The United States Patent and Trademark Office
PATENT TRIAL AND APPEAL BOARD

DANIELLE L. HERRITT
MCCARTER & ENGLISH LLP,
265 FRANKLIN STREET
BOSTON, MA 02110

Appeal No:	2014-007,671
Appellant:	DANIELLE L. HERRI TT(3RD.PTY.REQ.), BIO
Reexam Control No:	DELIVERY SCIENCE INTERNATIONet al.
Hearing Room:	95/002,170
Hearing Docket:	B
Hearing Date:	A
Hearing Time:	Wednesday, November 05, 2014
Location:	01:00 PM
	Madison Building - East Wing
	600 Dulany Street, 9th Floor
	Alexandria, Virginia 22313-1450

NOTICE OF HEARING
RESPONSE REQUIRED WITHIN 21 DAYS

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Request: ELMO Projector

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Kia L. Freeman (Reg. No. 47,577)

Danielle L. Herritt — 43,670

Typed or Printed Name of Attorney/Agent/Appellant — Registration No.

( ) PATENT OWNER (X) THIRD PARTY REQUESTER

/Danielle L. Herritt/ — November 4, 2014

Signature of Attorney/Agent/Appellant — Date

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cc: Patent Owner

HOFFMANN & BARON LLP
6900 JERICHO TURNPIKE
SYOSSET, NY 11791

US Patent No. 7,897,080
Appeal No. 2014-007,671
Reexamination No.: 95/002,170
117744-00023

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Daniel A. Scola, Jr.

HOFFMANN & BARON, LLP

6900 JERICHO TURNPIKE

SYOSSET, NY 11791

By: /Danielle L. Herritt/
Danielle L. Herritt
Registration No. 43,670
Attorney for Third Party Requester

Electronic Acknowledgement Receipt

EFS ID:	20598225
Application Number:	95002170
International Application Number:	
Confirmation Number:	6418
Title of Invention:	POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM
First Named Inventor/Applicant Name:	7897080
Customer Number:	23869
Filer:	Danielle L. Herritt/Maureen Tierney
Filer Authorized By:	Danielle L. Herritt
Attorney Docket Number:	117744-00023
Receipt Date:	04-NOV-2014
Filing Date:	10-SEP-2012
Time Stamp:	11:08:31
Application Type:	inter partes reexam

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		080THIRDUpdatedHearingConfirmation2014NOV4.PDF	1084338 cd9572cb8a48233f01ed5ff79fea63522be8c6f7	yes	4

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Reexam Miscellaneous Incoming Letter	1	3
	Reexam Certificate of Service	4	4
Warnings:			
Information:			
	Total Files Size (in bytes):	1084338	

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New International Application Filed with the USPTO as a Receiving Office
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UPDATED -- UPDATED -- UPDATED

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Deborah M. Vernon (Reg. No. 55,699)

Danielle L. Herritt — 43,670

Typed or Printed Name of Attorney/Agent/Appellant — Registration No.

( ) PATENT OWNER (X) THIRD PARTY REQUESTER

/Danielle L. Herritt/ — November 3, 2014

Signature of Attorney/Agent/Appellant — Date

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cc: Patent Owner

HOFFMANN & BARON LLP
6900 JERICHO TURNPIKE
SYOSSET, NY 11791

US Patent No. 7,897,080
Appeal No. 2014-007,671
Reexamination No.: 95/002,170
117744-00023

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Daniel A. Scola, Jr.

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6900 JERICHO TURNPIKE

SYOSSET, NY 11791

By: /Danielle L. Herritt/
Danielle L. Herritt
Registration No. 43,670
Attorney for Third Party Requester

Electronic Acknowledgement Receipt

EFS ID:	20586357
Application Number:	95002170
International Application Number:	
Confirmation Number:	6418
Title of Invention:	POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM
First Named Inventor/Applicant Name:	7897080
Customer Number:	23869
Filer:	Danielle L. Herritt/Maureen Tierney
Filer Authorized By:	Danielle L. Herritt
Attorney Docket Number:	117744-00023
Receipt Date:	03-NOV-2014
Filing Date:	10-SEP-2012
Time Stamp:	12:29:39
Application Type:	inter partes reexam

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		080UpdatedHearingConfirmation2014NOV3.PDF	1107256 0652a7d5f46dcfac52e946e6140a3301921de2a8	yes	4

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Reexam Miscellaneous Incoming Letter	1	3
	Reexam Certificate of Service	4	4
Warnings:			
Information:			
	Total Files Size (in bytes):	1107256	

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US Patent No. 7,897,080
Appeal No. 2014-007,671
Reexamination No.: 95/002,170
117744-00023

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Daniel A. Scola, Jr.

HOFFMANN & BARON, LLP

6900 JERICHO TURNPIKE

SYOSSET, NY 11791

By: /Danielle L. Herritt/
Danielle L. Herritt
Registration No. 43,670
Attorney for Third Party Requester

Electronic Acknowledgement Receipt

EFS ID:	20595766
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International Application Number:	
Confirmation Number:	6418
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First Named Inventor/Applicant Name:	7897080
Customer Number:	23869
Filer:	Danielle L. Herritt/Maureen Tierney
Filer Authorized By:	Danielle L. Herritt
Attorney Docket Number:	117744-00023
Receipt Date:	03-NOV-2014
Filing Date:	10-SEP-2012
Time Stamp:	20:35:14
Application Type:	inter partes reexam

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		080SECONDUpdatedHearingConfirmation2014NOV3.PDF	1106481 7e59f1c3b37be069d63380f35a2829cfff482887	yes	4

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Reexam Miscellaneous Incoming Letter	1	3
	Reexam Certificate of Service	4	4
Warnings:			
Information:			
	Total Files Size (in bytes):	1106481	

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Appeal No. 2014-007671 of	)	
Inter Partes Reexamination of:	)	
US Patent No. 7,897,080	)	Confirmation No.: 6418
	)	
Named Inventor: Robert K. Yang *et al.*	)	Group Art Unit: 3991
	)	
Control No. 95/002,170	)	Examiner: Alan D. Diamond
	)	
Request Filed: September 10, 2012	)	M&E Docket: 117744-00023
	)	
Title: POLYETHYLENE OXIDE-BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM	)	H&B Docket: 1199-26 RCE/CON/REX

PATENT TRIAL and APPEAL BOARD
UNITES STATES PATENT AND TRADEMARK OFFICE
P.O. Box 1450
Alexandria, Virginia 22313-1450

UPDATE ON RELATED APPEAL

Both parties identified the appeal of the *inter partes* reexamination of US Patent No. 7,824,588 as a Related Appeal. See Appellant (MonoSol) Appeal Brief, March 10, 2014, at pp. 1-2 (referencing Appeal No. 2014-000547 of Reexamination Control No. 95/001,753); and BDSI's Respondent Brief in *Inter Partes* Reexamination, April 10, 2014, at p. 2 (with three exceptions, agreeing to Patent Owner's identification of Related Appeals and Interferences). Requester now updates the Board on the resolution of that related appeal and, for the Board's reference, provides the attached Decision on Appeal No. 2014-000547.

The attached Decision issued on April 17, 2014—after the respondent's brief was filed in this appeal. The attached Decision did not become final until June 17, 2014—after the briefing concluded in this appeal. The attached Decision on Appeal is relevant to issues in this appeal.

Respectfully submitted,

Attorneys for Requester, McCarter & English, LLP

Dated: October 17, 2014

By: /Danielle L. Herritt/

Danielle L. Herritt (Reg. No. 43,670)
Kia L. Freeman (Reg. No. 47,577)
Direct Dial: 617-449-6513

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Daniel A. Scola, Jr.

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6900 JERICHO TURNPIKE

SYOSSET, NY 11791

By: /Danielle L. Herritt/
Danielle L. Herritt
Registration No. 43,670
Attorney for Respondent

UNITED STATES PATENT AND TRADEMARK OFFICE

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United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
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www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
95/001,753	09/12/2011	7,824,588	117744-00016	6620

23869 7590 04/17/2014

Hoffmann & Baron LLP
6900 Jericho Turnpike
Syosset, NY 11791

EXAMINER	
DIAMOND, ALAN D	
ART UNIT	PAPER NUMBER
3991	

MAIL DATE	DELIVERY MODE
04/17/2014	PAPER

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The time period for reply, if any, is set in the attached communication.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE PATENT TRIAL AND APPEAL BOARD

BIODELIVERY SCIENCES INTERNATIONAL, INC.
Requester

v.

MONOSOL RX, LLC
Patent Owner and Appellant

Appeal 2014-000547
Reexamination Control 95/001,753
Patent 7,824,588 B2
Technology Center 3900

Before CHUNG K. PAK, JEFFREY B. ROBERTSON, and RAE LYNN P. GUEST, *Administrative Patent Judges*.

GUEST, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on appeal by the Patent Owner from the Patent Examiner's decision to reject pending claims in an *inter partes* reexamination of U.S. Patent 7,824,588 B2 (herein after the "'588 patent").[1]

[1] The '588 patent issued November 2, 2010, to Robert K. Yang, et al.

The Board's jurisdiction for this appeal is under 35 U.S.C. §§ 6(b), 134, and 315. We AFFIRM.

I. BACKGROUND

A request for *inter partes* reexamination under 35 U.S.C. §§ 311-318 and 37 C.F.R. §§ 1.902-1.997 for the '588 patent was filed on September 12, 2011, by a Third-Party Requester, BioDelivery Sciences International, Inc. (hereinafter "Requester"). *See* Request for *Inter Partes* Reexamination 1 (hereinafter "Request"); Requester's Respondent Brief, dated July 24, 2013 (hereinafter "Res. Br."). The Patent Owner and Appellant is MonoSol Rx, LLC (hereinafter "Patent Owner"). Patent Owner's Appeal Br. 1, dated June 24, 2013 (hereinafter "App. Br.").

The '588 patent is the subject of a litigation proceeding in the United States District Court for the District of New Jersey styled *MonoSol Rx, LLC v. BioDelivery Sciences Int'l, Inc.*, 10-cv-5695. The litigation is currently stayed pending the outcome of this Reexamination proceeding. *See* App. Br. 2.

An oral hearing was held March 26, 2014. A transcript of the hearing will be entered into the record in due course.

The '588 patent is directed to a method for forming a rapidly dissolving film containing an active ingredient evenly or uniformly distributed throughout the film. '588 patent, col. 1, ll. 35-42. According to the '588 patent, "uniform distribution is achieved by controlling one or more parameters, and particularly the elimination of air pockets prior to and during film formation and the use of a drying process that reduces

aggregation or conglomeration of the components in the film as it forms into a solid structure." *Id.* at col. 1, ll. 37-42.

The '588 patent originally contained claims 1-191. During reexamination, Patent Owner amended claim 1 and added new independent claims 192 and 193. Claims 1-193 are currently rejected by the Examiner.

Although Patent Owner appeals the rejection of all of the claims so rejected, with respect to independent claims 25 and 50 and the claims that depend therefrom, Patent Owner does not address the Examiner's specific findings and conclusions articulated in the rejections or explain why these positions are deficient. PO App. Br. 4. Accordingly, we summarily affirm the Examiner's rejections of claims 25 and 50 and the claims that depend therefrom.

Consistent with the arguments presented by Patent Owner, we address the rejections of claims 1-24, 75, 78, 81, 84, 87, 90, 93, 96, 99, 102, 105, 106, 111-132, 177, 178, 183, 186, 189, 192, and 193. *Id.*

Claims 1, 192 and 193 are at issue in this appeal and read as follows (with underlining showing additional language over the original patented claim):

> 1. A method of making a self-supporting therapeutic active-containing film comprising:
>
> (a) Mixing at least one edible polymer component, a therapeutic active composition, and at least one polar solvent to form a matrix;
>
> (b) Forming a wet film from said matrix, <u>said wet film having a substantially uniform content of therapeutic active composition throughout said wet film</u>;
>
> (c) Removing said polar solvent from said matrix with heat and/or radiation energy by exposing said matrix to a

temperature greater than the degradation temperature of said therapeutic active composition to form a self-supporting film;

wherein the temperature of the matrix is 100° C. or less during said step of removing said polar solvent from said matrix;

wherein the resulting self-supporting film maintains the substantially uniform content of therapeutic active composition per unit of film.

192. A method of making a self-supporting therapeutic active-containing film comprising:

(a) Mixing at least one edible polymer component, a therapeutic active composition and at least one polar solvent to form a matrix;

(b) Forming a wet film from said matrix, said wet film having a substantially uniform content of therapeutic active composition throughout said wet film;

(c) Removing said polar solvent from said matrix with heat and/or radiation energy by heating said matrix to a temperature that is less than the boiling point of said at least one polar solvent so as to form a viscoelastic film;

wherein the resulting viscoelastic film maintains the substantially uniform content of therapeutic active composition per unit of film.

193. A method of making a self-supporting therapeutic active-containing film comprising:

(a) Mixing at least one edible polymer component, a therapeutic active composition, and at least one polar solvent to form a matrix;

(b) Forming a wet film from said matrix, said wet film having a substantially uniform content of therapeutic active composition throughout said wet film;

(c) Using heat and/or radiation energy to remove said polar solvent from said matrix to form a self-supporting therapeutic active-containing film without forming bubbles;

wherein the resulting self-supporting film maintains the substantially uniform content of therapeutic active composition per unit of film.

REJECTIONS OF CLAIMS BASED ON SECTION 112

Claims 1-24, 75, 78, 81, 84, 87, 90, 93, 96, 99, 102, 105, 106, 111-132, 177, 178, 183, 186, 189, 192 and 193 stand rejected under 35 U.S.C. § 112, first and second paragraphs as indefinite, lacking in written description support, and lacking an enabling disclosure.

Claim 1 was amended during reexamination to recite a self-supporting therapeutic active-containing film in which there is "a substantially uniform content of therapeutic active composition" in both the wet film and maintained in the resulting self-supporting film "per unit of film." Claims 192 and 193 are new claims and have similar language to that added to claim 1.

The Examiner found that "[i]t is not clear exactly what is encompassed by a substantially uniform content of therapeutic active composition, and the '588 patent does not provide a definition for a substantially uniform content of therapeutic active composition." RAN at 9. The Examiner thus rejects the claim as being indefinite under 35 U.S.C. § 112, second paragraph, and as lacking adequate written descriptive support and lacking an enabling disclosure in the '588 patent under 35 U.S.C. § 112, first paragraph. *Id.* at 9-10. The Examiner further explains that "it is not clear how close to being uniform the product must be in order to be considered 'substantially uniform'. 'Substantially uniform' is not defined in the '588 patent." *Id.* at 68-69.

Patent Owner argues that the phrase "substantially uniform content of therapeutic active composition" means "a film having a degree of uniformity of ± 10% from the FDA label amount for the active per dosage unit." App. Br. 20.[2] In other words, the Patent Owner is arguing that the substantially uniform content must be defined with respect to a particular active content recognized and labeled by the FDA as a proper "dosage."

In support of this meaning, the Patent Owner points to the background of the '588 patent where the process of Fuchs is discussed as follows:

> dosage forms formed by processes such as Fuchs, would not likely meet the stringent standards of governmental or regulatory agencies, such as the U.S. Federal Drug Administration ("FDA"), relating to the variation of active in dosage forms. Currently, as required by various world regulatory authorities, dosage forms may not vary more than 10% in the amount of active present. When applied to dosage units based on films, this virtually mandates that uniformity in the film be present.

'588 patent, col. 2, ll. 25-44.

We disagree with the Patent Owner's interpretation of the phrase "substantially uniform content of therapeutic active composition." The

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[2] *Cf.* App. Br. 24 (defining the phrase as "a degree of uniformity sufficient to maintain the amount of active in each dosage unit within 10% of the FDA amount of active."); App. Br. 15 (defining only the term *uniformity* as "the amount of active present may not vary more than 10% from amount of the active set by the FDA, for example, in a unit dose (per unit of film, i.e. in a film unit)"); Patent Owner's Rebuttal Brief 3, dated September 9, 2013 (hereinafter "Reb. Br.") (defining the phrase as "a degree of uniformity consistent with FDA pharmaceutical products and must include the limited variation such that the amount of active present may not vary more than 10% from the amount of the active set by the FDA per unit of film, i. e. per therapeutic dosage unit.").

FDA standard identified by Patent Owner in the portion of the '588 patent reproduced supra, is not again referenced. In the remaining parts of the '588 patent, uniformity is characterized not with respect to an FDA recognized dosage, but with respect to the lack of agglomeration of active material in any part of the film. For example, the '588 patent states that the active material is "evenly distributed throughout the film," which is "achieved by . . . the use of a drying process that reduces aggregation or conglomeration of the components in the film as it forms into a solid structure." '588 patent, col. 1, ll. 37-42. An objective of the process is "a substantially non-self-aggregating uniform heterogeneity throughout the area of the films." *Id.* at col. 4, ll. 5-9. The '588 patent further describes "a substantially reduced occurrence of, i.e. little or no, aggregation or conglomeration of components within the film as is normally experienced when films are formed by conventional drying methods." *Id.*, col. 6, ll. 25-32. The process of the '588 patent provides "uniform distribution of components *for any given area in the film*." *Id.* at col. 7, ll. 26-29 (emphasis added).

Requiring a particular film to have an amount of active relative to a FDA recognized dosage considers the active amount in each individual "dosage unit" as compared to a particularly preferred or desired dosage. Patent Owner's interpretation disregards whether or not the active is agglomerated within the film and considers only a total amount of active material per dosage sized film rather than uniformity at *any given area in the film*, be it a small selected area, an area of the film consistent with a particular dosage, or an entire roll of film. Accordingly, the sentence relied

upon by the Patent Owner, stating that uniformity is "virtually mandated" by FDA requirements that the actual dosage be within a range of the labeled dosage, does not provide a definition of what would be considered "uniform," in light of the description of the '588 patent.

Further, the '588 patent describes three tests for determining uniformity. The first test was a visual inspection by "either the naked eye or under slight magnification. By viewing the films it was apparent that they were substantially free of aggregation, i.e. the carrier and the actives remained substantially in place and did not move substantially from one portion of the film to another." *Id.* at col. 28, ll. 1-9. This first test is not consistent with the Patent Owner's interpretation because the test does not measure the active content with respect to any particular desired dosage. Further, Patent Owner's interpretation does not exclude the presence of agglomerated particles, which is the purpose of the visual appearance test.

The second test involved cutting out "dosage forms" "from random locations throughout the film" and additively weighing the randomly selected dosage forms. *Id.* at col. 28, ll. 10-16. Table 2 shows that with each additional dosage form, the weight increased by exactly 0.04g. *Id.* at col. 28, ll. 19-65. The '588 patent explains that "each component has a unique density. Therefore, when the components of different densities are combined in a uniform manner in a film, as in the present invention, individual dosages forms from the same film of substantially equal dimensions, will contain the same mass." *Id.* at col. 29, ll. 3-9. This second test also is not consistent with the Patent Owner's interpretation because the test does not measure the active content with respect to any particular

desired dosage. Rather, the second test is directed towards comparing the active content at various locations on the same film.

The third test involved dissolving "individual doses" and testing for the amount of active in films of particular size. *Id.* at col. 29, ll. 10-12. The '588 patent states that "[t]his demonstrates that films of substantially similar size cut from different locations on the same film contain substantially the same amount of active." *Id.* at col. 29, ll. 13-15. Although the third test determines the actual amount of active within a dosage sized film, the third test also is not consistent with Patent Owner's interpretation because the test does not measure the active content with respect to any particular desired dosage. Rather, the third test is directed towards comparing the active content at various locations on the same film.

Accordingly, we conclude that the term "uniform" in the claims is not directed to uniformity as compared to a particular FDA dosage as proposed by Patent Owner, but rather non-agglomerated and evenly dispersed active content for any area of a given film.

This claim interpretation is more consistent with the Examiner's interpretation of the phrase "unit of film," with which the Patent Owner agrees. App. Br. 17. The Examiner determined that the phrase "unit of film" was broad, but definite, and indicated that "[i]t could be a roll of finished film, it could be a standard area of dried film before being cut, or it could be a dosage unit. Any size can be a unit." RAN 11.

Further, we agree with the Examiner that, while the term "uniform" appears definite in light of the '588 patent, we are not instructed as to the scope to which a film may be "substantially uniform." We are not provided

a degree of agglomeration or an amount of unevenly dispersed active material for which the film would still be acceptable. Considering that the second, additive-weight-based test shows only complete uniformity, with no additional films weighing more or less than exactly 0.04g, we are not instructed as to what deviation in weight would be considered "substantially uniform." Further, we are not provided the results of the dissolution test as evidence of a range of acceptable uniformity.

Words of degree may lack precision, but they do not necessarily render a claim indefinite. *Seattle Box Co., Inc. v. Indus. Crating & Packing, Inc.*, 731 F.2d 818, 826 (Fed. Cir. 1984) (A term of degree is definite if the specification "provides some standard for measuring that degree. . . . that is, whether one of ordinary skill in the art would understand what is claimed when the claim is read in light of the specification."). As discussed above, under the proper interpretation of the term "uniform," the '588 patent provides no standard or guidance by which the term "substantially" can be measured or determined. Nor is there any intrinsic and/or extrinsic evidence relied upon by Patent Owner to show that such term has a known meaning in the art. Thus, we agree with the Examiner that such relative expression, amenable to any number of plausible claim constructions, is deemed indefinite within the meaning of 35 U.S.C. § 112, second paragraph. *Ex parte Miyazaki*, 89 USPQ2d 1207, 1211 (BPAI 2008) ("[During prosecution of a patent application,] if a claim is amenable to two or more plausible claim constructions [upon giving it the broadest reasonable interpretation consistent with the Specification], the USPTO is justified in requiring the applicant to more precisely define the metes and bounds of the

claimed invention by holding the claim unpatentable under 35 U.S.C. § 112, second paragraph, as indefinite."); *see also In re Morris*, 127 F.3d 1048, 1056 (Fed. Cir. 1997) ("It is the applicants' burden to precisely define the invention, not the PTO's. *See* 35 U.S.C. § 112, ¶ 2 . . . . [T]his section puts the burden of precise claim drafting squarely on the applicant.").

Since we are unable to determine an acceptable degree of agglomeration or degree of uniformity for any area of a given film to be considered "substantially uniform," we decline to reach the question of whether the '588 patent provides written descriptive support and an enabling disclosure under 35 U.S.C. § 112, first paragraph. *In re Wilson*, 424, F.2d 1382, 1385 (CCPA 1970); *In re Steele*, 305 F.2d 859, 862 (CCPA 1962). However, we will address the propriety of the certain prior art rejections maintained by the Examiner for the sake of administrative and judicial efficiency because we need not understand the exact scope of "substantially uniform" to resolve certain prior art rejections and/or can give a certain conditional interpretation of "substantially uniform" to resolve certain prior art rejections as is readily apparent from the discussions below. *See, e.g., Ex parte Saceman*, 27 USPQ2d 1472, 1474 (Bd. Pat. App. & Int. 1993); *Ex parte Ionescu*, 222 USPQ 537, 540 (Bd. Pat. App. & Int. 1984).

REJECTIONS BASED ON CHEN

Claims 192 and 193 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Chen.[3] Claim 1 and the claims that depend therefrom stand

[3] WO 00/42992, published July 27, 2000, naming Li-Lan Chen et al. as inventors.

rejected under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious over Chen, either alone or view of additional prior art.[4] Patent Owner does not argue for the separate patentability of any dependent claims. Accordingly, the dependent claims stand or fall with claim 1.

Patent Owner contends that Chen fails to disclose a step of removing the polar solvent "by exposing the matrix to a temperature greater than the degradation temperature of said therapeutic active composition," as recited in claim 1.[5] Patent Owner argues that Chen teaches away from drying a film at a temperature above the degradation temperature of the therapeutic active composition. PO App. Br. 25-27. Patent Owner relies on the statement in Chen that the film is "dried under aeration at a temperature between 40-100°C so as to avoid destabilizing the agents contained within the formulation." *Id.* at 27; Chen, p. 15, ll. 19-29. Patent Owner argues that by this statement "Chen says such temperatures should be avoided" and that "Chen is concerned about keeping the temperature low to avoid destabilizing active agents." App. Br. 26 and 27.

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[4] Other additional art combined with Chen includes Le Person (Le Person, et al., "Near infrared drying of pharmaceutical thin films: experimental analysis of internal mass transport," Chem. Eng. Processing, Vol. 37, pp. 257-263 (1998)), Bernstein (US 5,656,297, issued August 12, 1997), Staab (US 5,393,528, issued February 28, 1995) and Hijiya (US 4,562,020, issued December 31, 1985).

[5] Patent Owner does not present separate the arguments with respect to claims 1, 192, and 193. However, only claim 1 includes a requirement that the temperature be greater than the degradation temperature of the therapeutic active composition.

We disagree with Patent Owner that Chen's statement suggests that higher temperatures "should be avoided" or "keeping the temperature low." Rather, Chen teaches a temperature range in order "to avoid destabilizing the agents contained within the formulation." Chen, p. 15, ll. 28-29. We disagree with Patent Owner that this statement would have suggested the skilled artisan limit the drying temperature to any particular temperature within the recited range of 40-100°C, provided that the film does not, in fact, result in degraded active ingredients. Thus, we find this statement in Chen consistent with the '588 patent. *See* '588 patent, col. 12, ll. 33-43.

Moreover, we agree with the Examiner that the skilled artisan would "have optimized Chen's drying step by using as high a drying temperature as possible within Chen's disclosed the range of 40-100°C without destabilizing the active agent because temperature is a results-effective variable with respect to active agent destabilization as taught by Chen; and so as to dry Chen's film as quickly as possible." RAN 28-29 and 74. We note that the example in Chen of drying for only 9 minutes (Chen, p. 17, ll. 13-15) is consistent with the description in the '588 patent of "drying the film within about 10 minutes or fewer." '588 patent, col. 7, ll. 33-35; *see* RAN 74. Patent Owner has not persuasively rebutted the Examiner's rationale as to the skilled artisan's reasonable optimization of temperatures within the range disclosed in Chen.

With respect to all of the claims on appeal, Patent Owner contends that Chen fails to disclose a film having a "substantially uniform content of therapeutic active composition per unit of film." According to Patent Owner, Chen does "not indicate or establish that the substantially uniform

content of the components is such that, for example, the amount of the active in individual dosage units varies by no more than 10% with respect to the desired/label amount for a particular film." App. Br. 28. Patent Owner argues that "[t]he actual degree of uniformity must be established through a determination of the actual amount of therapeutic active in at least samples of dosage units, which Chen does not disclose." *Id.* at 28 and 31-32. Patent Owner further argues that Figure 5 of Chen demonstrates that "in six instances the amount of active released from Chen's films is greater than 110% of the expected/desired amount." *Id.* at 30; Reb. Br. 5-6.

Initially, we note that Patent Owner's arguments substantially rely on Patent Owner's proposed claim interpretation which emphasizes uniformity with respect to a FDA-recognized dosage. For example, Patent Owner emphasizes a lack of evidence to support that the films of Chen are inherently within 10% of a recognized FDA dosage. Reb. Br. 5-6 Also, Patent Owner's arguments with respect to Figure 5 are exclusively related to release of an amount of active being more than 110% of "an expected/desired amount of pharmaceutical active for that drug." Reb. Br. 5.

We did not adopt the Patent Owner's proposed claim interpretation for the reasons discussed above and determine that the term "uniform content of therapeutic active composition" means non-agglomerated and evenly dispersed active content for any area of a given film, with the qualifier "substantially" expanding the scope to encompass some undefined agglomeration or some undefined degree of unevenly dispersed active material to also be acceptable. Accordingly, we do not find Patent Owner's arguments, including those regarding the release data over time in Figure 5

of Chen, to be compelling of a lack of uniformity. Figure 5 does not suggest agglomerated or unevenly dispersed active content for any area of a given film. Figure 5 merely indicates that different amounts of active material releases from the Chen films at various times, which is not shown to be an indicator that the active material is agglomerated or unevenly dispersed.

We agree with the Examiner that there is sufficient evidence to find that Chen inherently discloses a film with a substantially uniform content of therapeutic active composition per unit of film. RAN 21, 69-73, and 75.

In a case such as this where patentability rests upon a property of the claimed material not disclosed within the art, the PTO has no reasonable method of determining whether there is, in fact, a patentable difference between the prior art materials and the claimed material. Therefore, where the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily possess the characteristics of his claimed product. *In re Spada*, 911 F.2d 705, 708 (Fed. Cir. 1990); *In re Best*, 562 F.2d 1252, 1255 (CCPA 1977). However, the initial burden of presenting a case of unpatentability remains with the Requester and Examiner. If that burden is met, only then does the burden of coming forward with evidence or argument shift to the Patent Owner. *See In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992).

Although Patent Owner argues that the drying process of Chen is a conventional drying method that is distinguishable from the drying process of the '588 patent (App. Br. 29; Reb. Br. 14-15), we find that Chen describes

a substantially identical process to that described in the '588 patent. RAN 70 and 75.

Claim 1 does not recite any particular film drying steps. The evidence does not support Patent Owner's contention that the processes disclosed in Chen and in the '588 patent are clearly distinguishable. The '588 patent describes its drying process generally and does not clearly identify how a drying step can vary from a conventional drying process and avoid agglomerations of the active ingredients. For example, the '588 patent states that agglomerations form from "conventional drying methods such as a high-temperature air-bath using a drying oven, drying tunnel, vacuum drier, or other such drying equipment." However, the description of non-agglomerating drying methods in the '588 patent does not clearly distinguish such drying equipment. *See* col. 14, ll. 13-14 ("the inventive process is not limited to any particular apparatus for the above-described desirable drying."). The '588 patent is not limited to any particular drying methods but rather includes a variety of drying methods. *Id.* col. 7, ll. 6-25; col. 25, ll. 15-16 ("When a controlled or rapid drying process is desired, this may be through a variety of methods."). The only process clearly distinguished by the '588 patent is "uncontrolled air currents, either above or below the film" which "can create non-uniformity in the final film product." *Id.*, col. 7, ll. 19-21; *see also* col. 6, ll. 50-61; col. 12, ll. 47-57 ("The films are Controllably dried to prevent aggregation and migration of components, as well as preventing heat build up within."); col. 10, l. 67-col. 11, l. 4; col. 13, ll. 13-15; col. 25, ll. 2-8. The '588 patent does not exclude top air flow (*id.* at col. 11, ll. 6-23) nor does the '588 patent require bottom directed

drying, since it only describes this process as either exemplary or preferable. *See id.* at col. 6, ll. 53-58; col. 7, ll. 6-8; col. 12, ll. 56-57; col. 25, ll. 22-23.

Chen describes a process in which a film is dried in a "drying oven with aeration controller" as illustrated in Figure 2. Chen, p. 6, l. 2. Figure 2 is reproduced below.

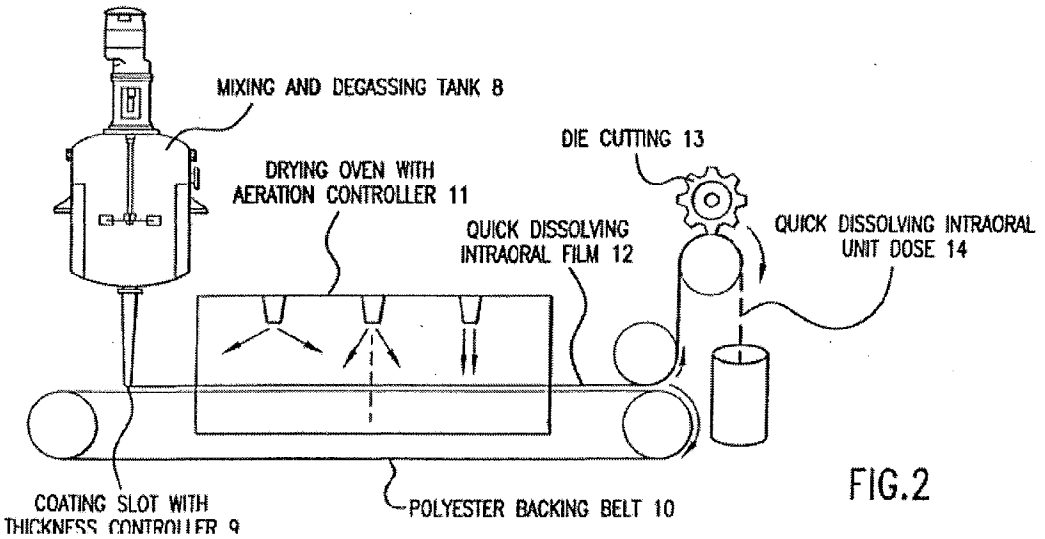

Figure 2 depicts a schematic of a manufacturing process for a dosage unit. Chen, p. 5, l. 31-p. 6, l. 3.

Figure 2 shows that at the initial drying stage, air currents are not directed onto the top of the film. Thus, we find that Chen teaches controlled drying and avoiding air currents directed onto the top surface of a film. The drying process of Chen is not sufficiently distinguished from the general drying method of the '588 patent.

Patent Owner's position is supported by the testimony of Dr. Rounds,[6] who testifies that Chen uses "a high presence of air flowing over the surface(s) of the wet film product" and that "uneven air currents flow[ing] over the wet film surface . . . can cause disruption of the fluid matrix and the components held therein, causing compositional non-uniformity of active content in the final, resulting film product." Rounds Decl. ¶ 16. We give little weight to Dr. Rounds' testimony because neither the "hot air circulating oven" nor the controlled air flow of Chen is distinguished from the equipment of the '588 patent. Dr. Rounds does not address Figure 2 which appears to show air diverted from the wet film surface consistent with the requirement for "controlled drying" in the '588 patent.

Moreover, the Examiner also finds that Chen's Table 4 describes weight per dosage film, thickness, density and water content measurements with minimal deviation as evidence that substantially uniform content of therapeutic active is inherent in the films described by Chen. RAN 15 and 71; *see* Chen p. 20, Table 4. The measured weight per dosage film as described in Chen is consistent with the additive weight test described in the '588 patent for determining uniformity. Specifically, the '588 patent states: "when the components of different densities are combined in a uniform manner in a film, as in the present invention, individual dosages forms from the same film of substantially equal dimensions, will contain the same mass." '588 patent, col. 29, ll. 4-9. Because the claims require only a "substantially uniform" film, which is broader than complete uniformity, but

[6] Declaration of Rhyta S. Rounds, dated January 9, 2012 and entered into the record on January 10, 2012 with Patent Owner's Response (hereinafter "Rounds Declaration" or "Rounds Decl.").

indefinite as to the degree of agglomeration or unevenly dispersed active material that would still be considered substantially uniform, for the purpose of applying art to the claims, we find that a weight deviation of ± 0.001 satisfies the limitation of "substantially uniform" active content. This amount is well within the less than 10% variation of active content per film unit requirement of claim 3.[7] Patent Owner does not persuasively show a distinction between the additive weight test of the '588 patent and the consistent weight measurements of Chen.

Accordingly, the Examiner's finding of inherency based on the processes of Chen and the '588 patent being "substantially identical" is supported by the evidence of record, as well as the Examiner's finding that Chen teaches films with consistent weight per unit film. Accordingly, the burden was properly shifted to Patent Owner to demonstrate that the process of Chen does not, in fact, teach a film having a substantially uniform content of therapeutic active composition per unit of film.

REJECTIONS BASED ON PEH

Claims 192 and 193 stand rejected under 35 U.S.C. § 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious over Peh,[8] either alone or in view of additional prior art.[9]

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[7] While Patent Owner does not clearly argue the limitation of claim 3 separately from independent claims 1, 192 and 193, we note that Patent Owner refers to claim 3 in distinguishing the scope over that of claim 1. App. Br. 23; Reb. Br. 3.

[8] Kok Khiang Peh et al., "Polymeric Films as Vehicle for Buccal Delivery: Swelling, Mechanical, and Bioadhesive Properties," J. Pharm. Pharmaceut. Sci., Vol. 2, No. 2, pp. 53-61 (1999).

In affirming the rejection of claims 192 and 193 as anticipated by Chen under 35 U.S.C. § 102(b) and as unpatentable under 35 U.S.C. § 112, it is unnecessary to address the additional rejections maintained by the Examiner for claims 192 and 193. *See In re Gleave*, 560 F.3d 1331, 1338 (Fed. Cir. 2009) (holding that obviousness rejections need not be reached upon affirming a rejection of all claims as anticipated).

SUMMARY

For the reasons discussed above, we affirm the Examiner's rejections of:

1. Claims 1-24, 75, 78, 81, 84, 87, 90, 93, 96, 99, 102, 105, 106, 111-132, 177, 178, 183, 186, 189, 192, and 193, under 35 U.S.C. § 112, as being indefinite;
2. Claims 25-28, 30-33, 35, 36, 40, 42-53, 55-58, 60, 61, 65, 67-74, 76, 77, 79, 80, 82, 83, 85, 86, 88, 89, 91, 92, 94, 95, 97, 98, 100, 101, 103, 104, 107-110, 133-139, 141-143, 155-161, 163-165, 179-182, 184, 185, 187, 188, 190-193 under 35 U.S.C. § 102(b) as being anticipated by Chen;
3. Claims 1-3, 5-8, 10, 11, 15, 17-24, 75, 78, 81, 84, 87, 90, 93, 96, 99, 102, 105, 106, 111-117, 119-121, 177, 178, 183, 186, and 189 under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious over Chen;
4. Claims 4, 14, 29, 39, 54, 64, 118, 140, and 162 under 35 U.S.C. § 103(a) as being unpatentable over Chen;
5. Claims 1, 122-132, 144-154 and 166-176 under 35 U.S.C. § 103(a) as being unpatentable over the combination of Chen and Le Person;
6. Claims 2, 5, 8, 9, 12, 15, 16, 18, 34, 37, 41, 59, 62, 66, 84, 99, 113, and 121 under 35 U.S.C. § 103(a) as being unpatentable over the combination of Chen and Bernstein;

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[9] Other additional art combined with Peh includes Le Person, Staab, Chen, Strobush (U.S. 5,881,476, issued March 16, 1999), Bernstein, and Hijiya.

7. Claims 13, 14, 17, 38, 39, 42, 63, 64 and 67 under 35 U.S.C. § 103(a) as being unpatentable over Chen in combination with Staab or Hijiya;
8. Claims 2, 5, 8, 15, 84, 99 and 113 under 35 U.S.C. § 103(a) as being unpatentable over the combination of Chen and Hijiya.

For the reasons discussed above, we do not reach the Examiner's rejections based on 35 U.S.C. § 112, first paragraph, or the Examiner's rejections based on the teachings of Peh alone or in view of additional prior art.

TIME PERIOD FOR RESPONSE

In accordance with 37 C.F.R. § 41.79(a)(1), the "[p]arties to the appeal may file a request for rehearing of the decision within one month of the date of: . . . [t]he original decision of the Board under § 41.77(a)." A request for rehearing must be in compliance with 37 C.F.R. § 41.79(b). Comments in opposition to the request and additional requests for rehearing must be in accordance with 37 C.F.R. § 41.79(c) & (d), respectively. Under 37 C.F.R. § 41.79(e), the times for requesting rehearing under paragraph (a) of this section, for requesting further rehearing under paragraph (d) of this section, and for submitting comments under paragraph (c) of this section may not be extended.

An appeal to the United States Court of Appeals for the Federal Circuit under 35 U.S.C. §§ 141-144 and 315 and 37 C.F.R. § 1.983 for an *inter partes* reexamination proceeding "commenced" on or after November 2, 2002 may not be taken "until all parties' rights to request rehearing have been exhausted, at which time the decision of the Board is final and appealable by any party to the appeal to the Board." 37 C.F.R.

§ 41.81. *See also* MPEP § 2682 (8th ed., Rev. 7, July 2008). In the event neither party files a request for rehearing within the time provided in 37 C.F.R. § 41.79, and this decision becomes final and appealable under 37 C.F.R. § 41.81, a party seeking judicial review must timely serve notice on the Director of the United States Patent and Trademark Office. *See* 37 C.F.R. §§ 90.1 and 1.983.

AFFIRMED

ak

PATENT OWNER:

Hoffmann & Baron, LLP
6900 Jericho Turnpike
Syosset, NY 11791

THIRD-PARTY REQUESTER:

McCarter & English, LLP
265 Franklin Street
Boston, MA 02110

Electronic Acknowledgement Receipt

EFS ID:	20450825
Application Number:	95002170
International Application Number:	
Confirmation Number:	6418
Title of Invention:	POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM
First Named Inventor/Applicant Name:	7897080
Customer Number:	23869
Filer:	Danielle L. Herritt/Maureen Tierney
Filer Authorized By:	Danielle L. Herritt
Attorney Docket Number:	117744-00023
Receipt Date:	17-OCT-2014
Filing Date:	10-SEP-2012
Time Stamp:	16:52:15
Application Type:	inter partes reexam

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Miscellaneous Incoming Letter	080UpdateOnRelatedAppealW588DecisionFINAL2014OCT17.PDF	1226067 41527131f7d795e12ccf33e7528a9e99bd58d6ba	no	26

Warnings:	
Information:	

Total Files Size (in bytes):	1226067

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

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New International Application Filed with the USPTO as a Receiving Office

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The United States Patent and Trademark Office
PATENT TRIAL AND APPEAL BOARD

DANIELLE L. HERRITT
MCCARTER & ENGLISH LLP,
265 FRANKLIN STREET
BOSTON, MA 02110

Appeal No:	2014-007,671
Appellant:	DANIELLE L. HERRI TT(3RD.PTY.REQ.), BIO
Reexam Control No:	DELIVERY SCIENCE INTERNATIONet al.
Hearing Room:	95/002,170
Hearing Docket:	B
Hearing Date:	A
Hearing Time:	Wednesday, November 05, 2014
Location:	01:00 PM
	Madison Building - East Wing
	600 Dulany Street, 9th Floor
	Alexandria, Virginia 22313-1450

NOTICE OF HEARING
RESPONSE REQUIRED WITHIN 21 DAYS

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CONFIRMATION OF ATTENDANCE OR WAIVER OF THE HEARING IS REQUIRED WITHIN **21 DAYS** OF THE MAILING DATE OF THIS NOTICE. Failure to respond will be treated as a waiver of your request to participate in the oral hearing. If you are no longer interested in participating in the oral hearing, you must still file a waiver of oral hearing with the Board. This allows the panel to promptly act on the appeal without waiting for the oral hearing date.

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http://www.uspto.gov/patents/process/file/efs/

2. Facsimile transmitted to: The USPTO Central fax number (official copy): **(571) 273-8300**
and the PTAB Hearing fax number (courtesy copy): **(571) 273-9797.**

3. By mail at the PTAB mailing address: Patent Trial and Appeal Board
United States Patent and Trademark Office
P.O. BOX 1450
Alexandria, Virginia 22313-1450

In all communications relating to this appeal, please identify the appeal by its number.

CHECK ONE:

(X) I previously filed my oral hearing request pursuant to 37 C.F.R. § 41.73(b).

( ) I am now filing my initial request to participate in the oral hearing pursuant to 37 C.F. R. § 41.73(d). A request for oral hearing and the fee set forth in 37 C.F.R. § 41.20(b)(3) are either attached to this hearing communication or have already been submitted.

CHECK ONE:

(X) IN-PERSON HEARING - ATTENDANCE CONFIRMED *(EFS-Web selection: Confirmation of Hearing by Appellant)*

( ) TELEPHONIC HEARING - ATTENDANCE CONFIRMED *(EFS-Web selection: Confirmation of Hearing by Appellant)*

( ) VIDEO HEARING - ATTENDANCE CONFIRMED *(EFS-Web selection: Confirmation of Hearing by Appellant)*

( ) HEARING ATTENDANCE WAIVED *(EFS-Web selection: Waiver of Hearing by Appellant)*

To aid the oral hearings staff in scheduling hearing rooms, please indicate the total number of participating and observing attendees if more than three are expected: _____
To aid the judges in determining whether any conflicts exist that may require a recusal, please list in the 'Comments' section the names of any additional person(s) who will be participating in the oral hearing. (Upon arrival, all persons presenting arguments must sign in at the Usher's desk.)

Comments/Special Requests:

Request: ELMO Projector

Danielle L. Herritt — 43,670

Typed or Printed Name of Attorney/Agent/Appellant — Registration No.

( ) PATENT OWNER (X) THIRD PARTY REQUESTER

/Danielle L. Herritt/ — October 2, 2014

Signature of Attorney/Agent/Appellant — Date

The 'Hearings' tab of the PTAB webpage http://www.uspto.gov/ip/boards/bpai/index.jsp provides additional information about oral hearings.

Please direct other inquiries to the PTAB Hearings Clerk at 571-272-9797.

cc: Patent Owner

HOFFMANN & BARON LLP
6900 JERICHO TURNPIKE
SYOSSET, NY 11791

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
95/002,170	09/10/2012	7897080	117744-00023	6418

23869 7590 09/16/2014

Hoffmann & Baron LLP
6900 Jericho Turnpike
Syosset, NY 11791

EXAMINER	
DIAMOND, ALAN D	
ART UNIT	PAPER NUMBER
3991	

MAIL DATE	DELIVERY MODE
09/16/2014	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

DRL - EXHIBIT 1007
DRL050

CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of the foregoing Third Party Requester's Confirmation of Attendance at Oral Hearing was served on October 2, 2014, by first class mail, directed to the patent owner at the correspondence address of record for the subject patent, that is:

Daniel A. Scola, Jr.

HOFFMANN & BARON, LLP

6900 JERICHO TURNPIKE

SYOSSET, NY 11791

By: /Danielle L. Herritt/
Danielle L. Herritt
Registration No. 43,670
Attorney for Third Party Requester

Electronic Acknowledgement Receipt

EFS ID:	20310915
Application Number:	95002170
International Application Number:	
Confirmation Number:	6418
Title of Invention:	POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM
First Named Inventor/Applicant Name:	7897080
Customer Number:	23869
Filer:	Danielle L. Herritt/Maureen Tierney
Filer Authorized By:	Danielle L. Herritt
Attorney Docket Number:	117744-00023
Receipt Date:	02-OCT-2014
Filing Date:	10-SEP-2012
Time Stamp:	13:48:05
Application Type:	inter partes reexam

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Reexam Miscellaneous Incoming Letter	080IPRxConfirmationOfAttendance2014OCT2.PDF	1107471 a223e7546a38b22d80e91a09f55dfb35ef776fed	no	4

Warnings:	
Information:	

2	Reexam Certificate of Service	080COSforConfirmationOfHearing2014OCT2.PDF	16036 03be71507f275d2cd70eea60aacac82e1e3f332f	no	1

Warnings:	
Information:	
Total Files Size (in bytes):	1123507

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The United States Patent and Trademark Office
PATENT TRIAL AND APPEAL BOARD

HOFFMANN & BARON LLP
6900 JERICHO TURNPIKE
SYOSSET, NY 11791

Appeal No:	2014-007,671
Appellant:	MONOSOL RX, LLC(OWNER), et al.
Reexam Control No:	95/002,170
Hearing Room:	B
Hearing Docket:	A
Hearing Date:	Wednesday, November 05, 2014
Hearing Time:	01:00 PM
Location:	Madison Building - East Wing 600 Dulany Street, 9th Floor Alexandria, Virginia 22313-1450

NOTICE OF HEARING
RESPONSE REQUIRED WITHIN 21 DAYS

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2. Facsimile transmitted to: The USPTO Central fax number (official copy): **(571) 273-8300**
and the PTAB Hearing fax number (courtesy copy): **(571) 273-9797.**

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United States Patent and Trademark Office
P.O. BOX 1450
Alexandria, Virginia 22313-1450

In all communications relating to this appeal, please identify the appeal by its number.

CHECK ONE:
(X) I previously filed my oral hearing request pursuant to 37 C.F.R. § 41.73(b).
( ) I am now filing my initial request to participate in the oral hearing pursuant to 37 C.F. R. § 41.73(d). A request for oral hearing and the fee set forth in 37 C.F.R. § 41.20(b)(3) are either attached to this hearing communication or have already been submitted.

CHECK ONE:
(X) IN-PERSON HEARING - ATTENDANCE CONFIRMED *(EFS-Web selection: Confirmation of Hearing by Appellant)*
( ) TELEPHONIC HEARING - ATTENDANCE CONFIRMED *(EFS-Web selection: Confirmation of Hearing by Appellant)*
( ) VIDEO HEARING - ATTENDANCE CONFIRMED *(EFS-Web selection: Confirmation of Hearing by Appellant)*
( ) HEARING ATTENDANCE WAIVED *(EFS-Web selection: Waiver of Hearing by Appellant)*

To aid the oral hearings staff in scheduling hearing rooms, please indicate the total number of participating and observing attendees if more than three are expected: 6
To aid the judges in determining whether any conflicts exist that may require a recusal, please list in the 'Comments' section the names of any additional person(s) who will be participating in the oral hearing. (Upon arrival, all persons presenting arguments must sign in at the Usher's desk.)

Comments/Special Requests:

ADDITIONAL PARTICIPANT: MICHAEL I. CHAKANSKY (REG. No. 31,600)
REQUEST: USE OF AN ELMO PROJECTOR & AV EQUIPMENT TO DISPLAY POWERPOINT SLIDES WITH USB CONNECTION

DANIEL A. SCOLA, JR. — 29,855
Typed or Printed Name of Attorney/Agent/Appellant — Registration No.

(X) PATENT OWNER ( ) THIRD PARTY REQUESTER

Signature of Attorney/Agent/Appellant

9/22/14
Date

The 'Hearings' tab of the PTAB webpage http://www.uspto.gov/ip/boards/bpai/index.jsp provides additional information about oral hearings.

Please direct other inquiries to the PTAB Hearings Clerk at 571-272-9797.

cc: Third Party Requester

DANIELLE L. HERRITT
MCCARTER & ENGLISH LLP,
265 FRANKLIN STREET
BOSTON, MA 02110

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
95/002,170	09/10/2012	7897080	117744-00023	6418

23869 7590 09/16/2014

Hoffmann & Baron LLP
6900 Jericho Turnpike
Syosset, NY 11791

EXAMINER	
DIAMOND, ALAN D	
ART UNIT	PAPER NUMBER
3991	

MAIL DATE	DELIVERY MODE
09/16/2014	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

CERTIFICATE OF FIRST CLASS SERVICE

It is certified that a copy of the foregoing Patent Owner's Confirmation of Attendance at Oral Hearing was served, by first class mail, postage prepaid, on September 22, 2014, in its entirety on the Respondent, Third Party Requester (Respondent) as provided in 37 CFR § 1.903, 37 CFR § 1.248 and 37 C.F.R. § 41.73(b) at the address below.

DANIELLE L. HERRITT
McCARTER & ENGLISH LLP
265 FRANKLIN STREET
BOSTON, MASSACHUSETTS 02110

/Michael I. Chakansky/
Michael I. Chakansky
Registration No.: 31,600
Attorney for the Patentee/Appellant

Electronic Acknowledgement Receipt

EFS ID:	20200964
Application Number:	95002170
International Application Number:	
Confirmation Number:	6418
Title of Invention:	POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM
First Named Inventor/Applicant Name:	7897080
Customer Number:	23869
Filer:	Michael I. Chakansky
Filer Authorized By:	
Attorney Docket Number:	117744-00023
Receipt Date:	22-SEP-2014
Filing Date:	10-SEP-2012
Time Stamp:	12:00:11
Application Type:	inter partes reexam

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Confirmation of Hearing by Appellant	PatentOwnersConfirmation.pdf	1722712 1f3252299a946da668adf805ff5a386f146a9a2b	no	5

Warnings:	
Information:	

Total Files Size (in bytes):	1722712

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

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UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
95/002,170	09/10/2012	7897080	117744-00023	6418

23869 7590 09/16/2014

Hoffmann & Baron LLP
6900 Jericho Turnpike
Syosset, NY 11791

EXAMINER	
DIAMOND, ALAN D	

ART UNIT	PAPER NUMBER
3991	

MAIL DATE	DELIVERY MODE
09/16/2014	PAPER

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The United States Patent and Trademark Office
PATENT TRIAL AND APPEAL BOARD

DANIELLE L. HERRITT
MCCARTER & ENGLISH LLP,
265 FRANKLIN STREET
BOSTON, MA 02110

Appeal No:	2014-007,671
Appellant:	DANIELLE L. HERRI TT(3RD.PTY.REQ.), BIO
Reexam Control No:	DELIVERY SCIENCE INTERNATIONet al.
Hearing Room:	95/002,170
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Comments/Special Requests:

_____

_____

Typed or Printed Name of Attorney/Agent/Appellant	Registration No.

( ) PATENT OWNER ( ) THIRD PARTY REQUESTER

Signature of Attorney/Agent/Appellant	Date

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cc: Patent Owner

HOFFMANN & BARON LLP
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
95/002,170	09/10/2012	7897080	117744-00023	6418

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DIAMOND, ALAN D	

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SYOSSET, NY 11791

Appeal No:	2014-007,671
Appellant:	MONOSOL RX, LLC(OWNER), et al.
Reexam Control No:	95/002,170
Hearing Room:	B
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RESPONSE REQUIRED WITHIN 21 DAYS

Your attention is directed to 37 CFR § 41.73. The above identified appeal will be heard by the Patent Trial and Appeal Board on the date indicated. Hearings will commence at the time set, and as soon as the argument in one appeal is concluded, the succeeding appeal will be taken up. **The time allowed for argument is 30 minutes** for each appellant or respondent who has requested an oral hearing, unless additional time is requested and approved before the argument commences. **As the hearing relates to an appeal of a reexamination, the hearing will be open to the public.**

Pursuant to § 41.73(d), if any other party to the appeal desires to participate in the oral hearing, but did not request an oral hearing pursuant to § 41.73(d), i.e., within two months after the mailing date of the Examiner's Answer, then this other party will be permitted to participate in the hearing by filing a separate request for oral hearing and the fee set forth in 37 C.F.R. § 41.20(b)(3) within 21 DAYS of the mailing date of this Notice, as well as a confirmation of attendance at the oral hearing.

CONFIRMATION OF ATTENDANCE OR WAIVER OF THE HEARING IS REQUIRED WITHIN **21 DAYS** OF THE MAILING DATE OF THIS NOTICE. Failure to respond will be treated as a waiver of your request to participate in the oral hearing. If you are no longer interested in participating in the oral hearing, you must still file a waiver of oral hearing with the Board. This allows the panel to promptly act on the appeal without waiting for the oral hearing date.

Confirmation or waiver of the hearing should be indicated by completing the form below and returning it to the Board. This form may be filed with the Board by any one of the following three alternative methods:

1. ***PREFERRED***: Via the USPTO Electronic Filing System (EFS) at

http://www.uspto.gov/patents/process/file/efs/

2. Facsimile transmitted to: The USPTO Central fax number (official copy): **(571) 273-8300**
and the PTAB Hearing fax number (courtesy copy): **(571) 273-9797.**

3. By mail at the PTAB mailing address: Patent Trial and Appeal Board
United States Patent and Trademark Office
P.O. BOX 1450
Alexandria, Virginia 22313-1450

In all communications relating to this appeal, please identify the appeal by its number.

CHECK ONE:
( ) I previously filed my oral hearing request pursuant to 37 C.F.R. § 41.73(b).
( ) I am now filing my initial request to participate in the oral hearing pursuant to 37 C.F. R. § 41.73(d). A request for oral hearing and the fee set forth in 37 C.F.R. § 41.20(b)(3) are either attached to this hearing communication or have already been submitted.

CHECK ONE:
( ) IN-PERSON HEARING - ATTENDANCE CONFIRMED *(EFS-Web selection: Confirmation of Hearing by Appellant)*
( ) TELEPHONIC HEARING - ATTENDANCE CONFIRMED *(EFS-Web selection: Confirmation of Hearing by Appellant)*
( ) VIDEO HEARING - ATTENDANCE CONFIRMED *(EFS-Web selection: Confirmation of Hearing by Appellant)*
( ) HEARING ATTENDANCE WAIVED *(EFS-Web selection: Waiver of Hearing by Appellant)*

To aid the oral hearings staff in scheduling hearing rooms, please indicate the total number of participating and observing attendees if more than three are expected: ____
To aid the judges in determining whether any conflicts exist that may require a recusal, please list in the 'Comments' section the names of any additional person(s) who will be participating in the oral hearing. (Upon arrival, all persons presenting arguments must sign in at the Usher's desk.)

Comments/Special Requests:

_____

_____

_____ _____
Typed or Printed Name of Attorney/Agent/Appellant Registration No.

( ) PATENT OWNER ( ) THIRD PARTY REQUESTER

_____ _____

Signature of Attorney/Agent/Appellant Date

The 'Hearings' tab of the PTAB webpage http://www.uspto.gov/ip/boards/bpai/index.jsp provides additional information about oral hearings.

Please direct other inquiries to the PTAB Hearings Clerk at 571-272-9797.

cc: Third Party Requester

DANIELLE L. HERRITT
MCCARTER & ENGLISH LLP,
265 FRANKLIN STREET
BOSTON, MA 02110

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
95/002,170	09/10/2012	7897080	117744-00023	6418

23869 7590 07/12/2014

Hoffmann & Baron LLP
6900 Jericho Turnpike
Syosset, NY 11791

EXAMINER
DIAMOND, ALAN D

ART UNIT	PAPER NUMBER
3991	

MAIL DATE	DELIVERY MODE
07/12/2014	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

United States Patent and Trademark Office

Under Secretary of Commerce for Intellectual Property and
Director of the United States Patent and Trademark Office
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

HOFFMANN & BARON LLP
6900 JERICHO TURNPIKE
SYOSSET, NY 11791

Appeal No: 2014-007671
Inter Partes Reexamination
Control No: 95/002,170
Appellant: 7897080 et al.

Patent Trial and Appeal Board Docketing Notice

Inter Partes Reexamination Control No. 95/002,170 was received from the Technology Center at the Board on July 08, 2014 and has been assigned Appeal No: 2014-007671.

In all future communications regarding this appeal, please include both the Inter Partes Reexamination Control Number and the appeal number.

The mailing address for the Board is:

PATENT TRIAL and APPEAL BOARD
UNITED STATES PATENT AND TRADEMARK OFFICE
P.O. BOX 1450
ALEXANDRIA, VIRGINIA 22313-1450

Telephone inquiries can be made by calling 571-272-9797 and referencing the appeal number listed above.

By order of the Patent Trial and Appeal Board.

JAG

cc: Third Party Requester

DANIELLE L. HERRITT
MCCARTER & ENGLISH LLP,
265 FRANKLIN STREET

BOSTON, MA 02110

PTO/AIA/32 (03-13)
Approved for use through 03/31/2013. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under thePaperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

REQUEST FOR ORAL HEARING BEFORE THE PATENT TRIAL AND APPEAL BOARD

Docket Number (Optional): 117744-00023

I hereby certify that this correspondence is being facsimile transmitted to the USPTO, EFS-Web transmitted to the USPTO, or deposited with the United States Postal Service with sufficient postage in an envelope addressed to "Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450" [37 CFR 1.8(a)]

on June 25, 2014.

Signature /Danielle L. Herritt/

Typed or printed name Danielle L. Herritt

In re Application of
Yang et al. (USPN 7,897,080)

Application Number	Filed
95/002,170	September 10, 2012

For
POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM

Art Unit	Examiner
3991	Alan D. Diamond

Applicant hereby **requests an oral hearing** before the Patent Trial and Appeal Board in the appeal of the above-identified application.

The fee for this Request for Oral Hearing is (37 CFR 41.20(b)(3)) $ 1,300.00

☐ Applicant asserts small entity status. See 37 CFR 1.27. Therefore, the fee shown above is reduced by 50%, and the resulting fee is: $ _____

☐ Applicant certifies micro entity status. See 37 CFR 1.29. Therefore, the fee shown above is reduced by 75%, and the resulting fee is: $ _____
Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☑ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. 50-4876.

☐ Payment made via EFS-Web.

☐ A petition for an extension of time under 37 CFR 1.136(b) (PTO/SB/23 or equivalent) is enclosed.
For extensions of time in reexamination proceedings, see 37 CFR 1.550.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

I am the

☐ applicant

☑ attorney or agent of record
Registration number 43,670

☐ attorney or agent acting under 37 CFR 1.34
Registration number _____

Signature /Danielle L. Herritt/

Typed or printed name Danielle L. Herritt

Telephone Number 617-449-6513

Date June 25, 2014

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.

☑ * Total of 1 forms are submitted.

This collection of information is required by 37 CFR 41.20(b)(3). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11, 1.14 and 41.6. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of the foregoing Respondent's Request for Oral Hearing (PTO/AIA/32) was served on June 25, 2014, by first class mail, directed to the patent owner at the correspondence address of record for the subject patent at the following address:

Daniel A. Scola, Jr.

HOFFMANN & BARON, LLP

6900 JERICHO TURNPIKE

SYOSSET, NY 11791,

By: /Danielle L. Herritt/
Danielle L. Herritt
Registration No. 43,670
Attorney for Respondent

Electronic Patent Application Fee Transmittal

Application Number:	95002170
Filing Date:	10-Sep-2012
Title of Invention:	POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM
First Named Inventor/Applicant Name:	7897080
Filer:	Danielle L. Herritt/Maureen Tierney
Attorney Docket Number:	117744-00023

Filed as Large Entity

inter partes reexam Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Request for Oral Hearing	1403	1	1300	1300
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**1300**

Electronic Acknowledgement Receipt

EFS ID:	19406732
Application Number:	95002170
International Application Number:	
Confirmation Number:	6418
Title of Invention:	POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM
First Named Inventor/Applicant Name:	7897080
Customer Number:	23869
Filer:	Danielle L. Herritt/Maureen Tierney
Filer Authorized By:	Danielle L. Herritt
Attorney Docket Number:	117744-00023
Receipt Date:	25-JUN-2014
Filing Date:	10-SEP-2012
Time Stamp:	13:49:55
Application Type:	inter partes reexam

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$1300
RAM confirmation Number	13453
Deposit Account	504876
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Oral Hearing Request - Third Party Requester	080RequestforOralHearing2014JUN25.PDF	321333 43fe781ca644cca14239ba2f398ed58fa230adec	no	2
Warnings:					
Information:					
2	Reexam Certificate of Service	080COSforRequestforOralHearing2014JUN25.PDF	5691 c36aa7cf417168fcc2463514a000816c4d2076ae	no	1
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	30054 44af82b34f1a4f2912ed6da07701f202596b0214	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	357078		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inter Partes Reexamination of Yang et al.	Examiner: Alan D. Diamond
U.S. Patent No. 7,897,080	Group Art Unit: 3991
Reexamination Control No. 95/002,170	Confirmation No. 6418
Filed: September 10, 2012	H&B Docket: 1199-26 RCE/CON/REX M&E Docket: 117744-00023

For: POLYETHYLENE-OXIDE BASED FILMS AND
DRUG DELIVERY SYSTEMS MADE THEREFROM

REQUEST FOR ORAL HEARING

Mail Stop *Inter Partes* Reexam
Central Reexamination Unit
Commissioner for Patents
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

Certificate of EFS-Web Transmission
I hereby certify that this correspondence is being transmitted via the U.S. Patent and Trademark Office electronic filing system (EFS-Web) to the USPTO on June 17, 2014.

Signed: Michael I. Chakansky /Michael I Chakansky/Reg. No. 31,600

Dear Madame:

Patent owner MonoSol Rx, LLC (Appellant) hereby requests an oral hearing in the above-captioned proceeding. Appellant considers an oral hearing necessary and desirable for a proper presentation of its appeal. 37 C.F.R. § 41.73(a). This request is being timely submitted within two months after the examiner's answer, which was dated April 25, 2014, and includes a certification that same was served in its entirety on all other parties to the proceeding. Authorization is hereby provided to charge the fees due in connection with this submission to Deposit Account No. 08-2461. 37 C.F.R. § 41.73(b) and 37 C.F.R. § 41.20(b)(3).

Dated: June 17, 2014

Respectfully submitted,

/Daniel A. Scola, Jr./
Daniel A. Scola, Jr.
Registration No. 29,855

Michael I. Chakansky
Registration No. 31,600

HOFFMANN & BARON, LLP

6900 Jericho Turnpike
Syosset, New York 11791
(973) 331-1700

Attorneys for the Appellant, Patent Owner

CERTIFICATE OF FIRST CLASS SERVICE

It is certified that a copy of this **REQUEST FOR ORAL HEARING** has been served, by first class mail, postage prepaid, on June 17, 2014, in its entirety on the Respondent, Third Party Requester (Respondent) as provided in 37 CFR § 1.903, 37 CFR § 1.248 and 37 C.F.R. § 41.73(b) at the address below.

DANIELLE L. HERRITT
McCARTER & ENGLISH LLP
265 FRANKLIN STREET
BOSTON, MASSACHUSETTS 02110

/Michael I. Chakansky/
Michael I. Chakansky
Registration No.: 31,600
Attorney for the Patentee/Appellant

Electronic Patent Application Fee Transmittal

Application Number:	95002170
Filing Date:	10-Sep-2012
Title of Invention:	POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM
First Named Inventor/Applicant Name:	7897080
Filer:	Michael I. Chakansky
Attorney Docket Number:	117744-00023

Filed as Large Entity

inter partes reexam Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Request for Oral Hearing	1403	1	1300	1300
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**1300**

Electronic Acknowledgement Receipt

EFS ID:	19331811
Application Number:	95002170
International Application Number:	
Confirmation Number:	6418
Title of Invention:	POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM
First Named Inventor/Applicant Name:	7897080
Customer Number:	23869
Filer:	Michael I. Chakansky
Filer Authorized By:	
Attorney Docket Number:	117744-00023
Receipt Date:	17-JUN-2014
Filing Date:	10-SEP-2012
Time Stamp:	17:11:14
Application Type:	inter partes reexam

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$1300
RAM confirmation Number	4100
Deposit Account	
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if app.)

1	Oral Hearing Request-Owner	080RequestOralHearing.pdf	162438 7aea2ba861c83b6838d1be13a807bbc454ce6c3d	no	3
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30269 e84ebb6dafe6497274479287ef98d314af2efbf3	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	192707	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
95/002,170	09/10/2012	7897080	117744-00023	6418

23869 7590 06/04/2014

Hoffmann & Baron LLP
6900 Jericho Turnpike
Syosset, NY 11791

EXAMINER	
DIAMOND, ALAN D	

ART UNIT	PAPER NUMBER
3991	

MAIL DATE	DELIVERY MODE
06/04/2014	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

UNITED STATES DEPARTMENT OF COMMERCE
U.S. Patent and Trademark Office
Address : COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450

APPLICATION NO./ CONTROL NO.	FILING DATE	FIRST NAMED INVENTOR / PATENT IN REEXAMINATION	ATTORNEY DOCKET NO.
95/002,170	10 September, 2012	7897080	117744-00023

Hoffmann & Baron LLP
6900 Jericho Turnpike
Syosset, NY 11791

EXAMINER	
Alan Diamond	
ART UNIT	PAPER
3991	20140530

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner for Patents

The rebuttal brief filed May 27, 2014 by Patent Owner Appellant has been entered.

The rebuttal brief filed May 27, 2014 by Third Party Requester Appellant has been entered.

No further response by the specialist is appropriate. Any further reply/comments by any party will be not be considered, and may be returned to the party that submitted it. The reexamination proceeding is being forwarded to the Patent Trial and Appeal Board for decision on the appeal(s).

/Alan Diamond/
Patent Reexamination Specialist
Central Reexamination Unit 3991

PTO-90C (Rev.04-03)

Transmittal of Communication to Third Party Requester *Inter Partes* Reexamination	Control No.	Patent Under Reexamination	
	95/002,170	7897080	
	Examiner	Art Unit	
	Alan Diamond	3991	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address. --

(THIRD PARTY REQUESTER'S CORRESPONDENCE ADDRESS)

Danielle L. Herritt
McCarter & English LLP
265 Franklin Street
Boston, MA 02110

Enclosed is a copy of the latest communication from the United States Patent and Trademark Office in the above-identified reexamination proceeding. 37 CFR 1.903.

Prior to the filing of a Notice of Appeal, each time the patent owner responds to this communication, the third party requester of the *inter partes* reexamination may once file written comments within a period of 30 days from the date of service of the patent owner's response. This 30-day time period is statutory (35 U.S.C. 314(b)(2)), and, as such, it cannot be extended. See also 37 CFR 1.947.

If an *ex parte* reexamination has been merged with the *inter partes* reexamination, no responsive submission by any *ex parte* third party requester is permitted.

All correspondence relating to this inter partes reexamination proceeding should be directed to the **Central Reexamination Unit** at the mail, FAX, or hand-carry addresses given at the end of the communication enclosed with this transmittal.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re *Inter Partes* Reexamination of:	)	
	)	
US Patent No. 7,897,080	)	Confirmation No.: 6418
	)	
Named Inventor: Robert K. Yang *et al.*	)	Group Art Unit: 3991
	)	
Control No.: 95/002,170	)	Examiner: Alan D. Diamond
	)	
Request Filed: September 10, 2012	)	M&E Docket: 117744-00023
	)	
Title: POLYETHYLENE OXIDE-BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM	)	H&B Docket: 1199-26 RCE/CON/REX

Mail Stop *Inter Partes* Reexam
Attn: Central Reexamination Unit
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REBUTTAL BRIEF

BioDelivery Systems, Inc. ("BDSI") respectfully submits this rebuttal brief pursuant to 37 CFR 41.66 and 37 CFR 41.71 within one month of the Examiner's Answer.

Certificate Regarding Word Count Pursuant to 37 CFR 1.943(c)

I hereby certify that this Brief does not exceed 7,000 words in total length, based on WORD's count of the words beginning on page 1 and continuing through the end of the signature page in this brief.

Signed: Danielle L. Herritt /Danielle L. Herritt/ Reg. No. 43,670 Dated: May 27, 2014

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INTRODUCTION

In its April 10, 2014 Patent Owner's Cross-Respondent's Brief, MonoSol attempts to demonstrate that the newly-added recitations in the '080 patent are clear, enabled and/or supported by written description. But it does not do so by relying on the specification. Instead, MonoSol relies on unsupported attorney argument (*see*, *e.g.*, Section A below), third party declarations (*see*, *e.g.*, Section C), and/or inherency (*see*, *e.g.*, Section D). In other words, MonoSol has failed to present any arguments or rely on any evidence relevant to the proposed rejections under 35 USC 112. And MonoSol's interpretation of the claims, and in particular its interpretation of the newly-added recitations, has changed throughout this proceeding—making it difficult for the Office, and others, to understand how MonoSol's amended or new claims relate to, or are supported by, the specification of the '080 patent.

A. Claims Reciting the Term "*Suitable for Commercialization…*" Lack Clarity, Written Description, and Enablement.

MonoSol does not address BDSI's proposed rejections of the '080 claims containing the term "*suitable for commercialization and regulatory approval … including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage*

units" under 35 USC 112. MonoSol instead relies on several irrelevant arguments based on a mischaracterization of the Examining Panel's construction of this term. Nowhere does MonoSol identify the support from the '080 specification necessary to satisfy the requirements of Section 112.

1. MonoSol's shifting claim construction demonstrates the lack of clarity of the "*suitable for commercialization…*" term.

The newly-added claim term "*suitable for commercialization …*" is indefinite. *See* BDSI March 10, 2014 Appeal Brief in *Inter Partes* Reexamination ("Cross-Appeal Brief"), at 14-17, 20-21. By introducing yet another proposed construction of this added term, MonoSol further demonstrates the lack of clarity of this term.

a. *MonoSol's current proposed construction is inconsistent with the Panel's construction.*

In responding to BDSI's proposed rejection for lack of clarity, MonoSol mischaracterizes the Panel's construction of the "*suitable for commercialization…*" term. MonoSol claims "there is only one interpretation set forth by both the Examiner and MonoSol." MonoSol's April 10, 2014 Patent Owner's Cross-Respondent's Brief ("Cross-Respondent's Brief"), at 12:11-12.

However, as illustrated in the table below, the construction now proposed by MonoSol is not the Panel's construction.

Panel's Construction	MonoSol's Current Construction
"[T]he bright line test for such suitability is based on performing analytical chemical tests for uniformity of content of active, said tests showing a particular variation of active, for example, not more than 10%." RAN at 14:3-5.	"[S]uitability for commercialization and FDA approval in the context of the present invention is clearly directed to maintaining the uniformity of content of the pharmaceutical active from start to finish in the manufacture of the pharmaceutical resulting film. Moreover, commercialization inherently requires the ability to mass produce the films at scale and that film products from different manufacturing runs will fall within the FDA uniformity requirements." Cross-Respondent's Brief at 12:22-13:3.

There are multiple critical differences between MonoSol's current proposed construction and the Panel's construction. For example, the Panel's construction does not mention "mass production" or uniformity between "manufacturing runs." Neither the Panel's construction nor the claims mentions "maintaining the

uniformity of content of the pharmaceutical active" and the Panel's construction does not mention "maintaining" at all.[1]

b. *MonoSol's current proposed construction is inconsistent with its own previously proposed constructions.*

In its Cross-Respondent's Brief, MonoSol proposes a construction that is inconsistent with previous constructions it proposed during reexamination. Although MonoSol now argues that the term does not require that all requirements for FDA approval be met, MonoSol previously argued, in an attempt to distinguish the prior art, that the term should be construed to require compliance with FDA requirements. *See* March 13, 2013 Reply ("Reply-2") at 66:16-20 ("[BDSI] has not provided any proof that Chen's process examples … will provide a process suitable for commercial manufacture, a process which produces products which are regulatory approvable by the FDA…").

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[1] MonoSol criticizes the Clevenger Declaration for "not discussing suitability for FDA approval and commercialization in connection with *maintaining* the uniformity of content in the amount of active." Cross-Respondent's Brief at 15:2-5 (emphasis added). This criticism is misplaced. The Panel never defined "suitable for commercialization …" in terms of "maintaining" anything.

MonoSol's shifting and inconsistent construction of this term supports, rather than rebuts, BDSI's proposed rejection of the "*suitable for commercialization …*" term for lack of clarity under Section 112.

2. Lack of Written Description

MonoSol has not responded in substance to BDSI's proposed rejection for lack of written description for the "*suitable for commercialization…*" term. *See* Cross-Respondent's Brief at 12-15. MonoSol fails to identify any language in the '080 specification, examples, figures, or original claims purportedly supporting this newly-added recitation. *See id.*

For the sake of completeness, BDSI notes that MonoSol cites a single sentence from the '080 specification as alleged support for this recitation[2], which sentence reads "[o]ther factors, such as mixing techniques, also play a role in the manufacture of pharmaceutical film suitable for commercialization and regulatory approval." '080 patent at 3:58-60, *quoted in* Cross-Respondent's Brief at 8. This sentence by no means provides written description of "*suitable for commercialization …*," in particular in light of the Panel's construction of this term

[2] In addition to the preamble, MonoSol also relies on this single sentence as support for newly-added steps (e) and (f).

involving a "bright line test … based on performing analytical chemical tests." *See* RAN at 14:3-5.

3. Lack of Enablement

MonoSol has not responded in substance to BDSI's proposed rejection for lack of enablement for the newly-added term "*suitable for commercialization …*". *See* Cross-Respondent's Brief at 12-15.

Instead, MonoSol devotes over three pages of its Cross-Respondent's Brief to arguing that BDSI's interpretation of the Lin Declaration, together with its claim construction, is "absurd." *Id.* at 12-15. But MonoSol has failed to explain why. For example, BDSI has demonstrated that, when applying the standard outlined in the Lin Declaration—which mandates compliance with FDA requirements—the '080 patent is not enabled. Cross-Appeal Brief at 17-19. In response, MonoSol disavows its previous proposed construction, and does not explain how the '080 specification enables the newly-recited term under *any* construction. *See* Cross-Respondent's Brief at 12-15.

BDSI's proposed rejections based upon the newly-added "*suitable for commercialization…*" term are proper. The Panel erred by not adopting these rejections, as this newly-added term is not clear, is not described, and is not

enabled. MonoSol's Cross-Respondent Brief does not effectively rebut the lack of clarity, but demonstrates the lack of clarity by proposing yet another construction of this term.

B. Claims Reciting the Term "*Analytical Chemical Tests*" Lack Clarity and Written Description.

1. Lack of Clarity

MonoSol has not addressed BDSI's proposed rejection for lack of clarity of the "*analytical chemical tests*" term. *See* Cross-Appeal Brief at 16-19. Instead, MonoSol repeats and reproduces block quotations of the RAN. *Id.*

In the quoted passage from the RAN, the Panel found that the difference between chemical and physical testing is that chemical testing involves "direct testing for the amount of active." RAN at 16:24-26 *quoted in* Cross-Respondent's Brief at 17. MonoSol argues that Example M of the '080 patent is an example of analytical chemical testing because Example M describes the use of a spectrophotometer to measure light absorption, which produces measurements "directly related to the amount of active present." Cross-Respondent's Brief at 19. But MonoSol does not even say that the Example M testing is "direct *testing* for the amount of active." Accordingly, this passage does not support MonoSol's position or justify the Panel's failure to adopt this rejection.

2. Lack of Written Description

The term "*analytical chemical tests*" does not appear in the specification, a point which MonoSol does not dispute. *See* Cross-Respondent's Brief at 16-19.

MonoSol quotes several passages from the '080 specification, but none discusses the combination of "analytical" and "chemical" together in the context of testing for uniformity. Instead of demonstrating how the '080 patent provides written description, MonoSol merely relies upon the Panel's finding that "*analytical chemical tests*" requires direct testing for the amount of the claimed pharmaceutical and/or bioactive active. *Id.* at 17. MonoSol has failed to point out how the specification conveys to one of ordinary skill in the art this narrow definition of "*analytical chemical tests*." *See* MPEP 2163.02.

Further, in an attempt to distinguish the prior art, MonoSol argued for a narrower construction of "*analytical chemical tests*," one that excludes visual inspection and weight measurement. Reply-2 at 53-59. But MonoSol has not identified a single test in the '080 specification that meets its newly-invented criteria.

Instead, MonoSol only points to the use of a spectrophotometer to test for the concentration of dye in Example M. *See* Cross-Respondent's Brief at 19:4-5.

But it is undisputed that a dye is not a pharmaceutical or bioactive active, as claimed. *See* MonoSol September 3, 2013 Response to ACP, at 66. MonoSol has not explained how a test for the concentration of a dye would be useful in direct testing for a pharmaceutical or bioactive active, as claimed. Accordingly, MonoSol has failed to identify any written description in the '080 specification that supports the Examiner's non-adoption of BDSI's proposed rejection.

MonoSol claims that BDSI somehow admits that Example M "provides an actual example of using a chemical analytical test to determine directly the amount of active in films made by the '080 Patent processes." *See* Cross-Respondent's Brief at 19. BDSI admitted no such thing. It is unclear how MonoSol can make such a leap from the quoted language. A sentence stating that measuring active content would have been obvious does not support—or even suggest—that Example M of the '080 patent provides an example of "analytical chemical tests."

BDSI's proposed rejections based upon the newly-added term "analytical chemical tests" are proper. The Examiner erred by not adopting these rejections, as this newly-added term is neither clear nor described in the specification. For the reasons stated above, all claims should have been rejected under Section 112.

C. Claims Requiring that in a Film "*Active…Varies by No More Than 10%*" and "*Less than 5%| 2%|1%| 0.5%*" Lack Written Description, Clarity, and Enablement.

1. Lack of Written Description

MonoSol makes no substantive argument challenging BDSI's proposed rejection based on lack of written description for the recitations that "*active…varies by no more than 10%*" and "*less than 5%|2%|1%| 0.5%.*" *See* Cross-Respondent's Brief at 19:18-20:2. Instead, MonoSol alleges that BDSI raised this argument for the first time on appeal. This allegation is not true. BDSI made this argument during reexamination. *Compare* Apr. 12, 2013 Comment at 17:3-5 ("In over 100 examples, the '080 Patent never demonstrates that any disclosed method results in a film that satisfies the recited active variation limitation as determined by analytical chemical testing."), *with* Cross-Appeal Brief at 30:14-17 ("Again, despite over 100 examples and 150 total original pages of specification, the '080 patent discloses no method that results in a film that satisfied the new variation/uniformity recitation as verified by analytical chemical testing.").

Because MonoSol has not substantively addressed this proposed rejection, BDSI's arguments are apparently unopposed.

2. Lack of Clarity and Enablement

Although MonoSol purports to substantively challenge BDSI's proposed lack of enablement and clarity rejections based on recitations that active varies by no more than 10% and/or by less than 5%, 2%, 1%, or 0.5%—it does not make any arguments relevant to these proposed rejections. *See* Cross-Respondent's Brief at 19-26. Instead, MonoSol makes three irrelevant arguments: (a) that *Chen* allegedly teaches a process for producing films with 30% variation in weight, (b) that *Staab* allegedly teaches films that lack uniformity, and (c) that the Declaration of MonoSol's expert, Dr. Bogue, exemplifies the use of analytical chemical tests to show films with uniformity of content in the amount of active. *Id.* None of these arguments addresses BDSI's proposed lack of enablement and clarity rejections. Neither the teachings of the prior art references nor an expert's post-grant opinions cure the lack of enablement and clarity of the claims of the '080 patent.

a. Chen *does not cure the lack of clarity and enablement of claimed degrees of active uniformity within a film.*

MonoSol argues that *Chen* teaches that films made according to *Chen*'s process have a 30% variation in the amount of active between "separately manufactured films." Cross-Respondent's Brief at 22:2-4. This argument is irrelevant to the limitations at issue. The limitations at issue do not concern a

comparison between "separately manufactured films."[3] *See, e.g.*, step (f) of claim 1 and step (e) of claim 82.

Further, *Chen* discloses processes for manufacturing film with the recited "uniformity of content of said active in substantially equal sized individual dosage units of said visco-elastic film is such that the amount of the active varies by no more than 10%." *See Chen* Table 4, at 20 (disclosing that the dried film of *Chen*'s Example 1, when rounded to two decimal places, as in Table 2 of the '080 patent, is 0.03 g/ dosage film with a variation of 0%). Moreover, Dr. Reitman confirmed that film manufactured according to *Chen*'s Example 7 process featured that recited uniformity. *See* Declaration of Dr. Maureen Reitman, Exhibit 2 to Cross-Appeal Brief ("Reitman Decl."), at ¶7.

Most importantly, MonoSol's premise is flawed. Even if *Chen* did teach a manufacturing process that did not result in film with the recited uniformity, such teaching would not cure the lack of enablement and indefiniteness in the '080 patent claims.

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[3] The comparison is addressed with respect to the relevant limitation in section D below.

b. Staab *does not cure the lack of clarity and enablement of claimed degrees of active uniformity within a film.*

Similarly, MonoSol contends that *Staab* demonstrates film lacking the recited uniformity. Cross-Respondent's Brief at 23-24. Again, MonoSol's premise is flawed. Whether or not *Staab* discloses non-uniform films, the claims of the '080 patent reciting the claimed degrees of active uniformity within a film are still indefinite and not enabled.

Taking one line out of context in its effort to distinguish *Staab*, MonoSol extracts an incorrect desired amount of active for *Staab*. *See* Cross-Respondent's Brief at 23-24. MonoSol then argues that there is a 100% variation from that incorrect "desired" amount. *See id.* This is a new argument, which was never presented to the Panel.[4] But in any event, any difference with respect to a desired amount of active is not relevant because the limitation at issue is not directed to active variation *from a desired amount*.

MonoSol argues that *Staab* intended the exemplary film to contain 5% active (*i.e.*, 9.5 mg)—based on a misreading of the third line in the table on column 11 of *Staab*. *See* Cross-Respondent's Brief at 23 (relying on the line in *Staab*

[4] On the contrary, MonoSol argued to the Panel that *Staab*'s "perfect yield" was suspect. *See* Reply-2 at 69 (emphasis omitted).

"benzalkonium chloride (50% aqueous) … 10%"). But the sentence that introduces the relevant example in *Staab* identifies the intended amount as "19 mg of benzalkonium chloride." *Staab* at 11:24-25. And the following paragraph confirms that the amount intended was obtained: "[t]his procedure was utilized to produce two[-]inch square films each containing 19 mg benzalkonium chloride and about 190 mg in weight." *Id.* at 11:49-51. Thus, not only did *Staab* obtain 19 mg films, but *Staab* intended to do so.

According to *Staab*'s disclosure, the film dosages each contained 10% active—that is, the same active percentage. And importantly, by only addressing a difference from an alleged target, MonoSol does not dispute that the active in *Staab*'s film varies by no more than 10%, and/or by less than 5%, 2%, 1%, or 0.5%. *See* Cross-Respondent's Brief at 23-24.

c. *Example M and the declaration of MonoSol's expert cannot cure the lack of enablement and indefiniteness of the claims of the '080 patent.*

The third irrelevant argument raised by MonoSol, in an attempt to demonstrate clarity and/or enablement, is based upon an expert declaration submitted during the reexamination proceeding. Specifically, MonoSol relies upon the March 13, 2013 Declaration of Dr. Bogue to somehow support the Panel's non-

adoption of this rejection. Cross-Respondent's Brief at 25-26. It is unclear how this expert declaration providing uniformity data collected after the filing of the '080 patent could establish clarity or enablement.

Neither does MonoSol's reliance on Example M provide clarity and/or enablement for the multiple different degrees of uniformity of active claimed. *See, e.g.*, independent claims 1, 82, 315, and 318. Example M does not include a pharmaceutical and/or bioactive active and thus cannot enable the degrees of such active uniformity claimed.

For the reasons set forth in BDSI's Cross-Appeal Brief, the Panel erred by not adopting these rejections, as this newly-added term is not clear and is not enabled.

D. Claims Reciting the Term "*Repeating Steps (a) Through (e) to Form Additional Resulting Films…*" Lack Written Description, Enablement, and Clarity.

After MonoSol amended two of its claims to include a new step, step (f), wherein other methods steps are repeated to form additional films such that the active content in the resulting film and the additional films varies no more than 10% from the desired amount (*see* claims 82 and 315), BDSI properly raised

Section 112 rejections. This new step is not described anywhere in the '080 specification.

1. Lack of Written Description and Enablement

MonoSol neither addresses BDSI's proposed rejections nor demonstrates how the Panel's non-adoption is proper. Instead, MonoSol relies on irrelevant arguments that do not address written description and enablement.

a. *MonoSol fails to demonstrate written description or enablement.*

In an attempt to demonstrate written description and enablement, MonoSol cites a single passage from the background of the '080 specification. Cross-Respondent's Brief at 27. The passage reads: "[c]urrently, as required by various world authorities, dosage forms may not vary more than 10% in the amount of active present. When applied to dosage units based on films, this virtually mandates that uniformity in the film be present." '080 patent at 2:42-46, *quoted in* Cross-Respondent's Brief at 27. But this passage provides neither written description nor enablement for the "*repeating*" term, which includes the requirement that the resulting films and the additional films vary no more than 10% from the desired amount of active as indicated by analytical chemical tests. *See* '080 claims 82 and 315 at step (f).

MonoSol does not dispute BDSI's argument that there is no support in the '080 patent for a method that achieves one variation percentage within a resulting film, and second variation percentage between resulting films. *See* Cross-Appeal Brief at 34. This appears to be a post-grant idea.

Further, with respect to the lack of enablement, MonoSol cites part of claim 1 to somehow address the problem of maintaining uniformity. Cross-Respondent's Brief at 27-28 ("Moreover, the pending claims do enable by addressing the problem of maintaining uniformity. For example, claim 1 recites, *inter alia*, casting a flowable polymer matrix…"). With respect to enablement, MonoSol insists "No more is required." *Id.* at 28:7.

As an initial matter, claim 1 does not include the "*repeating*" step, which is the subject matter of this proposed 35 USC 112 rejection. Therefore, it is unclear how claim 1 enables this element or how, in MonoSol's words, "[n]o more is required." Specifically, if MonoSol's arguments or conclusion were true, then MonoSol has conceded that any prior art reference that discloses the claimed steps, such as *Chen*, is enabled and anticipates or renders obvious MonoSol's claims. In any event, as claim 1 does not enable this repeating step, MonoSol has failed to provide any explanation of why its claims are enabled.

As another irrelevant argument with respect to lack of enablement and written description, MonoSol appears to suggest that written description or enablement is not needed as it is inherent to its disclosure. Specifically, MonoSol states:

> Because the '080 Patent discloses processes which are suitable for commercialization, including scaling up and reproducibility, it is inherent that the process provides the same degree of uniformity in amount of active in dosage units produced from one manufacture of a resulting film to another manufacture of a resulting film and that the resulting films would be tested and should fall within the stated degree of uniformity.

Cross-Respondent's Brief at 28:13-18. As an initial matter, it is unclear how written description or enablement can be "inherent," and MonoSol fails to cite any authority for this proposition.

Further, this passage contains two apparent admissions. First, MonoSol appears to admit that any prior art reference that discloses the claimed materials and steps, such as *Chen*, inherently discloses the recited desired uniformity results between different manufacturing runs. Second, MonoSol appears to concede that the "analytical chemical testing" step implied in step (f) can be satisfied by performing the operative film-making process steps, without conducting an actual

analytical test. This is directly contrary to other arguments MonoSol has made. *See, e.g.*, MonoSol's March 10, 2014 Appeal Brief at 17:9-11 ("Only by analytical chemical testing is it possible to determine the actual amount of active present and hence whether uniformity of active content has been maintained during processing. This is the essence of the '080 Patent claims.").

b. Chen *does not cure the lack of written description and enablement of claimed active uniformity of separately manufactured films as compared to a target.*

MonoSol suggests that the newly-added "*repeating*" step is somehow enabled or described by the prior art *Chen* reference or the declaration of Dr. Reitman. Cross-Respondent's Brief at 27-28. This cannot be true. Prior art references and post-grant declarations do not provide written description or enablement for newly-added recitations to patents.

While more relevant to claims requiring separately manufactured films, MonoSol's misleading comparison of active in the *Chen* and Reitman films (*see* Cross-Respondent's Brief at 22:2-4) remains irrelevant to written description and enablement of those claims. MonoSol assumes a non-existent specific desired dosage weight for *Chen*'s Example 7—in its effort to distinguish *Chen*. *See* Cross-Respondent's Brief at 20-22. But *Chen* does not identify a desired dosage weight

for Example 7. On the contrary, *Chen* explains that "[t]he size of the film may be varied according to the dosage required." *Chen* at 16:5-6. *Chen* notes that "[t]he dosage form was 25-250 mg in various, shapes, sizes, and thicknesses." *Chen* at 17:18-19. In short, there is no basis for MonoSol's direct dosage weight comparison.

As a result, the only legitimate basis for comparison is the target active percentage, as recited in the limitation at issue. *See*, *e.g.*, '080 claims 82 and 315 at step (f). *Chen* discloses that the Example 7 coating solution includes 3.71% oxybutynin and 70.72% water. *See Chen* at 21:5-17, Table 5. *Chen* discloses that, after drying, the Example 7 film included 2.32% water. *See Chen* at 15:5, Table 6. The Example 7 film thus included 12.38% oxybutynin,[5] which may be considered the target oxybutynin percentage.

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[5] $composition_{film}$ = (other $ingredients_{solution}$ – $H_2O_{solution}$)+H_2O_{film}

= (100 – 70.72) + H_2O_{film} = 29.28 + H_2O_{film}

H_2O_{film} = 0.695 because 2.32% = H_2O_{film} / (29.28 + H_2O_{film})

$composition_{film}$ = 29.28 + 0.695 = 29.975

oxybutynin % = $oxybutynin_{film}$ / $composition_{film}$ = 3.71 / 29.975 = 12.38%

The oxybutynin percentage in each film that Dr. Reitman produced using *Chen*'s Example 7 process may be calculated for each sample, using the measured oxybutynin and the consistent sample weight. *See* Reitman Decl. ¶¶6-7 (for data). Dr. Reitman's samples A-E featured 12.94%[6], 12.94%, 12.65%, 12.94%, and 12.06% oxybutynin, respectively. *See id.* (for data). A comparison of the oxybutynin dosage percentages calculated from Dr. Reitman's data to the target oxybutynin percentage inferred from *Chen*'s Example 7 shows that Dr. Reitman's samples were each within 90 percent and 110 percent of the target (*i.e.*, within 11.14% and 13.61%). Indeed, the available data indicates that *Chen*'s process produces film featuring uniformity measures that are similar to those Dr. Bogue reported for SUBOXONE film lots. In short, Dr. Reitman's declaration provides additional objective evidence that film manufactured using *Chen*'s process features the active uniformity that MonoSol attempts to rely on to distinguish its claims.

In view of the foregoing, it was improper for the Panel not to adopt BDSI's proposed rejections for lack of enablement and written description. MonoSol's irrelevant arguments do not change this.

[6] 4.4 mg oxybutynin / 0.034 g total sample weight (1000 mg / 1 g) = 12.94%.

2. Lack of Clarity

MonoSol has not responded in substance to BDSI's proposed rejection for lack of clarity for the "*repeating*" recitation. *See* Cross-Respondent's Brief at 27-28.

Further, MonoSol's apparent admission described above—that step (f) can be satisfied without conducting an actual analytical test—further illustrates MonoSol's confusion and the resulting lack of clarity of this recitation. On one hand, when attempting to distinguish prior art, MonoSol argues that using analytical chemical tests to determine that the uniformity of active content has been maintained is the "essence" of the '080 patent. MonoSol's March 10, 2014 Appeal Brief at 17:9-11. On the other hand, when attempting to rebut rejections under Section 112, MonoSol argues that it is "inherent" that the claimed process produces uniformity of active content. *See* Cross-Respondent's Brief at 28:13-18. Either the act of analytical chemical testing is the "essence" of the claims or it is unnecessary. It cannot be both. MonoSol's inconsistent arguments further demonstrate the lack of clarity of claims reciting the "*repeating*" term.

E. Claims Reciting the Term "*Rapidly Increasing the Viscosity of Said Flowable Polymer Matrix*" Lack Clarity.

As explained in BDSI's Cross-Appeal Brief, the newly-added term "*rapidly increasing the viscosity of said flowable polymer matrix*" fails to recite any actual method step and creates ambiguity and confusion in the claims in which it appears. Cross-Appeal Brief at 35-37. MonoSol does not substantively address this proposed rejection.

Rather, MonoSol pastes into its Cross-Respondent's Brief the passage from the RAN describing the non-adoption of this proposed rejection, without any further explanation and without identifying any support for the Panel's decision. Cross-Respondent's Brief at 29:10-19. Then, after concluding without explanation that a case cited by BDSI is distinguishable, MonoSol cites another case for the proposition that "a comparative term…requires a reference point." *Id.* at 29:22-30:6 *quoting Playtex Prods., Inc. v. Procter & Gamble, Co.*, 400 F.3d 901, 908 (Fed. Cir. 2010). Finally, MonoSol concludes, without explanation, that "[i]n the instant claim recitation, rapidly's reference point is 'within about the first 4 minutes' of the start of evaporation of the solvent, and is therefore definite." Cross-Respondent's Brief at 30:6-8 (emphasis omitted). But simply referring to original claim language does not illuminate the meaning of the added claim language or somehow render it definite.

Because MonoSol has not substantively addressed this proposed rejection, BDSI's arguments are apparently unopposed.

F. Claims Reciting the Term "*Controlling Drying … During Said Drying Said Flowable Polymer Matrix Temperature is 100ºC or Less*" Lack Clarity.

During reexamination, the "controlling drying" step was amended to recite "*controlling drying … to form a visco-elastic film … wherein during said drying said flowable polymer matrix temperature is 100ºC or less.*" As explained in BDSI's Cross-Appeal Brief, it is unclear whether the "100ºC or less" recitation applies only the beginning or throughout the "controlling drying" step and therefore claims reciting that recitation lack clarity. Cross-Appeal Brief at 37-38. MonoSol has not substantively disputed this proposed rejection.

Instead, MonoSol quotes the passage of the RAN regarding the non-adoption of this proposed rejection and then reiterates the Panel's reasoning. Cross-Respondent's Brief at 31:8-13.[7] MonoSol does not offer support for the Panel's finding or dispute any of BDSI's arguments, instead concluding that the "claim language makes this clear." Cross-Respondent's Brief at 31:17-18.

[7] The relevance of MonoSol's comment—"[i]mportantly, the Examiner did not define visco-elasticity in terms of viscosity" (Cross-Respondent's Brief at

Because MonoSol has not substantively addressed this proposed rejection, BDSI's arguments are apparently unopposed.

G. (Adopted)

H. The Multiple New Expressions of Desired Variation/Uniformity Added to Different Steps and Combinations of Steps During Reexamination Lack Clarity, Written Description, and Enablement.

MonoSol does not dispute that the '080 patent includes no evidence or verification of uniformity of content of a pharmaceutical and/or bioactive active in the final step or in any of the intermediate steps where its new recitations require a specific uniformity. *Compare* Cross-Appeal Brief at 43 *with* Cross-Respondent's Brief at 34-35. It is true that working examples generally are not required, as noted correctly in the underlying reexamination. RAN at 21:27-28. But the '080 patent's failure to demonstrate the alleged key point of novelty creates problems in clarity, written description, and enablement because, in this case, MonoSol argues that its claims require a higher degree of uniformity than produced by the prior art, which disclose the same methods using the same materials and reporting the same uniformity using the same criteria as the instant claims. RAN at, *e.g.*, 82 (finding

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31:14)—is unclear. BDSI has not argued that visco-elastic and viscosity are identical.

Chen discloses the same methods using the same materials); *id.* at 77 (finding *Chen* achieves uniformity to the same degree using the same criteria set forth in the '080 patent). The alleged higher degree of uniformity is neither described nor demonstrated in the '080 patent specification. And it is unclear how the scope of the claimed methods differs from the methods disclosed in *Chen* and *Staab*.

1. Lack of Clarity

First, MonoSol states that "there are two ways to compare the amounts and both are correct depending upon the circumstance." Cross Respondent's Brief at 35. By that statement, MonoSol admits that there are at least two interpretations of their desired variation recitations. MonoSol's attorney argument about what "scientists" would know "depending upon the circumstance" is unsupported by evidence. *See id.* Because there are at least two interpretations of the desired variation recitations—recitations that MonoSol relies upon heavily in its arguments—claims containing this recitation lack clarity.

Second, MonoSol does not clarify whether the claims require testing with respect to the new recitations of uniformity in various intermediate steps, and if so, whether such testing may be analytical, visual or any other methods known in the art. *See* Cross Respondent's Brief at 34-35. This is especially important because

MonoSol has argued both for and against the criticality of directly measuring the amount of active.

Third, MonoSol did not clarify what "*indicating…*" in step (e) means or requires in the context of the uniformity recited thereafter. *Compare* Cross-Appeal Brief at 40:3-8 *with* Cross-Respondent's Brief at 34-35.

Finally, MonoSol has failed to point to any description of "additional films" or "resulting film" or how they relate to any methods or uniformity requirements, yet they have recited these features. *Compare* Cross-Appeal Brief at 40:9-18 *with* Cross-Respondent's Brief at 34-35.

2. Lack of Written Description

According to MonoSol, "[t]he '080 Patent expressly recognizes the need to test for uniformity by any and all means at various steps during the manufacturing process." Cross-Respondent's Brief at 34, *citing* '080 patent at 29:6-52. This statement has at least three problems.[8]

[8] Another problem is that it is unclear which discussion "supra" MonoSol references for support.

First, none of the claims broadly recite "testing by *any and all* means." MonoSol's statement, suggesting various uniformity recitations require testing by any and all means, introduces yet another clarity problem.

Second, "any and all means" is inconsistent with MonoSol's narrow definition of analytical chemical testing.

Third, again contrary to MonoSol's argument, this cited passage does not teach testing during intermediate steps. This passage clearly states that all samples are cut from the film *after drying*:

> A method for testing uniformity in accordance with the present invention includes conveying a film through a manufacturing process. This process may include subjecting the film to drying processes … the cut film *then* [*i.e.* after drying] may be sampled … [t]his can save time and expense because the process may be altered prior to completing an entire manufacturing run. For example, the drying conditions … may be changed. Altering the drying conditions may involve changing the temperature, drying time, moisture level, and dryer positioning, among others.

'080 Patent at 29:7-47 (emphasis added). The same is true for the block quotation at the bottom of page 34 of MonoSol's Cross Respondent's Brief, citing '080 patent at 29:47-52. This second quotation is completely silent with respect to testing for uniformity at intermediate steps.

In addition, MonoSol does not dispute the lack of written description for the claimed variation between "resulting" films and "additional" films. *Compare* Cross-Appeal Brief at 44 *with* Cross Respondent's Brief at 34-35. MonoSol fails to cite written support for "resulting" and "additional" films and other recitations identified at pages 43 and 44 in BDSI's Cross-Appeal Brief, such as "varying by no more than 10% from a desired target."

3. Lack of Enablement

First, apparently in an attempt to identify support for written description and/or enablement, MonoSol argues that testing at various steps "is an obvious step to add, for example, to ensure early on in the manufacturing process that the degree of uniformity is being maintained." Cross-Respondent's Brief at 35:13-17. This contrasts with MonoSol's amendment and arguments during the reexamination where MonoSol amended every independent claim and proposed four new independent claims with this "obvious" testing step, in an effort to overcome the prior art. *See* MonoSol's March 10, 2014 Appeal Brief at 17:9-11 ("*Only by analytical chemical testing* is it possible to determine the actual amount of active present and hence whether uniformity of active content has been maintained during processing. This is the essence of the '080 Patent claims.") (emphasis added); *see also* Reply-2 at 69:1-4.

Second, MonoSol does not dispute that it has added multiple new expressions of variation/uniformity to the claims, without reciting what new and non-obvious methods steps or conditions achieve them. *Compare* Cross-Appeal Brief at 38-39, *with* Cross-Respondent's Brief at 34-35. MonoSol does not dispute that, although the claimed methods have different uniformity requirements at different steps, there are no discernible operative process differences. *Compare* Cross-Appeal Brief at 39:6-8 *with* Cross Respondent's Brief at 34-35. For example, claim 16 recites "varies by no more than 10% " and claim 315 recites "varies by no more than 10% from the desired amount." But these two claims do not have different operative, film-making process steps: claims 315 and 316 are identical, except that 315 has the repeating step (which provides more films, but does not provide different films) and recites "desired amount." And these claims have no operative, film-making process steps that are not in the cited prior art.

Finally, MonoSol again does not dispute that the '080 patent lacks results of analytical chemical tests (as defined by MonoSol, *e.g.*, a dissolution test) measuring a pharmaceutical and/or bioactive active. *Compare* Cross-Appeal Brief at 43 *with* Cross Respondent's Brief at 34-35. Whether examples are required or optional (*see* Cross-Respondent's Brief at 35:12-13) is not relevant. MonoSol has (erroneously) criticized the prior art for not demonstrating the recited desired

results by direct measurement of pharmaceutical and/or bioactive active by assaying. Reply-2 at 51:4-8, 69:1-6. MonoSol has insisted that methods taught and exemplified in the '080 specification—visual inspection and dosage unit weights—"cannot be relied upon." *See* Reply-2 at 51:6. Therefore, according to MonoSol's own statements and definition, none of the '080 claims is enabled.

CONCLUSION

Because MonoSol has not substantively addressed the issues raised by BDSI in this Appeal, they are apparently unopposed.

In the event that any fee has been overlooked and is required, Commissioner is hereby authorized to charge all necessary fees to Deposit Account No. 50-4876 under Attorney Docket No. 117744-00023.

Respectfully submitted,

Attorneys for Requester, McCarter & English, LLP

Dated: May 27, 2014

By: /Danielle L. Herritt/

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of the Rebuttal Brief was served on May 27, 2014, by first class mail, directed to the patent owner at the correspondence address of record for the subject patent, that is:

Daniel A. Scola, Jr.

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Electronic Acknowledgement Receipt

EFS ID:	19138882
Application Number:	95002170
International Application Number:	
Confirmation Number:	6418
Title of Invention:	POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM
First Named Inventor/Applicant Name:	7897080
Customer Number:	23869
Filer:	Kia L. Freeman
Filer Authorized By:	
Attorney Docket Number:	117744-00023
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Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Rebuttal Brief - Requester	27March2014_BDSI080RebuttalBrief.pdf	142835 e5a414cd12f1d08147150e28fcc60e69ef0ef4ef	no	35

Warnings:

Information:

Total Files Size (in bytes):	142835

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inter Partes Reexamination of Yang et al.	Examiner: Alan D. Diamond
U.S. Patent No. 7,897,080	Group Art Unit: 3991
Reexamination Control No. 95/002,170	Confirmation No. 6418
Filed: September 10, 2012	H&B Docket: 1199-26 RCE/CON/REX M&E Docket: 117744-00023

For: POLYETHYLENE-OXIDE BASED FILMS AND
DRUG DELIVERY SYSTEMS MADE THEREFROM

PATENT OWNER'S
APPELLANT'S REBUTTAL BRIEF

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I hereby certify that this correspondence is being transmitted via the U.S. Patent and Trademark Office electronic filing system (EFS-Web) to the USPTO on May 27, 2014.

Signed: Michael I. Chakansky /Michael I Chakansky/Reg. No. 31,600

I hereby certify that, pursuant to 37 CFR § 1.943(c), based on the WordPerfect word count of 5868 words, plus a hand count of 362 words for the images on pages 18 and 19, for a total of 6230 words, Appellant's brief, counting the words on those pages beginning at page 1 (entitled Patent Owner's Appellant's Rebuttal Brief) and continuing through and including all words of the signature page (entitled Conclusion), does not exceed 7,000 words in length.

Signed: Michael I. Chakansky /Michael I Chakansky/Reg. No. 31,600

Dear Madame:

Patent owner MonoSol Rx, LLC (Appellant), pursuant to 37 C.F.R. § 41.71 and MPEP § 2678, hereby responds to the Examiner's Answer dated April 25, 2014, incorporating in its entirety the Right of Appeal Notice mailed December 6, 2013 (RAN), and BDSI's Respondent Brief in *Inter Partes* Reexamination mailed April 10, 2014 (BDSI's RB). This response (MRB)

filed and served on May 27, 2014, is timely as May 25, 2014 was a Sunday, and May 26, 2014 was Memorial Day, a federal holiday.

No fees are believed to be due. If however, there are any fees due in connection with this submission, authorization to charge such fees and authorization to credit any overpayments, to Deposit Account No. 08-2461, is hereby provided.

TABLE OF CONTENTS

PATENT OWNER'S APPELLANT'S REBUTTAL BRIEF

I. PRELIMINARY STATEMENT[1]

As noted in MonoSol's Appellant's Brief (MAB), the invention in U.S. Patent No. 7,897,080 (the " '080 Patent") is directed to novel and non-obvious processes for manufacturing pharmaceutical and bioactive active-containing films suitable for commercialization and regulatory approval by the U.S. Food and Drug Administration ("FDA"). The suitability is with respect to uniformity of content in the amount of active in the resulting films, such that:

(i) the degree of uniformity of content of the amount of active (*e.g.*, where the amount of active varies by no more that 10% between equally sized dosage units) throughout a single manufactured roll (lot) of resulting film can also be strictly maintained through the claimed processes; and

(ii) the degree of uniformity of content in the amount of active in individual dosage units (*e.g.*, where the amount of active in any equally sized dosage unit varies by no more than 10% from the expected or desired amount) taken from different manufactured rolls (lots) of resulting films can also be strictly maintained through the claimed processes.

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[1] This Rebuttal Brief offers additional arguments addressing the rejections and arguments set forth in the (i) Examiner's Answer dated April 25, 2014, which expressly incorporated in its entirety the Examiner's Right of Appeal Notice mailed December 6, 2013 (RAN), and (ii) BDSI's Respondent Brief in *Inter Partes* Reexamination mailed April 10, 2014 (BDSI's RB or BDSI's Respondent Brief). "The rebuttal brief of the owner may be directed to the examiner's answer and/or any respondent brief." 37 C.F.R. § 41.71(b)(1). As the Examiner's Answer incorporated the RAN in its entirety, MonoSol may and does direct the rebuttal brief herein to the RAN as well.

Moreover, commercialization requires the ability to mass produce the films at scale and to ensure that resulting film products from different manufactured lots (runs) reproducibly meet the requisite degree of uniformity in amount of drug.

As noted in Bogue Declaration I, EA-1, ¶ 4, **one manufactured lot of resulting film can contain 2,000,000 individual dosage units**. The claimed processes accomplish this feat while providing the necessary narrow ranges in variation of the amount of active in individual dosage units across all lots, *i.e.*, multiple rolls of resulting films and even narrower ranges of uniformity of content in amount of active within a single lot, *i.e.*, a single roll of resulting film. Thus, as claimed, the '080 Patent requires a uniformity of content in amount of active (i) in individual dosage units sampled from a single lot of resulting film of 10% or less (independent claims 1, 161 and 316-318, see Appendix A, Bogue Declaration I, EA-1), and (ii) in individual dosage units sampled from two or more lots of resulting films of +/-10% of the pre-determined desired amount (independent claims 82 and 315, see Appendix B, Bogue Declaration I, EA-1).

Processes for such control of content uniformity are not present in or taught or suggested by the prior art. The Examiner and BDSI both wrongly assumed the '080 Patent's claimed uniformity in the distribution of active, *e.g.*, was present in the prior art and thus provided a basis for the claims being rejected. As shown again below, the Examiner's and BDSI's assumed uniformity is not present in or taught or suggested by the prior art.

BDSI's Respondent Brief (BDSI's RB) focuses on the alleged findings in the RAN at pp. 30-44 (Chen), pp. 52-62 (Staab), pp. 63-71 (Le Person); Reitman Declaration; and Cohen

Declaration.[2] BDSI's RB, p. 7. However, the primary references **Chen, Staab and Le Person do not support a *prima facie* case of obviousness**. All three are relied on to support the claim that the prior art disclosed methods of achieving the degrees of uniformity claimed by the '080 Patent. All three were taken on their face as demonstrating such uniformity. However, a closer look at all three shows the exact opposite -- **the prior art did not teach nor achieve the '080 Patent's claimed uniformity**.

First, BDSI and the Examiner have both relied on the false assumption that uniformity of weight of equally sized film samples in Chen, *e.g.*, is, by itself, sufficient to demonstrate that the amount of active present in prior art references meets the '080 Patent's claimed uniformity of active. As a consequence of this improper assumption, BDSI's Reitman Declaration demonstrates that samples taken from Chen's Example 7, and samples taken from Reitman's declared exact copying of Chen's Example 7 process, differed in weight by 30% from the expected or desired sample weight and thus exhibited a 30% non-uniformity in weight of pharmaceutical active from the expected or desired amount as well. Uniformity in amount of active of +/- 10% from the desired amount of drug is necessary in order to be suitable for regulatory approval– outside the scope of the '080 Patent claims.

Second, BDSI and the Examiner have both relied on the false assumption that uniformity of weight of equally sized film samples in Staab, *e.g.*, is, by itself, sufficient to demonstrate that the amount of active present in prior art references meets the '080 Patent's claimed uniformity of

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[2] Chen (WO 00/42992) ("Chen"); Staab (U.S. 5,393,528) ("Staab"); and Le Person (*"Near infrared drying of pharmaceutical thin films: experimental analysis of internal mass transport,"* Chemical Engineering and Processing, Vol. 37, pp. 257-263 (1998)) ("Le Person").

active and that Staab's reported 0% variation on uniformity of active is sufficient to demonstrate that Staab meets the '080 Patent's claimed uniformity of active. However, Staab disclosure actually demonstrates non-uniformity of content in weight of active of between 90 and 100% from the expected or desired amount of active– again, outside the scope of the '080 Patent claims.

Third, Le Person demonstrates a maldistribution of active ranging from over 20% to over 150% when measured as the percent difference in amount of active, as disclosed in Example M of the '080 Patent, col. 33, l. 20 - col. 34, l. 24 – again, outside the scope of the '080 Patent claims.

Thus, as will be shown again *infra,* the primary references **Chen, Staab and Le Person do not support a *prima facie* case of obviousness**, which MonoSol herein further rebuts with **factually supported objective evidence gleaned from the very prior art references** used by the Examiner to support the *prima facie* case of obviousness. It was error for the Examiner to rely on Chen, Staab and Le Person for *prima facie* obviousness. In fact, on their own or even in combination with BDSI's Reitman Declaration, these references clearly and unambiguously demonstrate **the non-obviousness of the '080 Patent claims** subject to this reexamination (hereinafter the " '080 Patent claims").

Finally, as supported by the Bogue Declarations, the 1 billion dollars in sales of Suboxone in 2012 alone, demonstrates the commercial success of the '080 Patent's claimed invention, which provides for the first time for the sublingual oral drug delivery in a film format, capable of being mass produced with the necessary uniformity (quality) to meet regulatory

requirements.

Neither the Examiner nor BDSI have met their burden of proving anticipation or obviousness and the rejections set forth in the RAN should be reversed.

II. CLAIM REJECTIONS ADDRESSED HEREIN.

The following claim rejections and associated errors in rejecting same that are directly and/or indirectly addressed herein are listed below. Moreover, Appellant maintains all its early arguments addressing same.

A. Claims 1-11, 13-15, 17-71, 82-90, 92-94, 96-150, 161-172, 174-176, 178-232, 243-253, 256, 258-271, 274, 276-289, 292 and 294-318 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Chen (RAN, pp. 29-44).

B. Claims 2, 3, 32, 55, 72-81, 111, 134, 151-160, 193, 216 and 233-242 stand rejected under 35 U.S.C. §103(a) as being unpatentable over the combined teaching of Chen and Staab (RAN, pp. 45-48).

C. Claims 317 and 318 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over the combined teachings of Chen and Arter (RAN, pp. 48-50).

D. Claims 317 and 318 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over the combined teachings of Chen and Strobush (RAN, pp. 50-52).

E. Claims 1-5, 10, 13-15, 21, 24, 25, 32, 44-46, 54, 55, 59, 63-70, 72-75, 78-84, 89, 92-94,100,103,104,111,123-125,133,134,138, 142-149, 151-154, 157-166,171, 174-176, 182, 185, 186, 193, 205-207, 215, 216, 220, 224-231, 233-236, 239-242,

249-252, 258-260, 267-270, 276-278, 285-288 and 294-318 stand rejected under 35 U.S.C. § 102(b) as anticipated by or, in the alternative under 35 U.S.C. § 103(a) as being obvious over Staab (RAN, pp. 52-62).

F. Claims 8, 9, 76, 77, 87, 88, 155, 156, 169, 170, 237 and 238 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Staab are (RAN, pp. 62-63).

G. Claims 82, 89, 90, 92, 161, 171, 172, 174, 274, 292, 304-311 and 313-318 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Le Person (RAN, pp. 63-71).

III. RESPONDENT'S REITMAN DECLARATION DEMONSTRATES THAT **CHEN'S PROCESSES PRODUCE FILMS WHICH ARE 30% FROM THE EXPECTED OR DESIRED DOSAGE WEIGHT** AND **NOT** THE 10% OR LESS RELIED ON BY THE EXAMINER AND BDSI FOR PRIMA FACIE OBVIOUSNESS (RAN, pp. 36-37, 44, 74-75, 77, 85, 88, 97, 100, 104, etc.; BDSI's RB, pp. 7, 8, 9, 17-28, etc.).

BDSI and the Examiner have both relied on the false assumption that uniformity of weight of equally sized film samples in Chen, *e.g.*, is, by itself, sufficient to demonstrate that the amount of active present in prior art references meets the '080 Patent's claimed uniformity of active. *See, e.g.*, RAN, pp. 36-37, 44, 74-75, 77, 85, 88, 97, 100, 104, etc.; and BDSI's RB, pp. 7, 9, 17-18, 22, etc. As a consequence of this improper assumption, BDSI's Reitman Declaration (EA-3) instead clearly **demonstrates the inability of Chen to provide** film dosage units meeting the '080 Patent's claimed substantial uniformity across different manufactured resulting films (lots).

BDSI's Reitman declares that she and her team "**manufactured a film in accordance with Example 7 of *Chen***", *i.e.*, Chen Example 7 film (Reitman Declaration, EA-3, p. 2, ¶ 3, emphasis supplied).

Reitman further declares that her 5 cm^2 dosage unit samples of **Reitman's Chen Example 7 film ("Reitman's Chen Example 7 film") all weighed exactly 34 mg.** *See* Reitman Declaration, EA-3, Table 2, page 4, ¶ 6.

Chen provides all the information necessary to calculate the weight of the 5 cm^2 dosage unit samples of Chen's Example 7 film. Indeed, **Chen's 5 cm^2 dosage unit sample of Example 7 film ("Chen's Example 7 film") weighed 48.8 mg.**[3]

According to the Examiner and BDSI, Chen's process provides for the production of uniform films. Moreover, in accordance with the Examiner's and BDSI's "assumption" that the same size films should have the same distribution of components and thus weigh the same, any replication of Chen's Example 7 must, in accordance with this "assumption", result in the same size films having the same weight. Yet, instead of **Chen's Example 7 film weighing the same as Reitman's Chen Example 7 film, they differ in weight by 30%.**[4]

The findings of obviousness and inherency are based on this erroneous "assumption", *e.g.*, that purely physical characteristics, *e.g.,* weight, can determine the degree of uniformity of content in the amount of active. There is a **30% weight difference between Chen's Example 7 film samples and Reitman's Chen's Example 7 film samples**. The "assumption" requires there to be a 30% difference in the weight (amount) of active between Chen's and Reitman's samples. Thus, **Chen's Example 7 and Reitman's Chen's Example 7 demonstrate a lack of**

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[3] Chen provides the following information regarding its film formed in Chen Example 7 (Chen, p. 22, Table 6, and p. 16, l. 5): Thickness = 3.2 mil = 0.008128 cm (3.2 mil x 0.00254 cm/mil = 0.008128 cm.); Size = 5 cm^2; and Density = 1.2 gm/cm^3. From this information the weight of the dosage sample can be calculated. Area x Thickness x Density = Weight of Film Sample. 5 cm^2 x 0.008128 cm x 1.2 gm/cm^3 = 0.0488 gm = 48.8 mg. Thus, the weight of Chen's 5 cm^2 Example 7 sample is **48.8 mg**, and any duplication of this example is expected to produce same size samples having the same weight.

[4] Chen's Example 7 Weight of Samples was 48.8 mg. Reitman's Example 7 Weight of Samples was 34 mg. ((48.8 mg - 34 mg)/(48.8 mg)) = (14.8 mg)/(48.8 mg) = 30%.

active content uniformity of 30% between their separately manufactured films. This degree of dis-uniformity does not meet the claimed uniformity limitation, which requires that all dosage units vary by no more than 10% from a desired amount of the active, *i.e.*, contain amounts of active within +/- 10% of the desired amount for the particular drug for all manufactured films. Nor would the 30% degree of dis-uniformity from the desired amount meet the limitation that the amount of active varies by no more than 10% in dosage units taken from a single manufactured film.

Thus, the factual basis for the Examiner's determination of *prima facie* obviousness in connection with Chen's alleged demonstration of uniformity of content in amount of active has been overcome as incorrect based on factual and objective evidence. "The examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness. If the examiner does not produce a *prima facie* case, the applicant is under no obligation to submit evidence of nonobviousness." MPEP § 2142. The Examiner's and BDSI's allegations of obviousness and inherency cannot stand, and the rejections should be removed.

The claims of the '080 Patent are not obvious in view of Chen.

IV. **STAAB'S EXAMPLE DEMONSTRATES A 100% - 90% DIFFERENCE IN UNIFORMITY** AND **NOT** THE 10% OR LESS RELIED ON BY THE EXAMINER AND BDSI FOR PRIMA FACIE OBVIOUSNESS (RAN, pp. 54, 56-59, 62, 75, 85, 95, 113-114, etc.; BDSI's RB, pp. 7, 8, 17, 18, 23, 29-32, etc.).

BDSI and the Examiner have again both relied on the false assumption that uniformity of weight of equally sized film samples in Staab, *e.g.*, is, by itself, sufficient to demonstrate that the amount of active present in prior art references meets the '080 Patent's claimed uniformity of active. *See, e.g.*, RAN, pp. 54, 56-59, 62, 75, 85, 95, 113-114, etc.; BDSI's RB, pp. 7, 8, 18, 29-32, etc. However, this "assumption" is incorrect. At best, Staab's ability to double the amount of its starting active which, if believed on its face, is an example of the application of alchemy or, more likely, is merely a bad prophetic example. Staab demonstrates the lack of uniformity of content in amount of active exceeding 90% - 100% and thus cannot be relied upon as a reference to reject the current claims.

Staab states (Staab, col. 11, l. 22 to col. 12, l. 3) that, when he incorporated 10% of a 50% by weight benzalkonium chloride aqueous solution into a film-forming mixture, he obtained, after drying, a film product having exactly 19 mg benzalkonium chloride ("active") in all film samples weighing 190 mg each. According to BDSI and the Examiner, because all the film samples had 19 mg of active, this demonstrated a 0% variation in uniformity of content in the active, and the Examiner relied on this 0% in his rejections. The Examiner's and BDSI's conclusion of **0% is wrong! Staab's lack of degree of uniformity of active content is actually 100% from the desired amount**.

The following is based on Staab, col.11, lines 22-51, and assumes no water is driven off. Staab starts with **10% by weight of benzalkonium chloride (50% aqueous)**. Thus, Staab starts

with **5% by weight of benzalkonium chloride active and 5% by weight of water**.[5] Staab and any reader/POSA would expect that the resulting film would maintain the 5% by weight of benzalkonium chloride active.[6] This is the desired amount of active. Staab cut out 190 mg samples from his resulting film. If Staab maintained the 5% by weight of active, the expected or desired amount of active in a 190 mg film sample would be 9.5 mg of benzalkonium chloride active.

190 mg x 5% = **9.5 mg**[7] **= Staab's desired amount of active**.

Instead Staab's 190 mg samples each contained 19 mg of benzalkonium chloride active.

19 mg is Staab's "reported" amount of active.

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[5] The Examiner also relied on Staab starting with 5% water in his obviousness analysis. "The ingredients blended to prepare the film are 52.5% HPMC, 37.5% glycerin and 10.0% of a 50% aqueous solution of the benzalkonium chloride (see col. 11, lines 30-34). Since **the water content before drying is 5%** (i.e., half of the 10% of the 50% aqueous solution of benzalkonium chloride), the dried film must have a water content of 10% or less as here claimed." RAN, p. 55 (emphasis supplied).

[6] This is assuming that everything else stays the same except, perhaps, for the water content. In the extreme example where the 5% by weight of water is removed, the expected, desired amount of active becomes 5.26% (.0526) by weight of benzalkonium chloride. (5)/(100-5) = (5)/(95) = .0526.

[7] **So far we have assumed that no water was driven off because Staab says nothing about the water content of his films. But even if we assume that all the water is driven off, then the difference is still too much at 90%.** If all the 5% by weight of water was driven off, then 10.0 mg of active would be the desired amount of active (190 mg x .0526 = 9.994 mg), and Staab's 19 mg of active results in a 90% difference from the 10 mg desired amount. A 90% difference would not meet regulatory requirements either.

The variation in uniformity of distribution of benzalkonium chloride active in Staab's resulting films was 100% from the desired amount.

$$\frac{\text{19.0 mg (actual amount of active) - 9.5 mg (desired amount of active)}}{\text{9.5 mg (desired amount of active)}}$$

$$= (9.5)/(9.5) = \mathbf{100\%}.$$

Nor would the 100% (or even the 90%) degree of dis-uniformity from the desired amount meet the limitation that the amount of active varies by no more than 10% in dosage units taken from a single manufactured film.

Thus, the factual basis for the Examiner's determination of *prima facie* obviousness in connection with Staab's alleged demonstration of uniformity of content in amount of active has been overcome as incorrect based on factual and objective evidence. "The examiner bears the initial burden of factually supporting any prima facie conclusion of obviousness. If the examiner does not produce a *prima facie* case, the applicant is under no obligation to submit secondary evidence to show nonobviousness." MPEP § 2142. The Examiner's and BDSI's allegations of obviousness and inherency cannot stand, and the rejections should be removed.

The claims of the '080 Patent are neither anticipated by, nor obvious in view of, Staab.

V. LE PERSON FIGURE 10 DEMONSTRATES A DEGREE OF **MALDISTRIBUTION OF ACTIVE OF FROM OVER 20% TO OVER 150%** AND NOT THE 10% OR LESS RELIED ON BY THE EXAMINER AND BDSI FOR PRIMA FACIE OBVIOUSNESS (RAN, pp. 63-71, 75, 85, 95, 115-117, etc.; BDSI's RB, pp. 32-35, etc.).

Le Person has not been used to reject claim 1 or its dependencies.[8] As MonoSol has argued from the beginning, Le Person demonstrates the maldistribution of active in thin films.[9] The Examiner and BDSI allege that Le Person's maldistribution is irrelevant because Le Person only discusses and provides data on the maldistribution of active in the depth (Z-axis) of the films tested. But the Examiner has not considered two important facts. First, the degree of maldistribution in Le Person is enormous. Second, Le Person discusses the large degree of shrinkage (50%) of the film as components evaporate. Contractive forces attendant to such shrinkage can cause significant movement of the active in virtually any direction. The Examiner's disregard of the lack of uniformity in Le Person was thus clear error.

Moreover, the '080 Patent claims all require that the process ensures that the "substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film" is maintained throughout the manufacturing process. Substantial uniformity is not limited to uniformity only in the X-Y plane of the film, but the Z-axis as well. The fact that the testing steps are for total amount of active in

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[8] Also, "[n]either in the request for reexamination nor in the Comments filed 04/12/13 has Third Party Requester shown how Le Person alone teaches or renders obvious all the limitations in claim 1." RAN, p. 64.

[9] Please note that Le Person uses the term "enduction" which, according to an online dictionary, means "coating" in French.

individual dosage units is related to the need for its application as a delivery system for bioactives and pharmaceutical actives regulated by the FDA.

Moreover, as the Examiner premises his case for *prima facie* obviousness on the conclusion that MonoSol's claimed uniformity would necessarily result from Le Person's disclosure, the Examiner's distinction that Le Person's examination and disclosure of the maldistribution of active (lack of substantial uniform distribution of active) in its films was limited to the Z-axis is without merit and cannot be disregarded.

Certainly, Le Person's disclosure of the maldistribution in active in the Z-axis as determined by analytical chemical testing, with the concomitant 50% shrinkage, must reflect maldistribution in the X-Y plane of Le Person's films as well. "The coupling between studies performed, on the one hand on a temporal basis (chromatographic and coulometric analysis), and on the other hand on a spatial basis (LSCM) allows to propose a model of the constituent transports inside the film whose thickness shrinks from 100 to 50 μm during drying." Le Person, p. 263. Common sense dictates that the 50% reduction in thickness of the film causes the active to move not only in the Z-axis but in the X-Y plane as well. Such contractive forces are clearly not limited to a single axis. There is certainly no reason or evidence to believe that such enormous maldistribution is limited to the Z-axis, especially as the film shrinks and the active is forced to find a place to reside.

MonoSol provides herein, based on Le Person's own data, a quantitative aspect to the degree of maldistribution or lack of uniformity in the distribution of active in Le Person's films. The quantitative data from Le Person demonstrates that: (i) at 5 minutes, Le Person's films

exhibited a maldistribution of active of over **80%**; (ii) at 10 minutes, Le Person's films exhibited a maldistribution of active of over **150%**; and (iii) at 15 minutes, Le Person's films exhibited a maldistribution of active of over **20%**.

Thus, Le Person's films significantly exceed the claimed "**substantially uniform distribution of said active**" of the '080 Patent, as demonstrated by analytical chemical tests which clearly **do not indicate** that the "uniformity of content in the amount of the active varies by no more than 10% ". Finally, the '080 Patent claims explicitly provide for "locking-in" uniformity "within about the first 4 minutes." MonoSol has consistently and repeatedly emphasized the importance of this claim language in achieving its degree of uniformity. Neither Le Person, Chen, Staab, nor any other prior art reference recognizes this important claim feature, which clearly further distinguishes the references in so far as their inability to "lock-in" within "about the first 4 minutes." This is clearly established by Le Person's demonstration of the continual movement of the active mass during at least the first 15 minutes of drying. **Le Person Figure 10 unequivocally demonstrates that Le Person's films could not lock-in uniformity within 5 or even 10 minutes.**

A. Development of Le Person's quantitative disclosure of the maldistribution of active in its films.

Figure 10 of Le Person (Le Person, p. 262) shows the mass fraction of the active substance relative to the complete film coating measured at 2 micron intervals from the bottom of the film (the left side of Figure 10) to the top of the film (see "exposed surface" all the way to the right of Figure 10). Le Person prepared three films which were analyzed for variation in active relative to the Z-axis of the films. These films, indicated on Figure 10 by "◊", "□", and "**X**", were dried for 5 minutes, 10 minutes and 15 minutes, respectively. Figure 10 provides the mass fraction of active for each of the films at various depths of the films. Those data points appear in Chart I below. As a measure of quality control to ensure that the correct numbers were used for each data point, Appellant inputted the Chart I data into a Microsoft Excel spreadsheet and had Excel generate its own figure based on the data in Chart I. The Excel generated figure appears below a copy of Le Person Figure 10 on the next page and, as can be seen, both exactly match each other with respect to the data points. Hence, the data in Chart I accurately reflects the information provided in Le Person's Figure 10.

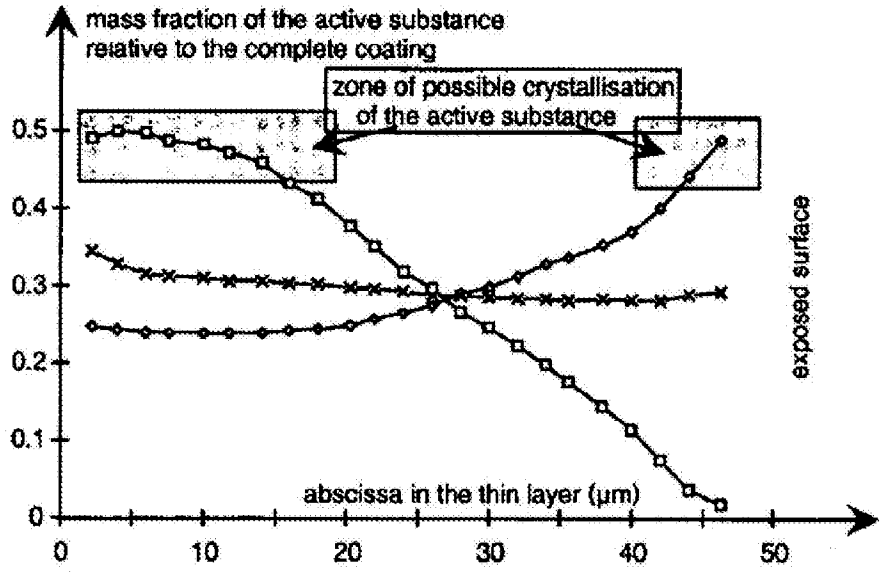
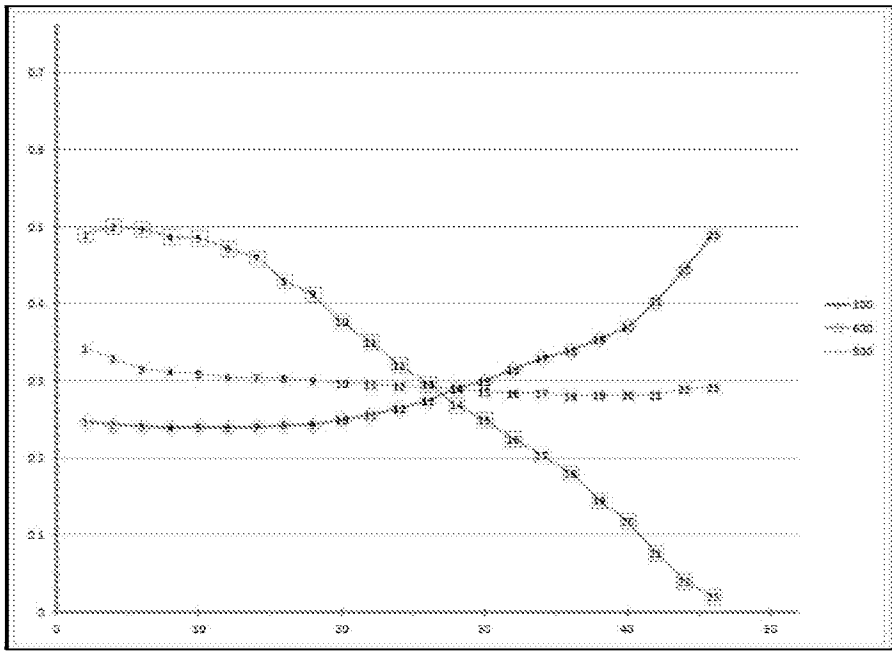


Fig. 10. Mass fraction fields of the active substance at three drying times (300 ◇, 600 □, 900 s x) during drying of a 100 µm thick coating under Short Infra Red drying process. Indications of the possible zones of crystallisation.



B. Le Person Figure 10 & Excel Reproduction of Le Person Figure 10 from Data Points in Chart I

C. Chart I - Data Points from Le Person Figure 10

Le Person Figure 10 Demonstrates Maldistribution of Active

Data Point	300 seconds 5 minutes ◊	600 seconds 10 minutes □	900 seconds 15 minutes X
1	0.247	0.490	0.343
2	0.244	0.500	0.329
3	0.241	0.497	0.315
4	0.240	0.487	0.312
5	0.240	0.485	0.309
6	0.240	0.472	0.305
7	0.240	0.460	0.304
8	0.243	0.430	0.303
9	0.244	0.413	0.301
10	0.250	0.377	0.297
11	0.256	0.350	0.296
12	0.265	0.330	0.293
13	0.275	0.296	0.292
14	0.291	0.269	0.290
15	0.299	0.250	0.286
16	0.315	0.225	0.284
17	0.329	0.204	0.284
18	0.339	0.180	0.281
19	0.354	0.145	0.282
20	0.370	0.118	0.282
21	0.403	0.077	0.282
22	0.445	0.040	0.285
23	0.490	0.020	0.292
MAX	0.490	0.500	0.343
MIN	0.240	0.020	0.281
AVG	0.298	0.309	0.298
(Max-Min)/Avg.	83.82%	155.38%	20.81%

As referred to above, these data points provide a quantitative measure to the degree of maldistribution of active in Le Person's films. The maldistribution differed for different drying times. The maldistribution of active of >80%, >150%, and >20% for films dried at 5 minutes, 10 minutes, and 15 minutes, respectively, clearly demonstrates that a "substantially uniform distribution of active" in Le Person's films had not been achieved within about 4 minutes as required by the '080 Patent claims. Moreover, even the film with the least maldistribution of active, the film dried for 15 minutes, namely >20%, does not support a degree of uniformity of active in individual dosage units which varies by no more than 10%.

Thus, the factual basis for the Examiner's determination of *prima facie* obviousness in connection with Le Person's alleged demonstration of uniformity of content in amount of active has been overcome as incorrect based on factual and objective evidence. "The examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness. If the examiner does not produce a *prima facie* case, the applicant is under no obligation to submit evidence of nonobviousness." MPEP § 2142. The Examiner's and BDSI's allegations of obviousness and inherency cannot stand and the rejections should be removed.

The claims of the '080 Patent are not obvious in view of Le Person.

VI. THUS, CHEN AND/OR STAAB AND/OR LE PERSON DO NOT RENDER THE '080 PATENT CLAIMS UNPATENTABLE.

Thus, Chen and/or Staab and/or Le person do not render the following '080 Patent claims unpatentable: claims 1-11, 13-15, 17-71, 21, 24, 25, 32, 44-46, 54, 55, 59, 63-70, 72-81, 82-84, 82-90, 92-94, 96-150, 151-160, 161-172, 174-176, 178-232, 233-242, 243-253, 256, 258-271, 274, 276-289, 292 and 294-318. It was error to reject same.

VII. ARTER AND STROBUSH DO NOT SUPPLY THE MISSING CLAIM ELEMENTS OF CHEN, STAAB AND LE PERSON (RAN, pp. 48-50, 50-52; BDSI's RB, 23-28)

Arter and Strobush[10] do not disclose the claim elements absent from Chen, Staab and/or Le Person and thus do not remedy their defects as references. Moreover, as noted above, Appellant maintains all its prior arguments regarding Arter and Strobush. *See, e.g.*, discussions in Appeal Brief.

A. Arter

The claim elements missing in Chen are not provided by Arter. Arter is cited for its disclosure of foraminous shields which form a "quiescent region" between the shields and the coated surface. Arter is a customized process and apparatus useful for making photographic coatings. Such a process and apparatus are not at all transferrable to drying methods for pharmaceutical films and, particularly, pharmaceutical films which are aqueous-based and self-supporting.

Arter is only concerned about the coatings appearance, not the degree of uniformity. At the very least, Arter is devoid of any suggestion whatsoever of the "locking-in" within "about the first 4 minutes" or the degree of uniformity as claimed.

B. Strobush

The claim elements missing in Chen are not provided by Strobush. Strobush teaches that evaporation of the solvent must be performed very slowly (low $h\Delta T$), in multiple stages, so that the silver atoms lined up on the coating's surface are not disturbed so as not to cause a mottled

[10] Arter (U.S. 4,365,423) ("Arter"); and Strobush (U.S. 5,881,476) ("Strobush")

appearance to the photographic coating. Strobush states "increasing the initial rate of heat transfer to the film ($h\Delta T_i$), increased the severity of mottle." Strobush, col. 20, ll. 39-41.

In contradistinction, the '080 Patent claims require **rapid evaporation of at least a portion of the solvent within about 4 minutes** so as to maintain the substantial uniformity in the distribution of active.

> "(c) controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus using air currents, which have forces below a yield value of said flowable polymer matrix during drying, to **evaporate at least a portion of said solvent** to form a visco-elastic film, having said active substantially uniformly distributed throughout, **within about the first 4 minutes** by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying **to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film**, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said visco-elastic film, varies by no more than 10%, and wherein during said drying said flowable polymer matrix temperature is 100 °C or less;".
>
> '080 Patent, claim 317, Appellant Brief, p. CA-39 (emphasis supplied).

See also, '080 Patent, claim 318, Appellant Brief, p. CA-40-41.

Again, as previously argued, Strobush is concerned about eliminating mottle to achieve a good appearance and is devoid of any teaching regarding "locking-in" within "about the first 4 minutes" or achieving the degree of uniformity claimed.

Thus, claims 317 and 318 are not rendered obvious over the combined teachings of Chen and Arter and/or Strobush. The Examiner's and BDSI's allegations of obviousness should and cannot stand and the rejections should be removed.

VIII. BOGUE DECLARATIONS AND COMMERCIAL SUCCESS – THE APPROPRIATE NEXUS TO THE CLAIMED INVENTION IS PRESENT (RAN, pp. 74, 78-80; BDSI's RB, pp. 10-18)

The Bogue Declarations provide ample evidence of the nexus between the commercially manufactured resulting films discussed in his declarations and the claimed invention as well as the commercial success of the claimed invention as exemplified by the sales of Suboxone. It was error not to do so. As set forth in Section II of Bogue Declaration I (AB, EA-1):

> II. Producing resulting films in accordance with the '080 Patent
>
> 4. Each of the 73 lots of resulting films (Lots 1-73) containing approximately 2,000,000 individual dosage units per lot discussed herein were manufactured: (i) for commercial use and regulatory approval; (ii) in compliance with U.S Food and Drug Administration ("FDA") standards and regulations, including those relating to analytical chemical testing for variation in active in individual dosage units; and (iii) in accordance with the invention disclosed in the '080 Patent, and as claimed by the '080 Patent both as issued and as amended in the Patentee's Reply to the Office Action; by:
>
> (a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and a pharmaceutical active, said matrix having a substantially uniform distribution of said active;
>
> (b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;
>
> (c) controlling drying through a process comprising conveying said polymer matrix through a drying apparatus and evaporating at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film wherein the polymer matrix temperature is 100 °C or less;

(d) forming the resulting pharmaceutical film from said visco-elastic film, wherein said resulting pharmaceutical film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained, such that uniformity of content in the amount of the active in substantially equal sized individual dosage units, sampled from different locations of said resulting pharmaceutical film, varies by no more than 10%; and

(e) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units of said sampled resulting pharmaceutical film, said tests indicating that uniformity of content in the amount of the active varies by no more than 10%, [see Appendix A] said resulting pharmaceutical film suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration.

5. Additionally, the uniformity of content in the amount of active as sampled from the 73 lots of resulting film varies no more than 10% from the desired amount of the active as indicated by said analytical chemical tests from 4(e) above. [See Appendix B]

Bogue Declaration I, ¶¶ 4 & 5, AB, EA-1.

In accordance with the process steps above, the ability to manufacture up to 2,000,000 films per lot of pharmaceutical-containing active with prescribed amount of active per unit dose provides the ability, for the first time, to provide a commercially viable FDA approved product, **(i) in a sub-lingual oral drug delivery film, (ii) in commercially sufficient quantities, and (iii) of sufficient quality (uniformity of active)** to enable Suboxone to have had sales of 1 billion dollars in 2012 alone. The combination of items (i), (ii) and (iii) alone at least provide the necessary nexus. Those sales figures have continued to increase, notwithstanding the entry into the marketplace of generic Suboxone tablets.

But for the process of the present invention as currently claimed, these sales would not be possible. Unless the uniformity of content in the amount of active as claimed is present, films

produced by the process claimed would not be marketable. The commercial success of the claimed film is directly related and conditioned upon achieving the claimed uniformity of active content in equally sized dosage units. These films were the first pharmaceutical sublingual film dosage units ever sold in the United States. Absent the ability to achieve the claimed uniformity, no pharmaceutical film could be commercially sold.

MonoSol submits that a clear nexus exists between the claims of the '080 Patent and its commercial success. Such evidence deserves full consideration and further supports secondary considerations relevant to the patentability of the claims.

IX. CONCLUSION

For the reasons set forth herein, all rejections should be withdrawn and a reexamination certificate issued.

If a reexamination certificate is not issued, Appellant requests that prosecution in this reexamination should be reopened and/or remanded, and the Examiner directed to respond with a non-final office action.

Appellant authorizes the Commissioner to charge all fees, if any, associated herewith to Deposit Account No. 08-2461.

Dated: May 27, 2014 Respectfully submitted,

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EVIDENCE APPENDIX

The below Reitman declaration was submitted by Third-Party Requester/Cross-Appellant. It was admitted in the record, and referred to in the Examiner's Right of Appeal Notice, mailed December 6, 2013, *see*, *inter alia*, pp. 2, 14, 75,77, 87-92, 94, 97, 100, 105.

3 BDSI's/Respondent's Declaration by Maureen Reitman, Sc.D. Under 37 C.F.R. § 1.132, dated February 28, 2013, filed April 12, 2013 ("Reitman Declaration")

3 BDSI's/Respondent's Declaration by Maureen Reitman, Sc.D. Under 37 C.F.R. § 1.132, dated February 28, 2013, filed April 12, 2013 ("Reitman Declaration")

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re *Inter Partes* Reexamination of:	)
US Patent No. 7,897,080	)
Issued: March 1, 2011	) Confirmation No.: 6418
Named Inventor: Robert K. Yang *et al.*	) Group Art Unit: 3991
Control No.: 95/002,170	) Examiner: Diamond, Alan D.
Filed: September 10, 2012	) M&E Docket: 117744-00023
Title: POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM	) H&B Docket: 1199-26 RCE/CON/REX

Mail Stop *Inter Partes* Reexam
Attn: Central Reexamination Unit
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION BY MAUREEN REITMAN, SC.D.
UNDER 37 CFR § 1.132

Sir/Madam:

I, Maureen Reitman, do hereby make the following declaration:

I. Technical Background

1. I am a Principal and the Director of the Polymer Science and Materials Chemistry Practice at Exponent. I hold two academic degrees: (1) a Bachelor of Science in Materials Science and Engineering from the Massachusetts Institute of Technology (MIT), and (2) a Doctor of Science in Materials Science and Engineering, with a thesis in the field of polymers, from MIT. I have been practicing in the field of polymer science and engineering for more than 20 years as a researcher at MIT, in a variety of technical roles at the 3M Company, and as a consultant with Exponent. I provide consulting engineering services in all aspects of polymer science and engineering including, but not limited to material selection, product design and development, mechanical and chemical testing, failure analysis, polymer chemistry, polymer

physics, and polymer processing. My specialties include formulation, processing and performance evaluation of polymeric materials, including films, coatings, adhesives and transdermal drug delivery systems. I have been directly involved in product development, product line extensions, transfer of new products to manufacturing, qualification of alternative materials and manufacturing equipment, evaluating field performance, and assessing intellectual property. I am a past chairman and continue to serve as a member of the board of directors of the Medical Plastics Division of the Society of Plastics Engineers. My *curriculum vitae* is provided in Appendix A.

2. While Exponent is being paid for my time, I am not an employee of, nor do I have any financial interest in, BioDelivery Sciences International, Inc.

3. I have been asked to carefully review International Publication No. WO 00/42992 ("*Chen*"), and manufacture a film as described in *Chen*. I carefully reviewed *Chen*. Under my direction, my team manufactured a film in accordance with Example 7 of *Chen*. I have also been asked to take samples and perform various analytical tests to confirm the uniform distribution of the pharmaceutical active in substantially equal sized individual dosage units of the film, which we did.

4. Manufacturing Example 7 of *Chen*

Chen states: "According to Examples 1-8, the hydrocolloid [Methocel E5(HPMC)] was dissolved in water under agitated mixing to form a uniform and viscous solution." Chen 17:7-8.

- Methocel E5(HPMC) was dissolved in water under agitated mixing to form a uniform and viscous solution, by my team.

Chen states: "Additional ingredients were then added sequentially to the viscous solution such as peppermint, aspartame, propyl[ene] glycol, benzoic acid and citric acid under agitated mixing until they were uniformly dispersed or dissolved in the hydrocolloid." Chen 17:8-11.

- Additional ingredients were then added sequentially to the viscous solution including peppermint oil, aspartame, propylene glycol, benzoic acid and citric acid under agitated mixing until they were uniformly dispersed or dissolved in the hydrocolloid, by my team.

- Kolliphor EL was also added to the viscous solution.

Chen states: "Therapeutic agents were added to the homogeneous mixture (coating solution) prior to forming the film." *Chen* 20:19-20.

- Oxybutynin chloride (the therapeutic agent of Example 7) was added to the homogeneous mixture (coating solution) prior to forming the film, by my team.

Chen's Table 5 specifies the composition for Example 7.

- We used the ingredients in the amounts identified in *Chen*'s Table 5. *See* Table 1.

Table 1			
Formulation, Ex. 7, Table 5, *Chen*	% Weight	Formulation, Prepared by Maureen Reitman Team	% Weight
Oxybutynin	3.71	Oxybutynin chloride	3.71
Methocel E5 (HPMC)	21.06	Methocel E5 Premium LV	21.06
Water	70.72	Water, distilled	70.72
Cremophor EL40	1	Kolliphor EL[1]	1
Propylene glycol	1	Propylene glycol	1
Peppermint	1	Peppermint oil	1
Aspartame	0.8	Aspartame	0.8
Benzoic acid	0.013	Benzoic acid	0.013
Citric acid	0.7	Citric acid, monohydrate	0.7

Chen states: "The resultant mixture was degassed in a vacuum chamber until trapped air bubbles were removed." Chen 17:11-12.

- The resultant mixture was degassed in a vacuum chamber until trapped air bubbles were removed, by my team.

Chen states: "The formulation was then coated on the non-siliconized side of a polyester film at a wet thickness of 10 mil and dried in a hot air circulating oven at 50°C for 9 minutes." Chen 17:13-15.

- The formulation was then coated on a non-siliconized side of a polyester film at a wet thickness of 10 mil and dried in a hot air circulating oven at 50°C for up to 9 minutes, on commercial manufacturing equipment by my team.

Chen states: "Methods for manufacturing the dosage unit include the solvent casting methods as shown in Figure 2." Chen 15:13-14. "The manufacturing process for forming the dosage unit is illustrated in Figure 2. The dry film formed by this process is a glossy, stand alone, self supporting, non-tacky and flexible film (12)." Chen 15:29-31.

- A solvent casting manufacturing process for forming the dosage unit as illustrated in Figure 2 was used[2], by my team.

[1] The Cremophor line of products now owned by BASF and renamed Kolliphor. Based on the naming convention of the Cremophor/ Kolliphor products, EL40 is Polyoxyl 40 Castor Oil and EL is Polyoxyl 35 Castor Oil (*i.e.*, they are based on a 1:40 and 1:35 ratio, respectively, of castor oil:ethylene oxide). They are different materials. However, one of skill in the art would recognize Kolliphor EL as an appropriate substitute, as Cremophor EL40 is no longer available.

- The film was manufactured using a controlled drying process.
- As illustrated in Figure 2, the drying oven featured aeration controller with 3 zones set such that in each successive zone air impingement on the surface of the film increased.
- The dry film formed by the process is a glossy, stand alone, self-supporting, non-tacky and flexible film.

Chen states: "A glossy, substantially transparent, stand alone, self-supporting, non-tacky and flexible film was obtained after drying." Chen 17:15-16.

- A glossy, substantially transparent, stand alone, self-supporting, non-tacky and flexible film was obtained after drying, by my team.

5. Verification of Content Uniformity – Visual Inspection

- By examination with the naked eye, uniformity was verified by my team.

6. Verification of Content Uniformity – Unit Dose Weight

- By weighing individual dosage units of substantially identical size, uniformity was verified by my team. *See* Table 2.

Table 2

Sample	Weight of 5 cm^2 dosage unit (grams)
1	0.034
2	0.034
3	0.034
4	0.034
5	0.034
6	0.034
7	0.034

7. Verification of Content Uniformity – Dissolution Test (HPLC)

- By dissolution of individual dosage units of substantially identical size and analysis by High Performance Liquid Chromatography (HPLC) active content uniformity was verified by my team. *See* Table 3.

[2] Our backing was not looped and we did not die cut in line, but the solvent casting and drying under aeration is matched.

Table 3	
Sample	Oxybutynin weight (mg)
A	4.4
B	4.4
C	4.3
D	4.4
E	4.1

- As can be seen in Table 3, the active varies by less than 10%.

8. Additional Observations

   - The components of the formulation, including the active component, were uniformly distributed in the viscous solution, which was used to cast the film, as was verified by my team.

   - The viscous solution, which was used to cast the film, exhibited the flow properties of honey (around 10,000 cps), as observed by my team.

   - Water content of the film was less than 10%, as verified by my team.

   - Within about 4 minutes after initiation of drying, the film was self-supporting, non-tacky, flexible and viscoelastic, as verified by my team.

9. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine, or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful statements may jeopardize the validity of the application or any patents issued thereon.

Dated: February 28, 2013

Maureen Reitman, Sc.D.

Appendix A

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Maureen T. F. Reitman, Sc.D.
Principal and Practice Director

Professional Profile

Dr. Maureen Reitman is a Principal and the Director of Exponent's Polymer Science and Material Chemistry practice. Her expertise includes polymer and composite technology, mechanics of materials, adhesion science, fiber mechanics, history and technology of plastics, and material failure analysis. She is skilled in the development and use of testing tools and methods and has applied them to plastic, rubber, textile, metal, glass, ceramic, and composite materials and systems. She is experienced in major aspects of product development, including materials selection, formulation, scale-up, end-use testing, failure analysis, certification procedures and issues related to intellectual property.

Dr. Reitman has conducted research in the areas of packaging and barrier materials; paints and coatings; plastic pipes; transdermal drug delivery; adhesives, sealants, and encapsulants; molding compounds; high temperature resins; nanoparticles; fibers and textiles; protective coatings and finishes; polymer chemical resistance; plastic insulation; connectors and splices; plastic packaging; medical devices; environmental effects on durability; and product aging. She has used her expertise to solve a broad range of problems related to coatings, fibers, films, and extruded and molded products, and their use in the telecom, electronics, electrical, transportation, construction, fire protection, medical, and consumer products markets.

Dr. Reitman is a member of the Board of Directors of the Medical Plastics Division of the Society of Plastics Engineers and an active member of two Underwriters Laboratories Standard Technical Panels, addressing Polymeric Materials (UL 94, UL 746, UL 1694) and Appliance Wiring (UL758).

Prior to joining Exponent, Dr. Reitman worked for the 3M Company in both research and management roles. Her activities included technology identification, materials selection and qualification, product development, customer support, program management, acquisition integration, intellectual property analysis, and patent litigation support.

Academic Credentials and Professional Honors

Sc.D., Materials Science and Engineering/ Program in Polymer Science and Technology, Massachusetts Institute of Technology, 1993
B.S., Materials Science and Engineering, Massachusetts Institute of Technology, 1990

National Academy of Engineering Frontiers of Engineering, 2009; Tau Beta Pi; Sigma Xi
John Wulff Award; Carl Loeb Fellowship; NCAA Postgraduate Scholarship;
Malcolm G. Kispert Award; GTE Academic All-American

Patents

Patent 6,311,524: Accelerated Method for Increasing the Photosensitivity of a Glassy Material, issued November 6, 2001.

European Patent EP0830428: Tackified Polydiorganosiloxane Polyurea Segmented Copolymers and a Process for Making Same, published March 25, 1998.

Patent 5,371,051: Fiber Optic Fusion Splice Protector Sleeve, issued March 24, 1998.

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Ezekoye OA, Lowman CD, Hulme-Lowe AG, Fahey MT. Polymer weld strength predictions using a thermal and polymer chain diffusion analysis. Polymer Engineering and Science 1998; 38(6):976–991, June.

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Book Contributions

Reitman M, Liu D, Rehkopf J. Chapter 38. Mechanical properties of polymers. In: Handbook of Measurement in Science and Engineering. Volume 2. Kutz, M (ed), John Wiley & Sons, Hoboken NJ, 2013. ISBN- 978-1-118-38464-0.

Reitman M, Jaekel D, Siskey R, Kurtz S. Morphology and crystalline architecture of polyarylketones, pp. 49-60. In: PEEK Biomaterials Handbook. Kurtz SM (ed), Elsevier William Andrews, Kidlington, Oxford, UK, 2012. ISBN 13:978-1-4377-4463-7

Tsuji JS, Mowat FS, Donthu S, Reitman M. Application of toxicology studies in assessing the health risks of nanomaterials in consumer products, pp. 543-580. In: Nanotoxicity: From In Vivo and In Vitro Models to Health Risks. Sahu S, and Casciano D. (eds), John Wiley & Sons, Chicester, West Sussex, UK, 2009. ISBN 978-0-470-74137-5.

Reitman MTF. The Plastics Revolution. In: Research and Discovery: Landmarks and Pioneers in American Science. Lawson RM (ed), Armonk NY: Sharpe Reference 2008. ISBN 978-0-7656-8073-0.

Klein SM. Mid-century plastic jewelry. Schiffer Publishing, Atglen, PA, 2005. (Technical advisor to author).

Selected Invited Presentations

Reitman MTF. Failure analysis tools. Workshop on Future Needs for Service Life Prediction of Polymeric Materials. NIST and Underwriters Laboratories, Gaithersburg, MD, October 2012.

Hoffman J, MacLean S, Ralston B, Reitman M, Ledwith P. Fractography of unfilled thermoplastic materials experiencing common mechanical failure modes. Materials Science & Technology 2012 Conference, Pittsburgh PA, October 2012.

Hoffman J, Reitman M, Ledwith P. Microscopic characterization of CPVC failure. Materials Science & Technology 2012 Conference, Pittsburgh PA, October 2012.

Reitman MTF. Polymer material properties for next generation medical devices. Invited Speaker: MedTech Polymers, UBM Canon, Chicago, IL, September 2012.

Reitman MTF. Polymers for medical applications. Fundamentals and Fellows Forum, ANTEC 2012, Orlando FL, April 2012.

Reitman MTF. Plastic and composite product failures. Invited lecture in Failure Analysis of Emerging Technologies. Stanford University Department of Materials Science and Engineering, Menlo Park, CA October 2009.

Reitman MTF. Factors for success: Plastics in injection molded medical devices. Part of *Injection Molding Works for Medical Design*, Design News Webcast, October 2008.

Reitman MTF. Plastic and composite product failures. Keynote Speaker: Third International Conference on Engineering Failure Analysis (ICEFA III), Elsevier, Sitges Spain, July 2008.

Reitman MTF. Multiphase materials for medical device applications, an overview. Medical Device and Manufacturing (MDM), Canon Communications, various locations, January- June 2008.

Reitman MTF. Nanotechnology and plastics for medical devices. Capitalizing on Nanoplastics, Intertek PIRA San Antonio TX, February 2008.

Reitman MTF. Nano additives in composites and coatings for medical device applications. Medical Device and Manufacturing Minneapolis, Canon Communications, Minneapolis MN, October 2007.

Reitman MTF, Swanger LA. Practical tips on how to manage your technical expert in patent disputes. Ropes & Gray IP Master Class, Live Teleconference, June 2007.

Reitman MTF, Kennedy E. Root cause failure analysis and accident investigation. Lorman Educational Services, Live Teleconference, November 2007.

Reitman MTF. Plastics failure analysis: Case studies. Baltimore/ Washington Chapter of SAMPE, October 2006.

Reitman MTF. Plastics failure analysis. Baxter Global Plastics Processing Conference 2005, Schaumburg IL, 2005.

Fahey MT. Fiber mechanics, corrosion, sealants: Tales of a 3M materials scientist. Class of 1960's Scholars Program, Williams College, 1999.

Fahey MT. Adhesives and sealants for the telecommunications industry. Riverwood V Conference, St. Paul MN, 1998.

Current Professional Appointments

- Underwriter's Laboratory Standards Technical Panel STP 746 (Polymeric Materials, includes UL94, UL 746 and UL1694)
- Underwriter's Laboratory Standards Technical Panel STP 758 (Appliance Wires/ UL758)
- Medical Plastics Division Board of Directors, Society of Plastics Engineers

Committee and Review Activities

- UL Forum on Initiatives to Improve the Long Term Aging Program, LTTA Tools Working Groups, Underwriters Laboratories
- Research and Engineering Technology Award Committee, Society of Plastics Engineers
- Reviewer, Medical Plastics Technical Program Committee, Society of Plastics Engineers
- Reviewer, Failure Analysis and Prevention Technical Program Committee, Society of Plastics Engineers
- Reviewer, various book proposals and submissions related to polymer science, ASM International, Elsevier, John Wiley

Professional Affiliations

- American Association for the Advancement of Science (member)
- American Association of Textile Chemists and Colorists—AATCC (senior member)
- American Chemical Society (member)
- ASTM International (member)
- Society for the Advancement of Material and Process Engineering (member)
- Society of Plastics Engineers (senior member)

CERTIFICATE OF SERVICE

It is certified that a copy of this PATENT OWNER'S APPELLANT'S REBUTTAL BRIEF has been served, by first class mail, postage prepaid, on May 27, 2014, in its entirety on the third party requester as provided in 37 CFR § 1.903 and 37 CFR § 1.248 at the address below.

DANIELLE L. HERRITT
McCARTER & ENGLISH LLP
265 FRANKLIN STREET
BOSTON, MASSACHUSETTS 02110

/Michael I. Chakansky/
Michael I. Chakansky
Registration No.: 31,600
Attorney for the Patentee/Appellant

Electronic Acknowledgement Receipt

EFS ID:	19140143
Application Number:	95002170
International Application Number:	
Confirmation Number:	6418
Title of Invention:	POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM
First Named Inventor/Applicant Name:	7897080
Customer Number:	23869
Filer:	Michael I. Chakansky
Filer Authorized By:	
Attorney Docket Number:	117744-00023
Receipt Date:	27-MAY-2014
Filing Date:	10-SEP-2012
Time Stamp:	21:30:57
Application Type:	inter partes reexam

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Rebuttal Brief - Owner	AppellantsRebuttalBrief.pdf	1869390 e4ae8c32870e5d47e495244a7cab0f9a66313b3d	no	45

Warnings:	
Information:	

Total Files Size (in bytes):	1869390

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
95/002,170	09/10/2012	7897080	117744-00023	6418

23869 7590 04/25/2014

Hoffmann & Baron LLP
6900 Jericho Turnpike
Syosset, NY 11791

EXAMINER
DIAMOND, ALAN D

ART UNIT	PAPER NUMBER
3991	

MAIL DATE	DELIVERY MODE
04/25/2014	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Transmittal of Communication to Third Party Requester *Inter Partes* Reexamination	Control No.	Patent Under Reexamination	
	95/002,170	7897080	
	Examiner	Art Unit	
	Alan Diamond	3991	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address. --

(THIRD PARTY REQUESTER'S CORRESPONDENCE ADDRESS)

Danielle L. Herritt
McCarter & English LLP
265 Franklin Street
Boston, MA 02110

Enclosed is a copy of the latest communication from the United States Patent and Trademark Office in the above-identified reexamination proceeding. 37 CFR 1.903.

Prior to the filing of a Notice of Appeal, each time the patent owner responds to this communication, the third party requester of the *inter partes* reexamination may once file written comments within a period of 30 days from the date of service of the patent owner's response. This 30-day time period is statutory (35 U.S.C. 314(b)(2)), and, as such, it cannot be extended. See also 37 CFR 1.947.

If an *ex parte* reexamination has been merged with the *inter partes* reexamination, no responsive submission by any *ex parte* third party requester is permitted.

All correspondence relating to this inter partes reexamination proceeding should be directed to the **Central Reexamination Unit** at the mail, FAX, or hand-carry addresses given at the end of the communication enclosed with this transmittal.

Inter Partes Reexamination Examiner's Answer	Application No.	Applicant(s)	
	95/002,170	7897080	
	Examiner	Art Unit	
	Alan Diamond	3991	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address. --

Incorporation by Reference of the Right of Appeal Notice

The Right of Appeal Notice (RAN) mailed on December 6, 2013, including all of the grounds of rejection, determinations of patentability, and explanations set forth in the RAN is incorporated by reference. Every ground of rejection and every determination not to make a proposed rejection set forth in the RAN are being maintained by the examiner.

This examiner's answer does not contain any new ground of rejection and any new determination not to make a proposed rejection.

Status of Amendment After Action Closing Prosecution

The amendment(s) filed on _____ has/have been entered.
The amendment(s) filed on 3 September 2013 has/have not been entered.

Period for providing a Rebuttal Brief

Appellant(s) is/are given a period of ONE MONTH from the mailing date of this examiner's answer within which to file a rebuttal brief in response to the examiner's answer. Prosecution otherwise remains closed.

The rebuttal brief of the patent owner may be directed to the examiner's answer and/or any respondent's brief. The rebuttal brief of the third party requester(s) may be directed to the examiner's answer and/or the respondent's brief of the patent owner. The rebuttal brief must (1) clearly identify each issue, and (2) point out *where* the issue was raised in the examiner's answer and/or in the respondent's brief. In addition, the rebuttal brief must be limited to issues raised in the examiner's answer or in the respondent's brief. The time for filing the rebuttal brief may not be extended. No further submission (other than the rebuttal brief(s)) will be considered, and any such submission will be treated in accordance with 37 CFR 1.939 and MPEP 2667.

☐ Attachment(s)

_____

☐ Other:

_____

All correspondence relating to this *inter partes* reexamination proceeding should be directed to the **Central Reexamination Unit** at one of the following addresses:

Please mail any communications to:
Attn: Mail Stop "Inter partes Reexam"
Central Reexamination Unit
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Please hand-deliver any communication to:
Customer Service Window
Attn: Central Reexamination Unit
Randolph Building, Lobby Level
401 Dulany Street
Alexandria VA 22314

Please FAX any communications to: (571) 273-9900

/Alan Diamond/
Patent Reexamination Specialist
Central Reexamination Unit 3991

/Jerry D. Johnson/
Patent Reexamination Specialist
Central Reexamination Unit 3991

/Deborah D. Jones/
Supervisory Patent Examiner, Art Unit 3991

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	95002170	7897080
	Examiner	Art Unit
	ALAN DIAMOND	3991

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

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	95002170	7897080
	Examiner	Art Unit
	ALAN DIAMOND	3991

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	10/08/2012	07/11/2013	11/25/2013	04/23/2014					
	217	✓	✓	✓	A					
	218	✓	✓	✓	A					
	219	✓	✓	✓	A					
	220	✓	✓	✓	A					
	221	✓	✓	✓	A					
	222	✓	✓	✓	A					
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	225	✓	✓	✓	A					
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Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
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CLAIM		DATE								
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CLAIM		DATE								
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	291	✓	-	-	-					
	292	✓	✓	✓	A					
	293	✓	-	-	-					
	294	✓	✓	✓	A					
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	317		✓	✓	A					
	318		✓	✓	A					

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re *Inter Partes* Reexamination of:	)	
	)	
US Patent No. 7,897,080	)	Confirmation No.: 6418
	)	
Named Inventor: Robert K. Yang *et al.*	)	Group Art Unit: 3991
	)	
Control No.: 95/002,170	)	Examiner: Alan D. Diamond
	)	
Request Filed: September 10, 2012	)	M&E Docket: 117744-00023
	)	
Title: POLYETHYLENE OXIDE-BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM	)	H&B Docket: 1199-26 RCE/CON/REX

Mail Stop *Inter Partes* Reexam
Attn: Central Reexamination Unit
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL OF PAYMENT OF RESPONDENT BRIEF FEE (37 C.F.R. § 41.20(b)(2)(ii))

Requester hereby submits payment of the fee for filing the respondent brief in support of the appeal of the above-identified *inter partes* reexamination on April 10, 2014. If additional fees are believed to be due, please charge our Deposit Account No. 50-4876, under Order No. 117744-00023 from which the undersigned is authorized to draw.

Respectfully submitted,
McCarter & English LLP

Dated: April 18, 2014

By: /Danielle L. Herritt/
Danielle L. Herritt Reg. 43,670
Kia Freeman Reg. 47,577
Direct Dial: 617-449-6513
Attorneys for Requester, BioDelivery Sciences International, Inc.

CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of the foregoing Transmittal of Payment of Respondent Brief Fee was served on April 18, 2014, by first class mail, directed to the patent owner at the correspondence address of record for the subject patent at the following address:

Daniel A. Scola, Jr.

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SYOSSET, NY 11791,

By: /Danielle L. Herritt/
Danielle L. Herritt
Registration No. 43,670
Attorney for Requester

Electronic Patent Application Fee Transmittal

Application Number:	95002170
Filing Date:	10-Sep-2012
Title of Invention:	POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM
First Named Inventor/Applicant Name:	7897080
Filer:	Danielle L. Herritt/Maureen Tierney
Attorney Docket Number:	117744-00023

Filed as Large Entity

inter partes reexam Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Filing Appeal Brief Inter Partes Reexam	1404	1	2000	2000
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**2000**

Electronic Acknowledgement Receipt

EFS ID:	18801479
Application Number:	95002170
International Application Number:	
Confirmation Number:	6418
Title of Invention:	POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM
First Named Inventor/Applicant Name:	7897080
Customer Number:	23869
Filer:	Danielle L. Herritt/kia freeman
Filer Authorized By:	Danielle L. Herritt
Attorney Docket Number:	117744-00023
Receipt Date:	18-APR-2014
Filing Date:	10-SEP-2012
Time Stamp:	19:44:58
Application Type:	inter partes reexam

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$2000
RAM confirmation Number	4077
Deposit Account	504876
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if app.)

1	Reexam Miscellaneous Incoming Letter	080BDSIRespondentIBriefFeeTransmittal.PDF	8779 37cde13ded906c1333c7949b9c18a0f3380f8a63	no	2
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30024 2087d8f1b02504f73f893ab67bb421f70f6af985	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	38803		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re *Inter Partes* Reexamination of:	)	
	)	
US Patent No. 7,897,080	)	Confirmation No.: 6418
	)	
Named Inventor: Robert K. Yang *et al.*	)	Group Art Unit: 3991
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Mailing Date: April 10, 2014	)	

Mail Stop *Inter Partes* Reexam
Attn: Central Reexamination Unit
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

BDSI'S RESPONDENT BRIEF IN *INTER PARTES* REEXAMINATION

BioDelivery Sciences International, Inc. ("BDSI") respectfully submits this Respondent's Brief pursuant to 37 CFR 41.66 and 41.68.

Certificate Regarding Word Count Pursuant to 37 CFR 1.943(c)

I hereby certify that, pursuant to 37 CFR 1.943(c), based on the Word version word count of 6,878 words, Respondent's Brief does not exceed 7,000 words in length.

Signed: Danielle L. Herritt /Danielle L. Herritt/ Reg. No. 43,670 Dated: April 10, 2014

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I. REAL PARTY IN INTEREST

BioDelivery Sciences International, Inc., the Requestor in the underlying *inter partes* reexamination, is the real party in interest for this brief.

II. RELATED APPEALS, INTERFERENCES, AND TRIALS

BDSI agrees with Patent Owner MonoSol's March 10, 2014 Appeal Brief (hereinafter "AB") except as follows.

- Neither US Patent No. 7,357,891 nor US Patent No. 7,425,292 successfully exited reexamination. No original or substantially identical claims were confirmed in either of the *ex parte* reexamination certificates.
- Requestor properly petitioned for *Inter Partes* Review of the new claims of '891C1 Patent and the substantially amended claims of the '292C1 Patent.
- BDSI presumes that MonoSol's reference to "the '150 Patent" is a reference to MonoSol's US Patent No. 8,017,150. In any event, to be clear, BDSI is not involved in any patent infringement action involving "the '150 Patent."

III. STATUS OF CLAIMS

BDSI agrees.

IV. STATUS OF AMENDMENTS

BDSI agrees.

V. SUMMARY OF CLAIMED SUBJECT MATTER

BDSI disagrees with the support cited by MonoSol for its newly added recitations and to any alleged distinction between the claimed methods and the prior art, whether based on uniformity, locking-in/preventing migration, performing analytical chemical testing, or any other claim element.

BDSI disputes, for example, that the invention is directed to methods "(i) where the degree of uniformity of content of active throughout a particular lot of resulting films, as well as (ii) where the degree of uniformity of content of active in dosage units taken from different lots of resulting films can also be strictly maintained through the claimed processes." AB at 5. None of the claims recite these alleged points of novelty, either "lot of resulting films" or "different lots of resulting films."

BDSI also disputes that "[p]rocesses for such control of content uniformity are not present in the prior art." AB at 5. None of MonoSol's claims recite "controlling content uniformity," nor do they provide any novel or non-obvious methods for controlling anything.

VI. ISSUES TO BE REVIEWED ON APPEAL

A. Whether the panel erred in rejecting the claims of the '080 patent when it relied upon substantial evidence and where MonoSol failed to dispute the findings underlying the panel's *prima facie* case.

B. Whether the panel erred in rejecting MonoSol's rebuttal arguments, where (i) no nexus has been established between the rebuttal evidence and the claimed invention, (ii) the rebuttal evidence is not commensurate with the scope of the claims, and (iii) MonoSol has not rebutted the substantial evidence that the newly-recited properties already existed in the prior art films.

VII. ARGUMENT

Preliminary Statement

The underlying issue of this reexamination is that if MonoSol has an inventive process, it has failed to claim it. MonoSol is unable to point to any claimed operative step or condition that is not taught or suggested by the prior art. And, despite several opportunities to do so, MonoSol is unable to explain why the prior art methods would not necessarily achieve the claimed desired results. The panel's *prima facie* case is also supported by extensive factual findings and substantial evidence. *See*, *e.g.*, RAN at 30-44 (*Chen*), 52-62 (*Staab*), 63-71 (*Le Person*); Reitman Declaration; Cohen Declaration.

And MonoSol has failed to rebut the panel's *prima facie* case. Instead, MonoSol argues that recitations of characteristics inherent to the prior art processes and/or recitations of well-known post-manufacturing steps render the claims novel and non-obvious. "However, arguments of counsel cannot take the place of factually supported objective evidence." MPEP 2145, *citing In re Huang*, 100 F.3d 135, 139-40 (Fed. Cir. 1996). With respect to all of its rebuttal evidence, *e.g.*, there is no nexus between the rebuttal evidence and the claimed invention. Many of MonoSol's arguments are presented without any discernible allegation of

error by the panel. Where no error has been alleged, MonoSol's arguments do not present proper issues for appeal. MonoSol is not entitled to *de novo* review.

A. Whether the panel erred in rejecting the claims of the '080 patent when it relied upon substantial evidence and where MonoSol failed to dispute the findings underlying the panel's *prima facie* case.

MonoSol's claims recite a process. As the panel has repeatedly found, MonoSol's process claims do not recite any process step or condition that can distinguish the methods disclosed in the prior art from the claimed methods. RAN at 74 (*Chen*), 82 (*Staab*). MonoSol is unable to point out any claimed operative step or condition that is not taught or suggested by the prior art. RAN at 82. Instead, MonoSol argues that two types of new recitations render the claims novel and non-obvious: (i) recitations of uniformity (which are inherent to the prior art processes) and (ii) recitations of a post-manufacturing testing step (which was well-known in the prior art).

"Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established." MPEP 2112.01(I), *citing In re Best*, 562 F.2d 1252, 1255 (CCPA 1977). The panel has met this burden.

In addition, the panel's findings are supported by substantial evidence, including: (i) the claimed uniformity disclosed in the *Chen* films (*Chen* at 17:15-16, and Table 4); (ii) the evidence in the Reitman Declaration reproducing Example 7 in *Chen* and confirming uniformity in the *Chen* films (Reitman Decl. ¶¶ 5-7); (iii) the evidence in the Cohen Declaration confirming the ability of one of ordinary skill to make uniform films when starting with a homogeneous polymer matrix or solution (Cohen Decl. ¶ 10); and (iv) the evidence in the Reitman Declaration demonstrating that MonoSol's newly-recited scientific theories are inherent in *Chen* (Reitman Decl. ¶ 8). Despite several opportunities to do so, MonoSol has been unable to respond to the panel's findings (RAN at 82-83) that the prior art methods would not necessarily achieve the claimed desired results or provide rebuttal evidence.

Finally, substantial evidence supports the panel's findings that the recited post-manufacturing steps were known in the prior art. MonoSol admits the worldwide regulatory requirement for consistent pharmaceutical dosages was known ('080 patent 2:38-45), and the panel correctly found motivation for the step of performing uniformity testing existed at the time the invention was made. RAN at 38-39. MonoSol also admits that the step of performing analytical chemical

testing for content uniformity was known in the prior art. '080 patent; *see also* 29:35-39 ("[a]ny conventional means for…testing…for example…use of analytical equipment,"); *see also* AB at 56 ("Le Person went on to support Patentee's position that the only way to actually determine uniformity of content in the amount of active is through assaying (analytical chemical testing)" (*citing Le Person* at 257, col. 2). The panel's finding of the same (RAN at 38-39) was not disputed in MonoSol's Appeal Brief.

B. Whether the panel erred in rejecting MonoSol's rebuttal arguments, where (i) no nexus has been established between the rebuttal evidence and the claimed invention, (ii) the rebuttal evidence is not commensurate with the scope of the claims, and (iii) MonoSol has not rebutted the substantial evidence that the newly-recited properties already existed in the prior art films.

Once the panel made its proper *prima facie* case, the burden of proof shifted to MonoSol to present rebuttal evidence and arguments. MPEP 2145, *citing In re Dillon*, 919 F.2d 688, 692 (Fed. Cir. 1990). Attorney argument cannot take the place of "factually supported objective evidence." MPEP 2145, *citing In re Huang*, 100 F.3d 135, 139-40 (Fed. Cir. 1996); MPEP 2145. "[T]o be entitled to substantial weight, the applicant should establish a nexus between the rebuttal

evidence and the claimed invention, *i.e.,* objective evidence of nonobviousness must be attributable to the claimed invention." MPEP 2145.

1. Bogue and Uniformity: there is no nexus between Bogue's lots and the claimed invention.

MonoSol argues that the panel did not give sufficient weight to the declarations of MonoSol's expert, Dr. Bogue, regarding the uniformity of "lots" of Suboxone® films. AB at 18 n.2. However, the panel fully considered and weighed Dr. Bogue's March 13, 2013 Declaration ("Bogue I") and September 3, 2013 Declaration ("Bogue II"), and found that MonoSol failed to establish a nexus between the process described in the Declarations and any of the claimed processes:

> Bogue Declaration I lacks specific details about the film production. For example, it is not clear in Bogue Declaration I which materials, e.g., the specific polymers and solvent, are used; it is not clear if other materials are present when preparing the films; it is not clear exactly what is done to form the flowable polymer matrix or how and on what it is casted, or, in particular, exactly how the controlled drying is performed and for what exact amount of time the drying is done, etc.

RAN at 74 (Bogue I); *see also* RAN at 78-80 (Bogue II). The Bogue Declarations merely recite general process steps and assert—without support—that the films

were made according to the '080 patent. Bogue I, ¶ 4; Bogue II, ¶ 4. Such statements do not establish a nexus. *See* RAN at 78-80, *citing* MPEP 716 and MPEP 716.03; *see also Ex Parte Standish*, 10 USPQ2d 1454, 1458 (BPAI 1988) (nexus is not established by generic statements regarding construction of products or process from declarants).

Thus, MonoSol failed to establish that Suboxone® is manufactured "in accordance with the '080 Patent" (AB at 33) or its claims; and the panel properly found that MonoSol had not established a nexus between the rebuttal evidence and the claimed invention. RAN at 78-79; MPEP 2145, *citing In re Huang*, 100 F.3d 135, 139-40 (Fed. Cir. 1996).

2. Bogue and Uniformity: Bogue's lots are not commensurate with the claim scope.

Even if Bogue established that the lots were made in accordance with even one claim—which it did not—it is unclear how a single product containing one polymer combination and one active can be commensurate in scope with claims covering hundreds of thousands of polymer combinations and actives.

3. Bogue Commercial Success: there is no nexus between the sales of Suboxone® and the claimed invention.

For the same reasons discussed above with respect to Bogue and uniformity, MonoSol failed to establish a nexus between the process described in its Declarations and any of the claimed processes. In its lengthy arguments relating to commercial success, MonoSol does not dispute the panel's findings that MonoSol failed to show a nexus between the evidence and the claimed methods and that the evidence is not commensurate in scope with claims (RAN at 80; AB at 18-25, 31-33).

Indeed, as stated in the RAN, the evidenced commercial success appears to be the result of product conversion, not the claimed invention. RAN at 79. The evidence of commercial success must be deemed to derive from the invention and not from an unrelated business event. RAN at 79, *citing* MPEP 716.03(b)(I). As explained in MonoSol's own exhibit, the tablet form of Suboxone® was recently discontinued. RAN at 79 (reproducing Exhibit 5 of the Response to ACP). As a result, existing users of the tablet form who were treating their opiate dependence and wanted to continue with the same branded drug were left with no option but to

convert to the Suboxone® film. *Id.* MonoSol did not dispute this in its brief or allege any error in the findings of the panel.

4. Bogue Commercial Success: one product is not commensurate with the claim scope.

The evidence of commercial success is not commensurate with the scope of the claims. As the panel found, "evidence of sales of Suboxone® film is not commensurate in scope with claims that are not limited to Suboxone®." RAN at 80. MonoSol does not dispute this finding.

5. The facts in *Leo* are the direct opposite of the facts in the instant appeal.

MonoSol relies heavily on *Leo Pharmaceutical Products, Ltd. v. Rea*, 726 F.3d 1346 (Fed. Cir. 2013) in constructing its rebuttal argument, contending that a person of ordinary skill would not have been able to optimize the necessary parameters recited in the claims of the '080 patent to arrive at the claimed invention. AB at 30-31.

First, even if MonoSol were to overcome the panel's conclusions regarding optimization (RAN at 37), it is unclear how that would advance MonoSol's

appeal. MonoSol failed to address the panel's primary conclusions that the claimed uniformity was explicitly or inherently disclosed. RAN at 36-37.

Second, the fact pattern in *Leo* is completely different from the facts in the present case. Some of the many differences between the facts in *Leo* and the present case are below:

Facts in *Leo* Relied upon by the Federal Circuit	**Facts in Present Case**
The prior art explicitly taught away from the claimed invention. *Leo*, 726 F.3d at 1353-54.	In contrast, the panel found that the prior art explicitly teaches the claimed invention. *See, e.g.*, RAN at 74 ("the prior art either explicitly, inherently and/or obviously performs the claimed generic manufacturing steps using the claimed generic ingredients"), 82 ("Despite multiple opportunities during these proceedings, *MonoSol has not explained what step or condition is claimed but not taught in the prior art*.")
The problem solved by the claimed invention was not recognized in the prior art. *Leo*, 726 F.3d at 1353.	MonoSol admits that the "problem" of content uniformity was recognized by the prior art, *i.e.*, *Le Person*. AB at 30. Further, the panel found that the solution was already provided by the prior art. RAN at 37; *see also* Cohen Decl., ¶ 10 ("When working with a homogeneous or completely dissolved coating mixtures as in

	Chen, it would be difficult for a person of ordinary skill in the film art ***not*** to obtain a film that has uniform content of active.") (emphasis added).
The elapsed time between the prior art and the patent's filing date was very long: 14 and 22 years. *Leo,* 726 F.3d at 1356.	The elapsed time between the prior art and the earliest priority date was a little more than one year. (*Chen, e.g.,* published July 27, 2000 and the first priority date of the '080 patent is October 12, 2001.)
The patent owner presented experimental evidence that the formulations disclosed in the prior art did not achieve the desired results. *Leo*, 726 F.3d at 1354.	In contrast, MonoSol presents no evidence that the methods of the prior art do not achieve its recited desired result. And MonoSol does not dispute the Reitman Declaration, which demonstrates that *Chen* achieved the desired results. (Reitman Decl., ¶¶ 5-7).

As such, the facts in *Leo* are the direct opposite of the facts in the instant appeal.

Even if the facts in *Leo* were not the direct opposite of the facts in the instant appeal, the Board has noted that *Leo* is only applicable in limited circumstances:

> [T]he Federal Circuit limited *Leo Pharm. Prods., Ltd.* to a situation where the applied prior art did not provide any apparent reason for one of ordinary skill in the art to arrive at the claimed subject matter not only due to the failure of the applied prior art to recognize and address

> the problem found by Appellants, but also due to the divergent teachings and express disclaimer in the applied prior art that would have precluded one of ordinary skill in the art from arriving at such combination.

Ex Parte Deorkar, 2013 WL 6217838, *2 (PTAB Nov. 27, 2013).

6. Example M has no nexus with the claimed invention, is not commensurate with the claimed invention, and, in any event, there is evidence that the prior art already teaches both uniformity and performing analytical testing.

MonoSol cites Example M of the '080 patent as evidence of the non-obviousness of the recited analytical chemical testing step to the claimed invention, relying on the proposition that there is no legal requirement that a patent disclose examples for each embodiment. AB at 27. In doing so, MonoSol admits that Example M is not covered by the claims and—therefore—there is no nexus and this example is not commensurate in scope with the claimed subject matter. It is not relevant whether or not Example M is an example of either "unexpected" uniformity or an analytical chemical test in both are in the prior art. MonoSol's argument does not address or rebut the panel's factual findings that the prior art disclosed the recited uniformity (RAN at 36-38 (discussing *Chen* at 17:15-16 and

Table 4); RAN at 56-57 (discussing *Staab* at cols. 1-13)) and that analytical chemical testing was well-known (RAN at 38-39, and 84).

For example, it is unclear how the disclosure of "degrees of uniformity … approaching 4%" (AB at 26) supports patentability when the prior art shows variation of 0% using the same criteria and to the same degree as the '080 patent. RAN at 36 (*Chen*) and 57 (*Staab*).

And, MonoSol cannot rely on recitation of the analytical claimed testing step itself to support non-obviousness of the claimed methods for making films. AB at 17 ("[o]nly by analytical chemical testing is it possible to determine the actual amount of active present ...[t]his is the essence of the '080 patent claims."). Even if Example M measured a pharmaceutical active—which it does not—the claimed testing step, by whatever method, is a known, post-manufacturing step. RAN at 38-39. With or without the performance of analytical chemical testing, the resulting film product made according to the claimed methods would be the same.

C. Claim Rejections Based on Sections 102 and/or 103

1. The panel did not err in rejecting claims 1-11, 13-15, 17-71, 82-90, 92-94, 96-150, 161-172, 174-176, 178-232, 243-253, 256, 258-271, 274, 276-289, 292, and 294-318 under 35 USC 103(a) over *Chen*.

a) *MonoSol's preliminary argument.*

According to MonoSol, "the Examiner has not even considered all of the elements of step (d) of Claim 1 or step (c) of Claims 82, 161 and 315-318." AB at 35. MonoSol asserts that the panel ignores that the claims require not only creation of viscoelastic film, but that it does so such that the active is "locked-in." AB at 36-37. But the panel did not ignore this requirement. The panel carefully considered this step and correctly and without error established its *prima facie* case with respect to "locked-in," by relying on *Chen*'s teaching of the same ingredients, homogeneously mixed, and the same process as the claimed invention. RAN at 36; 82-83. MonoSol has not explained why performing all of the claimed steps with the claimed materials, as the prior art does, would not dry a film such that active is "locked-in." RAN at 82. If there is a unique step for MonoSol's process, or if "locking-in" is meant to indicate a physical step or process condition, such step or condition has not yet been indentified and claimed. RAN at 82.

In addition, the Reitman Declaration reproduced *Chen* and provides evidence that "[w]ithin about 4 minutes after initiation of drying, the film was self-supporting, non-tacky, flexible, and viscoelastic." Reitman Decl. at ¶ 8. Therefore, Reitman demonstrates that the active in *Chen*'s films are locked-in within about 4 minutes after initation of drying and achieves the recited desired degrees of uniformity. Reitman at ¶ 5-8. MonoSol does not dispute Reitman.

b) Chen's *Figure 5 is not evidence of non-uniform films.*

Regarding Figure 5 in *Chen*, MonoSol fails to allege any panel error. Without addressing the findings of the panel, MonoSol merely repeats its old argument that Figure 5 in *Chen* discloses:

> in six instances the amount of pharmaceutical active released from Chen's unit dose films is greater than 110% *of the expected/desired amount of pharmaceutical active* for that drug and thus outside the '080 Patent's claim limitations.

AB at 39 (emphasis added).

As a preliminary matter, this argument is at best relevant only to independent claims 82 and 315, the only claims containing the limitation "varies by no more than 10% *from the desired amount of active*."

MonoSol's argument is entitled to little or no weight for several reasons.

First, MonoSol's own expert, Dr. Lin, stated "[t]hese data [in Figure 5] indicate that the test method used in the analysis is not reproducible ***and/or*** there is a lack of active agent content uniformity between individual dosage units." Lin Declaration ¶ 22 (emphasis added). That is, MonoSol's expert admits that the error bars in Figure 5 could indicate uncertainty in the testing measurement, rather than a variation regarding release. *Id.* "Reduced to its logical components, Lin's conclusion (X demonstrates B) does not follow from Lin's own premise (X indicates A and/or B). In other words, Lin's conclusion is logically invalid based on Lin's own stated premise." RAN at 92. In its brief, MonoSol does not mention, much less explain, its own expert's uncertainty.

Second, not only does the data in Figure 5 not support Lin's conclusion, it in fact supports the opposite conclusion, *i.e.*, that the error bars indicate uncertainty in the test measurement. The total release of hydromorphone decreases between 4 and 5 minutes, and again between 8 and 10 minutes and the total release of oxybutynin decreases between 6 and 8 minutes. But the total amount of active that has been released cannot decrease over time—no matter how irregular the film samples might be the drug cannot be "unreleased." If anything, these decreases in

total release over time support uncertainty in the test measurement. This point was made in the RAN (92-94), and MonoSol failed to rebut the panel's finding.

Third, Figure 5 is not relevant to the recited uniformity per dosage unit. Uniformity per dosage unit is not what is shown in Figure 5. Figure 5 shows cumulative active released over time, and it is not even clear that at 10 minutes the films are fully dissolved.

Finally, to the extent that MonoSol is claiming that "locking-in" uniform distribution and/or prevention of migration within the first 4 minutes is demonstrated by uniformity (AB at 40), *Chen* demonstrates it. MonoSol does not dispute that *Chen* discloses 0% variation using the same criteria and to the same degree as disclosed in the '080 patent in Table 4; 17:15-16 and that the Reitman Declaration confirms it (Reitman Decl. ¶¶ 5-6).

In view of the above, the rejection was proper and should be affirmed.

c) *MonoSol's optimization argument is based on* Leo*, a case that has no discernible relationship to the facts in the instant case.*

See detailed argument above with respect to the *Leo* case (Section VII(B)(5)).

2. The panel did not err in rejecting claims 2, 3, 32, 55, 72-81, 111, 134, 151-160, 193, 216 and 233-242 under 35 USC 103(a) over *Chen* in view of *Staab*.

MonoSol presents no arguments specific to the panel's findings of obviousness over *Chen* in view of *Staab*, other than to incorporate remarks from other sections relating to *Chen* and *Staab* separately. AB at 43. BDSI addresses these remarks above and below. *See* Sections (B) (rebuttal arguments), (C)(1) (*Chen*), and (C)(5) (*Staab*). MonoSol alleged no further panel error and did not challenge the motivation to combine *Chen* with *Staab*.

In view of the above, the rejection was proper and should be affirmed.

3. The panel did not err in rejecting claims 317 and 318 under 35 USC 103 over *Chen* in view of *Arter*

MonoSol incorporated its previous remarks relating to *Chen*, including "locking in," and alleging a lack of proof of uniformity of *Chen*'s films, and a lack of description of what happens to *Chen*'s films during the drying process. AB at 43-44. BDSI addresses these remarks above. *See* Section (C)(1) (*Chen*).

a) *The panel did not err in combining* Chen *with* Arter.

MonoSol argues that it is improper to combine *Arter* with *Chen* because "[*Arter*'s] process and apparatus is not at all transferrable to drying methods for

pharmaceutical films, and particularly pharmaceutical films which are aqueous-based and self-supporting." AB at 44-45. However, MonoSol failed to substantively address or point out any error in the RAN rejection, including the findings of the relevance and pertinence of *Arter*. *See* RAN at 103-06.

As noted in the RAN, it is not necessary to consider whether drying methods for organic solvent solutions are transferrable to aqueous solutions, because *Arter* plainly states the method of the invention can be useful in drying layers formed from "aqueous solutions of hydrophilic colloids." RAN at 105, *quoting Arter* at 9:8; *see also Arter* at 5:57-68 (including "cellulosic" polymers (*i.e.*, HPMC) and "aqueous composition").

Regarding "transferrable," *Arter*'s drying methods are "in no way limited to use in the manufacture of photographic materials, and can be advantageously employed in any process, used in the manufacture of any product, in which a gaseous drying medium is utilized in the drying of a coated layer…." *Arter* at 5:37-42. *Strobush,* which the Board has found to be pertinent art to the '080 patent family (*see* Section (C)(4)), cites and discusses *Arter*. *Strobush* at 2:60-3:9. Regarding "self-supporting," neither of the methods in claims 317 and 318 recite "self-supporting." Even if the claims did recite this limitation, MonoSol has not

disputed that *Chen* discloses a pharmaceutical "stand alone and self-supporting" film. *Chen* at 15; RAN at 3.

b) *MonoSol does not dispute* Arter's *teachings.*

In all of MonoSol's arguments, it did not dispute what the panel relies on *Arter* to teach. RAN at 48-50. For example, the panel found that "*Arter* teaches 'using air currents, which have forces below a yield value of the polymer matrix during drying, to evaporate at least a portion of said solvent'." RAN at 49.

The remaining arguments are irrelevant or immaterial. For example, in view of the explicit teachings above, whether or not "mottle" is the same as, related to, or different from MonoSol's so-called problem (AB at 45) is immaterial. *Chen* recognized and solved the content uniformity "problem," if there was one, so *Arter* need not do so. RAN at 105. Contrary to MonoSol's arguments (AB at 45), the panel did not rely on *Arter* to demonstrate either quantitative content uniformity, or a teaching of analytical chemical testing. RAN at 48-50.

In view of the above, the panel did not err in combining *Arter* and *Chen*. The rejection should be affirmed.

4. The panel did not err in rejecting claims 317 and 318 under 35 USC 103(a) over *Chen* in view of *Strobush.*

MonoSol presents previously-made arguments with respect to *Chen* regarding these rejections. AB at 46. BDSI addresses these remarks above. *See* Section (C)(1).

a) *The panel did not err in combining* Chen *with* Strobush.

In response to the panel's rejection of claims 317 and 318 over *Chen* in view of *Strobush,* MonoSol again argues that it is improper to combine *Strobush* with *Chen* because the films of *Strobush* are "photographic" and the films of '080 patent are pharmaceutical. AB at 46; MonoSol Response to ACP at 85. However, MonoSol fails to point out any specific error in the panel's findings and conclusion that it was proper to combine them. RAN at 109-11. For example, in rejecting similar arguments by MonoSol in an appeal of a related application, the Board found that "Strobush may…reasonably be considered to be within the field of Appellant's endeavor (as stated under the 'Field of the Invention' on page 1 of the Specification)." RAN at 110, *citing* Board Decision regarding U.S. Application No. 10/074,272 (which resulted in U.S. Patent No. 7,425,292, over which the '080 patent is terminally disclaimed), February 21, 2008, at 13:21-24. The fields of invention of the '080 patent and of the related '292 patent are "remarkably

similar," both relating to drying aqueous systems to achieve more uniformity, including uniform distribution of components. *See* RAN at 110. MonoSol did not appeal the Board Decision in the parent case and therefore has waived its right to reprise its arguments 6 years later in this appeal.

b) *The panel correctly relied upon* Strobush *for teachings of controlled and rapid drying with air currents so as not to exceed a yield value of the polymer matrix.*

MonoSol persists in misreading *Strobush*, repeating mischaracterizations that were refuted point-by-point in the RAN, without identifying any panel error. AB at 46-47; RAN at 107-111.

For example, contrary to MonoSol's argument (AB at 46-47), the panel has made a factual finding that *Strobush* teaches controlling the force of the air so as not to exceed a yield value of the polymer matrix. RAN at 108. And the panel has also found that *Strobush* further teaches that, without differential top airflow, there is no shearing force acting on the top of the wet coating, and thus the inherent viscosity of the wet film is not overcome. RAN at 110; *Strobush* at 16:18-22.

The panel has found that *Strobush* provides a drying oven with bottom-only drying (Fig. 12); and a drying oven with top and bottom air vents to permit controlled drying (RAN at 50-51, 107-08), for example "drying apparatus 10 can

be used such that no gas is supplied by the air bars 34 when top-side gas is not needed or desired." *Strobush* at 11:15-37, 16:14-22.

Contrary to MonoSol's argument (AB at 46), *Strobush* does not teach slow evaporation or low heat transfer rates. Actually, *Strobush* teaches how to maximize heat transfer rate and dry films rapidly. *See, e.g.*, RAN at 109; *Strobush* at 14:30-36 ("Figs. 21-22 show that by increasing the heat transfer rate to correspond to the increasing maximum allowable heat transfer rate, the rate of drying can be increased even more rapidly…").

MonoSol fails to point out any error in the panel's findings relating to *Strobush* and its conclusory arguments lack factual and evidentiary support.

c) *MonoSol's other arguments are irrelevant.*

MonoSol presents arguments that are irrelevant because the limitation is not found in the subject claims, for example, *Strobush's* films "are not self-supporting." AB at 47. The limitation "self-supporting" does not appear in any of the claims under this rejection, although it is explicitly taught by *Chen* at 15. MonoSol also argues alleged deficiencies of the prior art that are irrelevant because the panel did not rely on the cited art for that particular teaching or suggestion of a limitation, for example, "Strobush does not and cannot inherently form or make

obvious visco-elastic film…which locks in uniformity." *Compare* AB at 47 *with* RAN at 50-52. In view of the above, the rejection was proper and should be affirmed.

5. The panel did not err in rejecting claims 1-5, 10, 13-15, 21, 24, 25, 32, 44-46, 54, 55, 59, 63-70, 72-75, 78-84, 89, 92-94, 100, 103, 104, 111, 123-125, 133, 134, 138, 142-149, 151-154, 157-166, 171, 174-176, 182, 185, 186, 193, 205-207, 215, 216, 220, 224-231, 233-236, 239-242, 249-252, 258-260, 267-270, 276-278, 285-288, and 294-318 under 35 USC 102(b)/103(a) in view of *Staab*.

MonoSol repeats its previous arguments concerning *Leo* and optimization, analytical chemical testing, and the locking-in recitation. AB at 48-49, 52-53. BDSI addresses these remarks above. *See* Sections (B)(5) (*Leo*) and (C)(1) (*Chen*).

a) *The panel did not err in finding support for active uniformity in the examples of* Staab*, because MonoSol has misread* Staab.

MonoSol presents a new argument (never presented to the panel) regarding *Staab*'s film-making example at column 11, based on a misreading of *Staab* that takes the language out of context. AB at 50-52. MonoSol's argument is based on an allegedly 100% variation from a "desired" amount. AB at 50. Importantly, MonoSol does not dispute that the variation among films in *Staab* is 0%. *See id.* at

50-52. With two exceptions, none of the independent claims recite the limitation of a variation from a desired amount. At best, this argument pertains only to independent claims 82 and 315 (and claims depending therefrom).

The panel misread one line in *Staab*, the third line in the table on column 11 ("Benzalkonium chloride (50% aqueous) … 10%") and stated that the "water content [of *Staab*'s film] before drying is 5%." RAN at 55. Based on this misreading, MonoSol argues that *Staab* intended the films to contain 5% active, *i.e.*, 9.5 mg. AB at 49-52. But the sentence above the table cited by MonoSol—the first sentence of the example—explicitly states the intended amount, *i.e.*, "film containing 19 mg of [active]." *Staab*, at 11:24-25. The following paragraph, describing the example, confirms that the amount intended was obtained, "this procedure was utilized to produce 2 inch square films, each containing 19 mg [active] and about 190 mg in weight" (*Staab* 11:49-51), *i.e.*, film dosages each containing 10% active.

MonoSol attempts to manufacture an intended amount in *Staab*, which does not exist—*i.e.*, that *Staab* intended the films to contain 9.5 mg—but then obtained

twice that amount, or 19 mg films. Read in context, it is clear that, not only did *Staab* obtain 19 mg films, it intended to do so.

Again, MonoSol does not dispute the panel's finding that *Staab* shows 0% variation. RAN at 56.

b) *To the extent the panel erred, the error is harmless and does not affect any rejection.*

To the extent the panel erred in its misreading, any error is harmless. Again, the panel interpreted 10% active (50% aqueous solution) as 5% active and 5% water. RAN at 55. The panel reasoned that, because "the water content before drying is 5%," the dried film met the claim limitation of a water content of 10% or less. RAN at 55. As correctly read—the water content before drying is 10%—*Staab's* films still have a water content of 10% or less. RAN at 55. Thus, the panel's original rejection is still proper and any error harmless because under either interpretation, the claim recitation is anticipated.

In short, the panel was correct in relying on *Staab's* "19 mg" example to demonstrate the claimed degree of uniformity of content, and with respect to the water content of *Staab's* films, the panel did not err and should be affirmed.

6. The panel did not err in rejecting claims 8, 9, 76, 77, 87, 88, 155, 156, 169, 170, 237, and 238 under 35 USC 103(a) in view of *Staab*.

MonoSol referred to previous arguments without presenting any new arguments relating to *Staab*, without pointing out any error, and without arguing any claim separately. AB at 54. BDSI addresses these arguments above. *See* Section (C)(5) (*Staab*).

In view of the above, the rejection was proper and should be affirmed.

7. The panel did not err in rejecting claims 82, 89, 90, 92, 161, 171, 172, 174, 274, 292, 304-311, and 313-318 under 35 USC 103(a) in view of *Le Person*.

a) *MonoSol is not entitled to* de novo *review of the rejection.*

MonoSol asserts "[t]here is no **teaching in Le Person**, as to **how to make films** with the required degree of uniformity of content in the amount of active." AB at 56 (emphases in original). Without specifying any panel error, or substantiating its conclusion in any way, MonoSol then changes the topic in the next sentence.

In veiw of this, MonoSol fails to present a proper issue to be reviewed on appeal. MonoSol submits no discernible arguments or evidence, and does not

challenge even one finding in the detailed RAN rejection. *See* RAN at 64-71. It is unclear what aspect of the rejection MonoSol disputes.

b) *The facts in* Leo *are the direct opposite of the facts in the instant appeal.*

Without specifying any panel error, MonoSol makes the same arguments about variations and potential combinations and undue experimentation, *citing Leo*. AB at 54-55. BDSI addresses these remarks above. *See* Section (B)(5) (distinguishing *Leo*).

c) *Contrary to MonoSol's argument,* Le Person *does not teach the difficulty in making the claimed films.*

Presumably in an attempt to find prior art that "teaches away" (as in *Leo*), MonoSol argues that *Le Person* recognizes the "difficulties involved" (AB at 55) and quotes a passage from *Le Person*, but this passage mentions nothing about difficulty. *Id.*, first block quotation. Next, MonoSol quotes *Le Person*'s comment that diffusion in a system with two immiscible solvents "cannot be tracked by text book equations." AB at 55-56, *quoting Le Person* at 257. However, none of MonoSol's claims recite either two immiscible solvents or the cross-diffusivities caused by them. In any case, a person of ordinary skill is not limited to the knowledge of "text book equations."

d) *MonoSol points out how* Le Person *supports obviousness of the claimed invention.*

As explained above, contrary to MonoSol's argument, MonoSol itself admitted that *Le Person* recognized the problem of uniformity of content as recited in the claims. *See* Section (A)*; Le Person* at 257; *compare* AB at 55-56 *with* AB at 17.

Also, MonoSol reads *Le Person* as "support[ing] Patentee's position that the only way to actually determine uniformity of content in the amount of active is through assaying (analytical chemical testing)." AB at 56. Whether or not this is a correct characterization of *Le Person*, MonoSol's reading contradicts its argument in favor of non-obviousness based on analytical chemical testing. Elsewhere in the Brief, MonoSol argues that analytical chemical testing is "the essence" of the claims:

> Only by analytical chemical testing is it possible to determine the actual amount of active present and hence whether uniformity of active content has been maintained during processing. This is the essence of the '080 Patent claims.

AB at 17.

If this is the essence of the '080 invention, MonoSol appears to admit that the essence is in the prior art.

In view of the above, the rejection was proper and should be affirmed.

D. Claim Rejections Based on Section 112

MonoSol proposes, without any explanation, that the panel erred in not entering the proposed amendment to claim 318 filed September 3, 2013. AB at 34-35. But MonoSol failed to petition under 37 CFR § 1.182 for entry of that proposed amendment, which is the proper procedure for reconsideration of non-entry. Moreover, MonoSol could not, and has not, presented the required showing of good and sufficient reasons why the proposed amendment was necessary and was not presented earlier. *See* 37 CFR § 1.116(b)(3). MonoSol suggests that the amendments were necessitated by the introduction of "new" references and states that the amendments advance prosecution. Response to ACP at 44. Neither is true. First, the "new" references, *Strobush* and *Arter*—which was discussed in *Strobush*—were well-known to MonoSol. *See, e.g.*, Board Decision regarding U.S. Application No. 10/074,272 (which resulted in U.S. Patent No. 7,425,292, over which the '080 patent is terminally disclaimed), February 21, 2008, at 13:12-24 (finding *Strobush* to be within the field of endeavor).

Second, as pointed out in the RAN, the amendment would not advance prosecution or simplify issues for appeal. RAN at 3. Among the amendments

proposed, for example, MonoSol also attempted to add "self-supporting" to every independent claim. MonoSol acknowledged in its March 13, 2013 Remarks (at 75-76) that this limitation is disclosed in *Chen*. *Chen* specifically describes its films as "stand alone and self-supporting." *See* RAN at 3, *citing Chen* at 15, lines 30-31. Because this amendment regarding "self-supporting" would not have addressed any prior art rejection of record, nor simplified the issues on appeal, and because the amendments must be either entered or not entered as a whole, the panel did not err in refusing to enter the amendment relating to claim 318. RAN at 3.

1. The panel did not err in rejecting claim 318 under 35 USC 112 (pre-AIA) first paragraph.

MonoSol failed to identify any alleged error in the 112 rejection, and therefore waived its appeal of that rejection. *See* 37 CFR 41.67(c)(1)(vii). ("Any arguments…not included in the brief…will be refused consideration by the Board unless good cause is shown.")

Instead, MonoSol proposes, without any explanation or specificity, that the panel erred in not entering the proposed amendment to claim 318 filed September 3, 2013. AB at 34-35.

As discussed above, not only is this an inappropriate forum for reconsideration of non-entry of amendments, but also MonoSol has failed to dispute the panel's grounds for non-entry.

2. The panel did not err in rejecting claim 318 under 35 USC 112 (pre-AIA) second paragraph.

MonoSol failed to identify any alleged error in the 112 rejection, and therefore waived its appeal of that rejection. *See* 37 CFR 41.67(c)(1)(vii). ("Any arguments…not included in the brief…will be refused consideration by the Board unless good cause is shown.")

Instead, MonoSol proposes, without any explanation or specificity, that the panel erred in not entering the proposed amendment to claim 318 filed September 3, 2013. AB at 34-35.

As discussed above, not only is this an inappropriate forum for reconsideration of non-entry of amendments, but also MonoSol has failed to dispute the panel's grounds for non-entry.

Conclusion

MonoSol identified no error by the panel that would make any of the existing final rejections improper. Therefore, BDSI respectfully requests affirmation of all of the rejections.

Respectfully submitted,
McCarter & English LLP

Dated: April 10, 2014

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VIII. EVIDENCE APPENDIX

DECLARATION BY MAUREEN REITMAN, SC.D. UNDER 37 CFR § 1.132

This Declaration by Maureen Reitman, Sc.D. under 37 CFR. § 1.132, dated February 28, 2013 (Reitman Decl.), was submitted by BDSI/Third Party Requester in connection with its April 12, 2013 "Inter Partes Reexamination Comments Under 37 CFR § 1.947" to the Reply mailed on March 13, 2013. The Reitman Decl. was admitted in the record, and referred to in the Action Closing Prosecution, mailed July 31, 2013.

Pursuant to 37 CFR § 41.71, Third Party Requester is using this declaration which was admitted.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re *Inter Partes* Reexamination of:	)
US Patent No. 7,897,080	)
Issued: March 1, 2011	) Confirmation No.: 6418
Named Inventor: Robert K. Yang *et al.*	) Group Art Unit: 3991
Control No.: 95/002,170	) Examiner: Diamond, Alan D.
Filed: September 10, 2012	) M&E Docket: 117744-00023
Title: POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM	) H&B Docket: 1199-26 RCE/CON/REX

Mail Stop *Inter Partes* Reexam
Attn: Central Reexamination Unit
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION BY MAUREEN REITMAN, SC.D.
UNDER 37 CFR § 1.132

Sir/Madam:

I, Maureen Reitman, do hereby make the following declaration:

I. Technical Background

1. I am a Principal and the Director of the Polymer Science and Materials Chemistry Practice at Exponent. I hold two academic degrees: (1) a Bachelor of Science in Materials Science and Engineering from the Massachusetts Institute of Technology (MIT), and (2) a Doctor of Science in Materials Science and Engineering, with a thesis in the field of polymers, from MIT. I have been practicing in the field of polymer science and engineering for more than 20 years as a researcher at MIT, in a variety of technical roles at the 3M Company, and as a consultant with Exponent. I provide consulting engineering services in all aspects of polymer science and engineering including, but not limited to material selection, product design and development, mechanical and chemical testing, failure analysis, polymer chemistry, polymer

physics, and polymer processing. My specialties include formulation, processing and performance evaluation of polymeric materials, including films, coatings, adhesives and transdermal drug delivery systems. I have been directly involved in product development, product line extensions, transfer of new products to manufacturing, qualification of alternative materials and manufacturing equipment, evaluating field performance, and assessing intellectual property. I am a past chairman and continue to serve as a member of the board of directors of the Medical Plastics Division of the Society of Plastics Engineers. My *curriculum vitae* is provided in Appendix A.

2. While Exponent is being paid for my time, I am not an employee of, nor do I have any financial interest in, BioDelivery Sciences International, Inc.

3. I have been asked to carefully review International Publication No. WO 00/42992 ("*Chen*"), and manufacture a film as described in *Chen*. I carefully reviewed *Chen*. Under my direction, my team manufactured a film in accordance with Example 7 of *Chen*. I have also been asked to take samples and perform various analytical tests to confirm the uniform distribution of the pharmaceutical active in substantially equal sized individual dosage units of the film, which we did.

4. Manufacturing Example 7 of *Chen*

Chen states: "According to Examples 1-8, the hydrocolloid [Methocel E5(HPMC)] was dissolved in water under agitated mixing to form a uniform and viscous solution." Chen 17:7-8.

- Methocel E5(HPMC) was dissolved in water under agitated mixing to form a uniform and viscous solution, by my team.

Chen states: "Additional ingredients were then added sequentially to the viscous solution such as peppermint, aspartame, propyl[ene] glycol, benzoic acid and citric acid under agitated mixing until they were uniformly dispersed or dissolved in the hydrocolloid." Chen 17:8-11.

- Additional ingredients were then added sequentially to the viscous solution including peppermint oil, aspartame, propylene glycol, benzoic acid and citric acid under agitated mixing until they were uniformly dispersed or dissolved in the hydrocolloid, by my team.

- Kolliphor EL was also added to the viscous solution.

Chen states: "Therapeutic agents were added to the homogeneous mixture (coating solution) prior to forming the film." *Chen* 20:19-20.

- Oxybutynin chloride (the therapeutic agent of Example 7) was added to the homogeneous mixture (coating solution) prior to forming the film, by my team.

Chen's Table 5 specifies the composition for Example 7.

- We used the ingredients in the amounts identified in *Chen*'s Table 5. *See* Table 1.

Table 1			
Formulation, Ex. 7, Table 5, *Chen*	% Weight	Formulation, Prepared by Maureen Reitman Team	% Weight
Oxybutynin	3.71	Oxybutynin chloride	3.71
Methocel E5 (HPMC)	21.06	Methocel E5 Premium LV	21.06
Water	70.72	Water, distilled	70.72
Cremophor EL40	1	Kolliphor EL[1]	1
Propylene glycol	1	Propylene glycol	1
Peppermint	1	Peppermint oil	1
Aspartame	0.8	Aspartame	0.8
Benzoic acid	0.013	Benzoic acid	0.013
Citric acid	0.7	Citric acid, monohydrate	0.7

Chen states: "The resultant mixture was degassed in a vacuum chamber until trapped air bubbles were removed." Chen 17:11-12.

- The resultant mixture was degassed in a vacuum chamber until trapped air bubbles were removed, by my team.

Chen states: "The formulation was then coated on the non-siliconized side of a polyester film at a wet thickness of 10 mil and dried in a hot air circulating oven at 50°C for 9 minutes." Chen 17:13-15.

- The formulation was then coated on a non-siliconized side of a polyester film at a wet thickness of 10 mil and dried in a hot air circulating oven at 50°C for up to 9 minutes, on commercial manufacturing equipment by my team.

Chen states: "Methods for manufacturing the dosage unit include the solvent casting methods as shown in Figure 2." Chen 15:13-14. "The manufacturing process for forming the dosage unit is illustrated in Figure 2. The dry film formed by this process is a glossy, stand alone, self supporting, non-tacky and flexible film (12)." Chen 15:29-31.

- A solvent casting manufacturing process for forming the dosage unit as illustrated in Figure 2 was used[2], by my team.

[1] The Cremophor line of products now owned by BASF and renamed Kolliphor. Based on the naming convention of the Cremophor/ Kolliphor products, EL40 is Polyoxyl 40 Castor Oil and EL is Polyoxyl 35 Castor Oil (*i.e.*, they are based on a 1:40 and 1:35 ratio, respectively, of castor oil:ethylene oxide). They are different materials. However, one of skill in the art would recognize Kolliphor EL as an appropriate substitute, as Cremophor EL40 is no longer available.

- The film was manufactured using a controlled drying process.
- As illustrated in Figure 2, the drying oven featured aeration controller with 3 zones set such that in each successive zone air impingement on the surface of the film increased.
- The dry film formed by the process is a glossy, stand alone, self-supporting, non-tacky and flexible film.

Chen states: "A glossy, substantially transparent, stand alone, self-supporting, non-tacky and flexible film was obtained after drying." Chen 17:15-16.

- A glossy, substantially transparent, stand alone, self-supporting, non-tacky and flexible film was obtained after drying, by my team.

5. Verification of Content Uniformity – Visual Inspection

- By examination with the naked eye, uniformity was verified by my team.

6. Verification of Content Uniformity – Unit Dose Weight

- By weighing individual dosage units of substantially identical size, uniformity was verified by my team. *See* Table 2.

Table 2	
Sample	Weight of 5 cm^2 dosage unit (grams)
1	0.034
2	0.034
3	0.034
4	0.034
5	0.034
6	0.034
7	0.034

7. Verification of Content Uniformity – Dissolution Test (HPLC)

- By dissolution of individual dosage units of substantially identical size and analysis by High Performance Liquid Chromatography (HPLC) active content uniformity was verified by my team. *See* Table 3.

[2] Our backing was not looped and we did not die cut in line, but the solvent casting and drying under aeration is matched.

Table 3	
Sample	Oxybutynin weight (mg)
A	4.4
B	4.4
C	4.3
D	4.4
E	4.1

- As can be seen in Table 3, the active varies by less than 10%.

8. Additional Observations

   - The components of the formulation, including the active component, were uniformly distributed in the viscous solution, which was used to cast the film, as was verified by my team.

   - The viscous solution, which was used to cast the film, exhibited the flow properties of honey (around 10,000 cps), as observed by my team.

   - Water content of the film was less than 10%, as verified by my team.

   - Within about 4 minutes after initiation of drying, the film was self-supporting, non-tacky, flexible and viscoelastic, as verified by my team.

9. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine, or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful statements may jeopardize the validity of the application or any patents issued thereon.

Dated: February 28, 2013

Maureen Reitman, Sc.D.

Appendix A

Exponent
Failure Analysis Associates

Exponent
Phone Science Drive
Suite 200
Boston, Maryland 20878

Telephone 240-654-4000
Facsimile 240-654-4500
www.exponent.com

Maureen T. F. Reitman, Sc.D.
Principal and Practice Director

Professional Profile

Dr. Maureen Reitman is a Principal and the Director of Exponent's Polymer Science and Material Chemistry practice. Her expertise includes polymer and composite technology, mechanics of materials, adhesion science, fiber mechanics, history and technology of plastics, and material failure analysis. She is skilled in the development and use of testing tools and methods and has applied them to plastic, rubber, textile, metal, glass, ceramic, and composite materials and systems. She is experienced in major aspects of product development, including materials selection, formulation, scale-up, end-use testing, failure analysis, certification procedures and issues related to intellectual property.

Dr. Reitman has conducted research in the areas of packaging and barrier materials; paints and coatings; plastic pipes; transdermal drug delivery; adhesives, sealants, and encapsulants; molding compounds; high temperature resins; nanoparticles; fibers and textiles; protective coatings and finishes; polymer chemical resistance; plastic insulation; connectors and splices; plastic packaging; medical devices; environmental effects on durability; and product aging. She has used her expertise to solve a broad range of problems related to coatings, fibers, films, and extruded and molded products, and their use in the telecom, electronics, electrical, transportation, construction, fire protection, medical, and consumer products markets.

Dr. Reitman is a member of the Board of Directors of the Medical Plastics Division of the Society of Plastics Engineers and an active member of two Underwriters Laboratories Standard Technical Panels, addressing Polymeric Materials (UL 94, UL 746, UL 1694) and Appliance Wiring (UL758).

Prior to joining Exponent, Dr. Reitman worked for the 3M Company in both research and management roles. Her activities included technology identification, materials selection and qualification, product development, customer support, program management, acquisition integration, intellectual property analysis, and patent litigation support.

Academic Credentials and Professional Honors

Sc.D., Materials Science and Engineering/ Program in Polymer Science and Technology, Massachusetts Institute of Technology, 1993
B.S., Materials Science and Engineering, Massachusetts Institute of Technology, 1990

National Academy of Engineering Frontiers of Engineering, 2009; Tau Beta Pi; Sigma Xi
John Wulff Award; Carl Loeb Fellowship; NCAA Postgraduate Scholarship;
Malcolm G. Kispert Award; GTE Academic All-American

Patents

Patent 6,311,524: Accelerated Method for Increasing the Photosensitivity of a Glassy Material, issued November 6, 2001.

European Patent EP0830428: Tackified Polydiorganosiloxane Polyurea Segmented Copolymers and a Process for Making Same, published March 25, 1998.

Patent 5,371,051: Fiber Optic Fusion Splice Protector Sleeve, issued March 24, 1998.

Publications

Kurtz S, Siskey R, Reitman M. Accelerated aging, natural aging, and small punch testing of gamma-air sterilized polycarbonate urethane acetabular components. Journal of Biomedical Materials Research Part B: Applied Biomaterials 2010 May; 93B(2):422–447.

Hoffman JM, Reitman M, Donthu S, Ledwith P. Complimentary failure analysis methods and their application to CPVC pipe. Proceedings, ANTEC 2010, Society of Plastics Engineers, Orlando, FL, May 2010.

Hoffman JM, Reitman M, Donthu S, Ledwith P, Wills D. Microscopic characterization of CPVC failure modes. Proceedings, ANTEC 2009, Society of Plastics Engineers, Chicago, IL, June 2009. Best Paper Award in Failure Analysis & Prevention.

Kurtz SM, Ebert M, Siskey R, Ciccarelli L, Reitman M, Harper ML, Chan FW. Natural and accelerated aging of polyurethanes in the Bryan cervical disc. Poster No. P158. Transactions of Spineweek 2008, Geneva, Switzerland, May 26–31, 2008.

Reitman M, Ledwith P, Hoffman M, Moalli J, Xu T. Environmentally driven changes in nylon. Proceedings, ANTEC 2008, Milwaukee, WI, Society of Plastics Engineers, May 2008.

Hoffman JM, Reitman M, Ledwith P. Characterization of manufacturing defects in medical balloons. Proceedings, ANTEC 2008, Milwaukee, WI, Society of Plastics Engineers, May 2008.

Reitman, MTF, Moalli JE. Polymeric coatings for medical device. Medical Device and Manufacturing Technology, Touch Briefings, pp. 28–30, 2006.

Moalli JE, Moore CD, Robertson C, Reitman MTF. Failure analysis of nitrile radiant heating tubing. Proceedings, ANTEC 2006, Society of Plastic Engineers, Charlotte, NC, May 2006.

Reitman M, McPeak J. Protective coatings for implantable medical devices. Proceedings, ANTEC 2005, Society of Plastic Engineers, Boston MA, May 2005.

McPeak J, Reitman M, Moalli J. Determination of in-service exposure temperature of thermoformed PVC via TMA. Proceedings, 31st Annual North American Thermal Analysis Society Conference, Williamsburg, VA, 2004.

Reitman MTF, Moalli JE. Product development and standards organizations: Listings and certifications for plastic products. 8th Annual International Conference on Industrial Engineering Theory, Applications and Practice, Las Vegas, NV, 2003.

Potdar YK, Reitman MTF. The role of engineering consultants in failure analysis and product development. 8th Annual International Conference on Industrial Engineering Theory, Applications and Practice, Las Vegas, NV, 2003.

Ezekoye OA, Lowman CD, Hulme-Lowe AG, Fahey MT. Polymer weld strength predictions using a thermal and polymer chain diffusion analysis. Polymer Engineering and Science 1998; 38(6):976–991, June.

Fahey MT. Nonlinear and anisotropic properties of high performance fibers. MIT Thesis, 1993.

Fahey MT. Mechanical property characterization and enhancement of rigid rod polymer fibers. MIT Thesis, 1990.

Book Contributions

Reitman M, Liu D, Rehkopf J. Chapter 38. Mechanical properties of polymers. In: Handbook of Measurement in Science and Engineering. Volume 2. Kutz, M (ed), John Wiley & Sons, Hoboken NJ, 2013. ISBN- 978-1-118-38464-0.

Reitman M, Jaekel D, Siskey R, Kurtz S. Morphology and crystalline architecture of polyarylketones, pp. 49-60. In: PEEK Biomaterials Handbook. Kurtz SM (ed), Elsevier William Andrews, Kidlington, Oxford, UK, 2012. ISBN 13:978-1-4377-4463-7

Tsuji JS, Mowat FS, Donthu S, Reitman M. Application of toxicology studies in assessing the health risks of nanomaterials in consumer products, pp. 543-580. In: Nanotoxicity: From In Vivo and In Vitro Models to Health Risks. Sahu S, and Casciano D. (eds), John Wiley & Sons, Chicester, West Sussex, UK, 2009. ISBN 978-0-470-74137-5.

Reitman MTF. The Plastics Revolution. In: Research and Discovery: Landmarks and Pioneers in American Science. Lawson RM (ed), Armonk NY: Sharpe Reference 2008. ISBN 978-0-7656-8073-0.

Klein SM. Mid-century plastic jewelry. Schiffer Publishing, Atglen, PA, 2005. (Technical advisor to author).

Selected Invited Presentations

Reitman MTF. Failure analysis tools. Workshop on Future Needs for Service Life Prediction of Polymeric Materials. NIST and Underwriters Laboratories, Gaithersburg, MD, October 2012.

Hoffman J, MacLean S, Ralston B, Reitman M, Ledwith P. Fractography of unfilled thermoplastic materials experiencing common mechanical failure modes. Materials Science & Technology 2012 Conference, Pittsburgh PA, October 2012.

Hoffman J, Reitman M, Ledwith P. Microscopic characterization of CPVC failure. Materials Science & Technology 2012 Conference, Pittsburgh PA, October 2012.

Reitman MTF. Polymer material properties for next generation medical devices. Invited Speaker: MedTech Polymers, UBM Canon, Chicago, IL, September 2012.

Reitman MTF. Polymers for medical applications. Fundamentals and Fellows Forum, ANTEC 2012, Orlando FL, April 2012.

Reitman MTF. Plastic and composite product failures. Invited lecture in Failure Analysis of Emerging Technologies. Stanford University Department of Materials Science and Engineering, Menlo Park, CA October 2009.

Reitman MTF. Factors for success: Plastics in injection molded medical devices. Part of *Injection Molding Works for Medical Design*, Design News Webcast, October 2008.

Reitman MTF. Plastic and composite product failures. Keynote Speaker: Third International Conference on Engineering Failure Analysis (ICEFA III), Elsevier, Sitges Spain, July 2008.

Reitman MTF. Multiphase materials for medical device applications, an overview. Medical Device and Manufacturing (MDM), Canon Communications, various locations, January- June 2008.

Reitman MTF. Nanotechnology and plastics for medical devices. Capitalizing on Nanoplastics, Intertek PIRA San Antonio TX, February 2008.

Reitman MTF. Nano additives in composites and coatings for medical device applications. Medical Device and Manufacturing Minneapolis, Canon Communications, Minneapolis MN, October 2007.

Reitman MTF, Swanger LA. Practical tips on how to manage your technical expert in patent disputes. Ropes & Gray IP Master Class, Live Teleconference, June 2007.

Reitman MTF, Kennedy E. Root cause failure analysis and accident investigation. Lorman Educational Services, Live Teleconference, November 2007.

Reitman MTF. Plastics failure analysis: Case studies. Baltimore/ Washington Chapter of SAMPE, October 2006.

Reitman MTF. Plastics failure analysis. Baxter Global Plastics Processing Conference 2005, Schaumburg IL, 2005.

Fahey MT. Fiber mechanics, corrosion, sealants: Tales of a 3M materials scientist. Class of 1960's Scholars Program, Williams College, 1999.

Fahey MT. Adhesives and sealants for the telecommunications industry. Riverwood V Conference, St. Paul MN, 1998.

Current Professional Appointments

- Underwriter's Laboratory Standards Technical Panel STP 746 (Polymeric Materials, includes UL94, UL 746 and UL1694)
- Underwriter's Laboratory Standards Technical Panel STP 758 (Appliance Wires/ UL758)
- Medical Plastics Division Board of Directors, Society of Plastics Engineers

Committee and Review Activities

- UL Forum on Initiatives to Improve the Long Term Aging Program, LTTA Tools Working Groups, Underwriters Laboratories
- Research and Engineering Technology Award Committee, Society of Plastics Engineers
- Reviewer, Medical Plastics Technical Program Committee, Society of Plastics Engineers
- Reviewer, Failure Analysis and Prevention Technical Program Committee, Society of Plastics Engineers
- Reviewer, various book proposals and submissions related to polymer science, ASM International, Elsevier, John Wiley

Professional Affiliations

- American Association for the Advancement of Science (member)
- American Association of Textile Chemists and Colorists—AATCC (senior member)
- American Chemical Society (member)
- ASTM International (member)
- Society for the Advancement of Material and Process Engineering (member)
- Society of Plastics Engineers (senior member)

DECLARATION BY EDWARD D. COHEN, PH.D. UNDER 37 CFR § 1.132

This Declaration by Edward D. Cohen, Ph.D. under 37 CFR. § 1.132, dated September 6, 2012 (Cohen Decl.), was submitted by BDSI/Third Party Requester in connection with its September 10, 2012 "Request for Inter Partes Reexamination". The Cohen Decl. was admitted in the record, and referred to in the Action Closing Prosecution, mailed July 31, 2013.

Pursuant to 37 CFR § 41.71, Third Party Requester is using this declaration which was admitted.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re *Inter Partes* Reexamination of:	)	
	)	
US Patent No. 7,897,080	)	
	)	
Issued: March 1, 2011	)	
	)	
Named Inventor: Robert K. Yang *et al.*	)	Group Art Unit: To Be Assigned
	)	
Control No.: To Be Assigned	)	Examiner: To Be Assigned
	)	
Filed: September 10, 2012	)	
	)	
Title: Polyethylene-oxide based films and drug delivery systems made therefrom	)	

Mail Stop *Inter Partes* Reexam
Attn: Central Reexamination Unit
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION BY EDWARD D. COHEN, PH.D. UNDER 37 C.F.R. § 1.132

Sir/Madam:

I, Edward D. Cohen, Ph.D., do hereby make the following declaration:

I. Technical Background

1. I have worked for over 45 years in the field of coating and drying, in research, manufacturing, and more recently in industry consulting. I have a B.S. in Chemical Engineering from Tufts University and a Ph.D. in Physical Chemistry from the University of Delaware.

2. I have technical experience in thin film coating and drying process development, formulating coatings, coating machine design, new product process development, and troubleshooting manufacturing process problems. My experience includes more than 30 years at E.I. DuPont de Nemours and Co., from which I retired as a DuPont Fellow.

3. I have published extensively in the field of coating and converting, including several books and industry publications (see Appendix A for a shortened list of publications). I am a contributing editor for Converting Quarterly, a peer-reviewed journal. Converting is the field of coating and drying a substrate, and cutting the resulting product. I have chaired committees and symposia in both the American Institute of Chemical Engineers and the American Chemical Society. I was founding president of the International Society of Coating Science and Technology ("ISCST").

4. I have taught professional continuing education courses in the coating fields for more than 22 years, for the Association of Metallizers, Coaters, and Laminators ("AIMCAL); University of Minnesota; American Institute of Chemical Engineers; and the International Society of Coating Science and Technology.

5. My honors include the John Tallmadge Award for Contributions to Coating Technology; the AIMCAL President's Award in recognition of Meritorious Service to AIMCAL and the Converting Industry, and the ISCST Founders Award.

6. I am currently an independent consultant for the coating and converting industries and a Technical Consultant for AIMCAL. I was retained by BDSI as a consultant in 2011, for which I am paid on an hourly basis. I have been hired as a consultant by McCarter & English, LLP, to provide an expert analysis of certain issues in connection with the reexamination of U.S. Patent No. 7,897,080 ("'080 patent"). While I am being paid for my time, I am not an employee of BioDelivery Sciences, Inc., nor do I have any financial interest in BioDelivery Sciences, Inc.

7. I have read the '080 patent, and Chen *et al.* (PCT Publication No. WO2000/42992, or "Chen").

8. Chen provides coating mixtures containing active that are described as "homogeneous", "completely dissolved", or "completely dispersed". Drying such hydrocolloid coating mixtures would be expected to yield films with substantially uniform content of active per unit of film, where the unit of film is a typical dosage unit or per sheet of uncut film. It is my opinion that Chen teaches films with substantially uniform content of active per unit of film, where the unit of film is, for example, a dosage unit or an uncut sheet of film.

9. In general, as a homogeneous or completely dispersed coating mixture is dried, the solvent is removed, the viscosity increases and the active would be more firmly fixed in place. When working with a homogeneous or completely dissolved coating mixture, for example, it would be difficult for a person of

ordinary skill in the thin film art not to obtain a film that has uniform content of active.

10. It is my opinion that drying the film coating mixtures of Chen according to the drying methods of Chen would yield films with uniform content of active per unit dosage. When working with a homogeneous or completely dissolved or completely dispersed coating mixture, it is my opinion that the drying methods disclosed in Chen would not be expected to create any agglomeration, aggregation, or otherwise non-uniform content of active. There would have been a variety of drying processes or apparatus known in the art at the time the '080 Patent was filed, including bottom drying, that would have been able to provide a film with uniform content of active.

11. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine, or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful statements may jeopardize the validity of the application or any patents issued thereon.

Dated this 6 day of September, 2012. Edward D Cohen

Edward D. Cohen, Ph.D.

Appendix A

Publications List Condensed

Books

Cohen, E. and Lightfoot, E. J., 2011. Coating Processes, Kirk-Othmer Encyclopedia of Chemical Technology. 1-68.

Cohen, E. D. & Gutoff E. B., *Water and Solvent Based Coating Technology*, in J. R, Wagner, Jr., Multilayer Flexible Packaging, Elsevier, First edition, 2010.

Cohen, E. D. & Gutoff E. B., *Coating and Drying Defects Troubleshooting Operating Problems*, second edition, John Wiley and Sons, New York, 2006.

Cohen, E. D. & Gutoff E. B., *Coating and Drying Defects Troubleshooting Operating Problems*, John Wiley and Sons, New York, 1995.

Cohen, E. D. & Gutoff E. B., *Modern Coating & Drying Technology*, VCH Publishers, New York, April 1992.

Journal Articles

E. D. Cohen, *Web Coating Defects: Controlling Dryer Defects, Part2*, Converting Quarterly, 2011 Quarter 4.

E. D. Cohen, *What is the Impregnation-coating Process and Why is it Used?* Converting Quarterly, 2011 Quarter 3.

E. D. Cohen, *Why is Pre-metered Slot-die Coating Increasing in Popularity?* Converting Quarterly, 2011 Quarter 1.

E. D. Cohen, *Web Coating Defects: Streaks And How To Eliminate Them,* Converting Quarterly, 2011 Quarter 1.

E. D. Cohen, *Technology Trends,* Paper Film & Foil Converter, May 2010.

E. D. Cohen & D. Bemi, *Conserve Energy*, Paper Film & Foil Converter, February, 2009.

E. D. Cohen, *Older methods: Still effective for web coating*, Converting Magazine, June 2007.

E. D. Cohen & E. B. Gutoff, *Coating Process Survey*, Kirk Othmer Concise Encyclopedia of Chemical Technology, 4th Ed., John Wiley & Sons, Inc. NY (1999).

E. Cohen, E. J. Lightfoot, K. N. Christodoulou, *Important Issues in Drying of Thin Films: An Industrial Engineers Perspective*, Part 2 Models. Industrial Coating Research, Vol. 4, pp.47-72 (1998).

E. B. Gutoff & E. D. Cohen, R&*D Needs in the Drying of Coatings*, Drying Technology, 14(6), 1315-1328 (1996).

E. Cohen, E. J. Lightfoot, K. N. Christodoulou, *Important Issues in Drying of Thin Films: An Industrial Engineers Perspective*, Industrial Coating Research, Vol. 3, pp.45-68 (1995).

IX. RELATED PROCEEDINGS APPENDIX

None.

X. CERTIFICATE OF SERVICE

CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of the instant brief was served on April 10, 2014, by first class mail, directed to the patent owner at the correspondence address of record for the subject patent at the following address:

Daniel A. Scola, Jr.

HOFFMANN & BARON, LLP

6900 JERICHO TURNPIKE

SYOSSET, NY 11791,

By: /Danielle L. Herritt/
Danielle L. Herritt
Registration No. 43,670
Attorney for Respondent

Electronic Acknowledgement Receipt

EFS ID:	18732595
Application Number:	95002170
International Application Number:	
Confirmation Number:	6418
Title of Invention:	POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM
First Named Inventor/Applicant Name:	7897080
Customer Number:	23869
Filer:	Danielle L. Herritt/Maureen Tierney
Filer Authorized By:	Danielle L. Herritt
Attorney Docket Number:	117744-00023
Receipt Date:	10-APR-2014
Filing Date:	10-SEP-2012
Time Stamp:	17:37:11
Application Type:	inter partes reexam

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Respondent Brief - Requester	117744_00023_080_Respondent_Brief_FINAL_2014APR10.PDF	1102636 cd63f3422ee43816f6cc817c18e2987a5d99cf26	no	62

Warnings:

The page size in the PDF is too large. The pages should be 8.5 x 11 or A4. If this PDF is submitted, the pages will be resized upon entry into the Image File Wrapper and may affect subsequent processing

Information:

Total Files Size (in bytes):	1102636

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inter Partes Reexamination of Yang et al.	Examiner: Alan D. Diamond
U.S. Patent No. 7,897,080	Group Art Unit: 3991
Reexamination Control No. 95/002,170	Confirmation No. 6418
Filed: September 10, 2012	H&B Docket: 1199-26 RCE/CON/REX M&E Docket: 117744-00023

For: POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM

PATENT OWNER'S CROSS-RESPONDENT'S BRIEF

Mail Stop *Inter Partes* Reexam
Central Reexamination Unit
Commissioner for Patents
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

Certificate of EFS-Web Transmission
I hereby certify that this correspondence is being transmitted via the U.S. Patent and Trademark Office electronic filing system (EFS-Web) to the USPTO on April 10, 2014.

Signed: Michael I. Chakansky /Michael I Chakansky/Reg. No. 31,600

I hereby certify that, pursuant to 37 CFR § 1.943(c), based on the WordPerfect word count of 6,981 words, Patent Owner's Cross-Respondent's Brief, counting the words on those pages beginning at page 1 (entitled Patent Owner's Cross-Respondent's Brief) and continuing through and including all words of the signature page (entitled Conclusion), does not exceed 7,000 words in length.

Signed: Michael I. Chakansky /Michael I Chakansky/Reg. No. 31,600

Dear Madame:

On March 10, 2014, Third Party Requester BioDelivery Sciences International, Inc. ("BDSI" or "Third Party Requester" or "Cross-Appellant") filed its cross Appeal Brief in *Inter Partes* Reexamination ("BDSI's Brief") regarding certain claims rejections not adopted by the Examiner in the RAN. This Patent Owner's Cross-Respondent's Brief, filed April 10, 2014

("MonoSol's Brief") is timely.

MonoSol submits this brief in opposition to BDSI's Cross-Appeal, and authorizes the Commissioner to charge all fees associated therewith, including, without limitation, the $2,000.00 fee for filing this respondent's brief in an *inter partes* reexamination proceeding, pursuant to 37 C.F.R. § 41.20(b)(2), to Deposit Account No. 08-2461.

TABLE OF CONTENTS

TABLE OF AUTHORITIES

CASES

STATUTES

PTAB DECISIONS

PATENT OWNER'S CROSS-RESPONDENT'S BRIEF

I. Real Party in Interest

MonoSol Rx, LLC ("MonoSol"), owner of U.S. Patent No. 7,897,080 (the " '080 Patent"), is the real party in interest.

II. Related Appeals and Interferences

MonoSol commenced a patent infringement action asserting U.S. 7,824,588 (the " '588 Patent"), U.S. 7,357,891 (the " '891 Patent") and U.S. 7,425,292 (the " '292 Patent") against BDSI, *inter alia*, in the District of New Jersey, *MonoSol Rx, LLC v. BioDelivery Sciences International, Inc., MEDA Pharmaceuticals, Inc. and Aveva Drug Delivery Systems, Inc.*, 10-cv-5695 ("the Litigation"). Then, BDSI requested *inter partes* reexamination of the '588 Patent (95/001,753) and then *ex parte* reexamination of the '891 Patent (90/012,098) and the '292 Patent (90/012,097). The Court stayed the Litigation. The '891 Patent and the '292 Patent successfully exited reexamination with reexamination certificates, leaving the '588 Patent *inter partes* reexamination pending and currently on appeal to the PTAB. BDSI also requested *inter partes* reexamination of two additional patents of MonoSol, namely, the '080 Patent, herein, and US 7,666,337 (the " '337 Patent") (95/002,171). The '337 Patent reexamination is currently on appeal to the PTAB.

Several actions have been recently commenced for patent infringement arising from the

submission of ANDAs regarding U.S. 8,017,150 (" '150 Patent"), *inter alia*, in the U.S. District Court for the District of Delaware. The actions are 1:13-cv-014611; 1:13-cv-01674; and 1:13-cv-02003. The '150 Patent is a divisional of the application for the '337 Patent, of which the '080 Patent is a continuation.

III. Status of Claims

MonoSol accepts BDSI's statement that the following claims are pending and currently stand rejected: claims: 1-11, 13-15, 17-90, 92-94, 96-172, 174-176, 178-253, 256, 258-271, 274, 276-289, 292 and 294-318. Moreover, MonoSol is appealing all claims rejected and all the grounds therefor.

IV. Status of Amendments

MonoSol accepts BDSI's statement, except notes that the reply and amendment dated January 29, 2013 are not part of the record.

V. Summary of Claimed Subject Matter

MonoSol disputes BDSI's summary. MonoSol's invention is directed to novel and non-obvious processes for manufacturing pharmaceutical and bioactive (hereinafter, collectively "pharmaceutical") active-containing films suitable for commercialization and FDA approval. Suitability for commercialization and FDA approval in the context of the present invention is clearly directed to maintaining the uniformity of the pharmaceutical active from start to finish in the process of manufacturing pharmaceutical resulting film. Moreover, commercialization inherently requires the ability to mass produce the films at scale and that resulting film products from different manufacturing runs meet the requisite degree of uniformity in amount of drug.

The '080 Patent process steps require, *inter alia*, that the degree of uniformity be demonstrated by chemical testing using analytical equipment, that is, by analytical chemical testing. Although physical observations and testing are very useful to suggest **non-uniformity** of pharmaceutical active content (*see, e.g.*, '080 Patent, col. 29, ll. 20 through 47), only analytical chemical testing can determine the actual degree of **uniformity**[1] of pharmaceutical active content as required by the FDA. Importantly, the FDA requirements talk about both types of testing, but always require analytical chemical testing of samples to ensure the amount of pharmaceutical active.

[1] Of course, analytical chemical testing can be used determine non-uniformity as well.

BDSI correctly states that there are seven independent claims pending on appeal, *i.e.*, claims 1, 82, 161, 315, 316, 317 and 318. The independent claim language appears below.

A process for **manufacturing resulting films suitable for commercialization and regulatory approval,** said regulatory approval including analytical chemical testing which meets the **standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units**, said films having **a substantially uniform distribution of components comprising a substantially uniform distribution of [a desired amount of] said active in individual dosage units of said resulting films**, comprising the steps of:

[Preamble - Claims 82 and 315 included bracketed limitation; claim 161 adds "film capable of being administered to a body surface".]

(a) **forming a flowable polymer matrix** comprising a water-soluble polymer, a solvent and said active, said active selected from the group consisting **of bioactive actives, pharmaceutical actives and combinations thereof**, said matrix having a substantially uniform distribution of said active;

[(a) - Claim 1 does step (a) in 2 steps (a) and (b), generally by adding active last.]

(b) **casting said flowable polymer matrix**, said flowable polymer matrix having a **viscosity from about 400 to about 100,000 cps;**

[(b) - Claim 1's version is denoted step (c).]

(c) **controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus** [at a temperature of about **60 °C** and **using air currents,** which have **forces below a yield value of the polymer matrix during drying**,] to evaporate at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, **within about the first 4 minutes by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying** to **maintain said substantially uniform distribution** of said active **by locking-in** or substantially preventing migration of said active within said visco-elastic film[[, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said visco-elastic film, **varies by less than 5%,**]] and wherein during said drying said flowable **polymer matrix temperature is 100 °C or less**;

[(c) - Claim 1 does not have the bracketed limitations and it is denoted as step (d); in claims 82 and 161 the double bracketed percent is 10%; only claim 318 has single bracketed limitation of 60 °C .]

(d) **forming said resulting film from said visco-elastic film by further controlling drying** by continuing evaporation to a **water content of said resulting film of 10% or less** and wherein said **substantially uniform distribution of active by said locking-in** or substantially preventing migration of said active **is maintained**[, such that **uniformity of content** in the amount of said active in substantially equal sized individual dosage

units, sampled from different locations of said resulting film**, varies by no more than 10%**];

[(d) - Claim 1 denotes this as step (e); claims 1, 82 and 161 do not have bracketed limitation; claim 318 replaces bracketed "varies by no more than 10%" with "varies by less than 5%".]

(e) **performing analytical chemical tests for uniformity of content of said active** in said substantially equal sized individual dosage units of said sampled resulting film, said tests indicating that uniformity of content in the amount of said **active varies by no more than 10%** and said **resulting film is suitable for commercial and regulatory approval**, wherein said regulatory approval is provided by the U.S. Food and Drug Administration.

[(e) - Claim 1 denotes this as step (f); claim 318 replaces "varies by no more than 10%" with "varies by less than 5%".]

(f) **repeating steps (a) through (e)** to form additional resulting films, such that **uniformity of content** in the amount of said active in said resulting film and said additional resulting films **varies no more than 10%** from **the desired amount** of said active as indicated by said analytical chemical tests.

[(f) - only claims 82 and 315 have this step.]

(f) **administering said resulting film to a body surface**.

[(f) - only claim 161 has this step.]

BDSI alleges that there is no support for some of the above claim elements. MonoSol disagrees. Support for the claims may be found throughout the '080 Patent, for example:

***Preamble and Step (e); step (f) for claim 1*:** col. 3, ll. 58-60.

***Step (a); steps (a) and (b) for claim 1*:** col. 19, l. 30 through col. 21, l. 31.

***Steps (b) and (c); steps (c) and (d) for claim 1*:** col. 6, ll. 49-52; Figures 6, 7, 8, 35 and 36 and col. 14, ll. 20-25; col. 11, ll. 17-19; col. 11, ll. 21-23; col. 12, ll. 20-36, col. 13, ll. 37-38; col. 29, ll. 11-13; col. 33, l. 10 through col. 34, l. 24; col. 44, 11. 9-13; col. 6, ll. 52-60; col. 7, lines 5 through 16; col. 27, ll. 53-55; col. 41, ll. 49-50; col. 13, ll. 23-36; col. 16, l. 62 through col. 17, l. 3.

Step (e); step (f) for claim 1: col. 28, l. 66 through col. 29, l. 6; col. 29, ll. 20 through 47 ; col. 32, ll. 34-41; col. 33, l. 10 through col. 34, l. 24; col. 15, ll. 28-43.

***Step (f), only claims 82 and 315*:** col. 2, ll. 27-46.

***Step (f), only claim 161*:** col. 29, l. 64 to col. 30, l. 2.

VI. Issues to be Reviewed on Appeal

MonoSol disputes certain of the characterizations of the non-adoption of BDSI's proposed 35 U.S.C. § 112 rejections which form the sole basis for its Cross-Appeal. For example, BDSI in its appeal issue C proposes that the specified issue C recitation has no written description. Yet, BDSI did not propose, nor did the Examiner find, a lack of written description with respect to this recitation. RAN, pp. 17-20. Thus, it cannot be part of BDSI's Cross-Appeal. This is one example of the dispute. These are addressed and corrected by the counter statement *infra*.

Finally, many of the arguments made in BDSI's Brief are improper, self-serving arguments about the RAN's rejection of '080 Patent claims based on §§ 102 and 103. Such arguments exceed the scope of BDSI's Cross-Appeal, and should not be considered.

Issues to be Reviewed on Appeal

A. The Examiner did not err in finding that the recitation of "suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units" is enabled, definite and has written description (RAN, pp. 12-15).

B. The Examiner did not err in finding that the recitation of "chemical analytical tests" is clear and has written description (RAN pp. 15-16).

C. The Examiner did not err in finding that the recitation of "individual dosage units vary by no more than 10%, 5%, 2%, 1% or 0.5%" is clear and enabled (RAN, pp. 17 -20).

D. The Examiner did not err in finding that the recitation of the term "varies by no more than 10% from desired amount of active" is clear, enabled and has written description (RAN, pp. 20-22).

E. The Examiner did not err in finding that the recitation of the term "rapidly increasing the viscosity of said flowable polymer matrix" is clear (RAN, p. 22).

F. The Examiner did not err in finding that the recitation of "during said drying said flowable polymer matrix temperature is 100 °C or less" is clear (RAN, p. 23).

G. There is no section in the RAN regarding the non-adoption of BDSI's proposed § 112 rejections labeled "G".

H. The Examiner did not err in finding that the various recitations of the entered claim amendments requiring various degrees of uniformity are clear, enabled and have written description (RAN, pp. 24-27).

VII. ARGUMENT

Preliminary Statement

Due to space limitations and, *inter alia*, the overlapping nature of BDSI's arguments, each of the arguments made by MonoSol herein are hereby explicitly incorporated into all of the argument sections.

A. The Examiner did not err in finding that the recitation of "suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units" is enabled, definite and has written description (RAN, pp. 12-15; BDSI's Brief, pp. 14-21).

BDSI complains that the Examiner erred by not adopting BDSI's interpretation of "suitable for commercialization and regulatory approval...", and for not rejecting the recitation as lacking written description and enablement under that interpretation, and further for not rejecting the recitation for being susceptible to two interpretations -- the PTO's and MonoSol's. However, there is only one interpretation set forth by both the Examiner and MonoSol and that interpretation is supported by the specification, *see supra* and *infra*.

BDSI's interpretation, an interpretation that BDSI tries to attribute to MonoSol, is absurd. BDSI's argument that the recitation requires compliance with each and every FDA requirement for a drug to be accepted for use in humans, from determining the chemistry, through the manufacturing process, including requirements for packaging and presumably the labeling as well, is unfounded and unsupported. As the Examiner recognized, the '080 Patent and this recitation address maintaining the uniformity of content of the active in dosage units on a commercial scale so as to provide a drug-containing film suitable for FDA approval in that it can meet the FDA's uniformity of content requirements -- not how the dosage units are packaged! The recitation is definite.

Again, suitability for commercialization and FDA approval in the context of the present invention is clearly directed to maintaining the uniformity of content of the pharmaceutical active

from start to finish in the manufacture of the pharmaceutical resulting film. Moreover, commercialization inherently requires the ability to mass produce the films at scale and that film products from different manufacturing runs will fall within the FDA uniformity requirements. BDSI's attempt to create a strawman by morphing Dr. Lin's declaration into support for its wishful desire that the '080 Patent claims require a process meeting all the requirements of a "FDA CMC submission" (BDSI's Brief, p. 20) is just that -- wishful thinking. The term "FDA CMC" does not appear in the '080 Patent or its claims. It only appears in Dr. Lin's declaration in the paragraphs concerning his background experience and responsibilities. Lin Declaration, ¶¶ 4 & 5.

Although MonoSol's Dr. Lin discusses in the background section (Lin Declaration, p. 3) his experience with many of the U.S. regulatory requirements for a drug to be approved for marketing and distribution, his focus is clearly directed to meeting the requirement of maintaining the "uniformity of content of the drug active" so as to be suitable for FDA approval. This can be clearly seen by Dr. Lin's statements.

> "**the manufacture of films with uniformity of content (strength) of drug active required for FDA approval**." Lin Declaration ¶ 17 (emphasis supplied).

> "**the determination of the actual amount of drug (active) in individual dosage units**." Lin Declaration ¶ 18 (emphasis supplied).

> "As required for FDA approval . . . would not **ensure that films containing drug could be manufactured to meet specifications that ensure consistent strength [uniformity of content]**." Lin Declaration ¶ 19 (emphasis supplied).

> "the disclosure necessary **to provide for the manufacture of drug-containing films with the uniformity of content in amount of drug (active) in individual dosage units to make FDA approvable film products**." Lin Declaration ¶ 21 (emphasis supplied).

BDSI's argument that the recitation requires satisfaction of the full panoply of FDA requirements is illogical on its face. Taken to its illogical conclusion, BDSI is arguing that the recitation includes ensuring fulfillment of the FDA requirements regarding drug labeling! BDSI is just wrong. BDSI cites to MonoSol's Reply to the Non-Final Office Action, filed on March 13, 2013 ("MonoSol's Reply to OA" or "Reply-2"), as supporting its position. However, a more complete look at the sections cited by BDSI does not support BDSI's position, but rather supports MonoSol's and the Examiner's position. For example, the complete first two sentences provide:

> "As explained throughout the '080 Patent and as summarized above, the present invention is based upon the discovery that certain process parameters, such as, viscosity and controlled drying methods to **avoid non-uniformity of content in the amount of active must be employed to provide a commercially and FDA viable film product.** . . . See Lin Declaration, ¶¶ 17-22."

MonoSol's Reply to OA (Reply-2), p. 78, ll. 4-8 (emphasis supplied).

BDSI's reliance on Dr. Clevenger's declaration (BDSI's Brief, p. 21) is also misplaced. It is clear from the portion of the declaration cited by BDSI that Dr. Clevenger is not discussing suitability for FDA approval and commercialization in connection with maintaining the uniformity of content in the amount of active but, instead, is discussing something he describes as the "route to regulatory approval". Clevenger Declaration, ¶ 4.

BDSI's strawman has been shown to be without substance, or clothes for that matter and, for that reason alone, must fall.

For all of the above reasons, there was no error in the Examiner's refusal to apply BDSI's constructions to the recitation. The Examiner's finding that the recitation is enabled, definite and has written description must be affirmed.

B. The Examiner did not err in finding that the recitation of "chemical analytical tests" is clear and has written description (RAN pp. 15-16; BDSI's Brief, pp. 21-25).

BDSI complains that the Examiner erred in declining to adopt BDSI's proposed rejections for the term "analytical chemical tests" because, according to BDSI, the term is not used, not described, not defined, and not exemplified in the '080 patent. BDSI is wrong.

The '080 Patent expressly provides:

> "It may be **desirable to test the films of the present invention for chemical and physical uniformity during the film manufacturing process**. . . . Uniform films are desired, **particularly for films containing pharmaceutical active** components for safety and efficacy reasons."

'080 Patent, col. 28, l. 66 through col. 29, l. 6 (emphasis supplied).

> "After the end pieces, or sampling sections, are removed from **the film portion(s), they may be tested for uniformity in the content of components between samples**. Any conventional means for examining and testing the film pieces may be employed, such as, for example, visual inspection, **use of analytical equipment**, and any other suitable means known to those skilled in the art"

'080 Patent, col. 29, ll. 33-38 (emphasis supplied).

> "An alternative method of determining the uniformity of the active is to cut the film into individual doses. **The individual doses may then be dissolved and tested for the amount of active in films of particular size. This demonstrates that films of substantially similar size cut from different locations on the same film contain substantially the same amount of active**."
>
> '080 Patent, col. 32, ll. 34-41 (emphasis supplied).

MonoSol agrees with the Examiner's reasoning and findings. As the Examiner stated:

> "This proposed rejection is not adopted for the following reasons. As noted above in the Scope of Claims section, which cites to the '080 patent specification for support, the term "analytical chemical tests" means analytical tests for determining the amount of active content in the recited sample. **The distinguishing point between analytical chemical tests as here claimed and physical testing (analytical or nonanalytical)** is whether there is **direct testing for the amount of active**. Accordingly, the term "analytical chemical tests" is clear and has written description."
>
> RAN, p.16 (emphasis supplied).

In the Scope of the Claims section referred to *supra*, the Examiner stated:

> "It is clear that when the '080 patent refers to 'physical' uniformity it is referring to, for example, uniformity based on the appearance of the film or the weight of individual doses cut from the film. **Likewise, it is clear that when the '080 patent refers to 'chemical' uniformity, it is referring to uniformity with respect to the actual amount of active, *i.e.*, chemical, present in the sample. Accordingly, the term 'analytical chemical tests' when read in light of the '080 patent**

> **specification means analytical tests for determining the amount of active content in the recited sample.**"
>
> RAN, p. 8 (emphasis supplied).

The section of the RAN at pp. 86-87 that BDSI relies on to support its argument that the '080 Patent lacks written description for "analytical chemical tests" actually demonstrates written description for the above recitation. In particular, the following language quoted directly from BDSI's Comments filed 10/03/13, in which **BDSI relied on the '080 Patent disclosure**, clearly demonstrates written description for the above recitation for "chemical analytical tests". Thus, as quoted by the Examiner, BDSI in its Comments stated:

> "**Indeed, analytical chemical tests were among many known ways to measure the amount of active in each dosage form.** Reply at 64-66; **'080 patent, cols. 31-32.** Thus, the ACP does not and need not rely on Example M for the rejection of claims including the step of performing analytical chemical testing. Even in the interpretation most favorable to MonoSol--which may or may not be correct--Example M only confirms what is already admittedly known regarding this post-manufacturing step. **That is, measuring active content in samples from pharmaceutical commercial runs is obvious**. ACP at 37-38."
>
> RAN, p. 87, quoting BDSI's Comments (emphasis supplied).

Certainly, using BDSI's own argument above, BDSI admits that Example M from the '080 Patent provides an actual example of using a chemical analytical test to determine directly the amount of active in films made by the '080 Patent processes. '080 Patent, col. 33, l. 10 through col. 34, l. 24. The uniformity of content was measured using a spectrophotometer (analytical chemical testing) which measures light absorption and is directly related to the amount of active present. Example M used percent difference of active concentration as measured by light absorption found in equally sized samples. Highest minus lowest = 1.774 – 1.700 = .074; Average of 8 samples = 1.725; 0.074 divided by 1.725 = 0.043; = **4.3%** degree of uniformity.

For all of the above reasons, there is no error in the Examiner's refusal to apply BDSI's constructions to the recitation. The Examiner's finding that the recitation is definite and has written description must be affirmed.

C. The Examiner did not err in finding that the recitation of "individual dosage units vary by no more than 10%, 5%, 2%, 1% or 0.5%" is clear and enabled (RAN, pp. 17 -20; BDSI's Brief, pp. 25-32).

BDSI complains that the Examiner erred in declining to adopt BDSI's proposed rejections for the step of performing analytical tests to verify specific levels of uniformity because, in BDSI's words, this step is not used, not described, not defined, and not exemplified in the '080 patent. BDSI is wrong. Moreover, BDSI proposes in its issues on appeal, that the

recitation has no written description. Yet, BDSI never proposed a lack of written description with respect to this recitation and the Examiner never found it lacking. RAN, pp. 17-20. Thus, this ground should not be part of the Cross-Appeal. Additionally, BDSI once again improperly addresses §§ 102 and 103 matters outside the scope of its Cross-Appeal. These arguments should not be considered.

BDSI relies on Chen (as interpreted by Reitman) and Staab in its attempts to establish that the prior art provided examples of the recited claimed degrees of content uniformity, which it did not. Indeed, when relying just on physical measurements, Reitman's declaration demonstrates that samples taken from Chen's Example 7, and samples taken from Reitman's exact copying of Chen's Example 7 process, differed in weight by 30% from the desired weight and thus exhibited a 30% non-uniformity in weight of pharmaceutical active from the desired amount as well. Moreover, Staab's supposed 0% variation on uniformity of active turns out to be a variation in uniformity of content in weight of active of between 90 and 100% from the desired amount. See discussion below.

1. Respondent's Reitman Declaration (EA-4) demonstrates that Chen's processes produce films which are 30% from the desired dosage weight.

BDSI and the Examiner have both relied on the false assumption that uniformity of weight of equally sized film samples is, by itself, sufficient to demonstrate that the amount of active present in prior art references meets the '080 Patent claimed uniformity of active. *See. e.g.*, RAN, pp. 77, 97. However, using this "assumption," BDSI's Reitman Declaration (EA-4)

instead clearly demonstrates the inability of Chen to provide film dosage units meeting the '337 Patent's claimed substantial uniformity across different manufactured resulting films (lots).

BDSI's Reitman declares that she and her team "**manufactured a film in accordance with Example 7 of *Chen***", *i.e.*, Chen Example 7 film (Reitman Declaration, EA-4, p. 2, ¶ 3, emphasis supplied).

Reitman further declares that her 5 cm^2 dosage samples of **Reitman's Chen Example 7 film all weighed exactly 34 mg.** *See* Reitman Declaration, EA-4, Table 2, page 4, ¶ 6.

Chen provides enough information to calculate the weight of the 5 cm^2 dosage unit sample of Chen Example 7 film. Indeed, **Chen's 5 cm^2 dosage unit sample of Example 7 film weighed 48.8 mg**.[2]

Taking Chen's 5 cm^2 Example 7 film weight as the expected or desired dosage unit weight of Chen's Example 7 samples, **the weight difference between Chen's** Example 7 dosage units and **Reitman's** Chen Example 7 dosage units amounts to a 30% difference in weight.

Hence, in accordance with BDSI's and the Examiner's assumption that purely physical characteristics, *e.g.,* weight, can determine uniformity of content in the amount of active, as there is a **30% weight difference between Chen's Example 7 samples and Reitman's Chen's**

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[2] Chen provides the following information regarding its film formed in Chen Example 7 (Chen, p. 22, Table 6, and p. 16, l. 5): Thickness = 3.2 mil = 0.008128 cm; Size = 5 cm^2; and Density = 1.2 gm/cm^3. From this information the weight of the dosage sample can be calculated. Area x Thickness x Density = Weight of Film Sample. 5 cm^2 x 0.008128 cm x 1.2 gm/cm^3 = 0.0488 gm =48.8 mg. Thus, the weight of Chen's 5 cm^2 Example 7 sample is expected (desired) to be **48.8 mg.**

Example 7 samples, the assumption requires there to be a 30% difference in the weight (amount) of active between Chen's and Reitman's samples.[3] Thus, **Chen's Example 7 and Reitman's Chen's Example 7 demonstrates a lack of uniformity of content in the amount of active of 30% between their separately manufactured films.**

[3] Chen's Example 7 Weight of Samples was 48.8 mg. Reitman's Example 7 Weight of Samples was 34 mg. ((48.8 mg - 34 mg)/(48.8 mg)) = (14.8 mg)/(48.8 mg) = 30%.

2. Staab's example demonstrates a 100% - 90% difference in unformity

Staab states (Staab, col. 11, l. 22 to col. 12, l. 3) that when he incorporated 10% of a 50% by weight benzalkonium chloride aqueous solution into a film-forming mixture, he obtained, after drying, a film product having exactly 19 mg benzalkonium chloride ("active") in all 190 mg film samples. According to BDSI and the Examiner, as all the film samples had 19 mg of active, this demonstrated a 0% variation in uniformity of content in the active, and the Examiner relied on this 0% in his rejections. **0% is wrong! Staab's lack of degree of uniformity of active content is 100% from the desired amount**.

The following is based on Staab, col.11, lines 22- 51, and assumes no water is driven off. Staab starts with 10% by weight of benzalkonium chloride (50% aqueous). Thus, Staab's starts with **5%** by weight of benzalkonium chloride active. Staab and any reader would expect the resulting film would maintain the 5% by weight of benzalkonium chloride active.[4] Staab cut out 190 mg samples from his resulting film. If Staab maintained the 5% by weight of active, the expected or desired amount of active in a 190 mg sample would be 9.5 mg of benzalkonium chloride active.

[4] This is assuming that everything else stays the same, except perhaps for the water content. In the extreme example where all of the water is removed, the expected, desired amount of active becomes 5.26% (.0526) by weight of benzalkonium chloride.

190 mg x 5% = **9.5 mg**[5] **= Staab's desired amount of active**.

Instead Staab's 190 mg samples each contained 19 mg of benzalkonium chloride active.

19 mg is Staab's actual amount of active.

The variation in uniformity of distribution of benzalkonium chloride active in Staab's resulting films **was 100% from the desired amount**.

$$\frac{\text{19.0 mg (actual amount of active) - 9.5 mg (desired amount of active)}}{\text{9.5 mg (desired amount of active)}}$$

$$= (9.5)/(9.5) = \mathbf{100\%}!$$

[5] **So far we have assumed that no water was driven off because Staab says nothing about the water content of his films. But even if we assume that all the water is driven off, then the difference is still too much at 90%.** If all the water was driven off, then 10.0 mg of active would be the desired amount of active (190 mg x .0526 = 9.994 mg) and Staab's 19 mg of active results in a 90% difference from the 10 mg desired amount. A 90% difference would not meet the FDA requirements either.

3. Example M from the '080 Patent - Degree of Uniformity 4.3%

Example M of the '080 Patent exemplifies the use of analytical chemical testing demonstrating that active-containing films manufactured in accordance with the invention obtain **degrees of uniformity of content in the amount of active of 4.3%**. '080 Patent, col. 33, l. 10 through col. 34, l. 24. *See* discussion, *supra*.

MonoSol obtains even better degrees of uniformity of content with its commercial manufacturing production runs. As the Examiner stated in the RAN, pp. 19-20.

> **As seen in Appendices A and C of Bogue Declaration I [EA-1], a variation as low as 2% was obtained. The variation was calculated by taking the maximum active content of a lot minus the minimum active content of that lot, divided by the average active content of that lot (see ¶ 9).** While the red dye of the '080 Patent's Example M is not a pharmaceutical active or bioactive active, a similar calculation is made in Example M at col. 34, lines 18-20 based on absorbance measurements, which are directly related to concentration of the red dye (see also col. 33, lines 49-51). Further, ¶¶ 10-11 of Bogue Declaration I, citing Appendix B, allege that "the amount of active across different lots of resulting film varies no more than 10% from the desired amount of the active."

RAN, pp. 19-20 (emphasis supplied).

Finally, BDSI alleges that because MonoSol's Bogue declaration only provided "results" and not the underlying "data" it must be given little weight. BDSI Brief, pp. 29-30. Bogue provided the way the results were calculated. Bogue Declaration I, ¶¶ 9-11. Bogue also attested

that he "compiled individual dosage unit assay data for individual Lots 1 - 73, **all of which were disclosed in MonoSol's 2012 Annual Product Review to the FDA**." Bogue Declaration I, EA-1, ¶ 6 (emphasis supplied). The fact that MonoSol, in the ordinary course of business, disclosed the same data to the FDA to meet compliance regulations supports **the great weight that should be given to the Bogue declarations**.

For all of the above reasons, there is no error in the Examiner's refusal to apply BDSI's constructions to the recitation, and the Examiner's finding that the recitation is definite and enabled must be affirmed. The PTAB should also find that there is written description.

D. The Examiner did not err in finding that the recitation of the term "varies by no more than 10% from desired amount of active" is clear, enabled and has written description (RAN, pp. 20-22; BDSI's Brief, pp. 32-35).

BDSI complains that the Examiner erred in declining to adopt BDSI's proposed rejections based on its arguments that somehow requiring manufactured films to comply with the varies by no more than 10% from desired amount of active is not described, not defined, and not exemplified in the '080 patent. BDSI is wrong.

The '080 Patent expressly provides that:

> "Currently, as required by various world regulatory authorities, dosage forms may not vary more than 10% in the amount of active present. When applied to dosage units based on films, this virtually mandates that uniformity in the film be present."

'080 Patent, col. 2, ll. 42-46.

That being said, BDSI's argument as to the "repeating steps" is also without basis. BDSI argues that "[l]ogically, repeating a set of steps should produce more of the same film, but not change the quality of the film." BDSI Brief, p. 33. However, as demonstrated *supra*, using only physical characteristics, Reitman's repeat of Chen Example 7 steps produced film samples which were not uniform, when compared to Chen's Example 7 steps film samples. The difference in uniformity between the two separate productions of film was **30%**.

Moreover, the pending claims do enable by addressing the problem of maintaining uniformity. For example, claim 1 recites, *inter alia*, casting a flowable polymer matrix having a

viscosity from about 400 to about 100,000 cps and controlling drying by conveying said flowable polymer matrix through a drying apparatus and evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film within about the first 4 minutes by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, wherein during said drying said flowable polymer matrix temperature is 100 °C or less. No more is required.

Finally, as set forth *supra*, dosage units must not vary by more than 10% in the amount of pharmaceutical active prescribed by the FDA. The amount of pharmaceutical active prescribed is the amount desired to be delivered to the patient. The '080 Patent discloses that the amount of active is permitted to vary no more than 10% from the desired amount. In effect, although this can result in about a 20% range in amount of active between dosage units, there still is only a 10% difference in amount of active from the desired amount. Because the '080 Patent discloses processes which are suitable for commercialization, including scaling up and reproducibility, it is inherent that the process provides that same degree of uniformity in amount of active in dosage units produced from one manufacture of a resulting film to another manufacture of a resulting film and that the resulting films would be tested and should fall within the stated degree of uniformity.

For all of the above reasons, there is no error in the Examiner's refusal to apply BDSI's constructions to the recitation, and the Examiner's finding that the recitation is enabled, definite and has written description must be affirmed.

E. The Examiner did not err in finding that the recitation of the term "rapidly increasing the viscosity of said flowable polymer matrix" is clear (RAN, p. 22; BDSI's Brief, pp. 35-37).

BDSI complains that the Examiner erred in declining to adopt BDSI's conclusion that the scope of the claims cannot be determined because the newly-added "rapidly increasing the viscosity of said flowable polymer matrix" includes terms of degree both lacking a reference point and standards for comparison. BDSI is wrong.

MonoSol believes that the Examiner put it best when not adopting this proposed conclusion and rejection.

> "This proposed rejection is not adopted for the following reasons. The rapid increase in viscosity takes place during the step of evaporating the solvent from the flowable polymer matrix, and each of the independent claims sets forth the time period during evaporation in which the rapid increase takes place, *i.e.*, within the first 4 minutes. Thus, the rapid increase occurs within this time frame. The claims also set forth the reason for such an evaporation time, *i.e.,* 'to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film.' Accordingly, it is unnecessary to set forth a degree of viscosity increase for 'rapidly increasing the viscosity'."
>
> RAN, p. 22.

Cases cited by BDSI are inapposite. MonoSol's "rapidly" is not comparable to the "low level current" of *Sony Corporation, et al. v. Network-l Security Solutions, Inc.*, IPR2013-00092,

Paper 21, p. 8 (PTAB May 24,2013). It is closer to *Playtex Prods., Inc. v. Procter & Gamble, Co.*, 400 F.3d 901 (Fed. Cir. 2010) (*Playtex*) cited by *Sony*. "As 'substantially flattened surface' has unambiguous meaning in view of the intrinsic record, the district court erred in relying upon extrinsic evidence that directly contradicted that meaning. . . . The disputed claim term is clearly a comparative term. Comparison requires a reference point. Therefore, to flatten something, one must flatten it with respect to either itself or some other object. . . . " *Playtex* at 908. In the instant claim recitation, **rapidly's reference point is "within about the first 4 minutes" of the start of evaporation of the solvent**, and is therefore definite.

For all of the above reasons, there is no error in the Examiner's refusal to apply BDSI's constructions to the recitation, and the Examiner's finding that the recitation is definite must be affirmed.

F. The Examiner did not err in finding that the recitation of "during said drying said flowable polymer matrix temperature is 100 °C or less" is clear (RAN, p. 23; BDSI's Brief, pp. 37-38).

BDSI complains that the Examiner erred in determining that the "100 °C or less" in the "controlling drying" step clearly applies throughout the step. The Examiner did not err.

MonoSol believes that the Examiner again put it best when not adopting this proposed rejection.

> "This proposed rejection is not adopted for the following reasons. The recitation states 'during drying' the flowable polymer matrix temperature is 100°C or less. The claims specify that the flowable polymer matrix has a viscosity of about 400 to about 100,000 cps. As long as the polymer matrix has this viscosity during drying, it is a flowable polymer matrix and its temperature must be 100°C or less."
>
> RAN, p.23.

Importantly, the Examiner did not define visco-elasticity in terms of viscosity, but merely stated that, in accordance with the claims, during the time that the polymer matrix has a viscosity of about 400 to about 100,000 cps it is considered, for purposes of the claim, to be a flowable polymer matrix such that it is required to be at a temperature of 100°C or less. The following claim language makes this clear:

> "casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

> controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus . . . evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying . . ., wherein during said drying said flowable polymer matrix temperature is 100 °C or less...".

For all of the above reasons, there is no error in the Examiner's refusal to apply BDSI's constructions to the recitation. The Examiner's finding that the recitation is definite must be affirmed.

G. None, see issues *supra*.

H. The Examiner did not err in finding that the various recitations of the entered claim amendments requiring various degrees of uniformity are clear, enabled and have written description (RAN, pp. 24-27; BDSI's Brief, pp. 38-44).

BDSI complains that the Examiner erred in declining to adopt BDSI's proposed § 112 rejections for the uniformity requirements required in different steps and combinations of steps even though these requirements according to BDSI are not described, not defined, and not exemplified in the '080 patent. BDSI could not be more wrong. As to BDSI's inappropriate §§ 102 and 103 based argument, they are beyond the scope of BDSI's Cross-Appeal and should not be considered, see discussions *supra*.

The '080 Patent expressly recognizes the need to test for uniformity by any and all means at various steps during the manufacturing process, *see* discussion *supra*. One of the reasons given is to be able to stop the run early and attempt to correct any problems. Indeed, the '080 Patent spends almost an entire column on this issue ('080 Patent, col. 29, ll. 6-52). A small excerpt is quoted below.

> "**Moreover, it may be desirable to repeat the steps of sampling and testing throughout the manufacturing process. Testing at multiple intervals may ensure that uniform film dosages are continuously produced. Alterations to the process can be implemented at any stage to minimize non-uniformity between samples.**"

'080 Patent, col 29, ll. 47-52 (emphasis supplied).

BDSI appears loath to admit that, depending on whether or not the quantity being measured is known or desired, when scientists compare the amounts of a substance in different samples, there are two ways to compare the amounts and both are correct depending upon the circumstance. The methods differ depending upon what is desired to be measured. One method is when trying to compare the amount in a sample relative to a pre-determined desired amount, as is the case in pharmaceutical drug dosage units. The other method is where there is no predetermined desired amount, in which case the percent difference between amount of active in each sample is used. Both differences relate to the uniformity of content in the amount of active in the film from which the samples are cut. Hence we get the two 10% differences, one from the desired amount and one measuring the percent difference in amount. The '080 Patent processes can also achieve higher degrees of uniformity, hence the other percent differences.

MonoSol was not required to provide examples of tests for all these different degrees of uniformity, though it did for some. See Example M discussion, *supra*. However, whereas the '080 Patent specification and all the claims require the maintenance of the substantially uniform distribution of active by locking-in or substantially preventing migration of the active, testing for the same at various steps is an obvious step to add, for example, to ensure early on in the manufacturing process that the degree of uniformity is being maintained.

For all of the above reasons, there is no error in the Examiner's refusal to apply BDSI's constructions to the recitation. The Examiner's finding that the recitation is enabled, definite and has written description must be affirmed.

VIII. CONCLUSION

MonoSol respectfully submits that no error has been identified by BDSI or made by the Examiner in the RAN with respect BDSI's issues on Cross-Appeal and the Cross-Appeal should be dismissed and the Examiner affirmed on these issues.

Dated: April 10, 2014

Respectfully submitted,

/Daniel A. Scola, Jr./
Daniel A. Scola, Jr.
Registration No. 29,855

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EVIDENCE APPENDIX

1 MonoSol's/Cross-Respondent's Declaration of B. Arlie Bogue, Ph.D. Under 37 C.F.R. § 1.132, executed March 13, 2013, filed March 13, 2013 ("Bogue Declaration I")

2 MonoSol's/Cross-Respondent's Declaration of B. Arlie Bogue, Ph.D. Under 37 C.F.R. § 1.132, executed August 29, 2013, filed September 3, 2013 ("Bogue Declaration II")

3 MonoSol's/Cross-Respondent's Declaration of David T. Lin, Ph.D. Under 37 C.F.R. § 1.132, executed March 13, 2013, filed March 13, 2013 ("Lin Declaration")

The above declarations included below were submitted by MonoSol/ Respondent, they were admitted in the record, and referred to in the Examiner's Right of Appeal Notice, mailed December 6, 2013, *see*, *inter alia*, pp. 2, 68-69, 71-72, 83-84, 87-88. Pursuant to 37 C.F.R. § 41.71, MonoSol is using these declarations which ***were*** admitted.

The below Reitman declaration was submitted by Third-Party Requester/Cross-Appellant, it was admitted in the record, and referred to in the Examiner's Right of Appeal Notice, mailed December 6, 2013, *see*, *inter alia*, pp. 2, 14, 75,77,87-92, 94, 97, 100, 105.

4 BDSI's/Cross-Appellant's Declaration by Maureen Reitman, Sc.D. Under 37 C.F.R. § 1.132, dated February 28, 2013, filed April 12, 2013 ("Reitman Declaration")

MonoSol's/Cross-Respondent's Declaration of B. Arlie Bogue, Ph.D. Under 37 C.F.R. § 1.132, dated March 13, 2013 ("Bogue Declaration I")

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patentee:	Yang et al.	Examiner:	Diamond, Alan D.
Patent No.:	U.S. 7,897,080	Group Art Unit:	3991
Reexamination Control No.:	95/002,170	Confirmation No.	6418
Filed:	September 10, 2012	H&B Docket:	1199-26 RCE/CON/REX
Dated:	March 13, 2013	M&E Docket:	117744-00023

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Central Reexamination Unit
Commissioner for Patents
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

Certificate of EFS-Web Transmission
I hereby certify that this correspondence is being transmitted via the U.S. Patent and Trademark Office electronic filing system (EFS-Web) to the USPTO on
March 13, 2013.
Signed: Michael I. Chakansky /Michael I Chakansky/

DECLARATION OF B. ARLIE BOGUE, PH.D. UNDER 37 C.F.R. § 1.132

Madame:

I, B. Arlie Bogue, Ph.D., do hereby make the following declaration:

I. Technical Background

1. I have worked in the field of pharmaceutical development, and particularly oral dosage form development, for 22 years. I am employed by MonoSol Rx, LLC. ("Patentee" and/or "MonoSol"), the assignee of issued patent U.S. 7,897,080 ("the '080 Patent"), as Senior Director for Manufacturing Strategy and Innovation.

2. I have a BS in Physical Chemistry from Colorado State University and a Ph.D. in Chemical and BioEngineering from Arizona State University. I have participated in postdoctoral studies in Biochemical Engineering at the University of Virginia. During my career, I have been named as an inventor on over 23 U.S. patents and numerous foreign patents directed to the formulation,

processing and/or packaging of pharmaceutical oral disintegrating unit doses (tablets and film strips). I have direct experience with the commercial scale processing of pharmaceutical film systems as well as an understanding of the uniformity of content of active and methods for testing the same.

3. I have read the '080 Patent and the Office Action issued on November 29, 2012 in the reexamination of the '080 Patent ("Office Action") and the references cited therein, and I have also reviewed the amendment as to the independent claims set forth in Patentee's Reply to the Office Action concurrently filed herewith.

II. Producing resulting films in accordance with the '080 Patent

4. Each of the 73 lots of resulting films (Lots 1-73) containing approximately 2,000,000 individual dosage units per lot discussed herein were manufactured: (i) for commercial use and regulatory approval; (ii) in compliance with U.S Food and Drug Administration ("FDA") standards and regulations, including those relating to analytical chemical testing for variation in active in individual dosage units; and (iii) in accordance with the invention disclosed in the '080 Patent, and as claimed by the '080 Patent both as issued and as amended in the Patentee's Reply to the Office Action; by:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and a pharmaceutical active, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said polymer matrix through a drying apparatus and evaporating at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film wherein the polymer matrix temperature is 100 °C or less;

(d) forming the resulting pharmaceutical film from said visco-elastic film, wherein said resulting pharmaceutical film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained, such that uniformity of content in the amount of the active in substantially equal sized individual dosage units, sampled from different locations of said resulting pharmaceutical film, varies by no more than 10%; and

(e) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units of said sampled resulting pharmaceutical film, said tests indicating that uniformity of content in the amount of the active varies by no more than 10%, [see Appendix A] said resulting pharmaceutical film suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration.

5. Additionally, the uniformity of content in the amount of active as sampled from the 73 lots of resulting film varies no more than 10% from the desired amount of the active as indicated by said analytical chemical tests from 4(e) above. [See Appendix B]

III. Analytical Chemical Testing for Uniformity of Content of Patentee's Resulting Films

6. To demonstrate the uniformity of individual dosage unit films, I compiled individual dosage unit assay data for individual Lots 1- 73, all of which were disclosed in MonoSol's 2012 Annual Product Review to the FDA.

7. Ten (10) individual dosage units all having the same dimensions were cut out from different locations of each of the 73 lots of resulting films using a commercial packaging machine, thus providing 730 randomly sampled individual dosage units, ten each from the 73 separate lots. All samples were analyzed by a validated method, in compliance with FDA guidelines and regulations regarding same, using analytical chemical testing, in which the pharmaceutical active

was extracted and analyzed by High Performance Liquid Chromatography (HPLC) against an external standard to quantify the amount of active present in each individual dosage unit.

8. According to the inventive process set forth and claimed in the '080 Patent, and in accordance with FDA nomenclature, I have prepared tables shown as Appendices A, B and C, reflecting the uniformity of content of active of individual dosage units within particular lots and across different lots.

9. First, the uniformity of content of active in a lot is determined through establishing the amount of active ($A_{N(i)}$) actually present in each sampled individual dosage unit from the same lot (N) as determined by taking the difference between the amount of active in the sample with the most active ($Max_{LOT(N)}$) minus the amount of active in the sample with the least amount of active ($Min_{LOT(N)}$) and dividing the difference by the average amount of active in the lot samples ($Lot_{(N)}$ Sample Average). That is: $(Max_{LOT(N} - Min_{LOT(N)}) / ((A_{N(1)} + A_{N(2)} + + + A_{N(10)})/10)$. The results are shown in Appendix A.

10. Second, the uniformity of content across different lots is determined through establishing the amount of active actually present in each sampled individual dosage unit from all 73 lots and comparing that amount of active with a "target" or "desired" amount of active contained therein. The target amount of active, when it is a pharmaceutical, is referred to as the "Label Claim", thus identifying the amount of pharmaceutical active in the film to a user. The desired amount is 100% of the target amount. Each individual dosage unit film cut from any individual lot must have the desired content of pharmaceutical active, varying no more that 10% from the target or desired amount. See Appendix B.

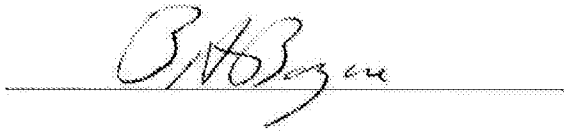
IV. '080 Patent Process Produces Films With Required Uniformity of Content of Active

11. The results shown in the appendices establish that the resulting films produced by the inventive method of the '080 Patent as disclosed and claimed have the required uniformity of content based on analytical chemical testing. First, the amount of active varies by no more than 10% between individual dosage units sampled from a particular lot of resulting film. See Appendix A.

Second, the amount of active across different lots of resulting film varies no more than 10% from the desired amount of the active. See Appendix B. Finally, the uniformity of content of the 73 lots of resulting film meets even more stringent standards, for example, the data shows: (i) 46 lots of resulting film wherein the uniformity of content of active is shown with the amount of active varying by less than 5%; (ii) 15 lots of resulting film wherein the uniformity of content of active is shown with the amount of active varying by less than 4%; 4 lots of resulting film wherein the uniformity of content of active is shown with the amount of active varying by less than 3%; and 1 lot of resulting film wherein the uniformity of content of active is shown with the amount of active varying by only 2%. See Appendix C.

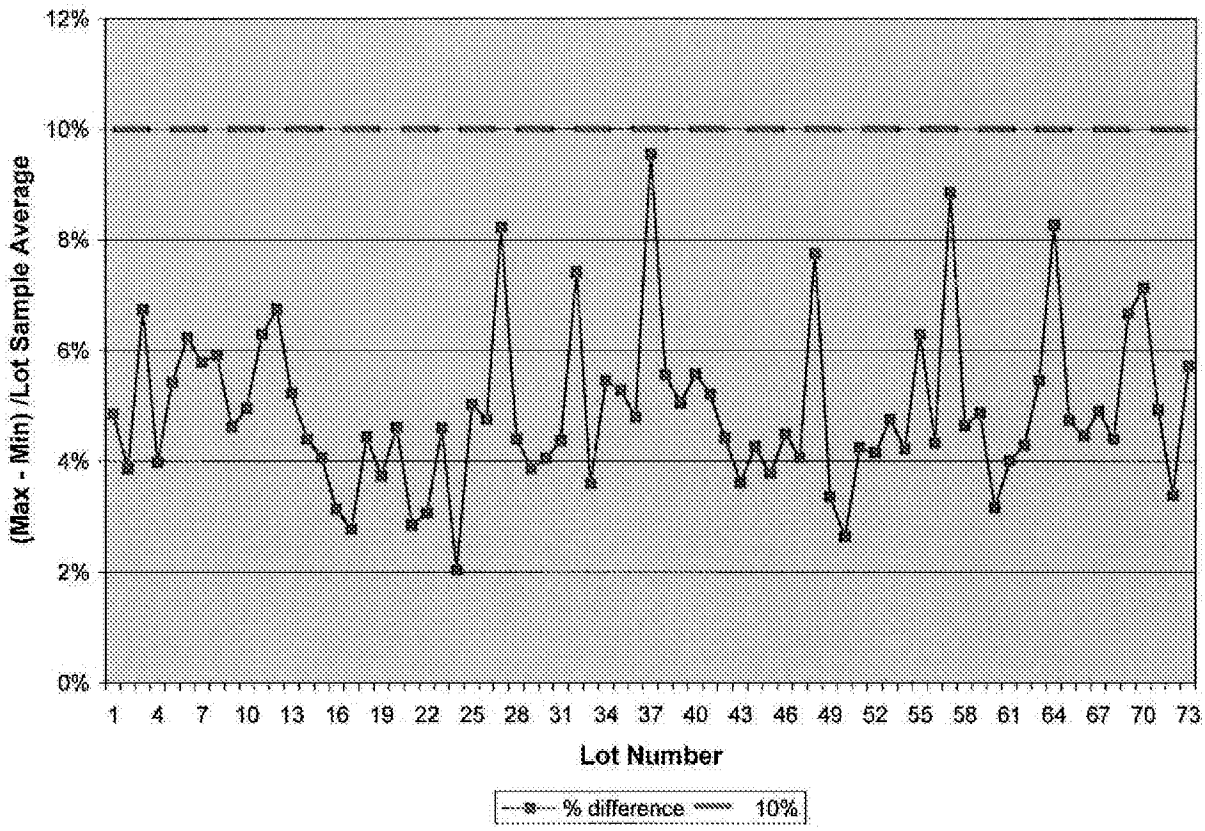
I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and. that such statements may jeopardize the validity of the application or any patents issued thereon.

Dated this 13th day of March, 2013

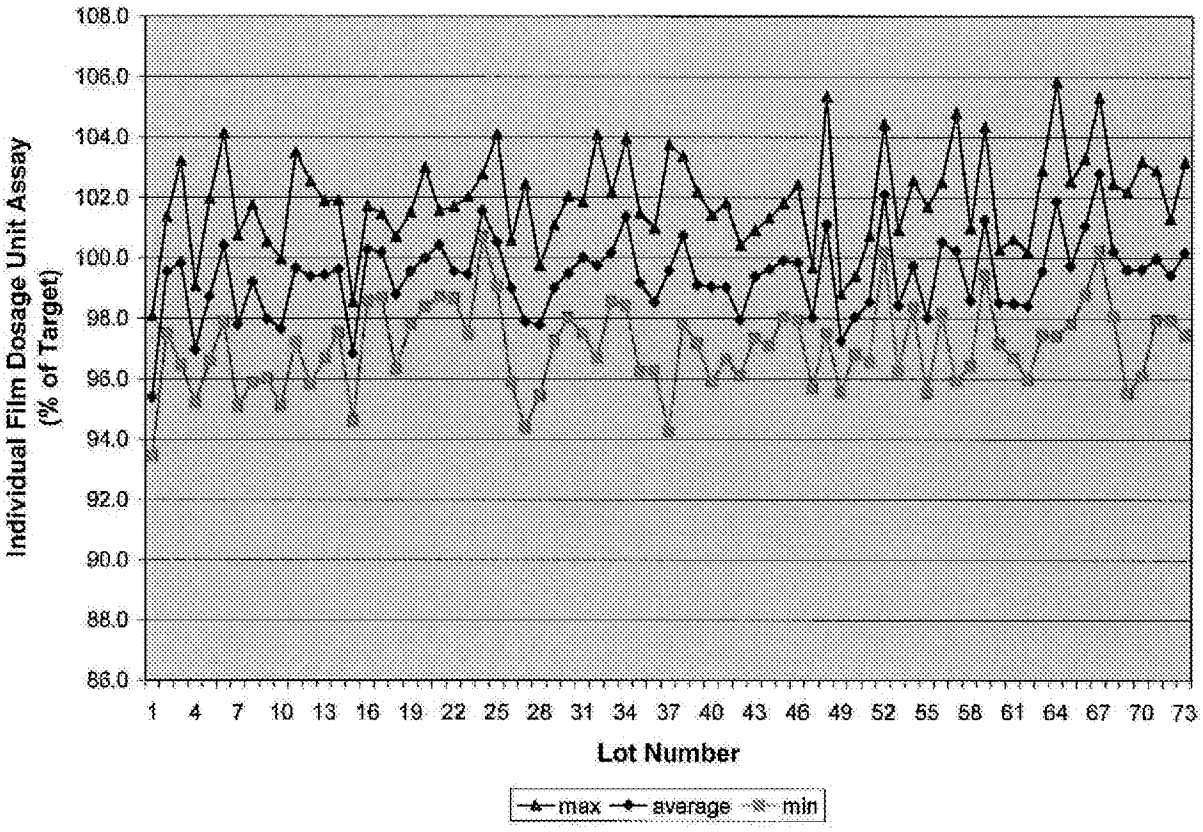


B. Arlie Bogue

APPENDIX A


12%
10%
8%
6%
4%
2%
0%
(Max - Min) /Lot Sample Average
1 4 7 10 13 16 19 22 25 28 31 34 37 40 43 46 49 52 55 58 61 64 67 70 73
Lot Number
% difference
10%

APPENDIX B


Individual Film Dosage Unit Assay
(% of Target)
108.0
106.0
104.0
102.0
100.0
98.0
96.0
94.0
92.0
90.0
88.0
86.0
1 4 7 10 13 16 19 22 25 28 31 34 37 40 43 46 49 52 55 58 61 64 67 70 73
Lot Number
max
average
min

APPENDIX C

Lots less than 5%			lots 5% to 10%	
Lot #	% Difference		Lot #	% Difference
24	2.0%		10	5.0%
45	2.6%		25	5.0%
17	2.8%		39	5.0%
21	2.8%		41	5.2%
22	3.1%		13	5.2%
16	3.1%		35	5.3%
60	3.2%		5	5.4%
50	3.4%		63	5.5%
72	3.4%		34	5.5%
33	3.6%		38	5.6%
43	3.6%		40	5.6%
19	3.7%		73	5.7%
46	3.8%		7	5.8%
29	3.9%		8	5.9%
2	3.9%		6	6.2%
4	4.0%		11	6.3%
61	4.0%		55	6.3%
30	4.0%		69	6.7%
48	4.1%		3	6.7%
15	4.1%		12	6.7%
52	4.2%		70	7.1%
54	4.2%		32	7.4%
51	4.2%		49	7.8%
44	4.3%		27	8.2%
62	4.3%		64	8.3%
56	4.3%		57	8.9%
31	4.4%		37	9.5%
28	4.4%			
14	4.4%			
68	4.4%			
42	4.4%			
18	4.4%			
66	4.5%			
47	4.5%			
23	4.6%			
20	4.6%			
9	4.6%			
58	4.6%			
65	4.7%			
26	4.8%			
53	4.8%			
36	4.8%			
1	4.9%			
59	4.9%			
67	4.9%			
71	4.9%			
total	46		total	27

MonoSol's/Cross-Respondent's Declaration of B. Arlie Bogue, Ph.D. Under 37 C.F.R. § 1.132, executed August 29, 2013 ("Bogue Declaration II")

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patentee:	Yang et al.	Examiner:	Diamond, Alan D.
Patent No.:	U.S. 7,897,080	Group Art Unit:	3991
Reexamination Control No.:	95/002,170	Confirmation No.	6418
Filed:	September 10, 2012	H&B Docket:	1199-26 RCE/CON/REX
Dated:	September 3, 2013	M&E Docket:	117744-00023

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Commissioner for Patents
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Signed: Michael I. Chakansky /Michael I Chakansky/

DECLARATION OF B. ARLIE BOGUE, PH.D. UNDER 37 C.F.R. § 1.132

Madame:

I, B. Arlie Bogue, Ph.D., do hereby make the following declaration:

I. Technical Background

1. I have worked in the field of pharmaceutical development, and particularly oral dosage form development, for 22 years. I am employed by MonoSol Rx, LLC. ("Patentee" and/or "MonoSol"), the assignee of issued patent U.S. 7,897,080 ("the '080 Patent"), as Senior Director for Manufacturing Strategy and Innovation.

2. I have a BS in Physical Chemistry from Colorado State University and a Ph.D. in Chemical and BioEngineering from Arizona State University. I have participated in postdoctoral studies in Biochemical Engineering at the University of Virginia. During my career, I have been named as an inventor on over 23 U.S. patents and numerous foreign patents directed to the formulation, processing and/or packaging of pharmaceutical oral disintegrating unit doses (tablets and film

strips). I have direct experience with the commercial scale processing of pharmaceutical film systems as well as an understanding of the uniformity of content of active and methods for testing the same.

3. My declaration dated March 13, 2013 was submitted in support of Patentee's response to the Office Action issued on November 29, 2012 in the reexamination of the '080 Patent ("Bogue Declaration I").

4. In Bogue Declaration I, I disclosed Patentee's method of producing resulting films in accordance with the '080 Patent and analytical chemical testing for uniformity of content thereof.

5. I hereby identify the resulting films in Bogue Declaration I as Suboxone® sublingual unit dose film products, and further declare that the Suboxone® sublingual unit dose film products were manufactured for Reckitt Benckiser Pharmaceuticals Inc. by Patentee, MonoSol.

6. Patentee is the exclusive source of Suboxone® sublingual unit dose film products for Reckitt Benckiser.

7. Suboxone® sublingual unit dose film products are FDA approved drug products.

8. In Patentee's production of unit dose film products, described in the '080 Patent, including its production of Suboxone® sublingual unit dose film products, the wet film thicknesses, from which the dry resulting products such as Suboxone® sublingual unit dose film products are produced, are always significantly greater in thickness than the dry resulting unit dose film products.

9. The Suboxone® sublingual unit dose film products made by MonoSol, and described in Bogue Declaration I, have dry thicknesses ranging from approximately 110 to approximately 175 microns, depending on the particular Suboxone® sublingual unit dose film product. Hence, the wet films from which these products are made have wet film thicknesses significantly greater than approximately 110 to approximately 175 microns.

10. I have reviewed the documents attached as Exhibits 7 and 8 to the Response by Patentee to the Action Closing Prosecution and referred to as Chapter <905> Uniformity of Dosage Units (2011) (Ex. 7) and Chapter <905> Uniformity of Dosage Units (2007) (Ex. 8).

11. Chapter <905> Uniformity of Dosage Units (2007), Ex. 8, specifies at p.1 that: "Content Uniformity is the default test and may be applied in all cases. The test for Weight Variation is applicable for dosage forms specified as W1, W2, W3, and W4.

12. Patentee's unit dose film products manufactured in accordance with the '080 Patent, including its Suboxone® sublingual unit dose film products are **not** dosage forms W1, W2, W3 or W4 as disclosed in the box on page 1, first column, in Chapter <905> Uniformity of Dosage Units (2011), Ex. 7.

13. Patentee's unit dose film products manufactured in accordance with the '080 Patent, including its Suboxone® sublingual unit dose film products are considered an "Others" dosage form for which CU or Content Uniformity with assaying is required. See, Table 1, second column, Chapter <905> Uniformity of Dosage Units (2011), Ex. 7.

14. Patentee's unit dose film products manufactured in accordance with the '080 Patent, including its Suboxone® sublingual unit dose film products, are **not** the "Tablets-Coated-with-a-Film" dosage forms in Table 1, Chapter <905> Uniformity of Dosage Units (2011), Ex. 7, second column.

15. **Weight Variation always requires that the relevant party "[c]arry out an assay for the drug substance(s) on a representative sample of the batch using an appropriate analytical method."** *See* Chapter <905> Uniformity of Dosage Units (2011), Ex. 7, p. 3, first column.

Dated this 29th day of August, 2013

B. Arlie Bogue

MonoSol's/Cross-Respondent's Declaration of David T. Lin, Ph.D. Under 37 C.F.R. § 1.132, executed March 13, 2013, filed March 13, 2013 ("Lin Declaration")

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patentee:	Yang et al.	Examiner:	Diamond, Alan D.
Patent No.:	U.S. 7,897,080	Group Art Unit:	3991
Reexamination Control No.:	95/002,170	Confirmation No.	6418
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Alexandria, VA 22313-1450

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March 13, 2013.
Signed: Michael I. Chakansky /Michael I Chakansky/

DECLARATION OF DAVID T. LIN, PH.D. UNDER 37 C.F.R. § 1.132

Madame:

I, David T. Lin, Ph.D. do hereby make the following declaration:

I. SUMMARY OF CREDENTIALS AND EXPERIENCE

1. Since January 2005, I have served as a Senior Consultant to Biologics Consulting Group, Inc. ("BCG"), a team of consultants who provide national and international regulatory and product development advice on the development and commercial production of small molecular weight synthetic drug, biotechnological and biological products.

2. While BCG is being paid for my time, I am not an employee of, nor do I have any financial interest in, MonoSol Rx, LLC ("Patentee" and/or "MonoSol").

3. Before joining BCG, I held various positions with the United States Food and Drug Administration ("FDA"). From 1997-2001, I was a Chemistry Reviewer in the Division of Reproductive and Urologic Drug Products, Center for Drug Evaluation and Research ("CDER"). In 2001, I became the Team Leader in the same Division and served in that role until 2003 when I was promoted to the position of acting Deputy Division Director in the Division of New Drug Chemistry III, Office of New Drug Chemistry (currently referred to as Office of New Drug Quality Assessment). In 2004, I was promoted to the position of acting Division Director.

4. As a Chemistry Reviewer at CDER, I was responsible for the comprehensive review of Chemistry, Manufacturing and Controls ("CMC") data for drugs being investigated during Phase 1, 2, and 3 clinical studies. I was also responsible for the review of CMC data in New Drug Applications and provided regulatory input to CMC reviewers responsible for review of Abbreviated New Drug Applications. This included providing scientific and regulatory guidance during development of small molecular weight drugs and biotechnological/biological drugs across a wide variety of dosage forms. I have reviewed CMC data submitted with respect to over 100 Investigational New Drug Applications and New Drug Applications (original and supplemental) as a chemistry reviewer, contributed to decisions regarding the approval of drugs, made presentations before scientific and regulatory conferences and participated in a variety of special FDA projects and committees, including serving as the co-Chair of the CMC Good Review Practices Committee.

5. As Team Leader, acting Deputy Division Director and acting Division Director in the Office of New Drug Chemistry, I was actively involved in directing the content of FDA guidances that pertained to CMC topics. As acting Deputy Division Director and Division Director, I was directly involved in discussions, regarding the content of the 2003 FDA draft guidance on Drug Product-Chemistry, Manufacturing, and Controls Information, with the committee responsible for writing this guidance. I had signatory authority for this draft guidance prior to public issuance by FDA. As acting Deputy Division Director and Division Director, I was involved in regular meetings with the supervisory staff in the Office of Generic Drugs to discuss regulatory and review policy issues that are common to both New Drug Applications and Abbreviated New Drug Applications.

6. I consider myself an expert in the fields of FDA practice and procedure as applicable to the testing requirements for drugs and review of Investigational New Drug Applications (INDs) and New Drug Applications (NDAs).

7. I received my B.A. in Biochemistry from the University of Pennsylvania in 1984, my Ph.D. in Organic Chemistry from the University of Maryland in 1989 and my M.B.A. from the University of Maryland's RH Smith School of Business in 2002. Attached hereto as Exhibit A is my curriculum vitae, including a list of my publications for the past ten years.

8. I have carefully reviewed Chen (WO 00/42992) ("Chen").

II. U.S. STATUTORY AND REGULATORY BACKGROUND FOR TESTING DRUGS FOR POTENCY AND DOSAGE UNITS FOR UNIFORMITY

9. From a US regulatory perspective, for a drug to be approved for commercial marketing and distribution, specifications necessary to ensure the identity, strength, quality, purity, potency, and bioavailability of the drug product must be provided in a New Drug Application.[1] In addition, reference to the current U.S. Pharmacopeia (USP) may satisfy these requirements.

10. Section 501(b) of the Food, Drug, and Cosmetic Act (the Act) deems an official drug (i.e., a drug represented as a drug which is recognized in the U.S. Pharmacopeia) to be adulterated if it fails to conform to compendial standards of quality, strength or purity. Compendial tests or assay methods are used when determining such conformance under 501(b); the standards are stated in individual monographs as well as portions of the General Notices section of the USP/NF. Standards and test methods have been established for such characteristics as potency and content uniformity.

11. Section 501(c) of the Act deems a drug that is not recognized in the USP to be adulterated if it fails to meet the strength, purity or quality which it is represented to possess.

[1] 21 CFR 314.50(d)(1)(ii)(a)

The applicable quality standards for a drug not recognized in the USP can be determined from such sources as the labeling of the drug (or drug product), the manufacturer's written specifications, and new drug applications.

12. The current good manufacturing practice (cGMP) regulations include the minimum requirements for the preparation of drug product for administration to humans. One of the requirements is that the strength[2] of the drug (active ingredient) in the drug product must be determined for each batch of drug product manufactured for commercial distribution.[3] Strength is taken to mean content or assay of the drug.

13. Batch uniformity of the drug products is ensured with procedures that describe the in-process controls, and tests, or examinations to be conducted on appropriate samples of in-process materials of each batch.[4] FDA also describes in guidance that it is expected the sampling plan for drug product is representative of the batch.[5]

14. Controls include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that the drug product conform to appropriate standards of identity, strength, quality, and purity.[6]

15. Regulatory specifications must be established to ensure that the dosage form will meet acceptable therapeutic and physicochemical standards throughout the shelf-life of the marketed product.[5] These specifications include tests for strength (content or assay) and uniformity of dosage units.

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[2] 21 CFR 210.3(b)(16)

[3] 21 CFR 211.165(a)

[4] 21 CFR 211.110(a)

[5] FDA Guideline for Submitting Documentation for the Manufacture and Controls for Drug Products, February 1987

[6] 21 CFR 211.160(b)

16. Testing to establish uniformity of dosage units is defined in the USP under the USP general chapter <905>.[7]

III. CHEN'S DISCLOSURE IS INSUFFICIENT

17. I have been asked to review Chen and render an opinion as to whether there is sufficient information contained within to allow regulatory FDA approval and commercialization of a drug product that is manufactured as described. After review of the patent in light of FDA practice and procedure, it is my opinion that there is insufficient disclosure to allow FDA to determine that a drug product as described can be manufactured for commercial distribution, manufactured in a consistent manner and meet specifications that will ensure the identity, strength, quality, purity, and potency of the drug product. In particular, Chen lacks any disclosure which would necessarily lead to the manufacture of films with uniformity of content (strength) of drug active required for FDA approval.

18. As would be required for FDA approval Chen does not disclose sufficient information that films containing drug can be produced consistently with respect to uniformity of content of the drug. No information was disclosed that demonstrated uniformity of content in the amounts of drug in individual dosage units. Chen discloses no specific test methods, and hence no test results, that could allow for the determination of the actual amount of drug (active) in individual dosage units.

19. As required for FDA approval, Chen's patent did not disclose sufficient information regarding the manufacturing process and process controls. The information disclosed by Chen would not ensure that films containing drug could be manufactured to meet specifications that ensure consistent strength.

20. Even if the information disclosed in Chen could be utilized to develop a manufacturing process for films containing drug, there is no information regarding the test methods that are necessary to determine the amount of drug in individual dosage units.

---

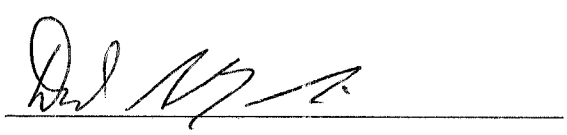
[7] USP General Chapter <905> Uniformity of Dosage Units

21. Therefore, Chen's disclosure is lacking, both explicitly and inherently, the disclosure necessary to provide for the manufacture of drug-containing films with the uniformity of content in amount of drug (active) in individual dosage units to make FDA approvable film products. It is my understanding that an inherent disclosure may not be established by probabilities or possibilities and that the mere fact that a certain thing may result from a given set of circumstances is not sufficient and that to be inherent requires that the missing disclosure is necessarily present.

22. Finally, Chen's patent discloses the release profiles of four active agents from films. See Chen, Figure 5. The release profile data presented in Figure 5 show a high degree of variability at each data point. For example, the release profile for nicotine containing film product show that the amount of nicotine released at the 5 minute and 8 minute time point can be as high as approximately 115-120%. This level of active agent is greater than the 110% level (from an expected amount of 100%) that is considered acceptable to FDA for regulatory approval of a product that purports to be manufactured consistently with acceptable content uniformity. These data indicate that the test method used in the analysis is not reproducible and/or there is a lack of active agent content uniformity between individual dosage units. These deficiencies demonstrate the lack of manufacturing consistency and lack of active agent content uniformity in the film.

23. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and. that such statements may jeopardize the validity of the application or any patents issued thereon.

Dated this 13th day of March, 2013



David T. Lin

EXHIBIT A

DAVID TSOCHUNG LIN

9121 Fall River Lane, Potomac, MD 20854 (301) 299-2853 dlin@bcg-usa.com

EXPERTISE

- 18+ years pharmaceutical regulatory experience.
  - 7+ years regulatory chemistry, manufacturing and controls (CMC) experience at CDER/FDA on small molecular-weight drugs, botanical drugs, peptide drugs, and protein drugs formulated in a broad range of sterile and non-sterile dosage forms.
  - 3+ years research experience at CBER/FDA.
  - 8+ years experience as regulatory CMC consultant.
- Unique combination of biologic/biotechnological and small molecular-weight drug regulatory experience, including device/drug and device/biologics combination products.
- Understanding of FDA regulatory requirements and expectations for drug development and marketing approval.
- Performed primary CMC review and assessment of drug products for treatment of reproductive and urologic disorders and diseases.
- Supervised CMC review activities in 7 CDER medical reviewing divisions including Reproductive/Urologic, Anti-viral, Dermatologic/Dental, Anti-inflammatory/ Analgesic/Ophthalmologic, Anti-infective, Special Pathogen/Immunologic, and Over-the-Counter drug products.
- Understanding of drug substance and drug product analytical method development and validation.
- Understanding of drug substance and drug product stability protocol development and stability data analysis.
- Understanding of current Good Manufacturing Practices (cGMPs)
- Experienced in chemical synthesis, small-scale and pilot-scale fermentation, biologics/ biotechnology, and protein chemistry.
- Experienced working in cross-functional teams (i.e., Pharmacology/toxicology, Clinical, Biostatistics, Biopharmaceutics, and Analytical).
- Ph.D. in Organic Chemistry; M.B.A. degree and training for managers.

EXPERIENCE

BIOLOGICS CONSULTING GROUP, INC. Alexandria, VA
January 2005 – Present
Senior Consultant

- Evaluate and provide advice on client CMC scientific and regulatory strategies for a wide range of therapeutic drug products (biologic and non-biologic) in dosage forms that include tablets, topicals, injectables, transdermals, implants, sprays, and inhalation, at all stages of product development, from pre-IND through post-NDA/BLA approval.
- Review and provide advice on IND and NDA/BLA submissions for suitability relative to FDA expectations for CMC data.
- Perform gap analysis audits for deficiencies relative to FDA expectations.
- Conduct regulatory and scientific due diligence audits for business acquisitions and licensing partnerships. Provide assessment of strengths and deficiencies.
- Represent clients in interactions with FDA.
- Prepare and write submissions to FDA, with focus on CMC sections.
- Represent client as FDA regulatory expert in legal proceedings.
- Advise clients on manufacturing contractor and vendor evaluation and selection.
- Provide management and technical oversight of contract manufacturing organizations (CMOs).
- Involved in business development to increase client base.
- Provide scientific and regulatory training and presentations at pharmaceutical/biopharmaceutical conferences.

FOOD & DRUG ADMINISTRATION, CENTER FOR DRUG EVALUATION AND RESEARCH, OFFICE OF NEW DRUG CHEMISTRY, DIVISION OF NEW DRUG CHEMISTRY III. Rockville, MD
July 2003 – December 2004
Division Director (acting) *March 2004 – December 2004*
Deputy Division Director (acting) *July 2003 – March 2004*

- Supervised 34 employees in 9 therapeutic product classes, includes 6 Team Leaders, review chemists and administrative staff. Responsible for employee work performance review and career development.
- Planned and set long-range plans and schedules for Division work. Directed and coordinated workload, and assured implementation of Division policies, goals and objectives.
- Evaluated budget and fiscal controls to manage Division functions.
- Made critical decisions and provided expert advice concerning regulatory, scientific and compliance approaches and options consistent with Office policies and objectives.
- Represented FDA in dealing and negotiating with the regulated industry, and professional and industry organizations.
- Participated as invited speaker at regulatory and scientific conferences on behalf of FDA.
- Served as the Chair of the Stability Guidance Technical Committee, Co-chair of the Conjugated Estrogens Working Group and Co-chair of the Good Review Practices Working Group.

FOOD & DRUG ADMINISTRATION, CENTER FOR DRUG EVALUATION AND RESEARCH, DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS. Rockville, MD
October 2001-July 2003
Lead Chemist (Team Leader)

- Managed a team of 4 review chemists in 2 therapeutic product classes.
- Responsible for secondary review, consistency of CMC reviews and adherence to FDA/ONDC policies and guidances.
- Coordinated reviewers' workload of IND and NDA submissions to ensure that reviews were conducted in timely manner.
- Interacted extensively with the regulated industry to provide regulatory direction during IND drug development and NDA post-approval activities.
- Active in the development of FDA guidances for industry and internal good review practices. Served as the Chair of the Stability Guidance Technical Committee, Co-chair of the Conjugated Estrogens Working Group and Co-chair of the Good Review Practices Working Group.

FOOD & DRUG ADMINISTRATION, CENTER FOR DRUG EVALUATION AND RESEARCH, DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS. Rockville, MD
April 1997-October 2001
Chemistry Reviewer

- Evaluated the quality of new drug products submitted to the FDA for approval.
- Integral part of a cross-functional review team responsible for evaluating the quality and effectiveness of reproductive and urologic drug products being investigated in clinical studies.
- Major contributor to committees responsible for establishing drug product quality standards and publishing guidances for pharmaceutical companies.
- Provided regulatory guidance to pharmaceutical company representatives during drug development.
- Mentored new reviewers.
- Served as computer focal point to facilitate and troubleshoot computer issues.

FOOD & DRUG ADMINISTRATION, CENTER FOR BIOLOGICS EVALUATION AND RESEARCH, LABORATORY OF PARASITIC BIOLOGY AND BIOCHEMISTRY. Bethesda, MD
February 1994-April 1997
National Research Council Fellow

- Investigated the biological role of specific proteins in the sexual differentiation of the malaria parasite. Published three research papers in peer-reviewed journals.
- Presented research data at three separate scientific conferences.
- Supervised the research projects of college students.
- Responsible for the coordination of instrument repairs and the ordering of laboratory supplies.

GENERAL ELECTRIC CO., CORPORATE RESEARCH & DEVELOPMENT, BIOLOGICAL SCIENCES LABORATORY. Schenectady, NY
July 1989-January 1994
Staff Scientist

- Developed recombinant biphenyl-metabolizing microorganisms capable of degrading environmental contaminants. Marketed this technology to the GE business units and government agencies responsible for environmental clean-up.
- Investigated the factors affecting aerobic biodegradation of indigenous PCBs in Hudson River sediment by various bacterial strains.
- Isolated and conducted mechanistic studies of the dioxygenase enzymes involved in biodegradation.
- Investigated the scientific and economic feasibility of biologically synthesizing aromatic monomers for use as a feedstock to produce biodegradable polymers.
- Supervised research projects of summer interns.
- Published research in peer-reviewed journals.
- Recruited at major East Coast universities. Interviewed and screened graduating science Ph.D. students for second round interviews at the Research Center.

UNIVERSITY OF MARYLAND, Dept. of Chemistry/Biochemistry. College Park, MD
May 1985-May 1989
Research Assistant

- Investigated mechanism of action of two bacterial enzymes, mandelate racemase and D-amino acid oxidase.
- Synthesized and tested novel halogenated aromatic hydroxy- and amino- acid analogs as potential irreversible inhibitors.
- Published research in peer-reviewed journals and co-authored one chapter in a biotechnology book. In addition, the research data was presented at two national scientific conferences.
- Served as the computer expert for the laboratory group.

EDUCATION

ROBERT H. SMITH SCHOOL OF BUSINESS. College Park, MD
University of Maryland
Master of Business Administration (MBA), *2002*
Concentration: Finance

UNIVERSITY OF MARYLAND. College Park, MD
Department of Chemistry and Biochemistry
Ph. D. -- Organic Chemistry, *1989*
Research Advisor -- Dr. John W. Kozarich

UNIVERSITY OF PENNSYLVANIA. Philadelphia, PA
Bachelor of Arts with Honors – Biochemistry, *1984*
Dean's List, Phi Lambda Upsilon Chemical Honor Society

TRAINING

- Facilitation Skills, CDER/FDA (Fall 2002)
- Six Sigma Strategy and Methods, Univ. of MD (Summer 2002)
- Group Decision-Making Techniques, CDER/FDA (Feb. 2002)
- Managing Written Communications for Team Leaders, CDER/FDA (Spring 2002)
- Organizational Behavior and Human Resources, Univ. of MD (Fall 1999)
- Management of Human Resources, Univ. of MD (Fall 1999)
- Introduction to Drug Law and Regulation, CDER/FDA (Nov. 1998)
- Basic Statistical Methods, CDER/FDA (Fall 1998)

HONORS/AWARDS

- CDER's Team Excellence Award (Nov 2004)
- FDA's Group Recognition Award (May 2004)
- CDER's Special Recognition Award (Nov 2002)
- CDER's Team Excellence Award (Nov 2002)
- OPS/ONDC Special Recognition Award (Dec 2001)
- CDER's Team Excellence Award (Nov 2000)
- OPS/ONDC Special Recognition Award (Jun 2000)
- CDER's Excellence in Mentoring Award (Nov 1999)

PRESENTATIONS

- Conducting Effective & Compliant Stability Programs for Pharmaceuticals & Biologics, "Stability Studies During Development", "Stability of Biopharmaceuticals", "Development of Specifications for Biopharmaceuticals", and "Extractables, Leachables, and Particulates – Safety Concern for Biotechnology Products", Dubai, UAE (Sep 2012).
- 4th DIA China Annual Meeting, "ICH Guidelines Q1D, Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products", and "Q1E, Evaluation of Stability Data", Shanghai, China (May 2012).
- IPA's Current Trends and Practices in Stability Testing, "Stability Testing Requirements for Biopharmaceutical Products", Montreal, Canada (Oct 2011)
- IPA's Current Trends and Practices in Stability Testing, "Stability Program for Combination Products", Montreal, Canada (Oct 2011)
- 3rd DIA China Annual Meeting, "Thinking About Comparability for Biosimilar Proteins", Beijing, China (May 2011).
- IPA's Current Trends and Practices in Stability Testing, "Stability Challenges for Combination Products", Boston, MA (May 2011).
- IPA's Current Trends and Practices in Stability Testing, "Country Specific Stability Requirements", Boston, MA (May 2011).
- Stability Programs Forum, "Stability Testing for Biotechnology/Biologic Products", Philadelphia, PA (Dec 2010).
- 11th Annual EuroTIDES/EuroPEPTIDES Conference, "Stability Considerations and Testing for Peptide-and Oligo-Based Therapeutics", Barcelona, Spain (Nov 2010).
- International Summit of China Pharmaceutical Industry, "FDA Requirements for Peptide Product Development: Considerations from Small Molecule and Biological Products", Hangzhou, China (Oct 2010).

- 7th Annual Method Validation Conference, "Ensure Method Validation Compliance through a Review of FDA Warning Letters", San Francisco, CA (Jul 2010).
- 6th Annual BioProcess International European Conference, "Extractables, Leachables and Particulates – Safety Concern for Biotechnology Products," Vienna, Austria (May 2010)
- ISPE-CSAC Meeting, "Biotechnological Drug Development and Interactions with CDER," Raleigh, NC (Oct 2009).
- Seminar on China International Bio-medicine Outsourcing Service, "Product Quality Issues with GLPs and GCPs," Hangzhou, China (Sep 2009).
- Informa Stability Testing for Biologics Conference, "Understanding Product Expiry and Shelf-Life," Prague, Czech Republic (Sep 2009).
- Informa Stability Testing for Biologics Conference Workshop, "Stability Testing Performed Over a Product Lifecycle," Prague, Czech Republic (Sep 2009).
- IVT Lab Compliance Conference, "Implement a Comprehensive and Compliant Stability Program," Philadelphia, PA (Aug 2009).
- OKBio ACCELERATE Workshop, "Product Development – Regulatory CMC Considerations," Oklahoma City, OK (Jun 2009).
- IVT Method Validation Conference, "Challenges in Understanding Impurities and Degradants for Biological/Biotechnological Products," San Francisco, CA (Oct 2008).
- IVT Method Validation Conference, "Strategies for Setting Biological Product Specifications," San Francisco, CA (Oct 2008).
- CBI 3rd Annual Stability Programs Conference, "Complex Stability Programs for Biologics," Philadelphia, PA (Jun 2008).
- IVT Lab Compliance Conference, "Stability Testing Fundamentals and Considerations in the Current Regulatory Environment," Baltimore, MD (Apr 2008).
- R&D Direction's 5th Annual Drug Development Summit, "Looking Forward in 2008: Regulatory Priorities and Considerations," Amelia Island, FL (Feb 2008).
- 2007 AAPS Annual Meeting, "Critical Stability Evaluation of Biopharmaceuticals During Clinical Development Stages," San Diego, CA (Nov 2007).
- 2007 DIA Annual Meeting, "The Impact of FDA's Quality by Design Initiative on Biologics Development," Atlanta, GA (Jun 2007).
- Institute for International Research: Formulation and Forced Degradation Strategies for Biomolecules, "Regulatory Requirements for Successful Product Development," San Diego, CA (Mar 2007).
- International Pharmaceutical Academy: Effective Management of Stability Programs, "Stability Design Considerations for Global Regulatory Filings," Toronto, Canada (Feb 2007).
- Cambridge Healthtech Institute's PepTalk: Optimizing Protein and Antibody Therapeutics, "Regulatory Considerations for the Development of Protein Therapeutic Products," San Diego, CA (Jan 2007).
- 2006 AAPS Annual Meeting, "The Impact of FDA Initiatives on the Development of Biological Products," San Antonio, TX (Nov 2006).
- SWE Enterprises: Stability Testing for the FDA Regulated Industry, "In-Use Testing of Biotechnological and Biologic Products," Boston, MA (Oct 2006).
- SWE Enterprises: Stability Testing for the FDA Regulated Industry, "Cost Efficient Design of Stability Studies," Boston, MA (Oct 2006).
- Institute for International Research: Chemistry Manufacturing & Controls, "Clarifying and Understanding ICH Guidance to Help Meet International Requirements for Submissions," Philadelphia, PA (July 2006).
- IVT Stability Testing: Implementing Effective Processes for Stability Program Development, "Cost Efficient Design of Stability Studies," San Diego, CA (June 2006).
- IVT Stability Testing: Implementing Effective Processes for Stability Program Development, "Stability Requirements for Global Regulatory Filings," San Diego, CA (June 2006).

- CBI Stability Programs: New Approaches to Test, Analyze and Document Data for Improved Program Design and Global Compliance, "In Use Testing of Biotechnological and Biological Products," Princeton, NJ (June 2006).
- IBC/TIDES: Oligonucleotide and Peptide Technology and Product Development, "Stability Considerations and Testing for Oligo- and Peptide-Based Therapeutics," Carlsbad, CA (May 2006).
- IBC Biopharm Manufacturing and Distribution Summit: Logistics for Biopharmaceutics, "Stability Studies to Support the Chain of Custody of Biotechnology Products," Reston, VA (Dec 2005).
- 2005 AAPS Annual Meeting: AAPS Short Course on Degradation and Stability in Small Molecule Active Pharmaceutical Ingredients/Stability Testing for Global Filings, "Stability Requirements for Global Regulatory Filings," Nashville, TN (Nov 2005).
- Therapeutic Strategies Against Neurodegenerative Conditions, "The Regulatory Product Development Process," Burlington, MA (Oct 2005).
- International Pharmaceutical Federation (FIP) Workshop: Harmonizing Clinical Trial GMP and Quality Requirements Across the EU and Beyond, "The US Investigational New Drug (IND) System," Noordwijk Zee, The Netherlands (Mar 2005).
- 2004 AAPS Annual Meeting, "Phase 2 and 3 IND CMC Guidance: FDA Perspective," Baltimore, MD (Nov 2004).
- 64th Annual World FIP Congress, "Clinical Trial Application Process – CMC: US FDA Perspective," New Orleans, LA (Sep 2004).
- AAPS Pharmaceutical Technologies 3rd Summer Conference: Optimizing the Global Clinical Trial Process, "IND Applications – FDA Perspective," Cherry Hill, NJ (Aug 2004).
- 2004 DIA Annual Meeting, "FDA Stability Guidance Update," Washington, DC (Jun 2004).
- DIA Meeting on CM&C/Regulatory and Technical Strategies, "Challenges and Opportunities in CMC Requirements for Phase 2-3," Bethesda, MD (Mar 2004).
- 2003 PDA Annual Meeting, "Draft FDA Stability Guidance," Atlanta, GA (Nov 2003).
- 2003 DIA Annual Meeting, "Product Quality of Non-clinical and Clinical Trial Materials," San Antonio, TX (Jun 2003).
- PARCS Meeting, "Managing CMC Requirements during IND," Irvine, CA (Apr 2003).
- PARCS Meeting, "Use of SUPAC Guidances during IND Development," Irvine, CA (Apr 2003).
- DIA Meeting on Global Chemistry, Manufacturing and Controls: Pre IND/CTX and IND/CTX Development Challenges, "FDA Perspective on Stability Testing during IND Development," Philadelphia, PA (Feb 2003).

PUBLICATIONS

- C. Syin, D. Parzy, F. Traincard, I. Boccaccio, M.G. Joshi, D.T. Lin, X.-M. Yang, K. Assemat, C. Doerig, and G. Langeley, "The H89 cAMP-dependent protein kinase inhibitor blocks *Plasmodium falciparum* development in infected erythrocytes," *Eur. J. Biochem. 268*, 4842 (2001).
- J.P. McDaniel, C. Syin, D.T. Lin, M.B. Joshi, S. Li, and N.D. Goldman, "Expression and characterization of a *Plasmodium falciparum* protein containing domains homologous to sarcalumenin and a tyrosine kinase substrate, eps15," *Int. J. Parasitol. 29*, 723 (1999).
- D.T. Lin, N.D. Goldman, and C. Syin, "Stage specific expression of a *Plasmodium falciparum* protein related to the eukaryotic mitogen-activated protein kinase," *Mol. Biochem. Parasitol. 78*, 67 (1995).
- M.R. Harkness, J.B. McDermott, D.A. Abramowicz, J.J. Salvo, W.P. Flanagan, M.L. Stephens, F.J. Mondello, R.J. May, J.H. Lobos, K.M. Carroll, M.J.Brennan, A.A. Bracco, K.M. Fish, G.L. Warner, P.R. Wilson, D.K. Dietrich, D.T. Lin, C.B. Morgan, and W.L. Gately, "*In situ* stimulation of aerobic PCB biodegradation in Hudson River sediments," *Science 259*, 503 (1993).
- D.T. Lin, V.M. Powers, L.J. Reynolds, C.P. Whitman, G.L. Kenyon and J.W. Kozarich, "Evidence for the generation of α-carboxy-α-hydroxy-*p*-xylylene from *p*-(bromomethyl)mandelate by mandelate racemase," *J. Am. Chem. Soc. 110*, 323 (1988).

- M.S. Lakshmikumaran, E. D'Ambrosio, L.A. Laimins, D.T. Lin and A.V. Furano, "Long interspersed repeat DNA(LINE) causes polymorphism at the rat insulin 1 locus," *Mol. Cell. Biol. 5*, 2197 (1985).

BOOK CHAPTER

- N.R. Schmuff and D.T. Lin, "Contents of Module 3 for an Electronic Common Technical Document Investigational New Drug Application," in Preparation and Maintenance of the IND Application in eCTD Format, W.K. Sietsema (ed.), FDAnews, Falls Church, VA, 117-134 (2008).
- N.R. Schmuff and D.T. Lin, "Chemistry, Manufacturing and Controls (CMC)," in Wiley Encyclopedia of Clinical Trials, (2008).
- J.A. Gerlt, G.L. Kenyon, J.W. Kozarich, D.T. Lin, D.C. Neidhart, G.A. Petsko, V.M. Powers, S.C. Ransom and A.Y. Tsou, "Structure-function relationships in mandelate racemase and muconate lactonizing enzyme," in Chemical Aspects of Enzyme Biotechnology, T.O. Baldwin, F.M. Raushel and A.I. Scott (eds.), Plenum, New York, NY, 9-21 (1990).

PROCEEDINGS OF MEETINGS

- D.T. Lin, N.D. Goldman, and C. Syin, "*Plasmodium falciparum* mitogen-activated protein kinase homologue contains an unusually large carboxyl terminal domain which is highly charged and homologous to merozoite surface antigens," Molecular Parasitology Meeting, Woods Hole, MA (1995).
- C. Syin, D. Lin, B. Krzyzanowska, and N.D. Goldman, "*Plasmodium* cGMP-dependent protein kinase," FDA Science Forum on Regulatory Sciences, Washington, D.C. (1994).
- J. H. Lobos, M. J. Brennan, J. T. Jackman and D. T. Lin, "*In situ* stimulation of PCB biodegradation in Hudson River sediment: III. enumeration and characterization of aerobic bacteria," ASM Meeting, New Orleans (1992).
- G.L. Kenyon, D.T. Lin, V.M. Powers, L.J. Reynolds, C.P. Whitman and J.W. Kozarich, "Generation of α-carboxy-α-hydroxy-*p*-xylylene from *p*-bromomethyl-mandelate by mandelate racemase-- further evidence for a carbanion mechanism," *FASEB J. 2*, 1329 (1988).
- D.T. Lin, V.M. Powers, L.J. Reynolds, C.P. Whitman, G.L. Kenyon and J.W. Kozarich, "Formation of *p*-xylylene species in the mandelate racemase catalyzed reaction of *p*-(bromomethyl)mandelate," *Fed. Proc. 46*, 2042 (1987)

BDSI's/Cross-Appellant's Declaration by Maureen Reitman, Sc.D. Under 37 C.F.R. § 1.132, dated February 28, 2013, filed April 12, 2013 ("Reitman Declaration")

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re *Inter Partes* Reexamination of:	)
US Patent No. 7,897,080	)
Issued: March 1, 2011	) Confirmation No.: 6418
Named Inventor: Robert K. Yang *et al.*	) Group Art Unit: 3991
Control No.: 95/002,170	) Examiner: Diamond, Alan D.
Filed: September 10, 2012	) M&E Docket: 117744-00023
Title: POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM	) H&B Docket: 1199-26 RCE/CON/REX

Mail Stop *Inter Partes* Reexam
Attn: Central Reexamination Unit
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION BY MAUREEN REITMAN, SC.D.
UNDER 37 CFR § 1.132

Sir/Madam:

I, Maureen Reitman, do hereby make the following declaration:

I. Technical Background

1. I am a Principal and the Director of the Polymer Science and Materials Chemistry Practice at Exponent. I hold two academic degrees: (1) a Bachelor of Science in Materials Science and Engineering from the Massachusetts Institute of Technology (MIT), and (2) a Doctor of Science in Materials Science and Engineering, with a thesis in the field of polymers, from MIT. I have been practicing in the field of polymer science and engineering for more than 20 years as a researcher at MIT, in a variety of technical roles at the 3M Company, and as a consultant with Exponent. I provide consulting engineering services in all aspects of polymer science and engineering including, but not limited to material selection, product design and development, mechanical and chemical testing, failure analysis, polymer chemistry, polymer

physics, and polymer processing. My specialties include formulation, processing and performance evaluation of polymeric materials, including films, coatings, adhesives and transdermal drug delivery systems. I have been directly involved in product development, product line extensions, transfer of new products to manufacturing, qualification of alternative materials and manufacturing equipment, evaluating field performance, and assessing intellectual property. I am a past chairman and continue to serve as a member of the board of directors of the Medical Plastics Division of the Society of Plastics Engineers. My *curriculum vitae* is provided in Appendix A.

2. While Exponent is being paid for my time, I am not an employee of, nor do I have any financial interest in, BioDelivery Sciences International, Inc.

3. I have been asked to carefully review International Publication No. WO 00/42992 ("*Chen*"), and manufacture a film as described in *Chen*. I carefully reviewed *Chen*. Under my direction, my team manufactured a film in accordance with Example 7 of *Chen*. I have also been asked to take samples and perform various analytical tests to confirm the uniform distribution of the pharmaceutical active in substantially equal sized individual dosage units of the film, which we did.

4. Manufacturing Example 7 of *Chen*

Chen states: "According to Examples 1-8, the hydrocolloid [Methocel E5(HPMC)] was dissolved in water under agitated mixing to form a uniform and viscous solution." Chen 17:7-8.

- Methocel E5(HPMC) was dissolved in water under agitated mixing to form a uniform and viscous solution, by my team.

Chen states: "Additional ingredients were then added sequentially to the viscous solution such as peppermint, aspartame, propyl[ene] glycol, benzoic acid and citric acid under agitated mixing until they were uniformly dispersed or dissolved in the hydrocolloid." Chen 17:8-11.

- Additional ingredients were then added sequentially to the viscous solution including peppermint oil, aspartame, propylene glycol, benzoic acid and citric acid under agitated mixing until they were uniformly dispersed or dissolved in the hydrocolloid, by my team.

- Kolliphor EL was also added to the viscous solution.

Chen states: "Therapeutic agents were added to the homogeneous mixture (coating solution) prior to forming the film." *Chen* 20:19-20.

- Oxybutynin chloride (the therapeutic agent of Example 7) was added to the homogeneous mixture (coating solution) prior to forming the film, by my team.

Chen's Table 5 specifies the composition for Example 7.

- We used the ingredients in the amounts identified in *Chen*'s Table 5. *See* Table 1.

Table 1			
Formulation, Ex. 7, Table 5, *Chen*	% Weight	Formulation, Prepared by Maureen Reitman Team	% Weight
Oxybutynin	3.71	Oxybutynin chloride	3.71
Methocel E5 (HPMC)	21.06	Methocel E5 Premium LV	21.06
Water	70.72	Water, distilled	70.72
Cremophor EL40	1	Kolliphor EL[1]	1
Propylene glycol	1	Propylene glycol	1
Peppermint	1	Peppermint oil	1
Aspartame	0.8	Aspartame	0.8
Benzoic acid	0.013	Benzoic acid	0.013
Citric acid	0.7	Citric acid, monohydrate	0.7

Chen states: "The resultant mixture was degassed in a vacuum chamber until trapped air bubbles were removed." Chen 17:11-12.

- The resultant mixture was degassed in a vacuum chamber until trapped air bubbles were removed, by my team.

Chen states: "The formulation was then coated on the non-siliconized side of a polyester film at a wet thickness of 10 mil and dried in a hot air circulating oven at 50°C for 9 minutes." Chen 17:13-15.

- The formulation was then coated on a non-siliconized side of a polyester film at a wet thickness of 10 mil and dried in a hot air circulating oven at 50°C for up to 9 minutes, on commercial manufacturing equipment by my team.

Chen states: "Methods for manufacturing the dosage unit include the solvent casting methods as shown in Figure 2." Chen 15:13-14. "The manufacturing process for forming the dosage unit is illustrated in Figure 2. The dry film formed by this process is a glossy, stand alone, self supporting, non-tacky and flexible film (12)." Chen 15:29-31.

- A solvent casting manufacturing process for forming the dosage unit as illustrated in Figure 2 was used[2], by my team.

[1] The Cremophor line of products now owned by BASF and renamed Kolliphor. Based on the naming convention of the Cremophor/ Kolliphor products, EL40 is Polyoxyl 40 Castor Oil and EL is Polyoxyl 35 Castor Oil (*i.e.*, they are based on a 1:40 and 1:35 ratio, respectively, of castor oil:ethylene oxide). They are different materials. However, one of skill in the art would recognize Kolliphor EL as an appropriate substitute, as Cremophor EL40 is no longer available.

- The film was manufactured using a controlled drying process.
- As illustrated in Figure 2, the drying oven featured aeration controller with 3 zones set such that in each successive zone air impingement on the surface of the film increased.
- The dry film formed by the process is a glossy, stand alone, self-supporting, non-tacky and flexible film.

Chen states: "A glossy, substantially transparent, stand alone, self-supporting, non-tacky and flexible film was obtained after drying." Chen 17:15-16.

- A glossy, substantially transparent, stand alone, self-supporting, non-tacky and flexible film was obtained after drying, by my team.

5. Verification of Content Uniformity – Visual Inspection

- By examination with the naked eye, uniformity was verified by my team.

6. Verification of Content Uniformity – Unit Dose Weight

- By weighing individual dosage units of substantially identical size, uniformity was verified by my team. *See* Table 2.

Table 2

Sample	Weight of 5 cm^2 dosage unit (grams)
1	0.034
2	0.034
3	0.034
4	0.034
5	0.034
6	0.034
7	0.034

7. Verification of Content Uniformity – Dissolution Test (HPLC)

- By dissolution of individual dosage units of substantially identical size and analysis by High Performance Liquid Chromatography (HPLC) active content uniformity was verified by my team. *See* Table 3.

[2] Our backing was not looped and we did not die cut in line, but the solvent casting and drying under aeration is matched.

Table 3	
Sample	Oxybutynin weight (mg)
A	4.4
B	4.4
C	4.3
D	4.4
E	4.1

- As can be seen in Table 3, the active varies by less than 10%.

8. Additional Observations

   - The components of the formulation, including the active component, were uniformly distributed in the viscous solution, which was used to cast the film, as was verified by my team.

   - The viscous solution, which was used to cast the film, exhibited the flow properties of honey (around 10,000 cps), as observed by my team.

   - Water content of the film was less than 10%, as verified by my team.

   - Within about 4 minutes after initiation of drying, the film was self-supporting, non-tacky, flexible and viscoelastic, as verified by my team.

9. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine, or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful statements may jeopardize the validity of the application or any patents issued thereon.

Dated: February 28, 2013

Maureen Reitman, Sc.D.

Appendix A

Exponent
Failure Analysis Associates

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Boston, Maryland 02215

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Maureen T. F. Reitman, Sc.D.
Principal and Practice Director

Professional Profile

Dr. Maureen Reitman is a Principal and the Director of Exponent's Polymer Science and Material Chemistry practice. Her expertise includes polymer and composite technology, mechanics of materials, adhesion science, fiber mechanics, history and technology of plastics, and material failure analysis. She is skilled in the development and use of testing tools and methods and has applied them to plastic, rubber, textile, metal, glass, ceramic, and composite materials and systems. She is experienced in major aspects of product development, including materials selection, formulation, scale-up, end-use testing, failure analysis, certification procedures and issues related to intellectual property.

Dr. Reitman has conducted research in the areas of packaging and barrier materials; paints and coatings; plastic pipes; transdermal drug delivery; adhesives, sealants, and encapsulants; molding compounds; high temperature resins; nanoparticles; fibers and textiles; protective coatings and finishes; polymer chemical resistance; plastic insulation; connectors and splices; plastic packaging; medical devices; environmental effects on durability; and product aging. She has used her expertise to solve a broad range of problems related to coatings, fibers, films, and extruded and molded products, and their use in the telecom, electronics, electrical, transportation, construction, fire protection, medical, and consumer products markets.

Dr. Reitman is a member of the Board of Directors of the Medical Plastics Division of the Society of Plastics Engineers and an active member of two Underwriters Laboratories Standard Technical Panels, addressing Polymeric Materials (UL 94, UL 746, UL 1694) and Appliance Wiring (UL758).

Prior to joining Exponent, Dr. Reitman worked for the 3M Company in both research and management roles. Her activities included technology identification, materials selection and qualification, product development, customer support, program management, acquisition integration, intellectual property analysis, and patent litigation support.

Academic Credentials and Professional Honors

Sc.D., Materials Science and Engineering/ Program in Polymer Science and Technology, Massachusetts Institute of Technology, 1993
B.S., Materials Science and Engineering, Massachusetts Institute of Technology, 1990

National Academy of Engineering Frontiers of Engineering, 2009; Tau Beta Pi; Sigma Xi
John Wulff Award; Carl Loeb Fellowship; NCAA Postgraduate Scholarship;
Malcolm G. Kispert Award; GTE Academic All-American

Patents

Patent 6,311,524: Accelerated Method for Increasing the Photosensitivity of a Glassy Material, issued November 6, 2001.

European Patent EP0830428: Tackified Polydiorganosiloxane Polyurea Segmented Copolymers and a Process for Making Same, published March 25, 1998.

Patent 5,371,051: Fiber Optic Fusion Splice Protector Sleeve, issued March 24, 1998.

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Kurtz S, Siskey R, Reitman M. Accelerated aging, natural aging, and small punch testing of gamma-air sterilized polycarbonate urethane acetabular components. Journal of Biomedical Materials Research Part B: Applied Biomaterials 2010 May; 93B(2):422–447.

Hoffman JM, Reitman M, Donthu S, Ledwith P. Complimentary failure analysis methods and their application to CPVC pipe. Proceedings, ANTEC 2010, Society of Plastics Engineers, Orlando, FL, May 2010.

Hoffman JM, Reitman M, Donthu S, Ledwith P, Wills D. Microscopic characterization of CPVC failure modes. Proceedings, ANTEC 2009, Society of Plastics Engineers, Chicago, IL, June 2009. Best Paper Award in Failure Analysis & Prevention.

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Fahey MT. Nonlinear and anisotropic properties of high performance fibers. MIT Thesis, 1993.

Fahey MT. Mechanical property characterization and enhancement of rigid rod polymer fibers. MIT Thesis, 1990.

Book Contributions

Reitman M, Liu D, Rehkopf J. Chapter 38. Mechanical properties of polymers. In: Handbook of Measurement in Science and Engineering. Volume 2. Kutz, M (ed), John Wiley & Sons, Hoboken NJ, 2013. ISBN- 978-1-118-38464-0.

Reitman M, Jaekel D, Siskey R, Kurtz S. Morphology and crystalline architecture of polyarylketones, pp. 49-60. In: PEEK Biomaterials Handbook. Kurtz SM (ed), Elsevier William Andrews, Kidlington, Oxford, UK, 2012. ISBN 13:978-1-4377-4463-7

Tsuji JS, Mowat FS, Donthu S, Reitman M. Application of toxicology studies in assessing the health risks of nanomaterials in consumer products, pp. 543-580. In: Nanotoxicity: From In Vivo and In Vitro Models to Health Risks. Sahu S, and Casciano D. (eds), John Wiley & Sons, Chicester, West Sussex, UK, 2009. ISBN 978-0-470-74137-5.

Reitman MTF. The Plastics Revolution. In: Research and Discovery: Landmarks and Pioneers in American Science. Lawson RM (ed), Armonk NY: Sharpe Reference 2008. ISBN 978-0-7656-8073-0.

Klein SM. Mid-century plastic jewelry. Schiffer Publishing, Atglen, PA, 2005. (Technical advisor to author).

Selected Invited Presentations

Reitman MTF. Failure analysis tools. Workshop on Future Needs for Service Life Prediction of Polymeric Materials. NIST and Underwriters Laboratories, Gaithersburg, MD, October 2012.

Hoffman J, MacLean S, Ralston B, Reitman M, Ledwith P. Fractography of unfilled thermoplastic materials experiencing common mechanical failure modes. Materials Science & Technology 2012 Conference, Pittsburgh PA, October 2012.

Hoffman J, Reitman M, Ledwith P. Microscopic characterization of CPVC failure. Materials Science & Technology 2012 Conference, Pittsburgh PA, October 2012.

Reitman MTF. Polymer material properties for next generation medical devices. Invited Speaker: MedTech Polymers, UBM Canon, Chicago, IL, September 2012.

Reitman MTF. Polymers for medical applications. Fundamentals and Fellows Forum, ANTEC 2012, Orlando FL, April 2012.

Reitman MTF. Plastic and composite product failures. Invited lecture in Failure Analysis of Emerging Technologies. Stanford University Department of Materials Science and Engineering, Menlo Park, CA October 2009.

Reitman MTF. Factors for success: Plastics in injection molded medical devices. Part of *Injection Molding Works for Medical Design*, Design News Webcast, October 2008.

Reitman MTF. Plastic and composite product failures. Keynote Speaker: Third International Conference on Engineering Failure Analysis (ICEFA III), Elsevier, Sitges Spain, July 2008.

Reitman MTF. Multiphase materials for medical device applications, an overview. Medical Device and Manufacturing (MDM), Canon Communications, various locations, January- June 2008.

Reitman MTF. Nanotechnology and plastics for medical devices. Capitalizing on Nanoplastics, Intertek PIRA San Antonio TX, February 2008.

Reitman MTF. Nano additives in composites and coatings for medical device applications. Medical Device and Manufacturing Minneapolis, Canon Communications, Minneapolis MN, October 2007.

Reitman MTF, Swanger LA. Practical tips on how to manage your technical expert in patent disputes. Ropes & Gray IP Master Class, Live Teleconference, June 2007.

Reitman MTF, Kennedy E. Root cause failure analysis and accident investigation. Lorman Educational Services, Live Teleconference, November 2007.

Reitman MTF. Plastics failure analysis: Case studies. Baltimore/ Washington Chapter of SAMPE, October 2006.

Reitman MTF. Plastics failure analysis. Baxter Global Plastics Processing Conference 2005, Schaumburg IL, 2005.

Fahey MT. Fiber mechanics, corrosion, sealants: Tales of a 3M materials scientist. Class of 1960's Scholars Program, Williams College, 1999.

Fahey MT. Adhesives and sealants for the telecommunications industry. Riverwood V Conference, St. Paul MN, 1998.

Current Professional Appointments

- Underwriter's Laboratory Standards Technical Panel STP 746 (Polymeric Materials, includes UL94, UL 746 and UL1694)
- Underwriter's Laboratory Standards Technical Panel STP 758 (Appliance Wires/ UL758)
- Medical Plastics Division Board of Directors, Society of Plastics Engineers

Committee and Review Activities

- UL Forum on Initiatives to Improve the Long Term Aging Program, LTTA Tools Working Groups, Underwriters Laboratories
- Research and Engineering Technology Award Committee, Society of Plastics Engineers
- Reviewer, Medical Plastics Technical Program Committee, Society of Plastics Engineers
- Reviewer, Failure Analysis and Prevention Technical Program Committee, Society of Plastics Engineers
- Reviewer, various book proposals and submissions related to polymer science, ASM International, Elsevier, John Wiley

Professional Affiliations

- American Association for the Advancement of Science (member)
- American Association of Textile Chemists and Colorists—AATCC (senior member)
- American Chemical Society (member)
- ASTM International (member)
- Society for the Advancement of Material and Process Engineering (member)
- Society of Plastics Engineers (senior member)

RELATED PROCEEDINGS APPENDIX

NONE.

CERTIFICATE OF SERVICE

It is certified that a copy of this **PATENT OWNER'S CROSS-RESPONDENT'S BRIEF** has been served, by first class mail, postage prepaid, on April 10, 2014, in its entirety on the third party requester as provided in 37 CFR § 1.903 and 37 CFR § 1.248 at the address below.

DANIELLE L. HERRITT
McCARTER & ENGLISH LLP
265 FRANKLIN STREET
BOSTON, MASSACHUSETTS 02110

/Michael I. Chakansky/
Michael I. Chakansky
Registration No.: 31,600
Attorney for the Patentee/MonoSol

Electronic Patent Application Fee Transmittal

Application Number:	95002170
Filing Date:	10-Sep-2012
Title of Invention:	POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM
First Named Inventor/Applicant Name:	7897080
Filer:	Michael I. Chakansky
Attorney Docket Number:	117744-00023

Filed as Large Entity

inter partes reexam Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Filing Appeal Brief Inter Partes Reexam	1404	1	2000	2000
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**2000**

Electronic Acknowledgement Receipt

EFS ID:	18734581
Application Number:	95002170
International Application Number:	
Confirmation Number:	6418
Title of Invention:	POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM
First Named Inventor/Applicant Name:	7897080
Customer Number:	23869
Filer:	Michael I. Chakansky
Filer Authorized By:	
Attorney Docket Number:	117744-00023
Receipt Date:	10-APR-2014
Filing Date:	10-SEP-2012
Time Stamp:	21:13:47
Application Type:	inter partes reexam

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$2000
RAM confirmation Number	7010
Deposit Account	
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if app.)

1	Respondent Brief - Owner	PORESPONDENTBRIEF.pdf	2715868 d3588755f1e73187176f64eaaac2e1c877714b2b	no	86
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30166 c70c3d4add45ac64e9931aae07c6b480ee291de7	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	2746034	

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re *Inter Partes* Reexamination of:	)	
	)	
US Patent No. 7,897,080	)	Confirmation No.: 6418
	)	
Named Inventor: Robert K. Yang *et al.*	)	Group Art Unit: 3991
	)	
Control No.: 95/002,170	)	Examiner: Alan D. Diamond
	)	
Request Filed: September 10, 2012	)	M&E Docket: 117744-00023
	)	
Title: POLYETHYLENE OXIDE-BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM	)	H&B Docket: 1199-26 RCE/CON/REX

Mail Stop *Inter Partes* Reexam
Attn: Central Reexamination Unit
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL OF PAYMENT OF APPEAL BRIEF FEE (37 C.F.R. § 41.20(b)(2)(ii))

Requester hereby submits payment of the fee for filing the brief in support of the appeal of the above-identified *inter partes* reexamination on March 10, 2014. If additional fees are believed to be due, please charge our Deposit Account No. 50-4876, under Order No. 117744-00023 from which the undersigned is authorized to draw.

Respectfully submitted,
McCarter & English LLP

Dated: April 1, 2014

By: /Danielle L. Herritt/
Danielle L. Herritt Reg. 43,670
Kia Freeman Reg. 47,577
Direct Dial: 617-449-6513
Attorneys for Requester, BioDelivery Sciences International, Inc.

Electronic Patent Application Fee Transmittal

Application Number:	95002170
Filing Date:	10-Sep-2012
Title of Invention:	POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM
First Named Inventor/Applicant Name:	7897080
Filer:	Danielle L. Herritt/Maureen Tierney
Attorney Docket Number:	117744-00023

Filed as Large Entity

inter partes reexam Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
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Petition:				
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Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**2000**

Electronic Acknowledgement Receipt

EFS ID:	18639818
Application Number:	95002170
International Application Number:	
Confirmation Number:	6418
Title of Invention:	POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM
First Named Inventor/Applicant Name:	7897080
Customer Number:	23869
Filer:	Danielle L. Herritt/Maureen Tierney
Filer Authorized By:	Danielle L. Herritt
Attorney Docket Number:	117744-00023
Receipt Date:	01-APR-2014
Filing Date:	10-SEP-2012
Time Stamp:	14:16:26
Application Type:	inter partes reexam

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$2000
RAM confirmation Number	493
Deposit Account	504876
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	080AppealBriefFeeTransmittal2014APR01.PDF	6764 9b27ec0e471ac28d6592fe3d75ffee9457b1724a	no	1
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30023 e24dc34b74d04389b720a7f133c9593e5364be7a	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	36787		

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<u>New Applications Under 35 U.S.C. 111</u>
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

<u>National Stage of an International Application under 35 U.S.C. 371</u>
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

<u>New International Application Filed with the USPTO as a Receiving Office</u>
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of the foregoing Transmittal of Payment of Appeal Brief Fee was served on April 1, 2014, by first class mail, directed to the patent owner at the correspondence address of record for the subject patent at the following address:

Daniel A. Scola, Jr.

HOFFMANN & BARON, LLP

6900 JERICHO TURNPIKE

SYOSSET, NY 11791,

By: /Danielle L. Herritt/
Danielle L. Herritt
Registration No. 43,670
Attorney for Requester

Electronic Acknowledgement Receipt

EFS ID:	18641248
Application Number:	95002170
International Application Number:	
Confirmation Number:	6418
Title of Invention:	POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM
First Named Inventor/Applicant Name:	7897080
Customer Number:	23869
Filer:	Danielle L. Herritt/Maureen Tierney
Filer Authorized By:	Danielle L. Herritt
Attorney Docket Number:	117744-00023
Receipt Date:	01-APR-2014
Filing Date:	10-SEP-2012
Time Stamp:	15:19:17
Application Type:	inter partes reexam

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Reexam Certificate of Service	080AppealBriefFeePaymentCOS.PDF	4946 770e72161972c089589f9b6f5c9f504a4970a2ca	no	1

Warnings:	
Information:	

Total Files Size (in bytes):	4946

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New Applications Under 35 U.S.C. 111

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EXHIBIT 1

US007897080B2

(12) **United States Patent**
Yang et al.

(10) **Patent No.: US 7,897,080 B2**
(45) **Date of Patent: *Mar. 1, 2011**

(54) **POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM**

(75) Inventors: **Robert K. Yang**, Flushing, NY (US); **Richard C. Fuisz**, McLean, VA (US); **Gary L. Myers**, Kingsport, TN (US); **Joseph M. Fuisz**, Washington, DC (US)

(73) Assignee: **MonoSol Rx, LLC**, Portage, IN (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **12/614,928**

(22) Filed: **Nov. 9, 2009**

(65) **Prior Publication Data**

US 2010/0092545 A1 Apr. 15, 2010

Related U.S. Application Data

(63) Continuation of application No. 10/856,176, filed on May 28, 2004, now Pat. No. 7,666,337, and a continuation-in-part of application No. 10/768,809, filed on Jan. 30, 2004, now Pat. No. 7,357,891, and a continuation-in-part of application No. PCT/US02/32575, filed on Oct. 11, 2002, and a continuation-in-part of application No. PCT/US02/32594, filed on Oct. 11, 2002, and a continuation-in-part of application No. PCT/US02/32542, filed on Oct. 11, 2002.

(60) Provisional application No. 60/473,902, filed on May 28, 2003, provisional application No. 60/443,741, filed on Jan. 30, 2003, provisional application No. 60/328,868, filed on Oct. 12, 2001, provisional application No. 60/386,937, filed on Jun. 7, 2002, provisional application No. 60/414,276, filed on Sep. 27, 2002, provisional application No. 60/371,940, filed on Apr. 11, 2002.

(51) **Int. Cl.**
B29C 39/14 (2006.01)

(52) **U.S. Cl.** **264/172.19**; 264/212; 264/217; 264/211.2; 264/234; 264/319; 264/344

(58) **Field of Classification Search** ..... None
See application file for complete search history.

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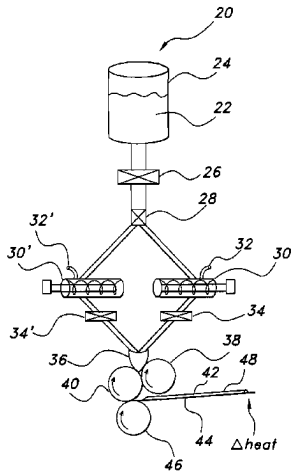
Primary Examiner—Edmund H. Lee
(74) *Attorney, Agent, or Firm*—Hoffmann & Baron, LLP

(57) **ABSTRACT**

The invention relates to the film products and methods of their preparation that demonstrate a non-self-aggregating uniform heterogeneity. Desirably, the films disintegrate in water and may be formed by a controlled drying process, or other process that maintains the required uniformity of the film. The films contain a polymer component, which includes polyethylene oxide optionally blended with hydrophilic cellulosic polymers. Desirably, the films also contain a pharmaceutical and/or cosmetic active agent with no more than a 10% variance of the active agent pharmaceutical and/or cosmetic active agent per unit area of the film.

299 Claims, 34 Drawing Sheets



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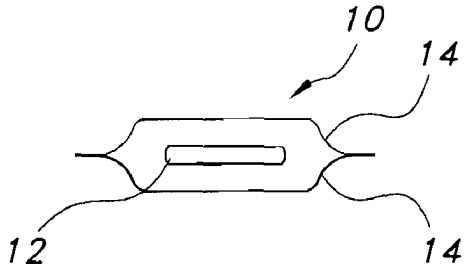


FIG. 1

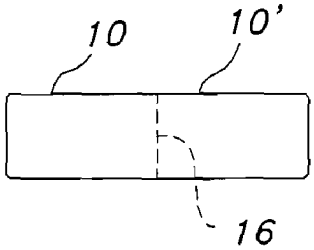


FIG. 2

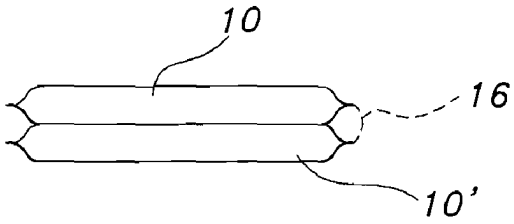
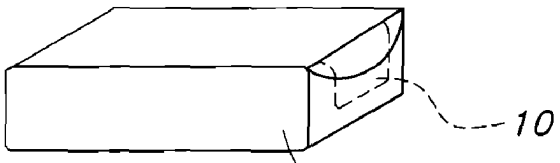


FIG. 3



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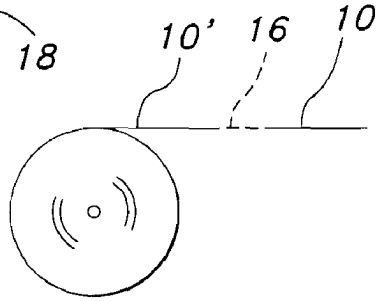

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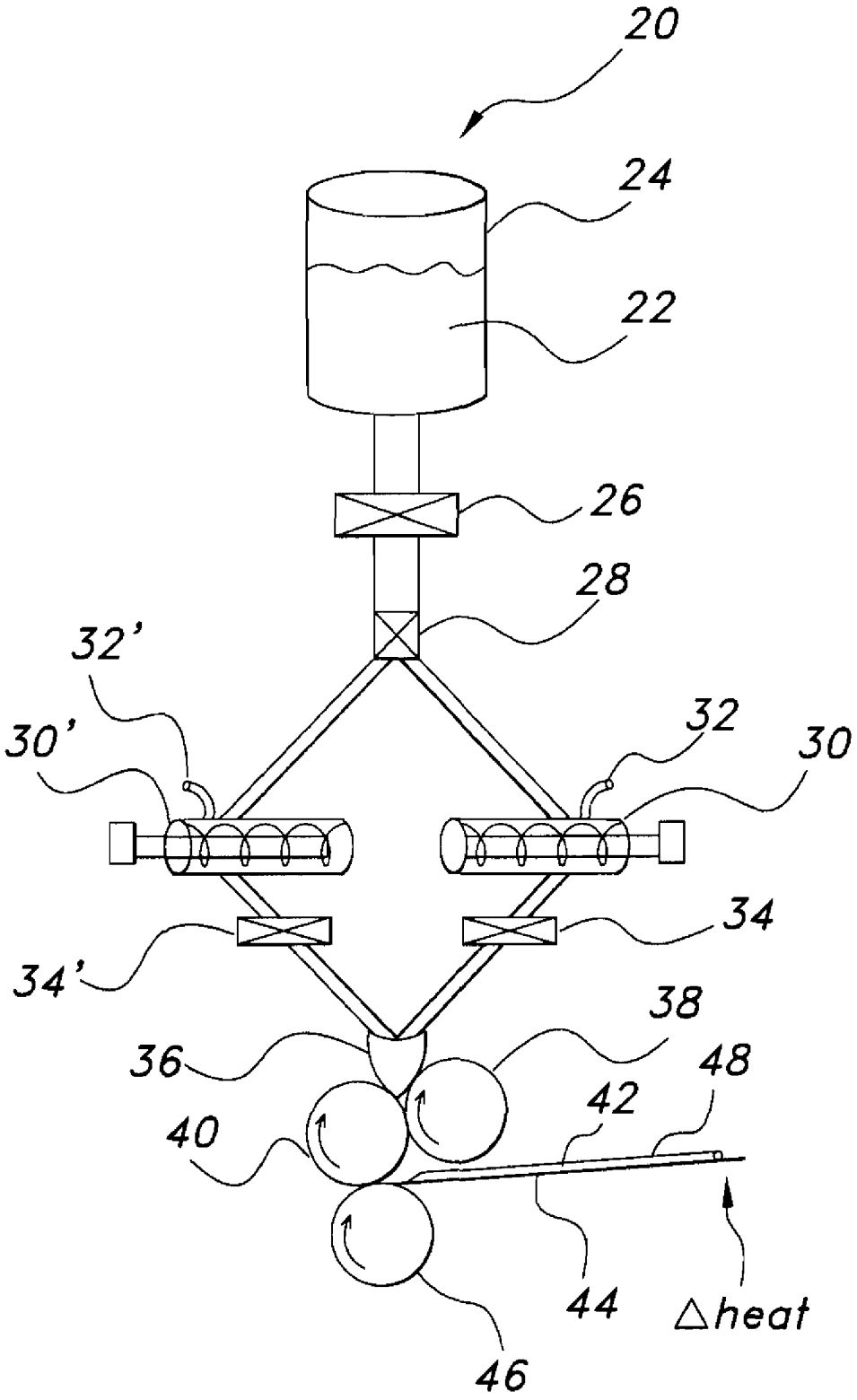

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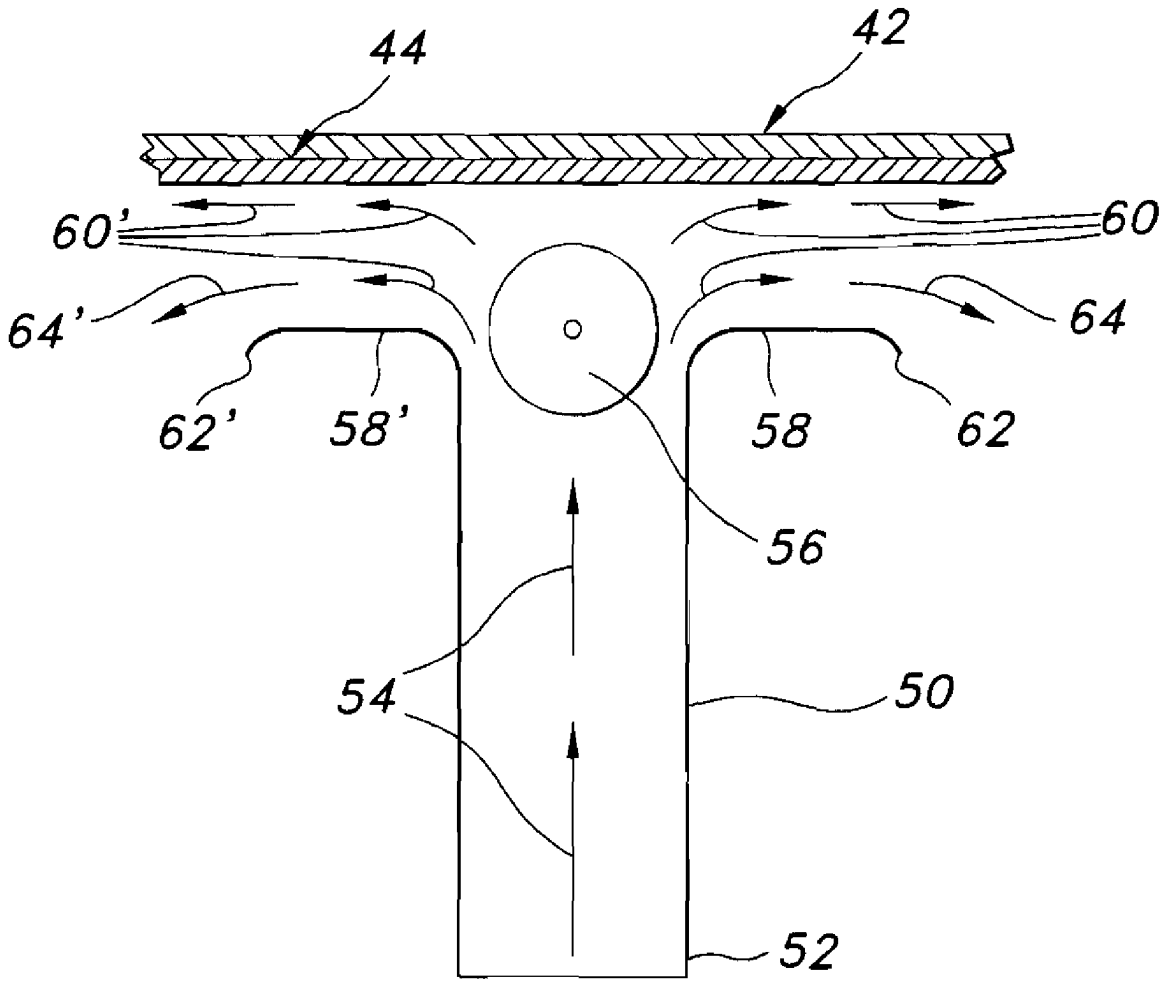

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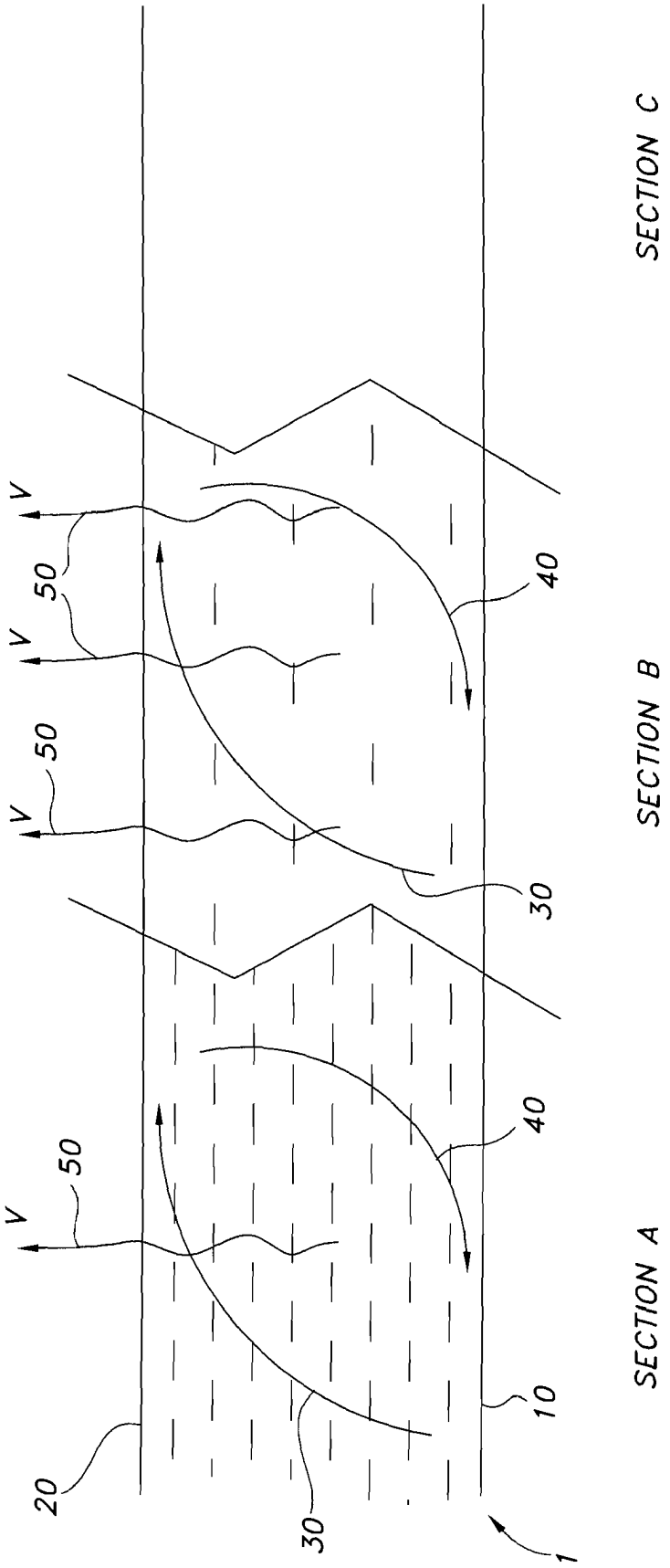

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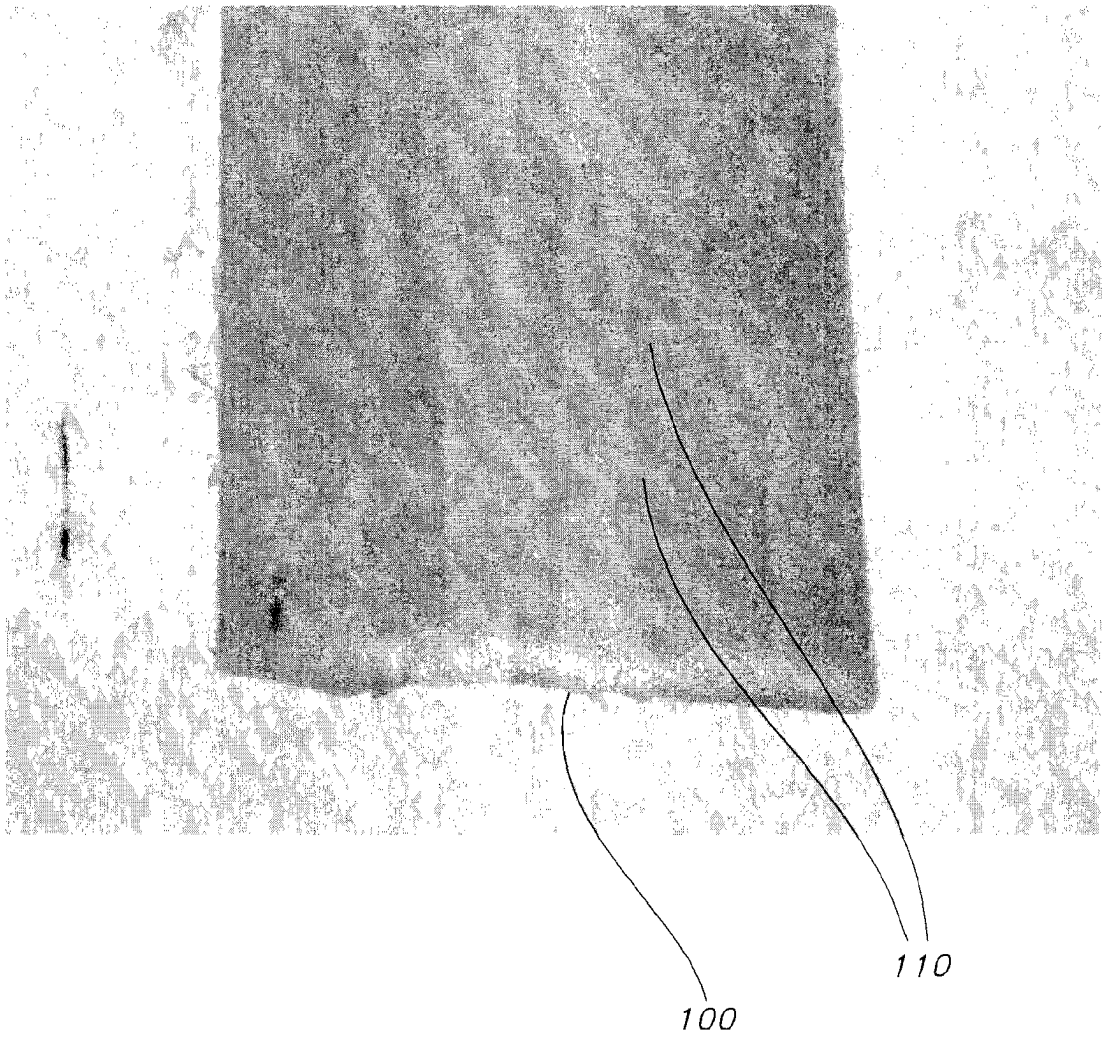

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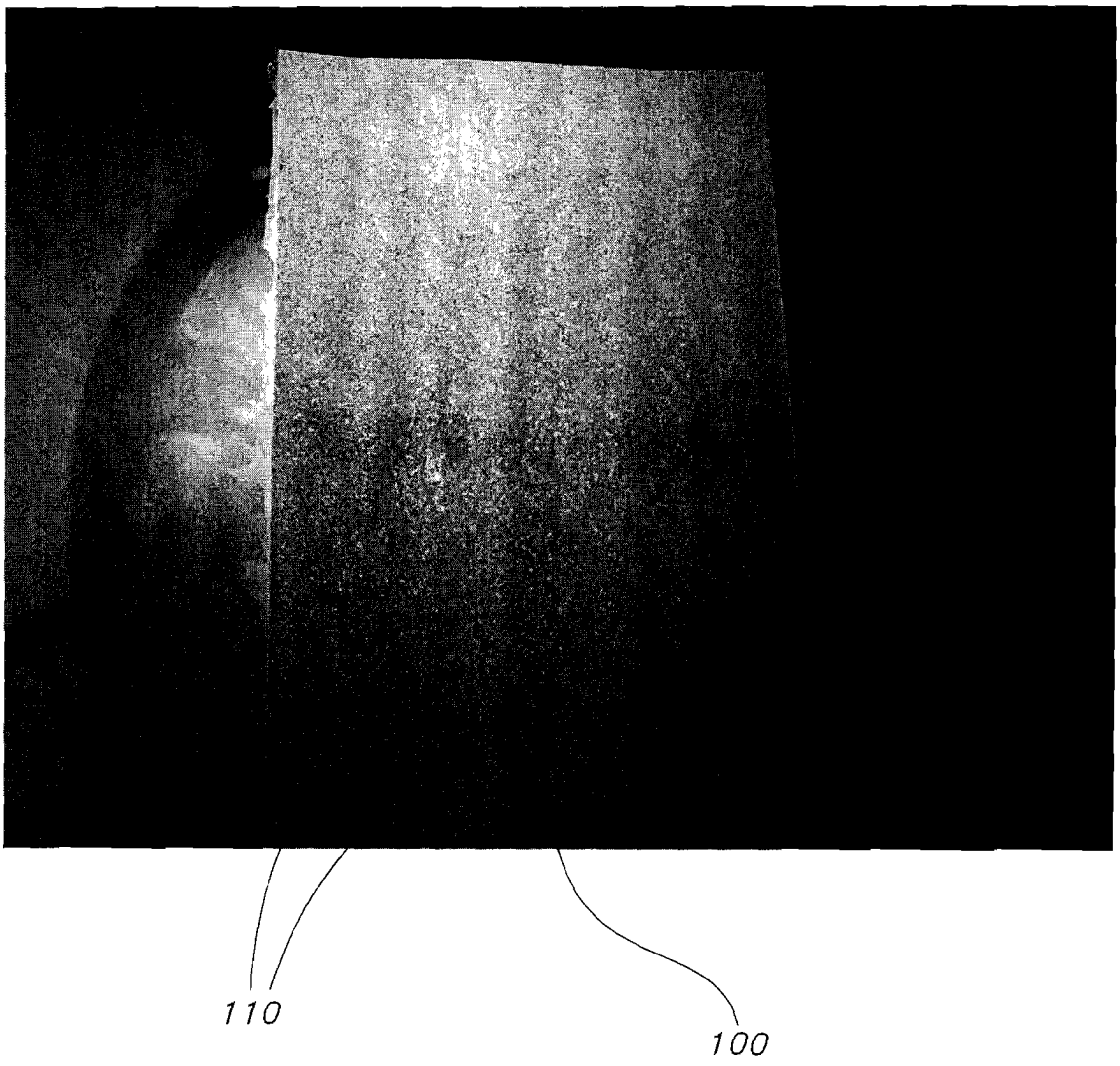
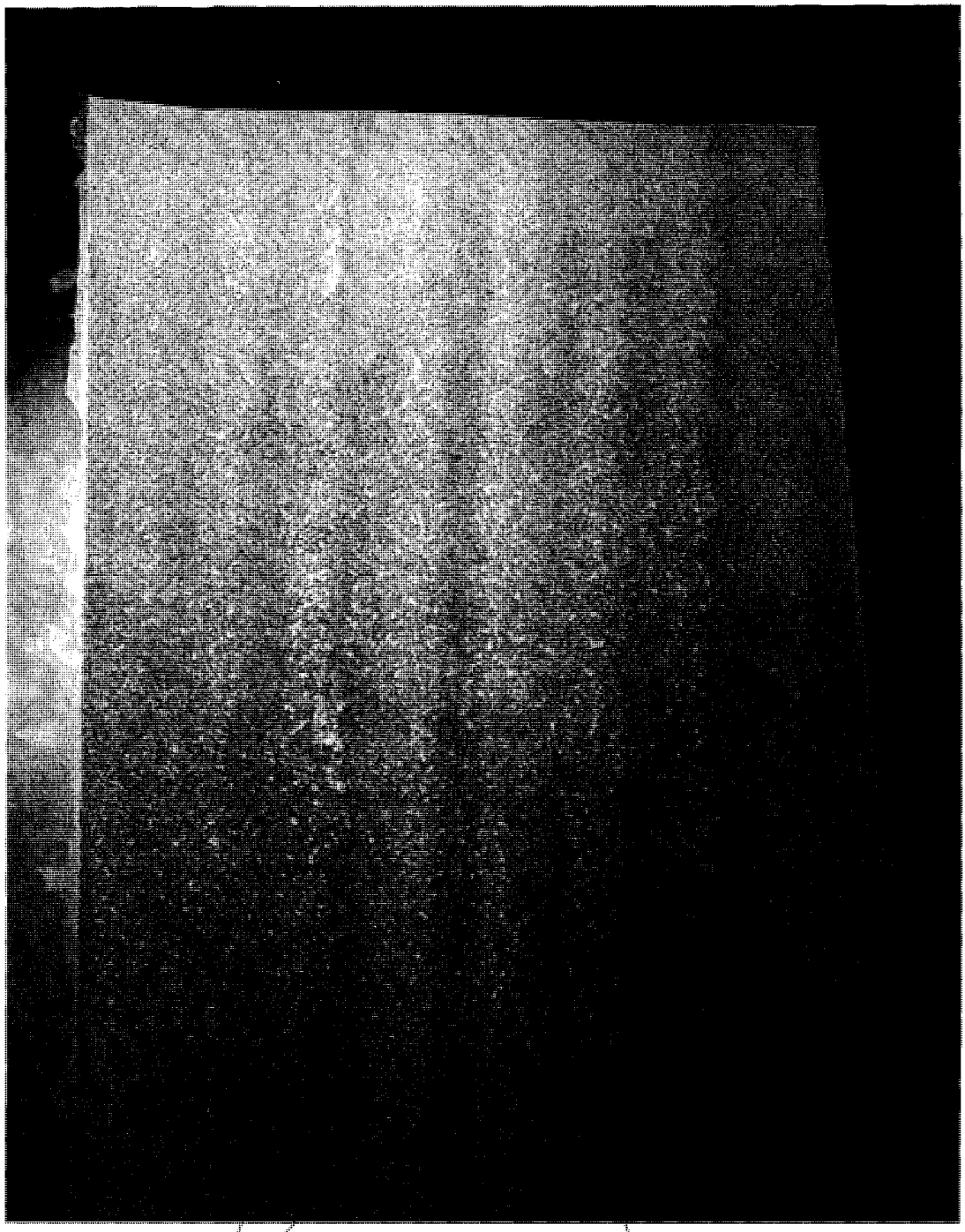


FIG. 10



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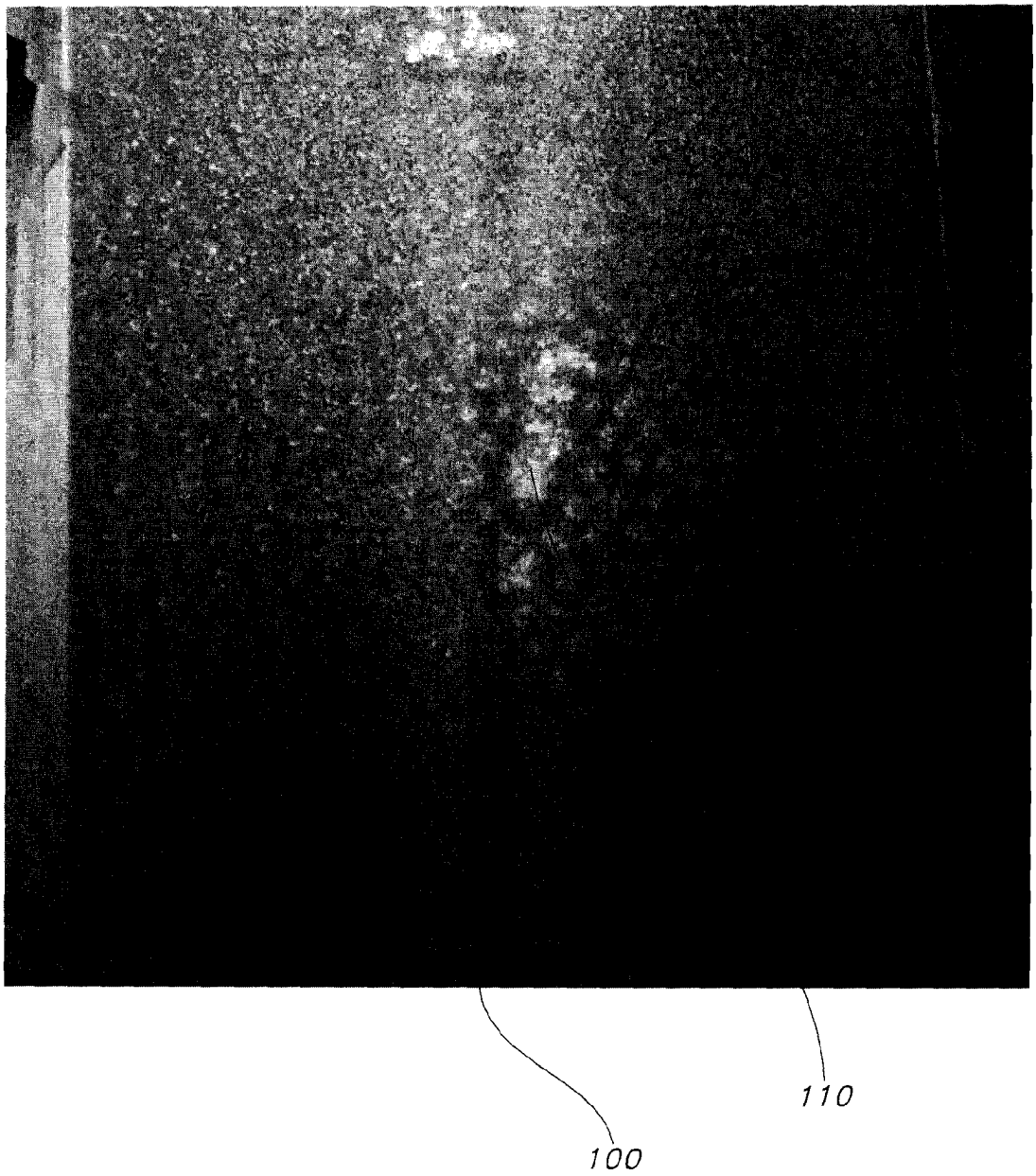

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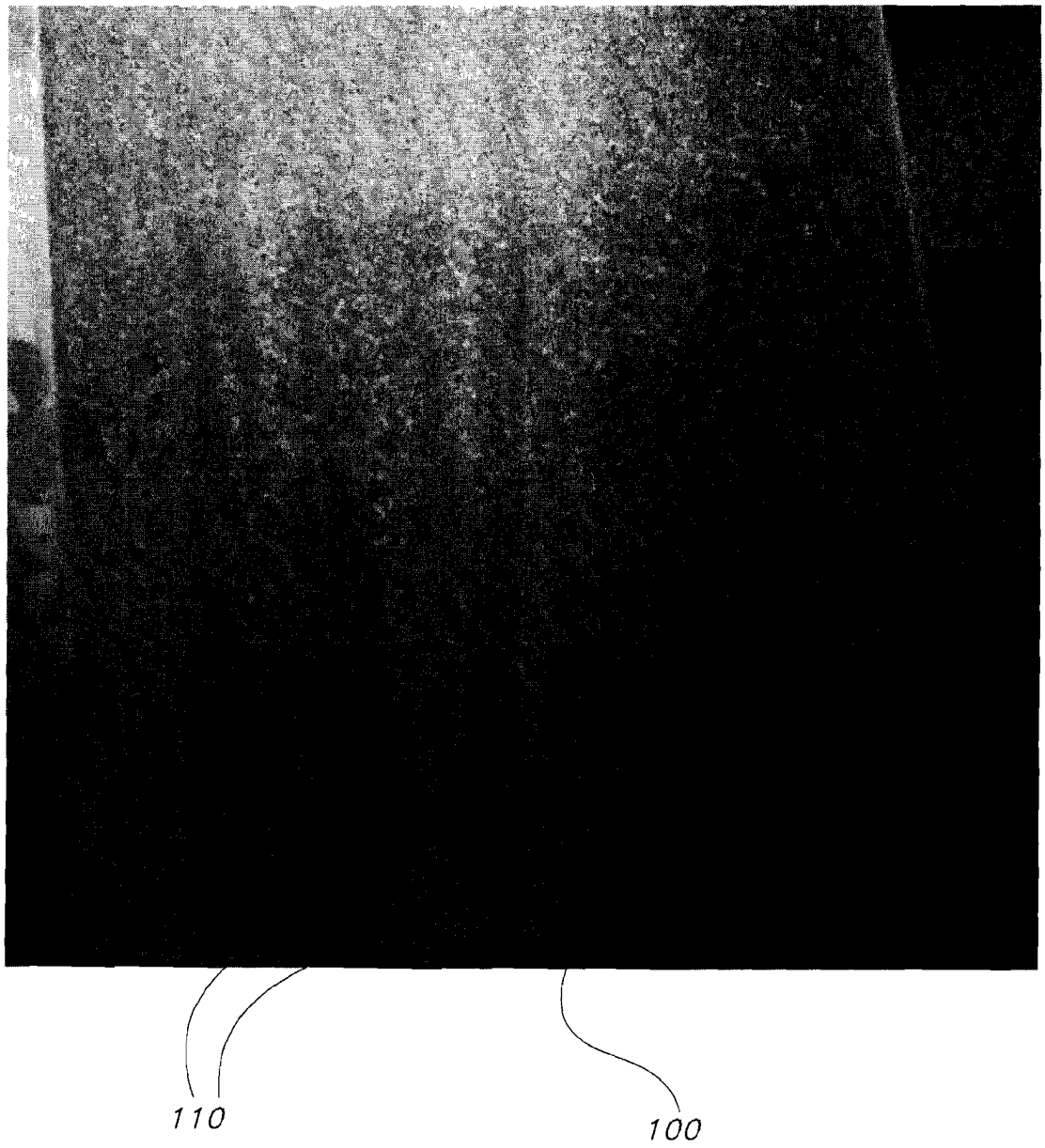
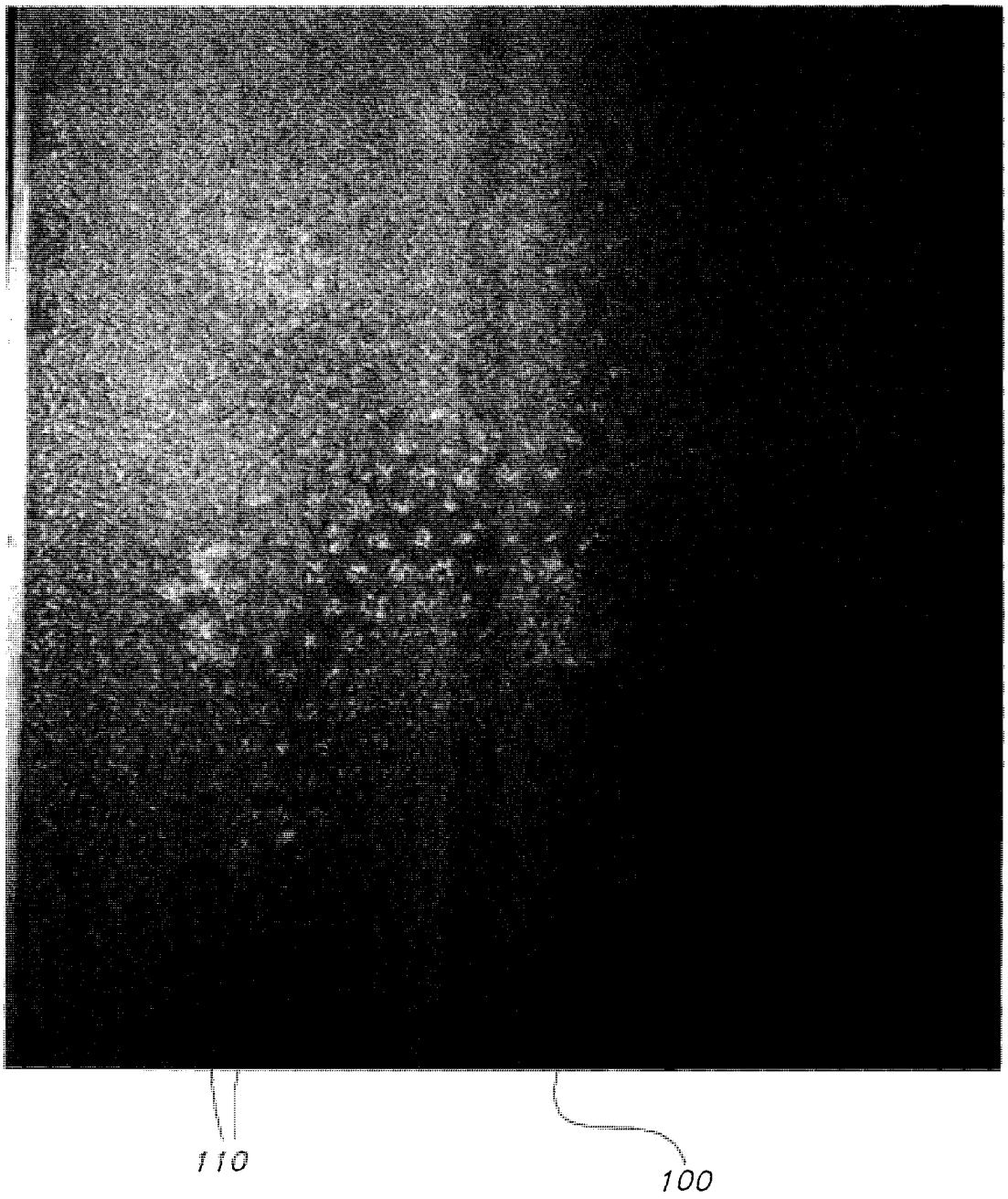


FIG. 13



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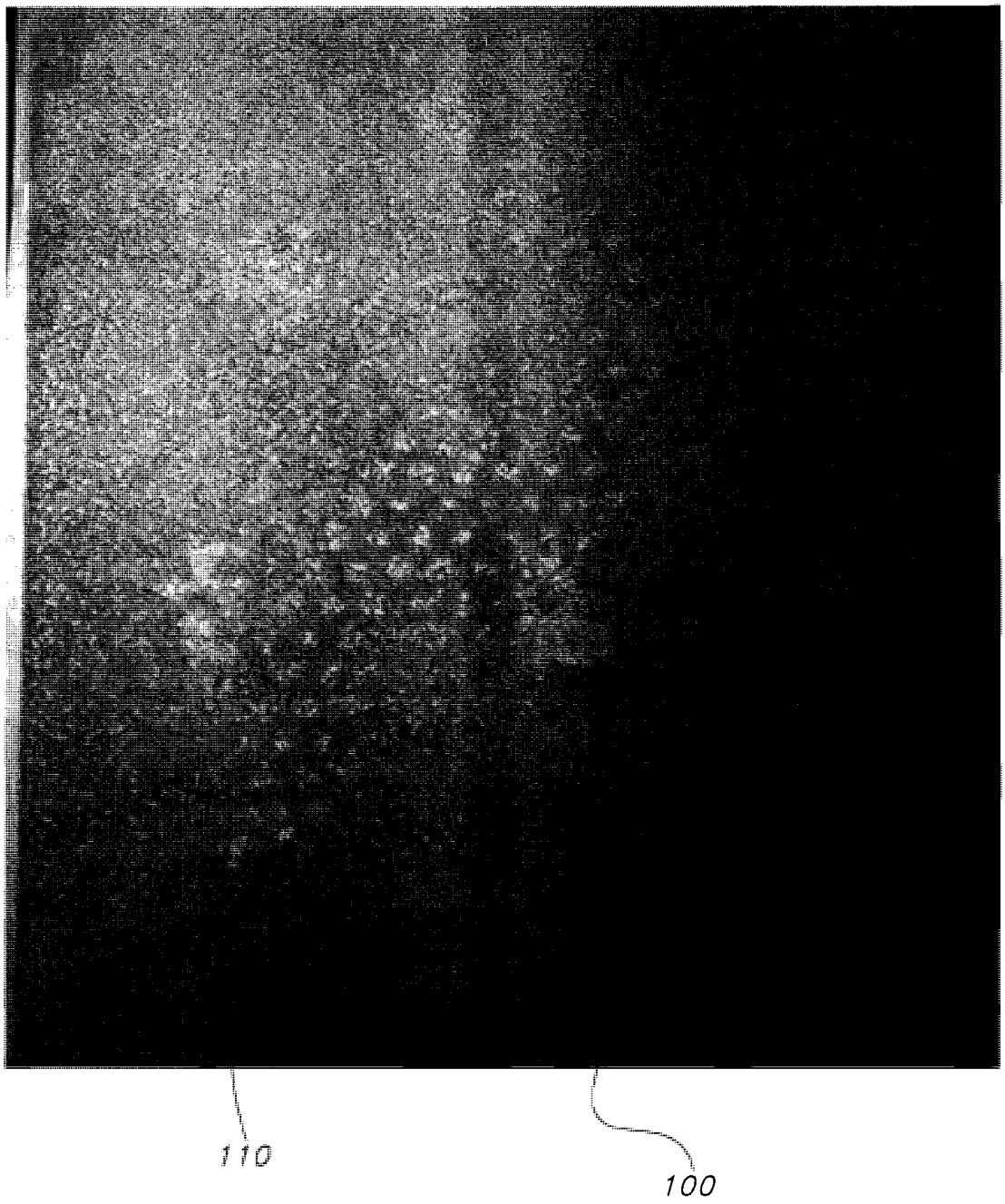

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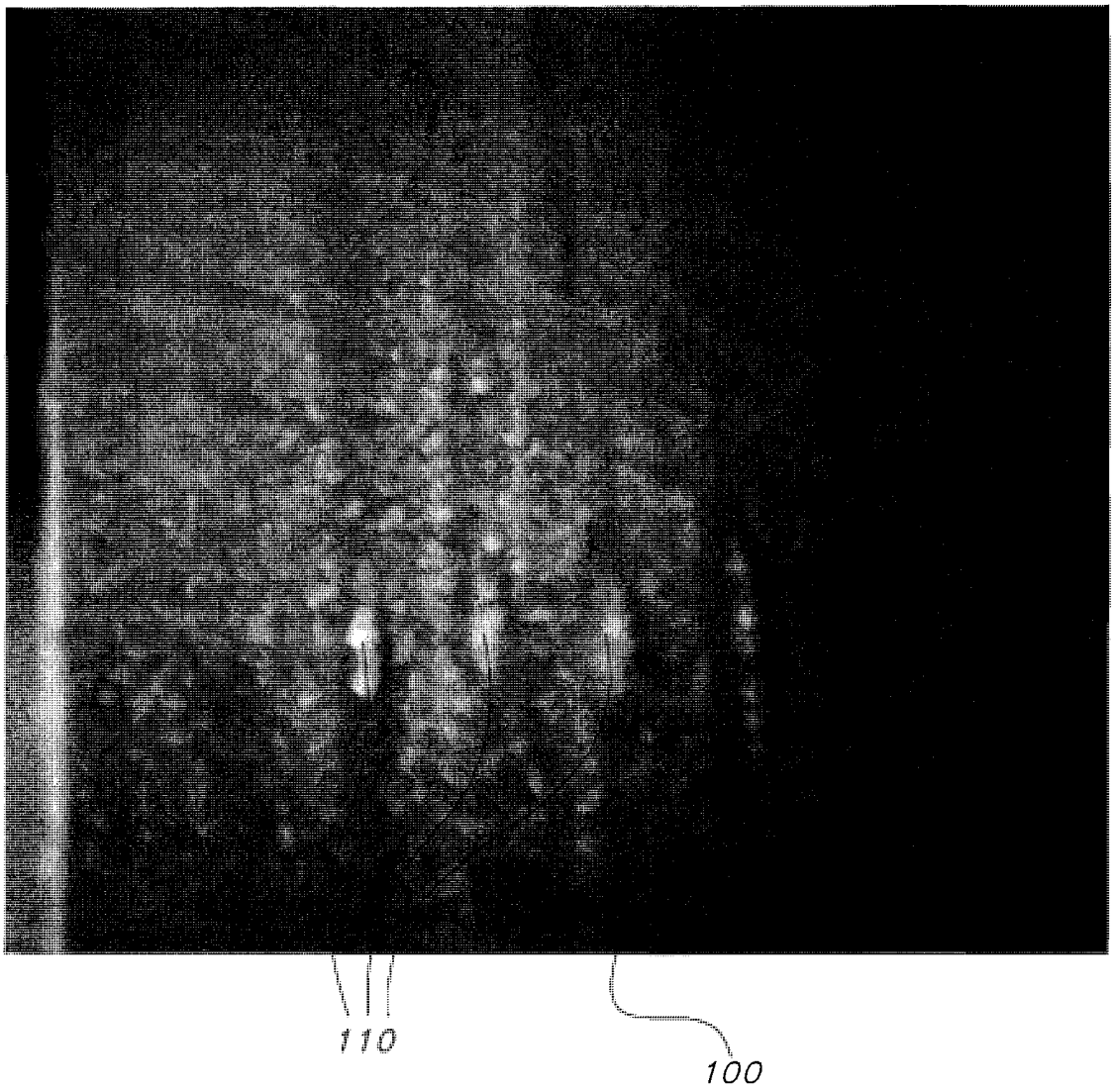

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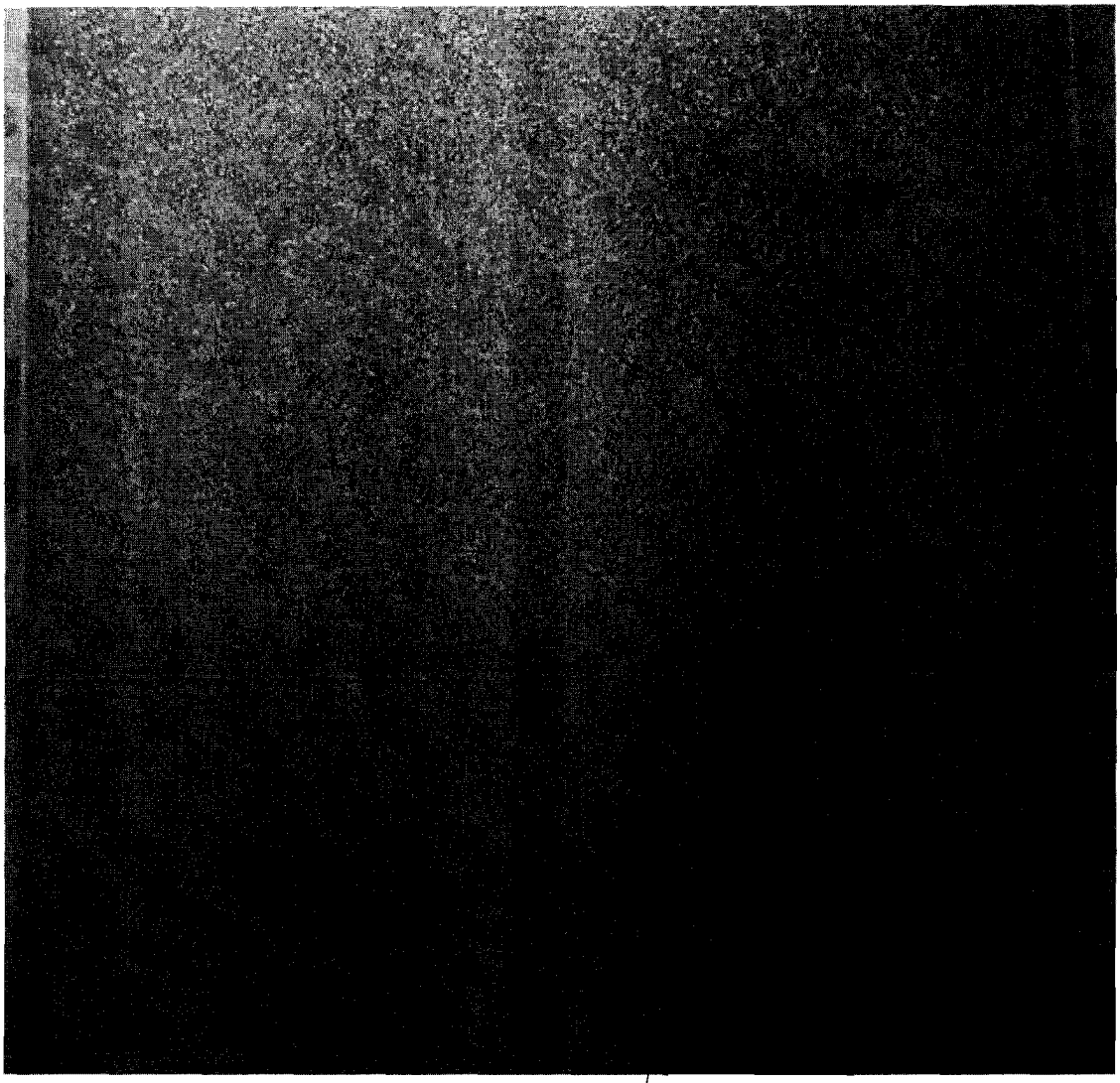

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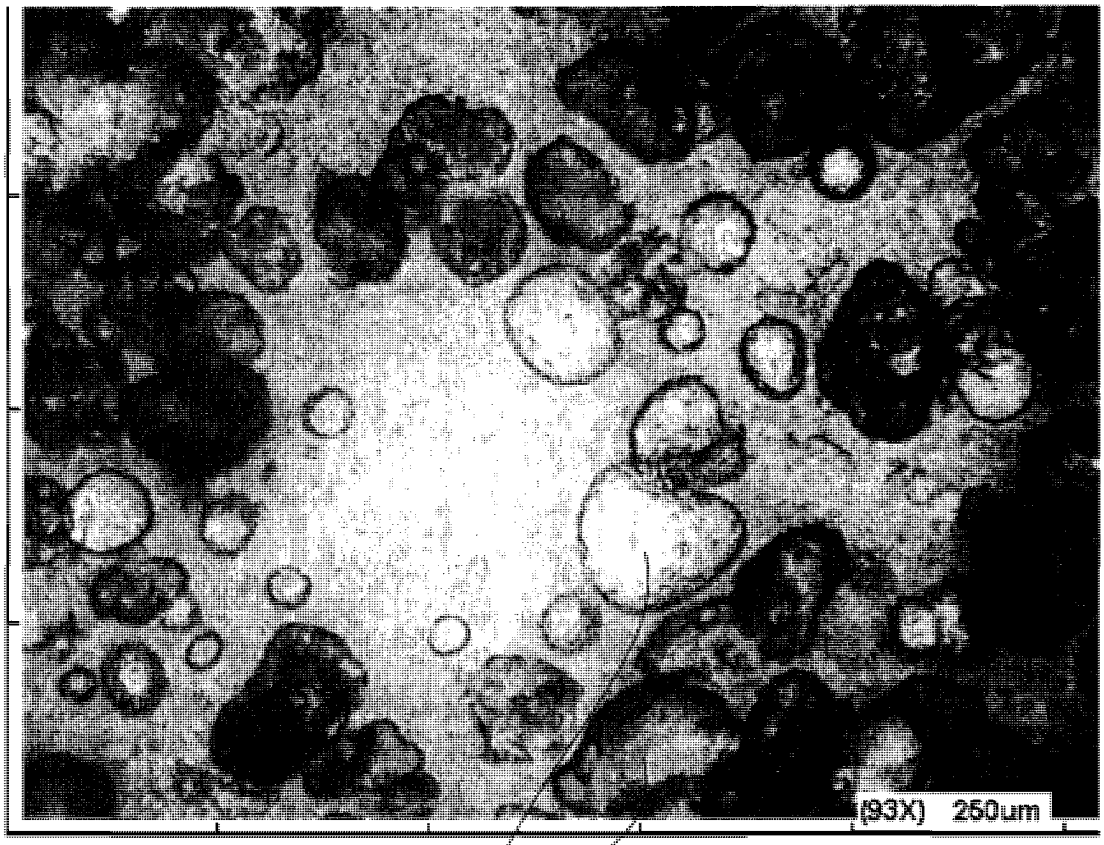

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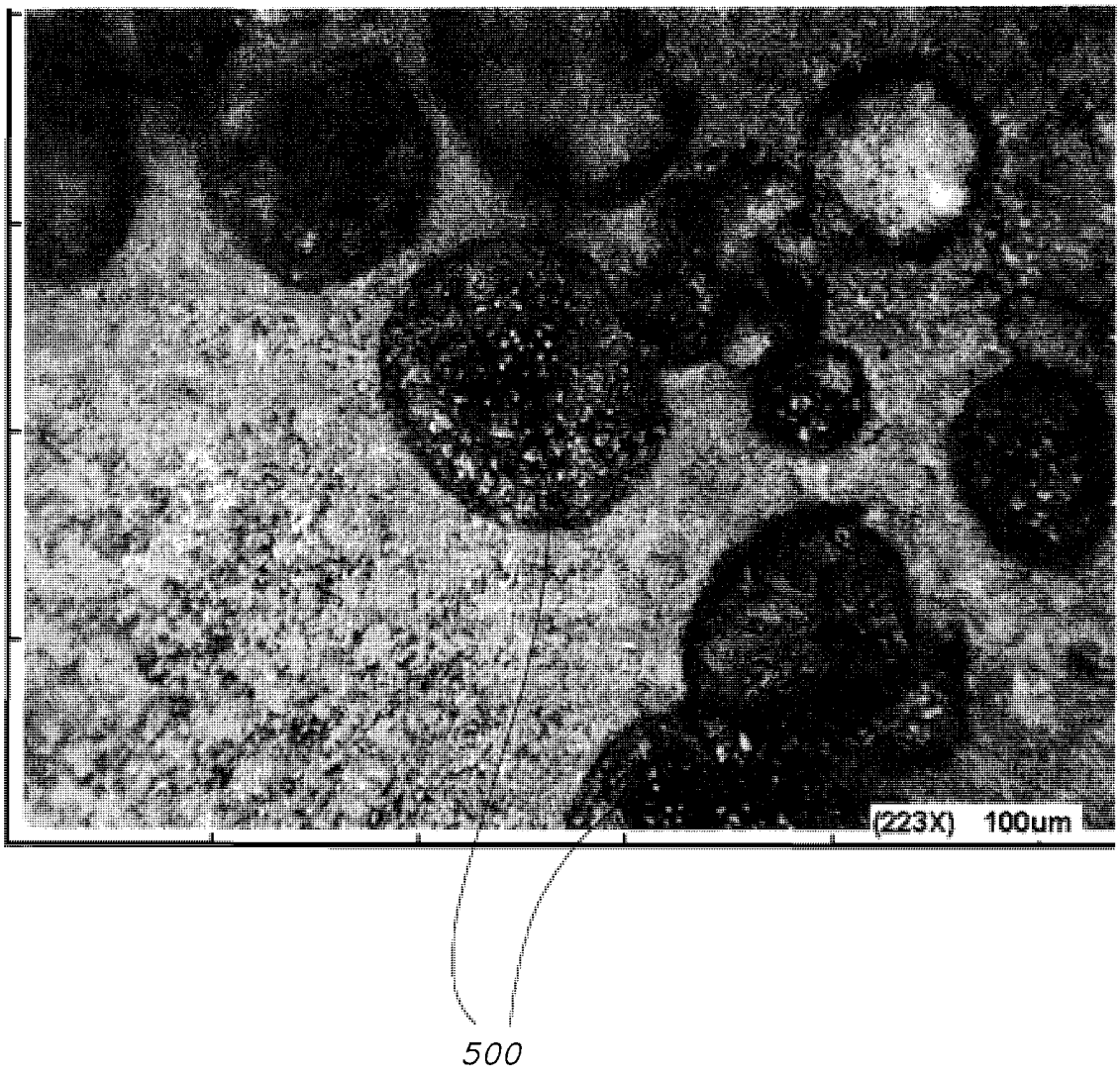

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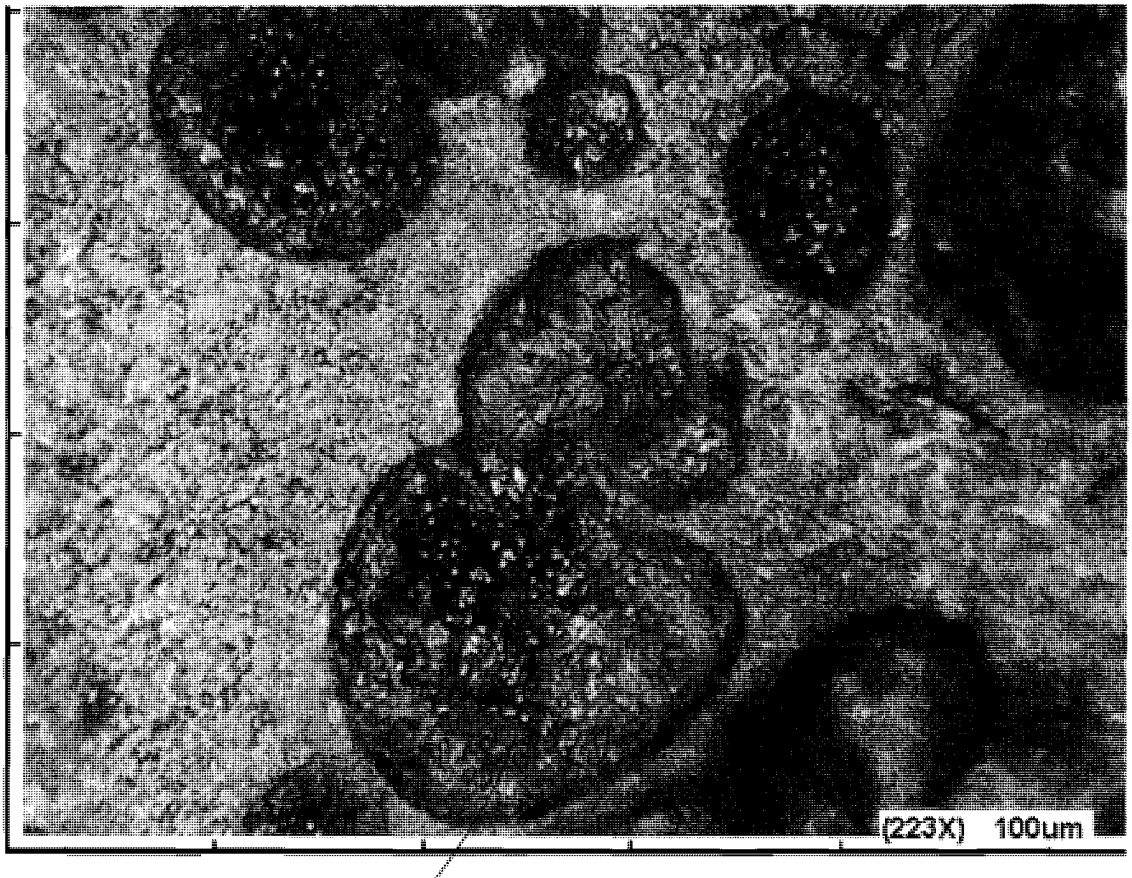

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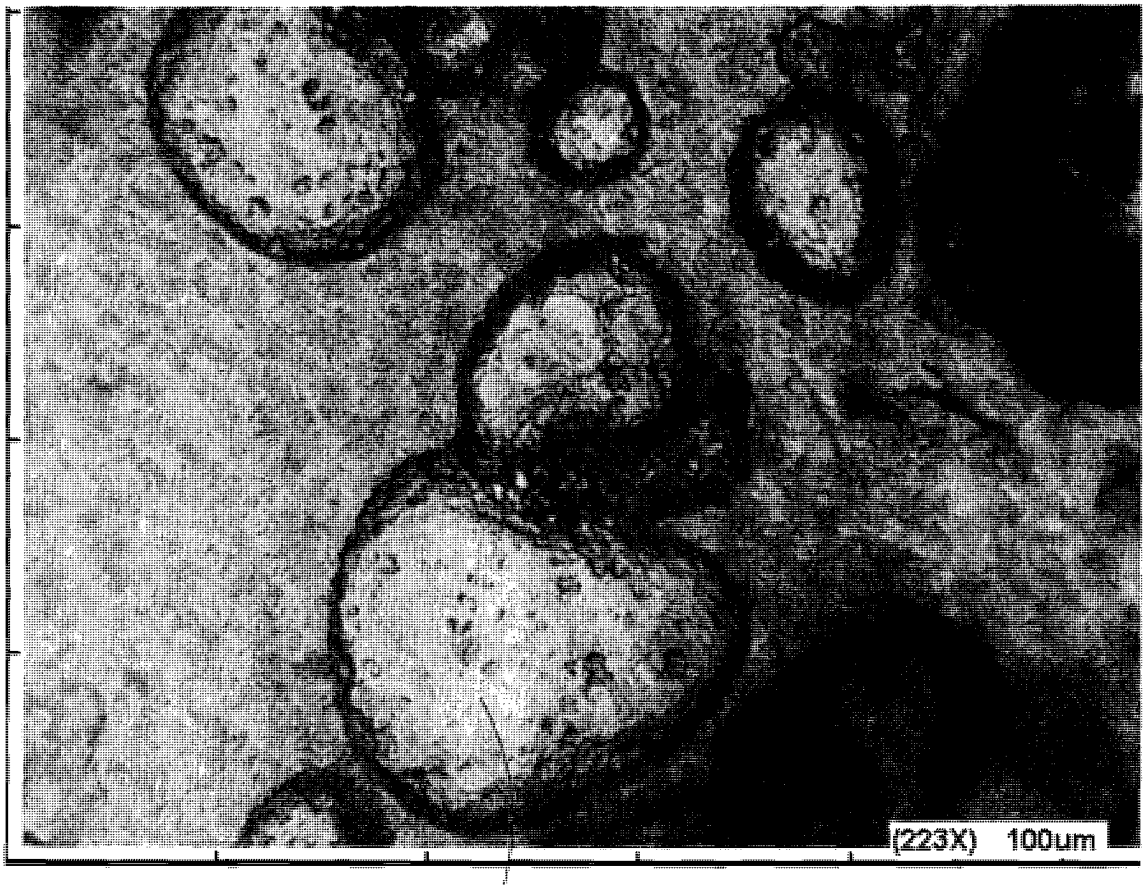

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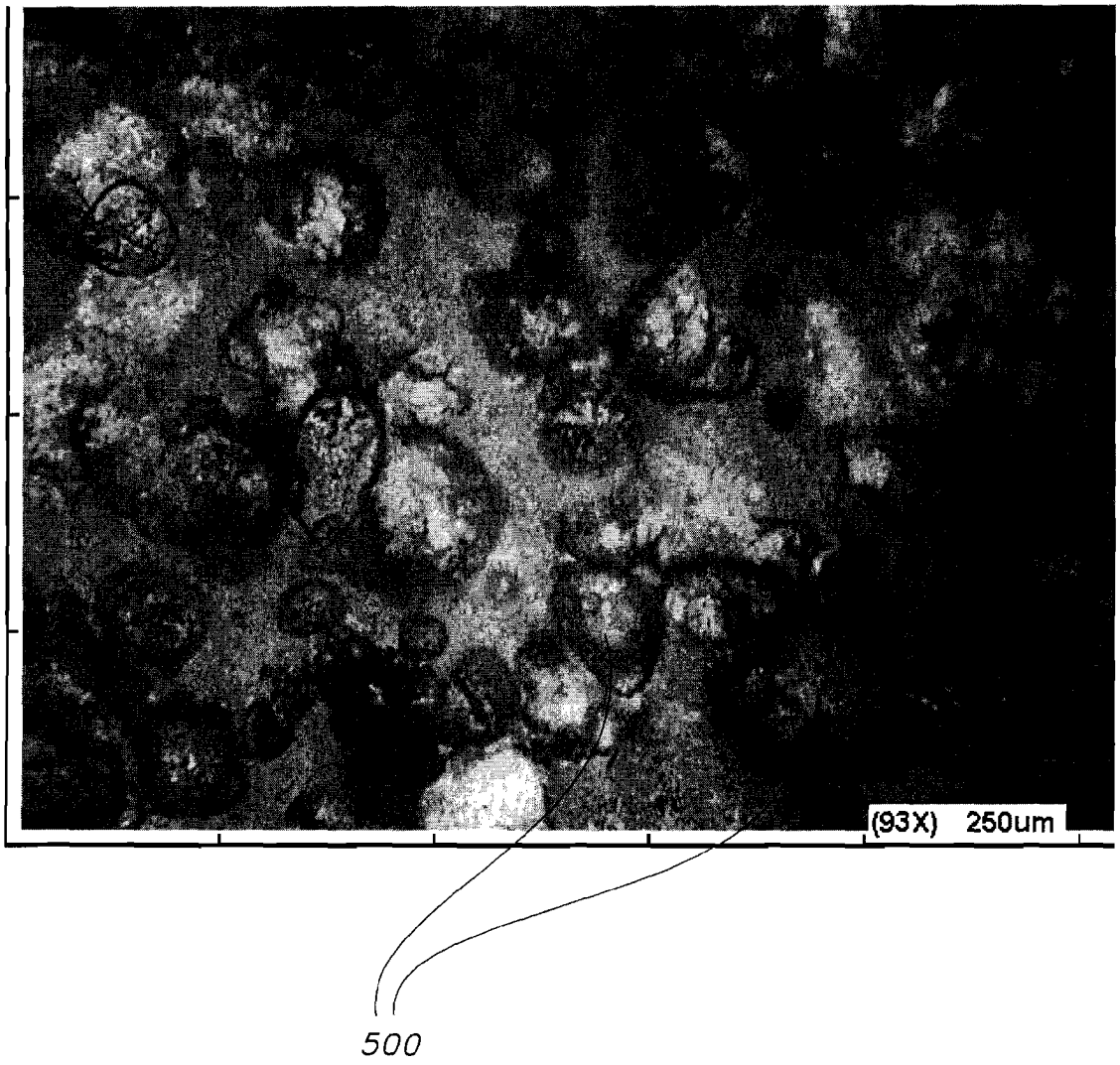
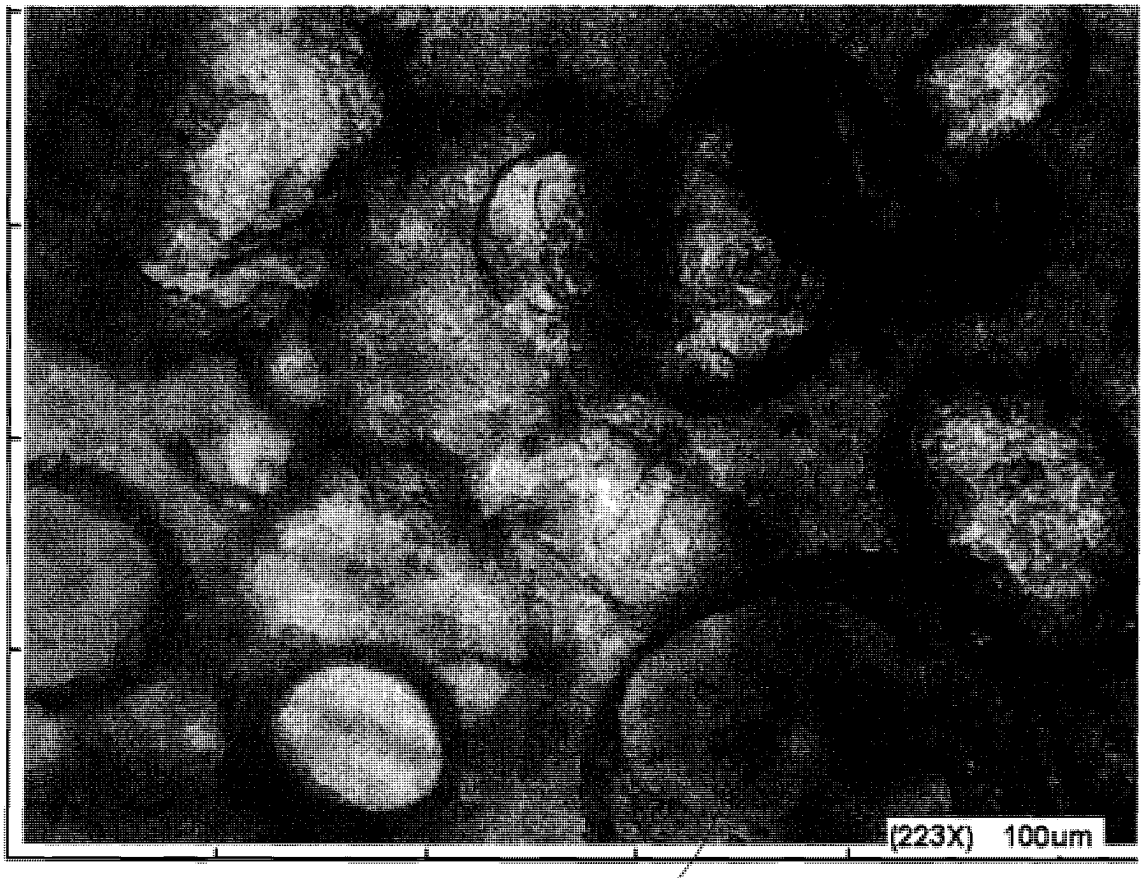


FIG. 22



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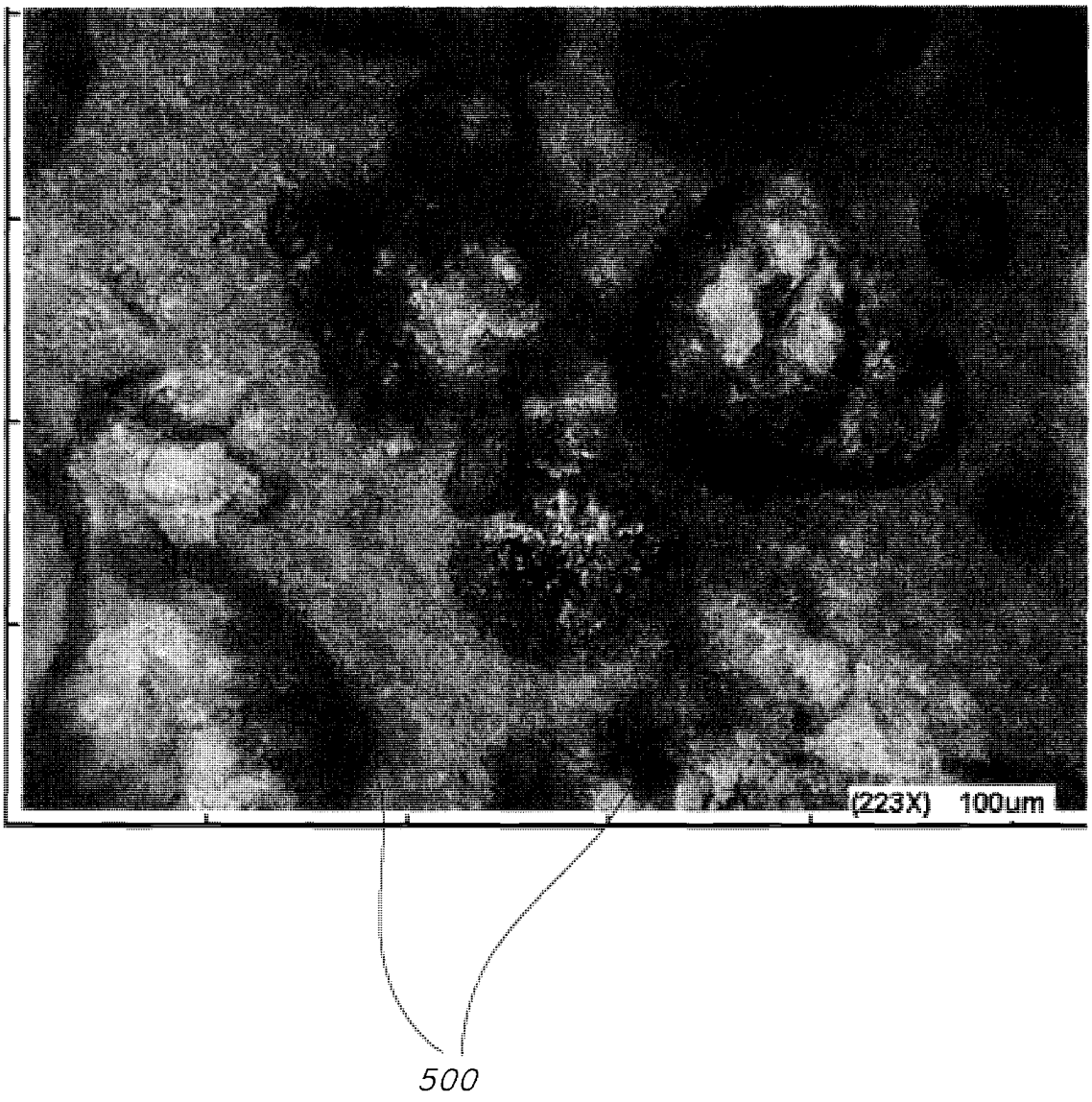

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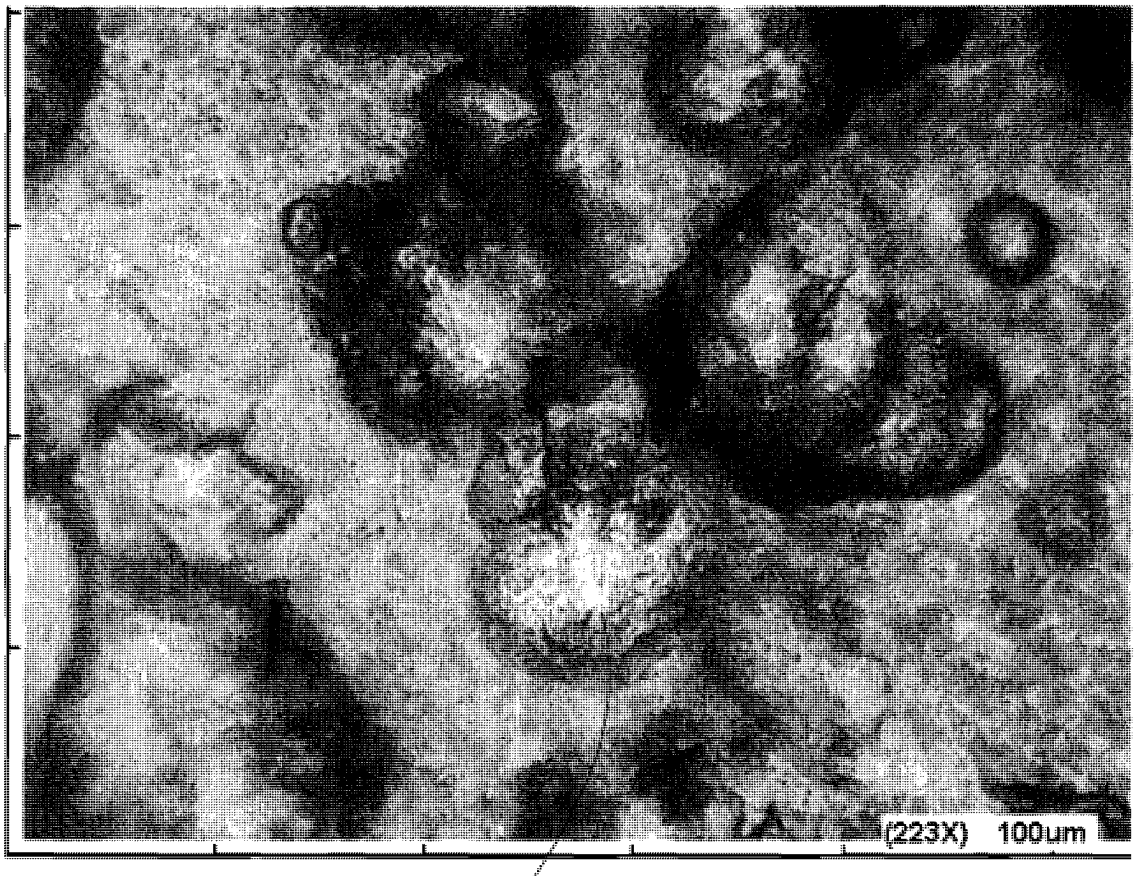

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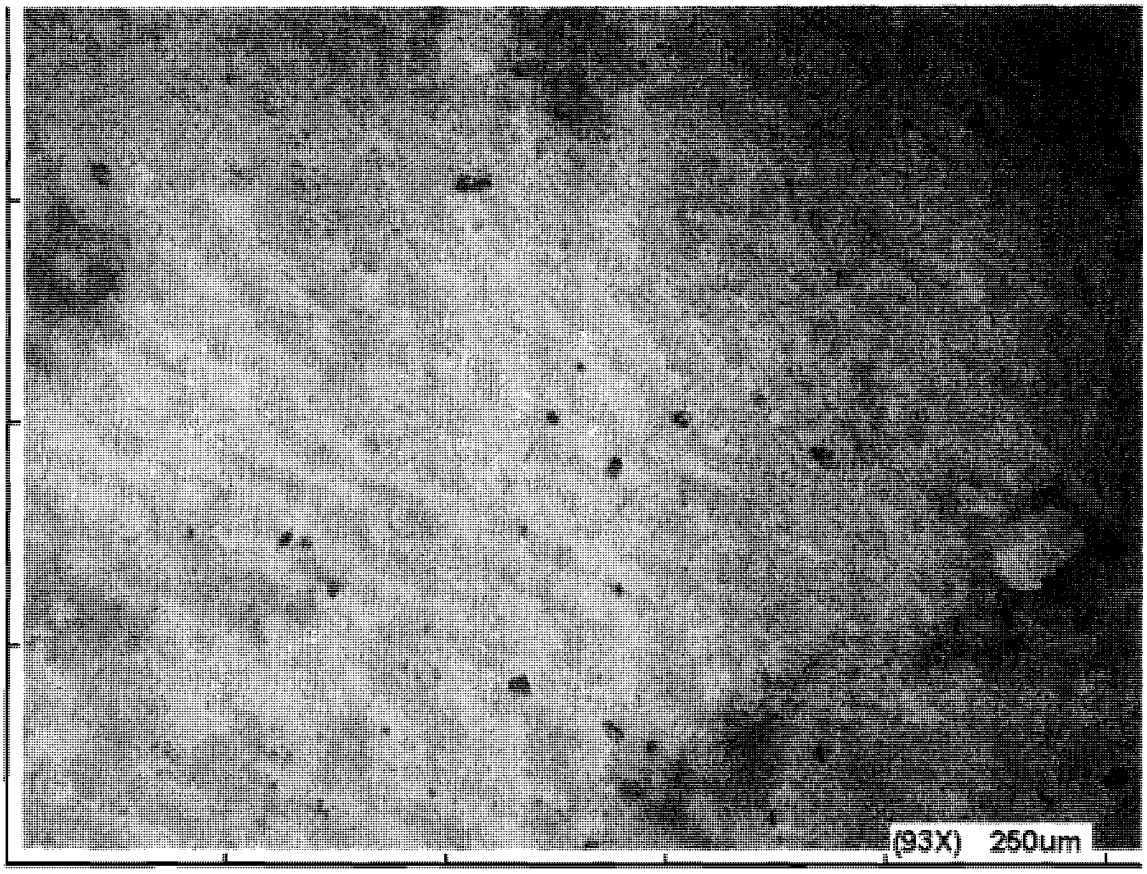


FIG. 26

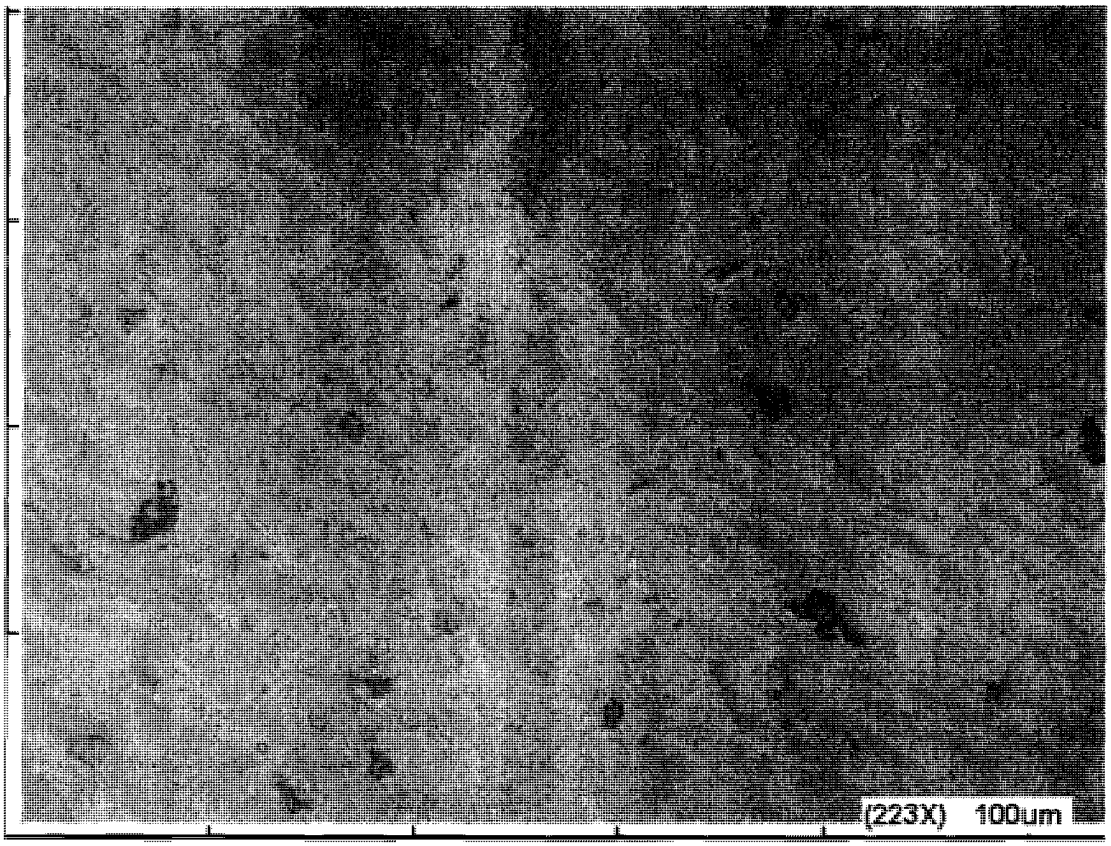
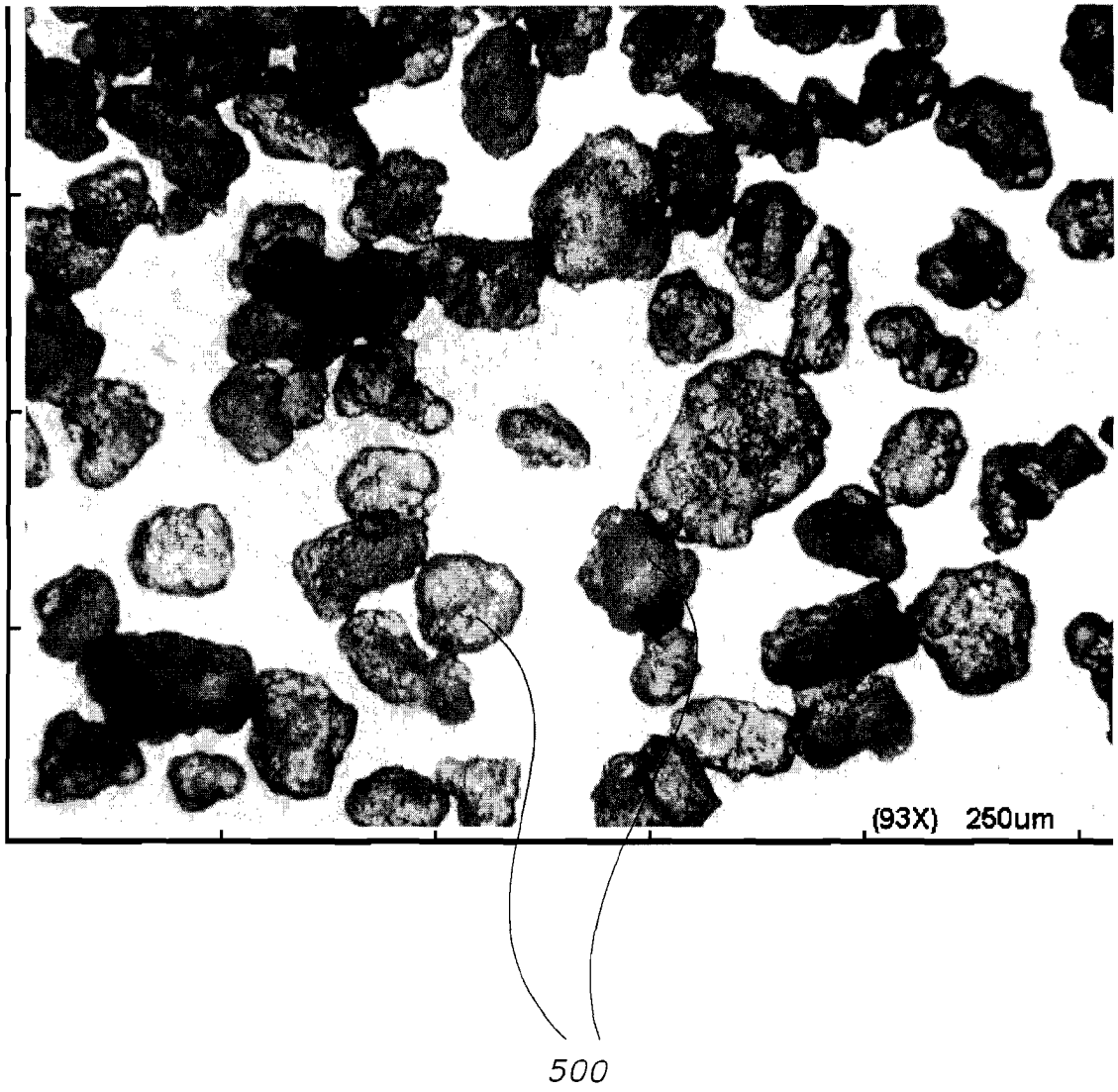


FIG. 27



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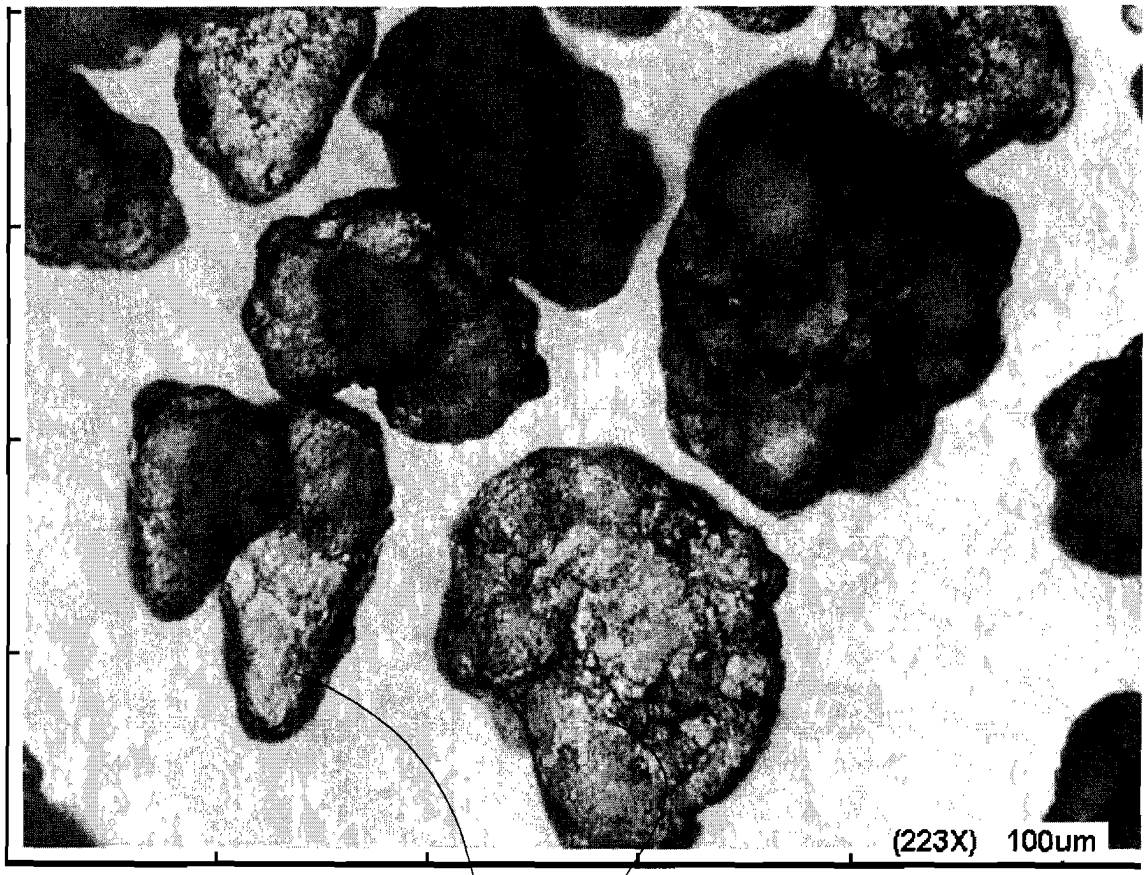

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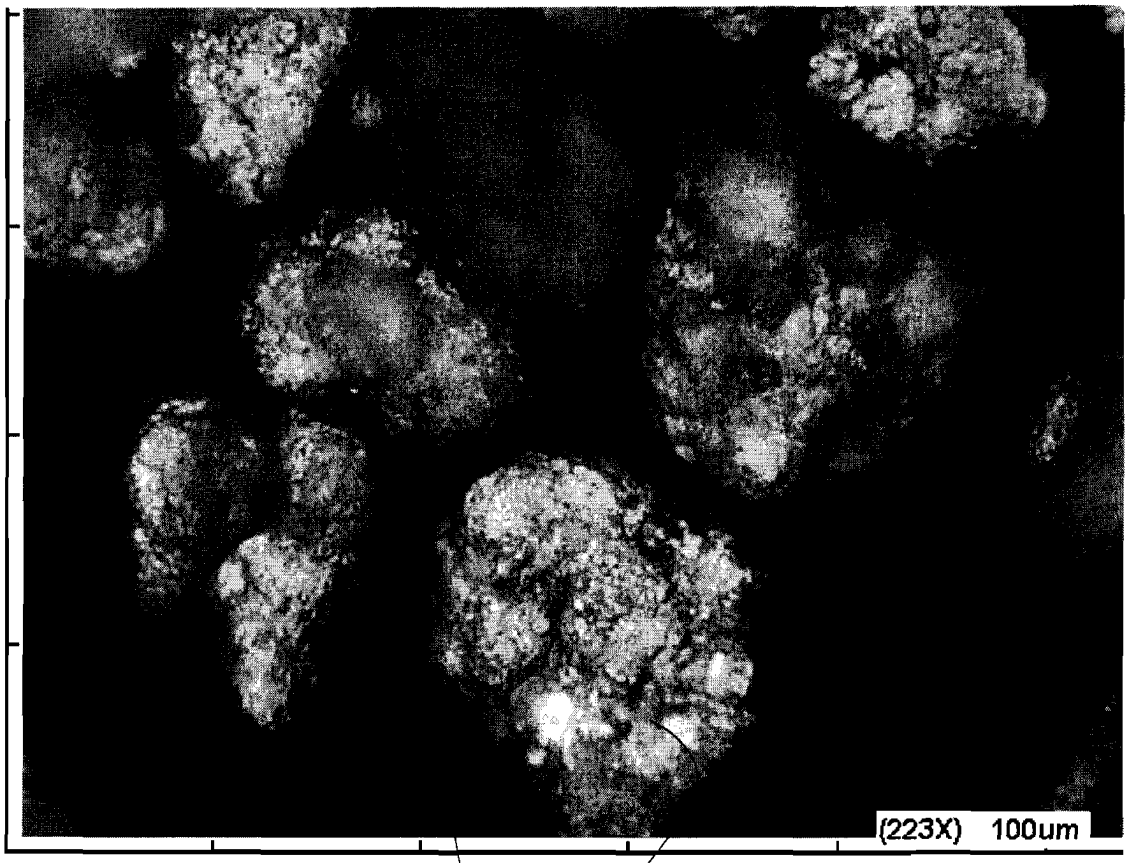

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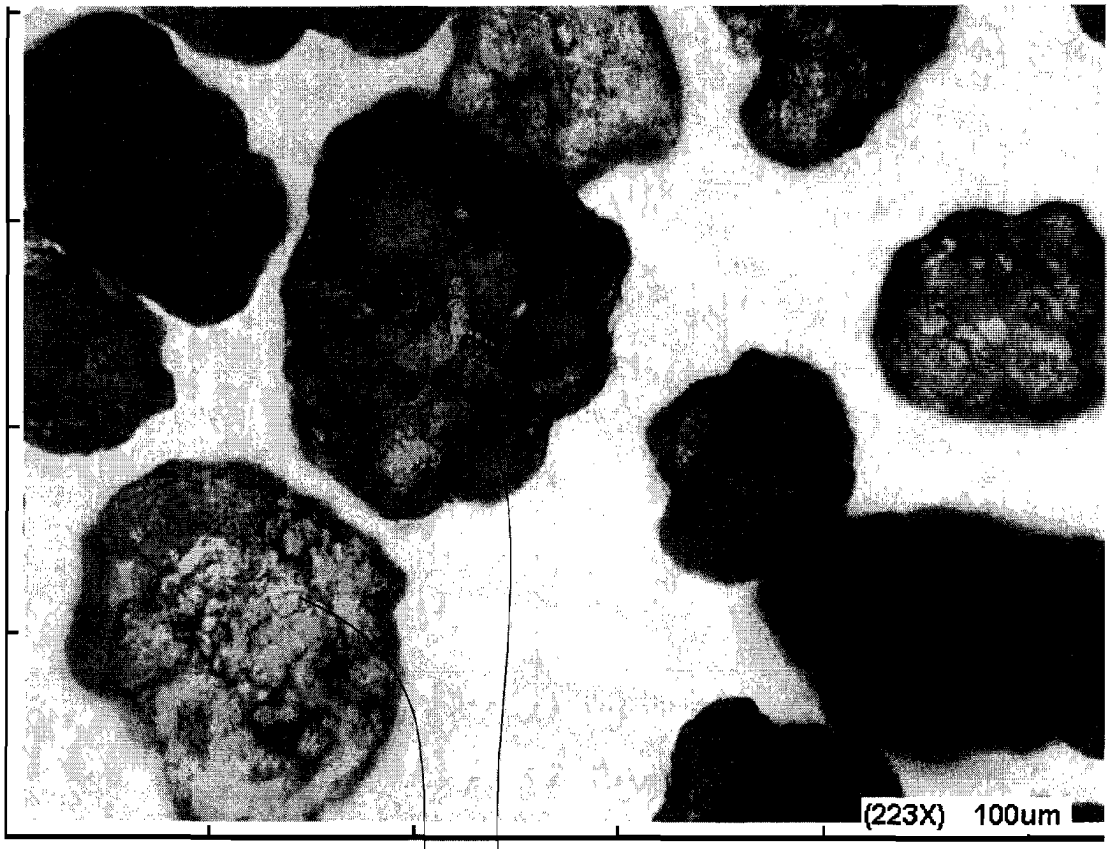
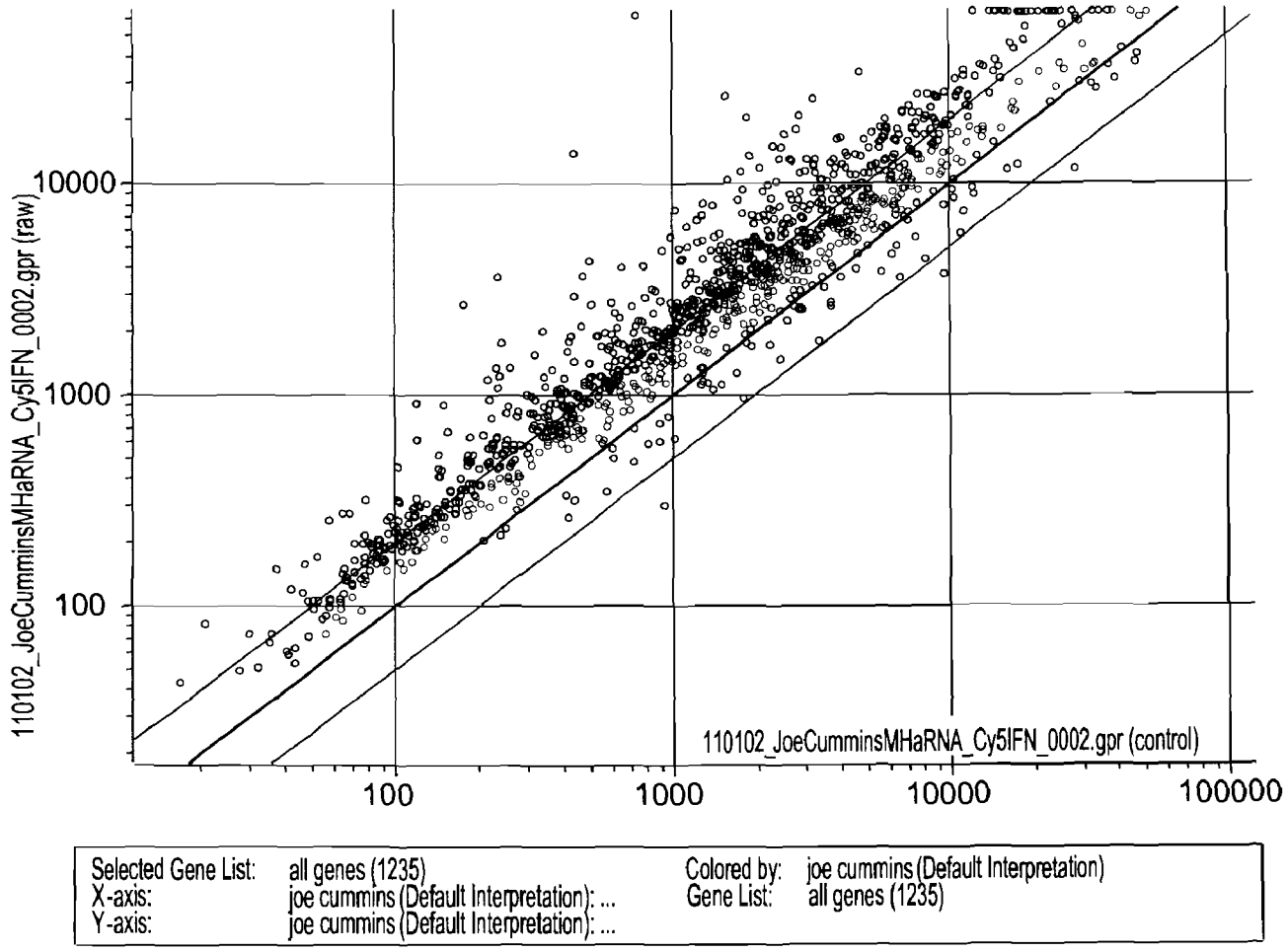
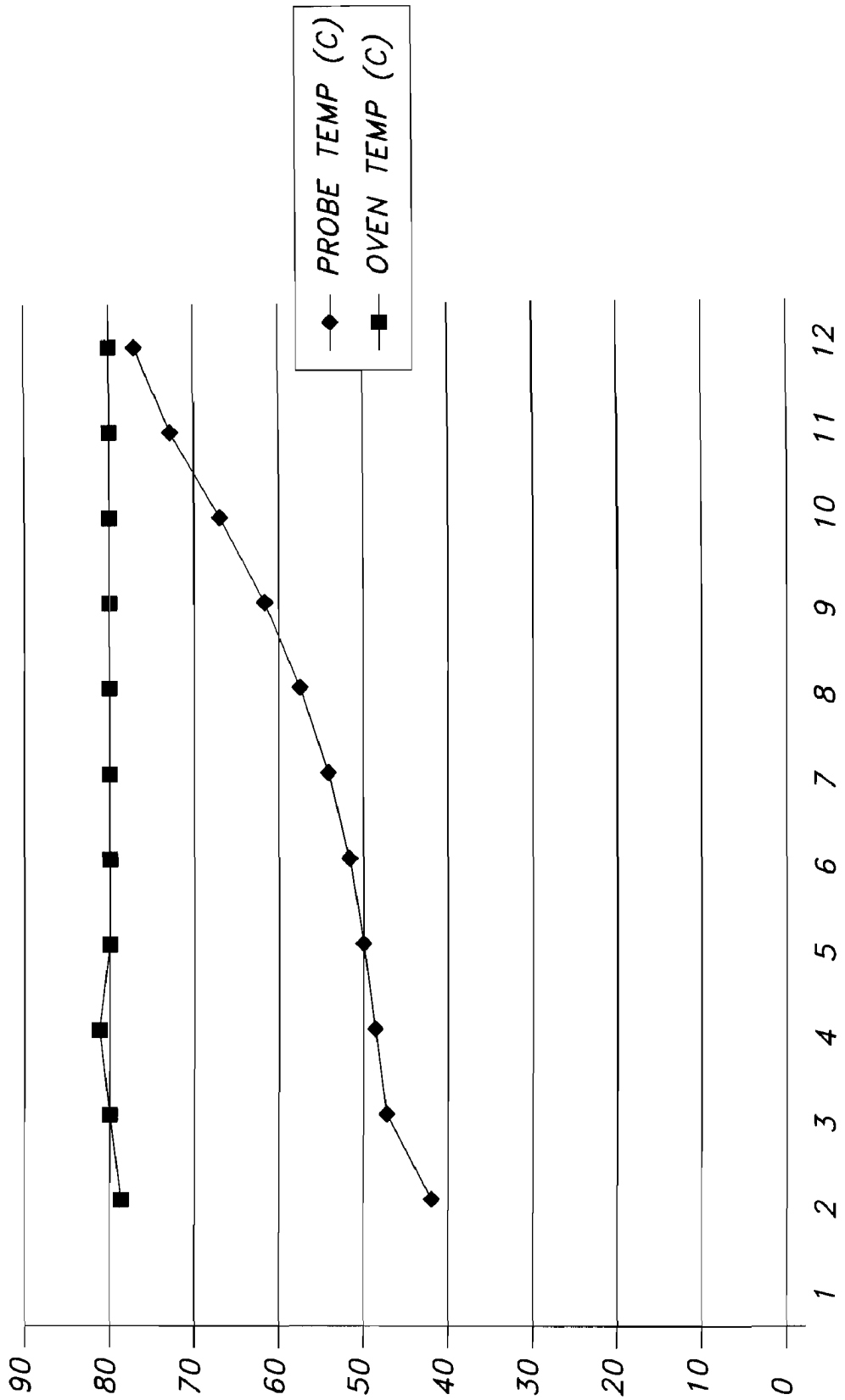


FIG. 31



Normalized to GAPDH, most of the ISGs are induced.

FIG. 32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OVEN TEMP (C)
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70
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30
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10
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1
2
3
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5
6
7
8
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11
12

FIG. 33

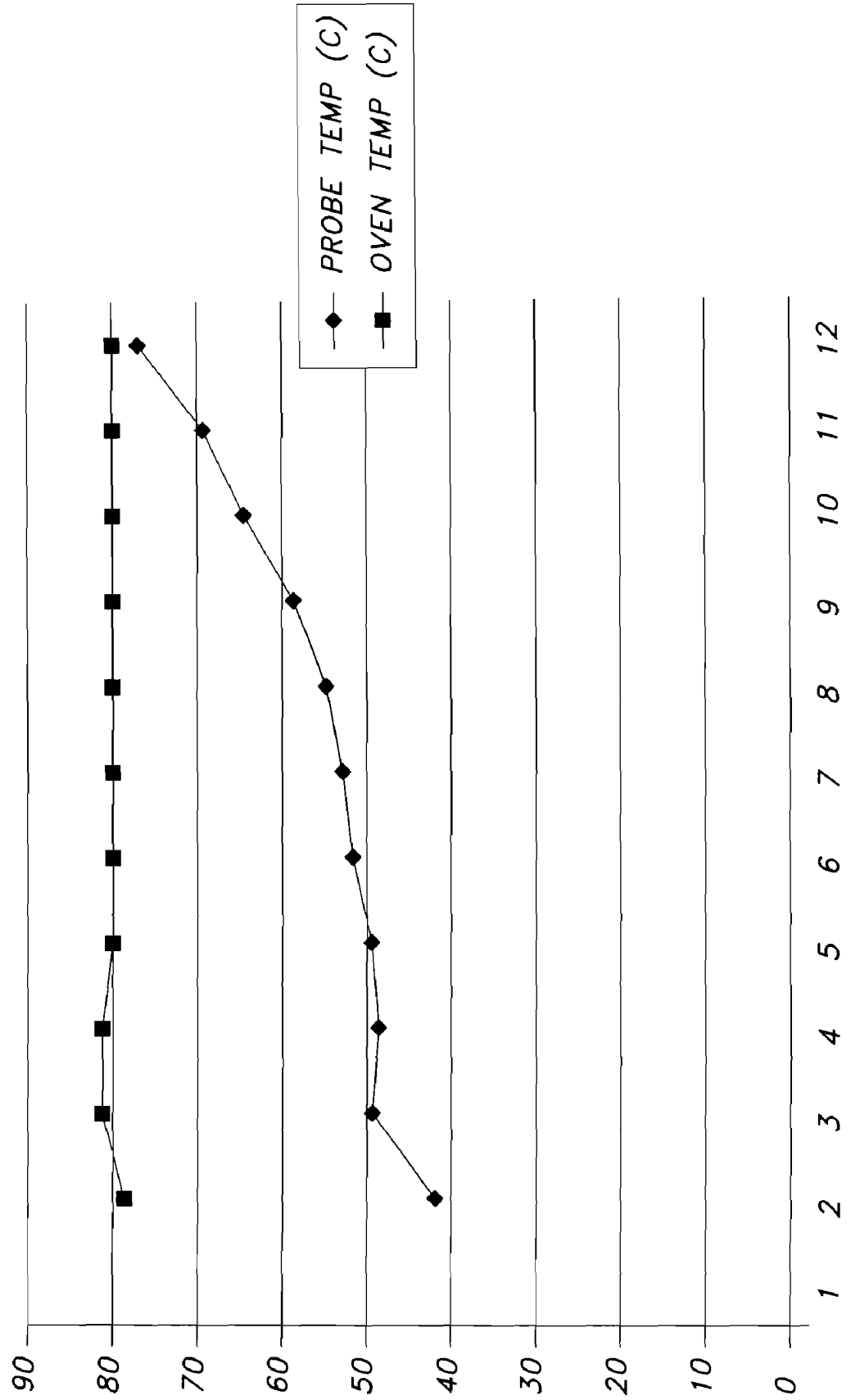
PROBE TEMP (C)
OVEN TEMP (C)
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FIG. 34

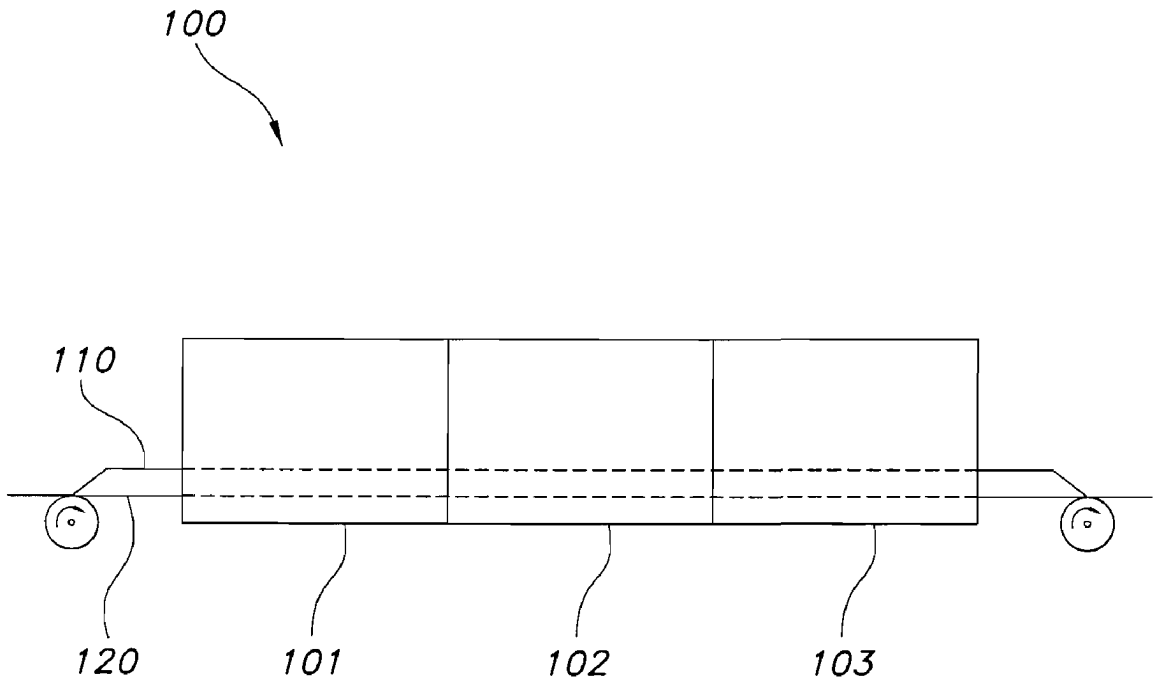


FIG. 35

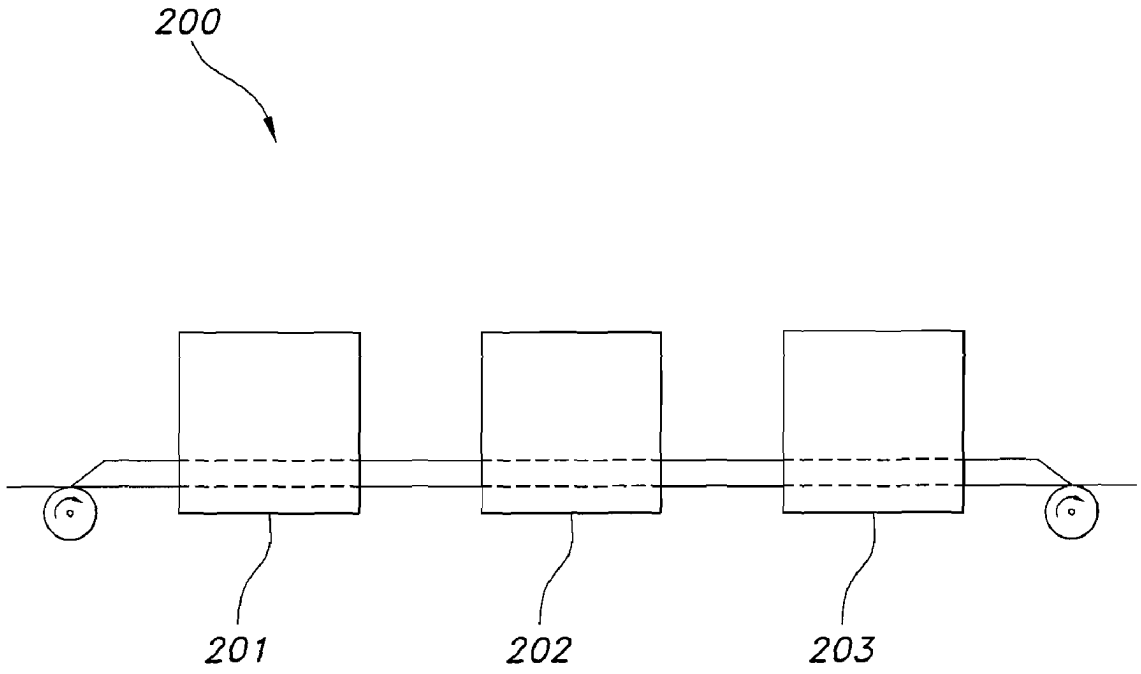


FIG. 36

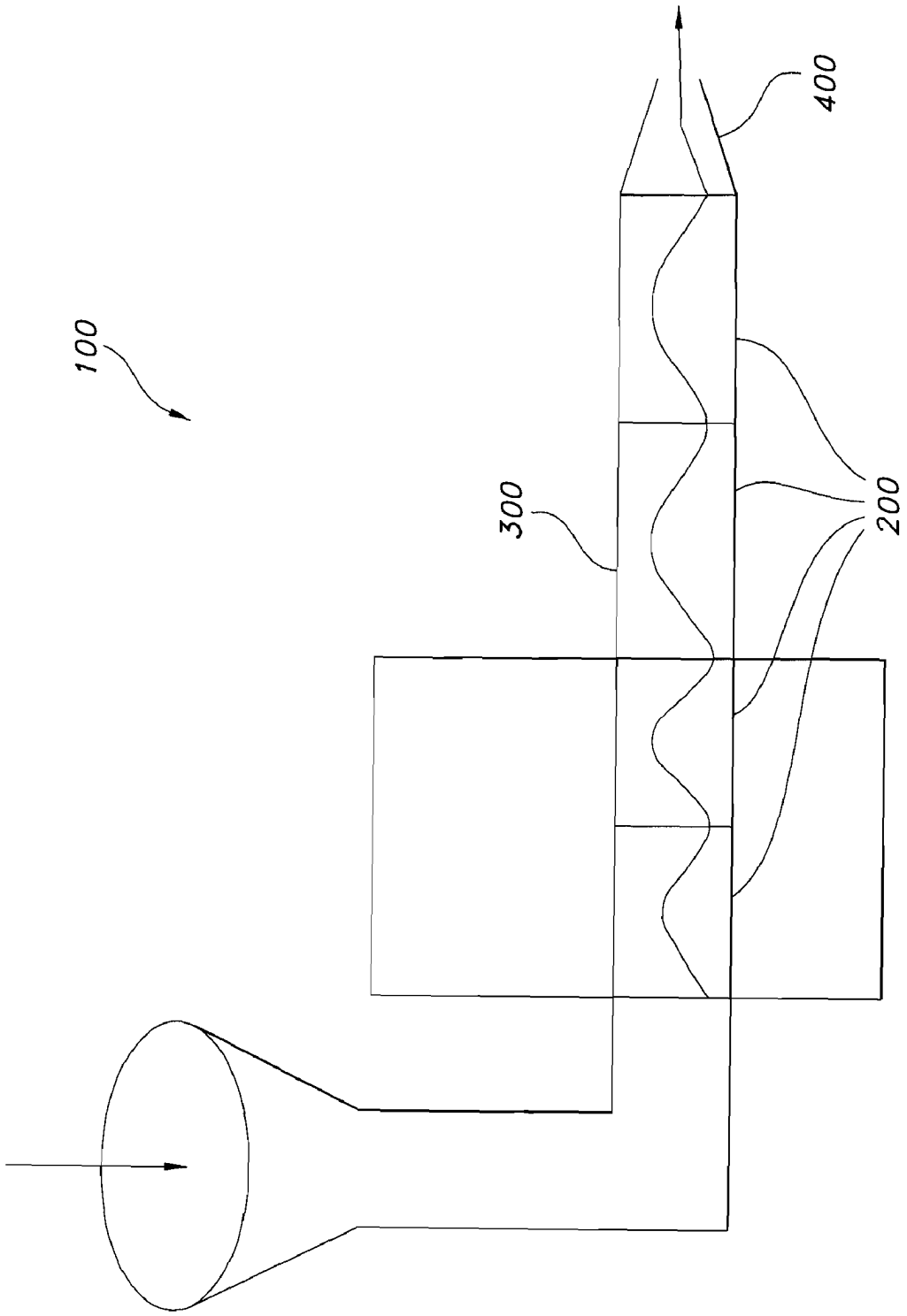


FIG. 37

FIG. 38

Ex.	Polymer Component Reference	% Solids of solution	Viscosity (cp) at 5 rpm	% moisture	Film thickness (mils)	Film strength	Tear Resistance	Tendency to go to roof of mouth	180° bend test	Film molding	Dis-solution (sec)	Rating of dissolution in mouth	Time in oven (min)
EI	PEO/PVP (60/40)	45.0	14800	2.21	3.8	Adequate	Excellent	Low	Passed	No	3	Fast to Moderate	9
EJ	PEO/PVP (40/60)	50.0	6600	2.86	4	Weak	Low to moderate	High	Passed	No	3	Fast	8
EK	PEO/Starch (80/20)	40.0	3440	2.27	4.5	Adequate to good	Excellent	High	Passed	No	3	Fast to Moderate	8
EL	PEO/CMC (80/20)	37.5	121,200	1.96	4.1	Good	Excellent	High	Passed	No	5	Slow	9
EM	PEO/CMC (60/40)	30.0	82,000	4.21	3.45	Weak	Good	High	Passed	No	3	Slow to Moderate	9
EN	PEO/CMC (40/60)	30.0	185,000	3.07	3.5	Adequate	Very low	High	Failed	No	4	Slow	9
EO	PEO/HPC (80/20)	37.5	21,200	1.65	4	Good	Excellent	High	Passed	No	4	Fast	8
EP	PEO/HPC (60/40)	37.5	17,000	2.84	3.8	Adequate	Excellent	High	Passed	No	4	Fast	9
EQ	PEO/HPC (40/60)	42.5	43,400	2.83	4.5	Poor to adequate	Poor to good	High	Passed	No	7	Fast to Moderate	7
ER	PEO/HPC (20/80)	42.5	46,400	2.33	4.4	Adequate to good	Poor	Low	Passed	No	14-15	Slow	9
ES	PEO/HPMC (80/20)	37.5	29,000	2.14	4.4	Adequate	Good	High	Passed	Yes	4	Fast to Moderate	8
ET	PEO/HPMC (60/40)	37.5	47,000	2.37	3.9	Poor to adequate	Slight	High	Passed	Yes	3	Fast to Moderate	9
EU	PEO/HPMC (40/60)	35.0	54,800	3.55	4.5	Adequate to good	Low	Low	Passed	Yes	8	Slow	8
EV	PEO/HPMC (20/80)	35.0	96,600	4.43	4.5	Good	Low	Low	Passed	No	22	Slow	10
EW	PEO/PVA (80/20)	37.5	41,600	2.92	9	Weak	Moderate	High	Passed	No	3	Moderate	10

POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. application Ser. No. 10/856,176, filed May 28, 2004 now U.S. Pat. No. 7,666,337, which claims the benefit of U.S. Provisional Application No. 60/473,902, filed May 28, 2003 and is a continuation-in-part of U.S. application Ser. No. 10/768,809, filed Jan. 30, 2004 now U.S. Pat. No. 7,357,891, which claims benefit to U.S. Provisional Application No. 60/443,741 filed Jan. 30, 2003 and is a continuation-in-part of:

(a) PCT/US02/32575 filed Oct. 11, 2002, which claims priority to: (1) U.S. application Ser. No. 10/074,272, filed Feb. 14, 2002 which claims benefit to U.S. Provisional Application No. 60/328,868, filed Oct. 12, 2001 and (2) U.S. Provisional Application No. 60/386,937, filed Jun. 7, 2002;

(b) PCT/US02/32594, filed Oct. 11, 2002, which claims priority to: (1) U.S. Provisional Application No. 60/414,276, filed Sep. 27, 2002, (2) U.S. application Ser. No. 10/074,272, filed Feb. 14, 2002, which claims benefit to U.S. Provisional Application No. 60/328,868, filed Oct. 12, 2001 and (3) U.S. Provisional Application No. 60/386,937, filed Jun. 7, 2002; and

(c) PCT/US02/32542, filed Oct. 11, 2002, which claims priority to: (1) U.S. Provisional Application No. 60/371,940, filed Apr. 11, 2002, (2) U.S. application Ser. No. 10/074,272, filed Feb. 14, 2002, which claims benefit to U.S. Provisional Application No. 60/328,868, filed Oct. 12, 2001 and (3) U.S. Provisional Application No. 60/386,937, filed Jun. 7, 2002.

FIELD OF THE INVENTION

The invention relates to rapidly dissolving films and methods of their preparation. The films contain a polymer component, which includes polyethylene oxide optionally blended with cellulosic polymers. The films may also contain an active ingredient that is evenly distributed throughout the film. The even or uniform distribution is achieved by controlling one or more parameters, and particularly the elimination of air pockets prior to and during film formation and the use of a drying process that reduces aggregation or conglomeration of the components in the film as it forms into a solid structure.

BACKGROUND OF THE RELATED TECHNOLOGY

Active ingredients, such as drugs or pharmaceuticals, may be prepared in a tablet form to allow for accurate and consistent dosing. However, this form of preparing and dispensing medications has many disadvantages including that a large proportion of adjuvants that must be added to obtain a size able to be handled, that a larger medication form requires additional storage space, and that dispensing includes counting the tablets which has a tendency for inaccuracy. In addition, many persons, estimated to be as much as 28% of the population, have difficulty swallowing tablets. While tablets may be broken into smaller pieces or even crushed as a means of overcoming swallowing difficulties, this is not a suitable solution for many tablet or pill forms. For example, crushing or destroying the tablet or pill form to facilitate ingestion, alone or in admixture with food, may also destroy the controlled release properties.

As an alternative to tablets and pills, films may be used to carry active ingredients such as drugs, pharmaceuticals, and the like. However, historically films and the process of making drug delivery systems therefrom have suffered from a number of unfavorable characteristics that have not allowed them to be used in practice.

Films that incorporate a pharmaceutically active ingredient are disclosed in expired U.S. Pat. No. 4,136,145 to Fuchs, et al. ("Fuchs"). These films may be formed into a sheet, dried and then cut into individual doses. The Fuchs disclosure alleges the fabrication of a uniform film, which includes the combination of water-soluble polymers, surfactants, flavors, sweeteners, plasticizers and drugs. These allegedly flexible films are disclosed as being useful for oral, topical or enteral use. Examples of specific uses disclosed by Fuchs include application of the films to mucosal membrane areas of the body, including the mouth, rectal, vaginal, nasal and ear areas.

Examination of films made in accordance with the process disclosed in Fuchs, however, reveals that such films suffer from the aggregation or conglomeration of particles, i.e., self-aggregation, making them inherently non-uniform. This result can be attributed to Fuchs' process parameters, which although not disclosed likely include the use of relatively long drying times, thereby facilitating intermolecular attractive forces, convection forces, air flow and the like to form such agglomeration.

The formation of agglomerates randomly distributes the film components and any active present as well. When large dosages are involved, a small change in the dimensions of the film would lead to a large difference in the amount of active per film. If such films were to include low dosages of active, it is possible that portions of the film may be substantially devoid of any active. Since sheets of film are usually cut into unit doses, certain doses may therefore be devoid of or contain an insufficient amount of active for the recommended treatment. Failure to achieve a high degree of accuracy with respect to the amount of active ingredient in the cut film can be harmful to the patient. For this reason, dosage forms formed by processes such as Fuchs, would not likely meet the stringent standards of governmental or regulatory agencies, such as the U.S. Federal Drug Administration ("FDA"), relating to the variation of active in dosage forms. Currently, as required by various world regulatory authorities, dosage forms may not vary more than 10% in the amount of active present. When applied to dosage units based on films, this virtually mandates that uniformity in the film be present.

The problems of self-aggregation leading to non-uniformity of a film were addressed in U.S. Pat. No. 4,849,246 to Schmidt ("Schmidt"). Schmidt specifically pointed out that the methods disclosed by Fuchs did not provide a uniform film and recognized that that the creation of a non-uniform film necessarily prevents accurate dosing, which as discussed above is especially important in the pharmaceutical area. Schmidt abandoned the idea that a mono-layer film, such as described by Fuchs, may provide an accurate dosage form and instead attempted to solve this problem by forming a multi-layered film. Moreover, his process is a multi-step process that adds expense and complexity and is not practical for commercial use.

Other U.S. patents directly addressed the problems of particle self-aggregation and non-uniformity inherent in conventional film forming techniques. In one attempt to overcome non-uniformity, U.S. Pat. No. 5,629,003 to Horstmann et al. and U.S. Pat. No. 5,948,430 to Zerbe et al. incorporated additional ingredients, i.e. gel formers and polyhydric alcohols respectively, to increase the viscosity of the film prior to drying in an effort to reduce aggregation of the components in

the film. These methods have the disadvantage of requiring additional components, which translates to additional cost and manufacturing steps. Furthermore, both methods employ the use the conventional time-consuming drying methods such as a high-temperature air-bath using a drying oven, drying tunnel, vacuum drier, or other such drying equipment. The long length of drying time aids in promoting the aggregation of the active and other adjuvant, notwithstanding the use of viscosity modifiers. Such processes also run the risk of exposing the active, i.e., a drug, or vitamin C, or other components to prolonged exposure to moisture and elevated temperatures, which may render it ineffective or even harmful.

In addition to the concerns associated with degradation of an active during extended exposure to moisture, the conventional drying methods themselves are unable to provide uniform films. The length of heat exposure during conventional processing, often referred to as the "heat history", and the manner in which such heat is applied, have a direct effect on the formation and morphology of the resultant film product. Uniformity is particularly difficult to achieve via conventional drying methods where a relatively thicker film, which is well-suited for the incorporation of a drug active, is desired. Thicker uniform films are more difficult to achieve because the surfaces of the film and the inner portions of the film do not experience the same external conditions simultaneously during drying. Thus, observation of relatively thick films made from such conventional processing shows a non-uniform structure caused by convection and intermolecular forces and requires greater than 10% moisture to remain flexible. The amount of free moisture can often interfere over time with the drug leading to potency issues and therefore inconsistency in the final product.

Conventional drying methods generally include the use of forced hot air using a drying oven, drying tunnel, and the like. The difficulty in achieving a uniform film is directly related to the rheological properties and the process of water evaporation in the film-forming composition. When the surface of an aqueous polymer solution is contacted with a high temperature air current, such as a film-forming composition passing through a hot air oven, the surface water is immediately evaporated forming a polymer film or skin on the surface. This seals the remainder of the aqueous film-forming composition beneath the surface, forming a barrier through which the remaining water must force itself as it is evaporated in order to achieve a dried film. As the temperature outside the film continues to increase, water vapor pressure builds up under the surface of the film, stretching the surface of the film, and ultimately ripping the film surface open allowing the water vapor to escape. As soon as the water vapor has escaped, the polymer film surface reforms, and this process is repeated, until the film is completely dried. The result of the repeated destruction and reformation of the film surface is observed as a "ripple effect" which produces an uneven, and therefore non-uniform film. Frequently, depending on the polymer, a surface will seal so tightly that the remaining water is difficult to remove, leading to very long drying times, higher temperatures, and higher energy costs.

Other factors, such as mixing techniques, also play a role in the manufacture of a pharmaceutical film suitable for commercialization and regulatory approval. Air can be trapped in the composition during the mixing process or later during the film making process, which can leave voids in the film product as the moisture evaporates during the drying stage. The film frequently collapse around the voids resulting in an uneven film surface and therefore, non-uniformity of the final film product. Uniformity is still affected even if the voids in the film caused by air bubbles do not collapse. This situation also provides a non-uniform film in that the spaces, which are not uniformly distributed, are occupying area that would otherwise be occupied by the film composition. None of the above-mentioned patents either addresses or proposes a solution to the problems caused by air that has been introduced to the film.

Therefore, there is a need for methods and compositions for film products, which use a minimal number of materials or components, and which provide a substantially non-self-aggregating uniform heterogeneity throughout the area of the films. Desirably, such films are produced through a selection of a polymer or combination of polymers that will provide a desired viscosity, a film-forming process such as reverse roll coating, and a controlled, and desirably rapid, drying process which serves to maintain the uniform distribution of non-self-aggregated components without the necessary addition of gel formers or polyhydric alcohols and the like which appear to be required in the products and for the processes of prior patents, such as the aforementioned Horstmann and Zerbe patents. Desirably, the films will also incorporate compositions and methods of manufacture that substantially reduce or eliminate air in the film, thereby promoting uniformity in the final film product.

SUMMARY OF THE INVENTION

The present invention is directed to rapid-dissolve film products containing at least one water-soluble polymer including polyethylene oxide alone or in combination with a hydrophilic cellulosic polymer, wherein the film product is free of added plasticizers.

Another embodiment of the rapid-dissolve film product includes at least one water-soluble polymer containing about 20% to 100% by weight polyethylene oxide, about 0% to 80% by weight hydroxypropylmethyl cellulose, and about 0% to 80% by weight hydroxypropyl cellulose; an active component; sucralose; precipitated calcium carbonate;

at least one flavoring; simethicone; water; and at least one colorant, wherein the film product is free of added plasticizers, surfactants, and polyalcohols.

Yet another embodiment of the present invention is directed to an edible water-soluble delivery system in the form of a film composition, which contains at least one water-soluble polymer comprising polyethylene oxide alone or in combination with a polymer selected from the group consisting of hydroxypropylmethyl cellulose and hydroxypropyl cellulose, wherein the edible water-soluble delivery system is essentially free of organic solvents, plasticizers, surfactants, and polyalcohols.

The present invention is also directed to processes for making a film having a substantially uniform distribution of components, including the steps of: (a) combining at least one water-soluble polymer comprising polyethylene oxide alone or in combination with a hydrophilic cellulosic polymer, a solvent, and an active component to form a matrix with a uniform distribution of the components; (b) forming a film from the matrix; and (c) drying the film, wherein the film is free of added plasticizers.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** shows a side view of a package containing a unit dosage film of the present invention.

FIG. **2** shows a top view of two adjacently coupled packages containing individual unit dosage forms of the present invention, separated by a tearable perforation.

FIG. **3** shows a side view of the adjacently coupled packages of FIG. **2** arranged in a stacked configuration.

FIG. **4** shows a perspective view of a dispenser for dispensing the packaged unit dosage forms, dispenser containing the packaged unit dosage forms in a stacked configuration.

FIG. **5** is a schematic view of a roll of coupled unit dose packages of the present invention.

FIG. **6** is a schematic view of an apparatus suitable for preparation of a pre-mix, addition of an active, and subsequent formation of the film.

FIG. **7** is a schematic view of an apparatus suitable for drying the films of the present invention.

FIG. **8** is a sequential representation of the drying process of the present invention.

FIG. **9** is a photographic representation of a film dried by conventional drying processes.

FIG. **10** is a photographic representation of a film dried by conventional drying processes.

FIG. **11** is a photographic representation of a film dried by conventional drying processes.

FIG. **12** is a photographic representation of a film dried by conventional drying processes.

FIG. **13** is a photographic representation of a film dried by conventional drying processes.

FIG. **14** is a photographic representation of a film dried by conventional drying processes.

FIG. **15** is a photographic representation of a film dried by conventional drying processes.

FIG. **16** is a photographic representation of a film dried by conventional drying

FIG. **17** is a photographic representation of a film dried by the inventive drying process.

FIG. **18** is a photomicrographic representation of a film containing fat coated particles dried by the inventive drying process.

FIG. **19** is a photomicrographic representation of a film containing fat coated particles dried by the inventive drying process.

FIG. **20** is a photomicrographic representation of a film containing fat coated particles dried by the inventive drying process.

FIG. **21** is a photomicrographic representation of a film containing fat coated particles dried by the inventive drying process.

FIG. **22** is a photomicrographic representation of a film containing fat coated particles dried by the inventive drying process.

FIG. **23** is a photomicrographic representation of a film containing fat coated particles dried by the inventive drying process.

FIG. **24** is a photomicrographic representation of a film containing fat coated particles dried by the inventive drying process.

FIG. **25** is a photomicrographic representation of a film containing fat coated particles dried by the inventive drying process.

FIG. **26** is a photomicrographic representation of fat coated particles not in film, heated for 9 minutes at 80° C.

FIG. **27** is a photomicrographic representation of fat coated particles not in film, heated for 9 minutes at 80° C.

FIG. **28** is a photomicrographic representation of fat coated particles at room temperature prior to processing.

FIG. **29** is a photomicrographic representation of fat coated particles at room temperature prior to processing.

FIG. **30** is a photomicrographic representation of fat coated particles at room temperature prior to processing.

FIG. **31** is a photomicrographic representation of fat coated particles at room temperature prior to processing.

FIG. **32** is a graphical representation of a microarray on the blood of a human after ingestion by the human of a film of the present invention containing a bovine derived protein.

FIG. **33** is a graphical representation of the temperature differential between the inside and outside of a film of the present invention during drying.

FIG. **34** is a graphical representation of the temperature differential between the inside and outside of a film of the present invention during drying.

FIG. **35** is a schematic representation of a continuously-linked zone drying apparatus in accordance with the present invention.

FIG. **36** is a schematic representation of a separate zone drying apparatus in accordance with the present invention.

FIG. **37** is a schematic representation of a extrusion device for use in producing films of the present invention.

FIG. **38** provides a table of various compositions of the invention, as well as certain properties.

DETAILED DESCRIPTION OF THE INVENTION

For the purposes of the present invention the term non-self-aggregating uniform heterogeneity refers to the ability of the films of the present invention, which are formed from one or more components in addition to a polar solvent, to provide a substantially reduced occurrence of, i.e. little or no, aggregation or conglomeration of components within the film as is normally experienced when films are formed by conventional drying methods such as a high-temperature air-bath using a drying oven, drying tunnel, vacuum drier, or other such drying equipment. The term heterogeneity, as used in the present invention, includes films that will incorporate a single component, such as a polymer, as well as combinations of components, such as a polymer and an active. Uniform heterogeneity includes the substantial absence of aggregates or conglomerates as is common in conventional mixing and heat drying methods used to form films.

Furthermore, the films of the present invention have a substantially uniform thickness, which is also not provided by the use of conventional drying methods used for drying water-based polymer systems. The absence of a uniform thickness detrimentally affects uniformity of component distribution throughout the area of a given film.

The film products of the present invention are produced by a combination of a properly selected polymer and a polar solvent, optionally including an active ingredient as well as other fillers known in the art. These films provide a non-self-aggregating uniform heterogeneity of the components within them by utilizing a selected casting or deposition method and a controlled drying process. Examples of controlled drying processes include, but are not limited to, the use of the apparatus disclosed in U.S. Pat. No. 4,631,837 to Magoon ("Magoon"), herein incorporated by reference, as well as hot air impingement across the bottom substrate and bottom heating plates. Another drying technique for obtaining the films of the present invention is controlled radiation drying, in the absence of uncontrolled air currents, such as infrared and radio frequency radiation (i.e. microwaves).

The objective of the drying process is to provide a method of drying the films that avoids complications, such as the noted "rippling" effect, that are associated with conventional drying methods and which initially dry the upper surface of the film, trapping moisture inside. In conventional oven drying methods, as the moisture trapped inside subsequently evaporates, the top surface is altered by being ripped open and

then reformed. These complications are avoided by the present invention, and a uniform film is provided by drying the bottom surface of the film first or otherwise preventing the formation of polymer film formation (skin) on the top surface of the film prior to drying the depth of the film. This may be achieved by applying heat to the bottom surface of the film with substantially no top air flow, or alternatively by the introduction of controlled microwaves to evaporate the water or other polar solvent within the film, again with substantially no top air flow. Yet alternatively, drying may be achieved by using balanced fluid flow, such as balanced air flow, where the bottom and top air flows are controlled to provide a uniform film. In such a case, the air flow directed at the top of the film should not create a condition which would cause movement of particles present in the wet film, due to forces generated by the air currents. Additionally, air currents directed at the bottom of the film should desirably be controlled such that the film does not lift up due to forces from the air. Uncontrolled air currents, either above or below the film, can create non-uniformity in the final film products. The humidity level of the area surrounding the top surface may also be appropriately adjusted to prevent premature closure or skinning of the polymer surface.

This manner of drying the films provides several advantages. Among these are the faster drying times and a more uniform surface of the film, as well as uniform distribution of components for any given area in the film. In addition, the faster drying time allows viscosity to quickly build within the film, further encouraging a uniform distribution of components and decrease in aggregation of components in the final film product. Desirably, the drying of the film will occur within about ten minutes or fewer, or more desirably within about five minutes or fewer.

The present invention yields exceptionally uniform film products when attention is paid to reducing the aggregation of the compositional components. By avoiding the introduction of and eliminating excessive air in the mixing process, selecting polymers and solvents to provide a controllable viscosity and by drying the film in a rapid manner from the bottom up, such films result.

The products and processes of the present invention rely on the interaction among various steps of the production of the films in order to provide films that substantially reduce the self-aggregation of the components within the films. Specifically, these steps include the particular method used to form the film, making the composition mixture to prevent air bubble inclusions, controlling the viscosity of the film forming composition and the method of drying the film. More particularly, a greater viscosity of components in the mixture is particularly useful when the active is not soluble in the selected polar solvent in order to prevent the active from settling out. However, the viscosity must not be too great as to hinder or prevent the chosen method of casting, which desirably includes reverse roll coating due to its ability to provide a film of substantially consistent thickness.

In addition to the viscosity of the film or film-forming components or matrix, there are other considerations taken into account by the present invention for achieving desirable film uniformity. For example, stable suspensions are achieved which prevent solid (such as drug particles) sedimentation in non-colloidal applications. One approach provided by the present invention is to balance the density of the particulate (ρ_p) and the liquid phase (ρ_1) and increase the viscosity of the liquid phase (μ). For an isolated particle, Stokes law relates the terminal settling velocity (Vo) of a rigid spherical body of radius (r) in a viscous fluid, as follows:

$$V_o=(2gr^r)(\rho_p-\rho_1)/9\mu$$

At high particle concentrations, however, the local particle concentration will affect the local viscosity and density. The viscosity of the suspension is a strong function of solids volume fraction, and particle-particle and particle-liquid interactions will further hinder settling velocity.

Stokian analyses has shown that the incorporation of a third phase, dispersed air or nitrogen, for example, promotes suspension stability. Further, increasing the number of particles leads to a hindered settling effect based on the solids volume fraction. In dilute particle suspensions, the rate of sedimentation, v, can be expressed as:

$$v/V_o=1/(1+\kappa\phi)$$

where κ=a constant, and ϕ is the volume fraction of the dispersed phase. More particles suspended in the liquid phase results in decreased velocity. Particle geometry is also an important factor since the particle dimensions will affect particle-particle flow interactions.

Similarly, the viscosity of the suspension is dependent on the volume fraction of dispersed solids. For dilute suspensions of non-interaction spherical particles, an expression for the suspension viscosity can be expressed as:

$$\mu/\mu_o=1+2.5\phi$$

where μ_o is the viscosity of the continuous phase and ϕ is the solids volume fraction. At higher volume fractions, the viscosity of the dispersion can be expressed as

$$\mu/\mu_o=1+2.5\phi+C_1\phi^2+C_2\phi^3+\ldots$$

where C is a constant.

The viscosity of the liquid phase is critical and is desirably modified by customizing the liquid composition to a viscoelastic non-Newtonian fluid with low yield stress values. This is the equivalent of producing a high viscosity continuous phase at rest. Formation of a viscoelastic or a highly structured fluid phase provides additional resistive forces to particle sedimentation. Further, flocculation or aggregation can be controlled minimizing particle-particle interactions. The net effect would be the preservation of a homogeneous dispersed phase.

The addition of hydrocolloids to the aqueous phase of the suspension increases viscosity, may produce viscoelasticity and can impart stability depending on the type of hydrocolloid, its concentration and the particle composition, geometry, size, and volume fraction. The particle size distribution of the dispersed phase needs to be controlled by selecting the smallest realistic particle size in the high viscosity medium, i.e., <500 μm. The presence of a slight yield stress or elastic body at low shear rates may also induce permanent stability regardless of the apparent viscosity. The critical particle diameter can be calculated from the yield stress values. In the case of isolated spherical particles, the maximum shear stress developed in settling through a medium of given viscosity can be given as

$$\tau_{max}=3V\mu/2r$$

For pseudoplastic fluids, the viscosity in this shear stress regime may well be the zero shear rate viscosity at the Newtonian plateau.

A stable suspension is an important characteristic for the manufacture of a pre-mix composition which is to be fed into the film casting machinery film, as well as the maintenance of this stability in the wet film stage until sufficient drying has occurred to lock-in the particles and matrix into a sufficiently solid form such that uniformity is maintained. For viscoelastic fluid systems, a rheology that yields stable suspensions for

extended time period, such as 24 hours, must be balanced with the requirements of high-speed film casting operations. A desirable property for the films is shear thinning or pseudoplasticity, whereby the viscosity decreases with increasing shear rate. Time dependent shear effects such as thixotropy are also advantageous. Structural recovery and shear thinning behavior are important properties, as is the ability for the film to self-level as it is formed.

The rheology requirements for the inventive compositions and films are quite severe. This is due to the need to produce a stable suspension of particles, for example 30-60 wt %, in a viscoelastic fluid matrix with acceptable viscosity values throughout a broad shear rate range. During mixing, pumping, and film casting, shear rates in the range of $10\text{-}10^5$ sec.$^{-1}$ may be experienced and pseudoplasticity is the preferred embodiment.

In film casting or coating, rheology is also a defining factor with respect to the ability to form films with the desired uniformity. Shear viscosity, extensional viscosity, viscoelasticity, structural recovery will influence the quality of the film. As an illustrative example, the leveling of shear-thinning pseudoplastic fluids has been derived as

$$\alpha^{(n-1/n)}=\alpha_o^{(n-1/n)}-((n-1)/(2n-1))(\tau/K)^{1/n}(2\pi/\lambda)^{(3+n)/n}h^{(2n+1)/n}t$$

where α is the surface wave amplitude, α_o is the initial amplitude, λ is the wavelength of the surface roughness, and both "n" and "K" are viscosity power law indices. In this example, leveling behavior is related to viscosity, increasing as n decreases, and decreasing with increasing K.

Desirably, the films or film-forming compositions of the present invention have a very rapid structural recovery, i.e. as the film is formed during processing, it doesn't fall apart or become discontinuous in its structure and compositional uniformity. Such very rapid structural recovery retards particle settling and sedimentation. Moreover, the films or film-forming compositions of the present invention are desirably shear-thinning pseudoplastic fluids. Such fluids with consideration of properties, such as viscosity and elasticity, promote thin film formation and uniformity.

Thus, uniformity in the mixture of components depends upon numerous variables. As described herein, viscosity of the components, the mixing techniques and the rheological properties of the resultant mixed composition and wet casted film are important aspects of the present invention. Additionally, control of particle size and particle shape are further considerations. Desirably, the size of the particulate a particle size of 150 microns or less, for example 100 microns or less. Moreover, such particles may be spherical, substantially spherical, or non-spherical, such as irregularly shaped particles or ellipsoidally shaped particles. Ellipsoidally shaped particles or ellipsoids are desirable because of their ability to maintain uniformity in the film forming matrix as they tend to settle to a lesser degree as compared to spherical particles.

A number of techniques may be employed in the mixing stage to prevent bubble inclusions in the final film. To provide a composition mixture with substantially no air bubble formation in the final product, anti-foaming or surface-tension reducing agents are employed. Additionally, the speed of the mixture is desirably controlled to prevent cavitation of the mixture in a manner which pulls air into the mix. Finally, air bubble reduction can further be achieved by allowing the mix to stand for a sufficient time for bubbles to escape prior to drying the film. Desirably, the inventive process first forms a masterbatch of film-forming components without active ingredients such as drug particles or volatile materials such as flavor oils. The actives are added to smaller mixes of the masterbatch just prior to casting. Thus, the masterbatch premix can be allowed to stand for a longer time without concern for instability in drug or other ingredients.

When the matrix is formed including the film-forming polymer and polar solvent in addition to any additives and the active ingredient, this may be done in a number of steps. For example, the ingredients may all be added together or a premix may be prepared. The advantage of a pre-mix is that all ingredients except for the active may be combined in advance, with the active added just prior to formation of the film. This is especially important for actives that may degrade with prolonged exposure to water, air or another polar solvent.

FIG. **6** shows an apparatus **20** suitable for the preparation of a pre-mix, addition of an active and subsequent formation of a film. The pre-mix or master batch **22**, which includes the film-forming polymer, polar solvent, and any other additives except a drug active is added to the master batch feed tank **24**. The components for pre-mix or master batch **22** are desirably formed in a mixer (not shown) prior to their addition into the master batch feed tank **24**. Then a pre-determined amount of the master batch is controllably fed via a first metering pump **26** and control valve **28** to either or both of the first and second mixers, **30**, **30'**. The present invention, however, is not limited to the use of two mixers, **30**, **30'**, and any number of mixers may suitably be used. Moreover, the present invention is not limited to any particular sequencing of the mixers **30**, **30'**, such as parallel sequencing as depicted in FIG. **6**, and other sequencing or arrangements of mixers, such as series or combination of parallel and series, may suitably be used. The required amount of the drug or other ingredient, such as a flavor, is added to the desired mixer through an opening, **32**, **32'**, in each of the mixers, **30**, **30'**. Desirably, the residence time of the pre-mix or master batch **22** is minimized in the mixers **30**, **30'**. While complete dispersion of the drug into the pre-mix or master batch **22** is desirable, excessive residence times may result in leaching or dissolving of the drug, especially in the case for a soluble drug. Thus, the mixers **30**, **30'** are often smaller, i.e. lower residence times, as compared to the primary mixers (not shown) used in forming the pre-mix or master batch **22**. After the drug has been blended with the master batch pre-mix for a sufficient time to provide a uniform matrix, a specific amount of the uniform matrix is then fed to the pan **36** through the second metering pumps, **34**, **34'**. The metering roller **38** determines the thickness of the film **42** and applies it to the application roller. The film **42** is finally formed on the substrate **44** and carried away via the support roller **46**.

While the proper viscosity uniformity in mixture and stable suspension of particles, and casting method are important in the initial steps of forming the composition and film to promote uniformity, the method of drying the wet film is also important. Although these parameters and properties assist uniformity initially, a controlled rapid drying process ensures that the uniformity will be maintained until the film is dry.

The wet film is then dried using controlled bottom drying or controlled microwave drying, desirably in the absence of external air currents or heat on the top (exposed) surface of the film **48** as described herein. Controlled bottom drying or controlled microwave drying advantageously allows for vapor release from the film without the disadvantages of the prior art. Conventional convection air drying from the top is not employed because it initiates drying at the top uppermost portion of the film, thereby forming a barrier against fluid flow, such as the evaporative vapors, and thermal flow, such as the thermal energy for drying. Such dried upper portions

serve as a barrier to further vapor release as the portions beneath are dried, which results in non-uniform films. As previously mentioned some top air flow can be used to aid the drying of the films of the present invention, but it must not create a condition that would cause particle movement or a rippling effect in the film, both of which would result in non-uniformity. If top air is employed, it is balanced with the bottom air drying to avoid non-uniformity and prevent film lift-up on the carrier belt. A balance top and bottom air flow may be suitable where the bottom air flow functions as the major source of drying and the top air flow is the minor source of drying. The advantage of some top air flow is to move the exiting vapors away from the film thereby aiding in the overall drying process. The use of any top air flow or top drying, however, must be balanced by a number of factors including, but not limited, to rheological properties of the composition and mechanical aspects of the processing. Any top fluid flow, such as air, also must not overcome the inherent viscosity of the film-forming composition. In other words, the top air flow cannot break, distort or otherwise physically disturb the surface of the composition. Moreover, air velocities are desirably below the yield values of the film, i.e., below any force level that can move the liquids in the film-forming compositions. For thin or low viscosity compositions, low air velocity must be used. For thick or high viscosity compositions, higher air velocities may be used. Furthermore, air velocities are desirable low so as to avoid any lifting or other movement of the film formed from the compositions.

Moreover, the films of the present invention may contain particles that are sensitive to temperature, such as flavors, which may be volatile, or drugs, proteins, or antigens, which may have a low degradation temperature. In such cases, the drying temperature may be decreased while increasing the drying time to adequately dry the uniform films of the present invention. Furthermore, bottom drying also tends to result in a lower internal film temperature as compared to top drying. In bottom drying, the evaporating vapors more readily carry heat away from the film as compared to top drying which lowers the internal film temperature. Such lower internal film temperatures often result in decreased drug degradation and decreased loss of certain volatiles, such as flavors.

During film preparation, it may be desirable to dry films at high temperatures. High heat drying produces uniform films, and leads to greater efficiencies in film production. Films containing sensitive active components, however, may face degradation problems at high temperatures. Degradation is the "decomposition of a compound . . . exhibiting well-defined intermediate products." The American Heritage Dictionary of the English Language (4^{th} ed. 2000). Degradation of an active component is typically undesirable as it may cause instability, inactivity, and/or decreased potency of the active component. For instance, if the active component is a drug or bioactive material, this may adversely affect the safety or efficacy of the final pharmaceutical product. Additionally, highly volatile materials will tend to be quickly released from this film upon exposure to conventional drying methods.

Degradation of an active component may occur through a variety of processes, such as, hydrolysis, oxidation, and light degradation, depending upon the particular active component. Moreover, temperature has a significant effect on the rate of such reactions. The rate of degradation typically doubles for every 10° C. increase in temperature. Therefore, it is commonly understood that exposing an active component to high temperatures will initiate and/or accelerate undesirable degradation reactions.

Proteins are one category of useful active ingredients that will degrade, denature, or otherwise become inactive when they are exposed to high temperatures for extended periods of time. Proteins serve a variety of functions in the body such as enzymes, structural elements, hormones and immunoglobulins. Examples of proteins include enzymes such as pancreatin, trypsin, pancrelipase, chymotrypsin, hyaluronidase, sutilains, streptokinaw, urokinase, altiplase, papain, bromelainsdiastase, structural elements such as collagen and albumin, hormones such as thyroliberin, gonadoliberin, adrenocorticottropin, corticotrophin, cosyntropin, sometrem, somatropion, prolactin, thyrotropin, somatostatin, vasopressin, felypressin, lypressin, insulin, glucagons, gastrin, pentagastrin, secretin, cholecystokinin-pancreozymin, and immunomodulators which may include polysaccharides in addition to glycoproteins including cytokines which are useful for the inhibition and prevention of malignant cell growth such as tumor growth. A suitable method for the production of some useful glycoproteins is disclosed in U.S. Pat. No. 6,281,337 to Cannon-Carlson, et al., which in incorporated herein in its entirety.

Temperatures that approach 100° C. will generally cause degradation of proteins as well as nucleic acids. For example some glycoproteins will degrade if exposed to a temperature of 70° C. for thirty minutes. Proteins from bovine extract are also known to degrade at such low temperatures. DNA also begins to denature at this temperature.

Applicants have discovered, however, that the films of the present invention may be exposed to high temperatures during the drying process without concern for degradation, loss of activity or excessive evaporation due to the inventive process for film preparation and forming. In particular, the films may be exposed to temperatures that would typically lead to degradation, denaturization, or inactivity of the active component, without causing such problems. According to the present invention, the manner of drying may be controlled to prevent deleterious levels of heat from reaching the active component.

As discussed herein, the flowable mixture is prepared to be uniform in content in accordance with the teachings of the present invention. Uniformity must be maintained as the flowable mass was formed into a film and dried. During the drying process of the present invention, several factors produce uniformity within the film while maintaining the active component at a safe temperature, i.e., below its degradation temperature. First, the films of the present invention have an extremely short heat history, usually only on the order of minutes, so that total temperature exposure is minimized to the extent possible. The films are controllably dried to prevent aggregation and migration of components, as well as preventing heat build up within. Desirably, the films are dried from the bottom. Controlled bottom drying, as described herein, prevents the formation of a polymer film, or skin, on the top surface of the film. As heat is conducted from the film bottom upward, liquid carrier, e.g., water, rises to the film surface. The absence of a surface skin permits rapid evaporation of the liquid carrier as the temperature increases, and thus, concurrent evaporative cooling of the film. Due to the short heat exposure and evaporative cooling, the film components such as drag or volatile actives remain unaffected by high temperatures. In contrast, skinning on the top surface traps liquid carrier molecules of increased energy within the film, thereby causing the temperature within the film to rise and exposing active components to high, potentially deleterious temperatures.

Second, thermal mixing occurs within the film due to bottom heating and absence of surface skinning. Thermal mixing occurs via convection currents in the film. As heat is applied to the bottom of the film, the liquid near the bottom increases

in temperature, expands, and becomes less dense. As such, this hotter liquid rises and cooler liquid takes its place. While rising, the hotter liquid mixes with the cooler liquid and shares thermal energy with it, i.e., transfers heat. As the cycle repeats, thermal energy is spread throughout the film.

Robust thermal mixing achieved by the controlled drying process of the present invention produces uniform heat diffusion throughout the film. In the absence of such thermal mixing, "hot spots" may develop. Pockets of heat in the film result in the formation of particle aggregates or danger areas within the film and subsequent non-uniformity. The formation of such aggregates or agglomerations is undesirable because it leads to non-uniform films in which the active may be randomly distributed. Such uneven distribution may lead to large differences in the amount of active per film, which is problematic from a safety and efficacy perspective.

Furthermore, thermal mixing helps to maintain a lower overall temperature inside the film. Although the film surfaces may be exposed to a temperature above that at which the active component degrades, the film interior may not reach this temperature. Due to this temperature differential, the active does not degrade.

For instance, the films of the present invention desirably are dried for 10 minutes or less. Drying the films at 80° C. for 10 minutes produces a temperature differential of about 5° C. This means that after 10 minutes of drying, the temperature of the inside of the film is 5° C. less than the outside exposure temperature. In many cases, however, drying times of less than 10 minutes are sufficient, such as 4 to 6 minutes. Drying for 4 minutes may be accompanied by a temperature differential of about 30° C., and drying for 6 minutes may be accompanied by a differential of about 25° C. Due to such large temperature differentials, the films may be dried at efficient, high temperatures without causing heat sensitive actives to degrade.

FIG. **8** is a sequential representation of the drying process of the present invention. After mechanical mixing, the film may be placed on a conveyor for continued thermal mixing during the drying process. At the outset of the drying process, depicted in Section A, the film **1** preferably is heated from the bottom **10** as it is travels via conveyor (not shown). Heat may be supplied to the film by a heating mechanism, such as, but not limited to, the dryer depicted in FIG. **7**. As the film is heated, the liquid carrier, or volatile ("V"), begins to evaporate, as shown by upward arrow **50**. Thermal mixing also initiates as hotter liquid, depicted by arrow **30**, rises and cooler liquid, depicted by arrow **40**, takes its place. Because no skin forms on the top surface **20** of the film **1**, as shown in Section B the volatile liquid continues to evaporate **50** and thermal mixing **30**/**40** continues to distribute thermal energy throughout the film. Once a sufficient amount of the volatile liquid has evaporated, thermal mixing has produced uniform heat diffusion throughout the film **1**. The resulting dried film **1** is a visco-elastic solid, as depicted in Section C. The components desirably are locked into a uniform distribution throughout the film. Although minor amounts of liquid carrier, i.e., water, may remain subsequent to formation of the visco-elastic, the film may be dried further without movement of the particles, if desired.

Furthermore, particles or particulates may be added to the film-forming composition or matrix after the composition or matrix is cast into a film. For example, particles may be added to the film **42** prior to the drying of the film **42**. Particles may be controllably metered to the film and disposed onto the film through a suitable technique, such as through the use of a doctor blade (not shown) which is a device which marginally or softly touches the surface of the film and controllably disposes the particles onto the film surface. Other suitable, but non-limiting, techniques include the use of an additional roller to place the particles on the film surface, spraying the particles onto the film surface, and the like. The particles may be placed on either or both of the opposed film surfaces, i.e., the top and/or bottom film surfaces. Desirably, the particles are securably disposed onto the film, such as being embedded into the film. Moreover, such particles are desirably not fully encased or fully embedded into the film, but remain exposed to the surface of the film, such as in the case where the particles are partially embedded or partially encased.

The particles may be any useful organoleptic agent, cosmetic agent, pharmaceutical agent, or combinations thereof. Desirably, the pharmaceutical agent is a taste-masked or a controlled-release pharmaceutical agent. Useful organoleptic agents include flavors and sweeteners. Useful cosmetic agents include breath freshening or decongestant agents, such as menthol, including menthol crystals.

Although the inventive process is not limited to any particular apparatus for the above-described desirable drying, one particular useful drying apparatus **50** is depicted in FIG. **7**. Drying apparatus **50** is a nozzle arrangement for directing hot fluid, such as but not limited to hot air, towards the bottom of the film **42** which is disposed on substrate **44**. Hot air enters the entrance end **52** of the drying apparatus and travels vertically upward, as depicted by vectors **54**, towards air deflector **56**. The air deflector **56** redirects the air movement to minimize upward force on the film **42**. As depicted in FIG. **7**, the air is tangentially directed, as indicated by vectors **60** and **60'**, as the air passes by air deflector **56** and enters and travels through chamber portions **58** and **58'** of the drying apparatus **50**. With the hot air flow being substantially tangential to the film **42**, lifting of the film as it is being dried is thereby minimized. While the air deflector **56** is depicted as a roller, other devices and geometries for deflecting air or hot fluid may suitable be used. Furthermore, the exit ends **62** and **62'** of the drying apparatus **50** are flared downwardly. Such downward flaring provides a downward force or downward velocity vector, as indicated by vectors **64** and **64'**, which tend to provide a pulling or drag effect of the film **42** to prevent lifting of the film **42**. Lifting of the film **42** may not only result in non-uniformity in the film or otherwise, but may also result in non-controlled processing of the film **42** as the film **42** and/or substrate **44** lift away from the processing equipment.

Monitoring and control of the thickness of the film also contributes to the production of a uniform film by providing a film of uniform thickness. The thickness of the film may be monitored with gauges such as Beta Gauges. A gauge may be coupled to another gauge at the end of the drying apparatus, i.e. drying oven or tunnel, to communicate through feedback loops to control and adjust the opening in the coating apparatus, resulting in control of uniform film thickness.

The film products are generally formed by combining a properly selected polymer and polar solvent, as well as any active ingredient or filler as desired. Desirably, the solvent content of the combination is at least about 30% by weight of the total combination. The matrix formed by this combination is formed into a film, desirably by roll coating, and then dried, desirably by a rapid and controlled drying process to maintain the uniformity of the film, more specifically, a non-self-aggregating uniform heterogeneity. The resulting film will desirably contain less than about 10% by weight solvent, more desirably less than about 8% by weight solvent, even more desirably less than about 6% by weight solvent and most desirably less than about 2%. The solvent may be water, a

polar organic solvent including, but not limited to, ethanol, isopropanol, acetone, methylene chloride, or any combination thereof.

In alternative embodiments, the film products of the present invention may be formed by extrusion rather than casting methods. Extrusion is particularly useful for film compositions containing polyethylene oxide-based polymer components, as discussed below. For instance, a single screw extrusion process may be employed in accordance with the present invention. According to such an extrusion process, pressure builds in the polymer melt so that it may be extruded through a die or injected into a mold.

As further explanation, a single screw extruder for use in the process of the present invention may include a barrel **300** containing a number of zones **200**, as shown in the extruder **100** depicted in FIG. **37**. These zones **200** may have varying temperatures and pressures. For instance, it may be desirable for the zones to increase in temperature as the composition proceeds through the barrel **300** to the extrusion die **400**. Any number of zones may be included in accordance with the present invention. In addition, the speed of extrusion may be controlled to produce desired film properties. For example, the extrusion composition may be held for an extended time period in the screw mixing chamber. Although this discussion is directed to single screw extrusion, other forms of extrusion are known to those skilled in the art and are considered well within the scope of the present invention.

Consideration of the above discussed parameters, such as but not limited to rheology properties, viscosity, mixing method, casting method and drying method, also impact material selection for the different components of the present invention. Furthermore, such consideration with proper material selection provides the compositions of the present invention, including a pharmaceutical and/or cosmetic dosage form or film product having no more than a 10% variance of a pharmaceutical and/or cosmetic active per unit area. In other words, the uniformity of the present invention is determined by the presence of no more than a 10% by weight of pharmaceutical and/or cosmetic variance throughout the matrix. Desirably, the variance is less than 5% by weight, less than 2% by weight, less than 1% by weight, or less than 0.5% by weight.

Film-Forming Polymers

The polymer may be water soluble, water swellable, water insoluble, or a combination of one or more either water soluble, water swellable or water insoluble polymers. The polymer may include cellulose or a cellulose derivative. Specific examples of useful water soluble polymers include, but are not limited to, polyethylene oxide (PEO), pullulan, hydroxypropylmethyl cellulose (HPMC), hydroxyethyl cellulose (HPC), hydroxypropyl cellulose, polyvinyl pyrrolidone, carboxymethyl cellulose, polyvinyl alcohol, sodium aginate, polyethylene glycol, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof. Specific examples of useful water insoluble polymers include, but are not limited to, ethyl cellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate and combinations thereof.

As used herein the phrase "water soluble polymer" and variants thereof refer to a polymer that is at least partially soluble in water, and desirably fully or predominantly soluble in water, or absorbs water. Polymers that absorb water are often referred to as being water swellable polymers. The materials useful with the present invention may be water soluble or water swellable at room temperature and other temperatures, such as temperatures exceeding room temperature. Moreover, the materials may be water soluble or water swellable at pressures less than atmospheric pressure. Desirably, the water soluble polymers are water soluble or water swellable having at least 20 percent by weight water uptake. Water swellable polymers having a 25 or greater percent by weight water uptake are also useful. Films or dosage forms of the present invention formed from such water soluble polymers are desirably sufficiently water soluble to be dissolvable upon contact with bodily fluids.

Other polymers useful for incorporation into the films of the present invention include biodegradable polymers, copolymers, block polymers and combinations thereof. Among the known useful polymers or polymer classes which meet the above criteria are: poly(glycolic acid) (PGA), poly (lactic acid) (PLA), polydioxanones, polyoxalates, poly(α-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof. Additional useful polymers include, stereopolymers of L- and D-lactic acid, copolymers of bis(p-carboxyphenoxy) propane acid and sebacic acid, sebacic acid copolymers, copolymers of caprolactone, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, copolymers of polyurethane and (poly(lactic acid), copolymers of polyurethane and poly(lactic acid), copolymers of α-amino acids, copolymers of α-amino acids and caproic acid, copolymers of α-benzyl glutamate and polyethylene glycol, copolymers of succinate and poly(glycols), polyphosphazene, polyhydroxy-alkanoates and mixtures thereof. Binary and ternary systems are contemplated.

Other specific polymers useful include those marketed under the Medisorb and Biodel trademarks. The Medisorb materials are marketed by the Dupont Company of Wilmington, Del. and are generically identified as a "lactide/glycolide co-polymer" containing "propanoic acid, 2-hydroxy-polymer with hydroxy-polymer with hydroxyacetic acid." Four such polymers include lactide/glycolide 100 L, believed to be 100% lactide having a melting point within the range of 338°-347° F. (170°-175° C.); lactide/glycolide 100 L, believed to be 100% glycolide having a melting point within the range of 437°-455° F. (225°-235° C.); lactide/glycolide 85/15, believed to be 85% lactide and 15% glycolide with a melting point within the range of 338°-347° F. (170°-175° C.); and lactide/glycolide 50/50, believed to be a copolymer of 50% lactide and 50% glycolide with a melting point within the range of 338°-347° F. (170°-175° C.).

The Biodel materials represent a family of various polyanhydrides which differ chemically.

Although a variety of different polymers may be used, it is desired to select polymers to provide a desired viscosity of the mixture prior to drying. For example, if the active or other components are not soluble in the selected solvent, a polymer that will provide a greater viscosity is desired to assist in maintaining uniformity. On the other hand, if the components are soluble in the solvent, a polymer that provides a lower viscosity may be preferred.

The polymer plays an important role in affecting the viscosity of the film. Viscosity is one property of a liquid that controls the stability of the active in an emulsion, a colloid or a suspension. Generally the viscosity of the matrix will vary from about 400 cps to about 100,000 cps, preferably from about 800 cps to about 60,000 cps, and most preferably from

about 1,000 cps to about 40,000 cps. Desirably, the viscosity of the film-forming matrix will rapidly increase upon initiation of the drying process.

The viscosity may be adjusted based on the selected active depending on the other components within the matrix. For example, if the component is not soluble within the selected solvent, a proper viscosity may be selected to prevent the component from settling which would adversely affect the uniformity of the resulting film. The viscosity may be adjusted in different ways. To increase viscosity of the film matrix, the polymer may be chosen of a higher molecular weight or crosslinkers may be added, such as salts of calcium, sodium and potassium. The viscosity may also be adjusted by adjusting the temperature or by adding a viscosity increasing component. Components that will increase the viscosity or stabilize the emulsion/suspension include higher molecular weight polymers and polysaccharides and gums, which include without limitation, alginate, carrageenan, hydroxypropyl methyl cellulose, locust bean gum, guar gum, xanthan gum, dextran, gum arabic, gellan gum and combinations thereof.

It has also been observed that certain polymers which when used alone would ordinarily require a plasticizer to achieve a flexible film, can be combined without a plasticizer and yet achieve flexible films. For example, HPMC and HPC when used in combination provide a flexible, strong film with the appropriate plasticity and elasticity for manufacturing and storage. No additional plasticizer or polyalcohol is needed for flexibility.

Additionally, polyethylene oxide (PEO), when used alone or in combination with a hydrophilic cellulosic polymer, achieves flexible, strong films. Additional plasticizers or polyalcohols are not needed for flexibility. Non-limiting examples of suitable cellulosic polymers for combination with PEO include HPC and HPMC. PEO and HPC have essentially no gelation temperature, while HPMC has a gelation temperature of 58-64° C. (Methocel EF available from Dow Chemical Co.). Moreover, these films are sufficiently flexible even when substantially free of organic solvents, which may be removed without compromising film properties. As such, if there is no solvent present, then there is no plasticizer in the films. PEO based films also exhibit good resistance to tearing, little or no curling, and fast dissolution rates when the polymer component contains appropriate levels of PEO.

To achieve the desired film properties, the level and/or molecular weight of PEO in the polymer component may be varied. Modifying the PEO content affects properties such as tear resistance, dissolution rate, and adhesion tendencies. Thus, one method for controlling film properties is to modify the PEO content. For instance, in some embodiments rapid dissolving films are desirable. By modifying the content of the polymer component, the desired dissolution characteristics can be achieved.

In accordance with the present invention, PEO desirably ranges from about 20% to 100% by weight in the polymer component. In some embodiments, the amount of PEO desirably ranges from about 1 mg to about 200 mg. The hydrophilic cellulosic polymer ranges from about 0% to about 80% by weight, or in a ratio of up to about 4:1 with the PEO, and desirably in a ratio of about 1:1.

In some embodiments, it may be desirable to vary the PEO levels to promote certain film properties. To obtain films with high tear resistance and fast dissolution rates, levels of about 50% or greater of PEO in the polymer component are desirable. To achieve adhesion prevention, i.e., preventing the film from adhering to the roof of the mouth, PEO levels of about 20% to 75% are desirable. In some embodiments, however, adhesion to the roof of the mouth may be desired, such as for administration to animals or children. In such cases, higher levels of PEO may be employed. More specifically, structural integrity and dissolution of the film can be controlled such that the film can adhere to mucosa and be readily removed, or adhere more firmly and be difficult to remove, depending on the intended use.

The molecular weight of the PEO may also be varied. High molecular weight PEO, such as about 4 million, may be desired to increase mucoadhesivity of the film. More desirably, the molecular weight may range from about 100,000 to 900,000, more desirably from about 100,000 to 600,000, and most desirably from about 100,000 to 300,000. In some embodiments, it may be desirable to combine high molecular weight (600,000 to 900,000) with low molecular weight (100,000 to 300,000) PEOs in the polymer component.

For instance, certain film properties, such as fast dissolution rates and high tear resistance, may be attained by combining small amounts of high molecular weight PEOs with larger amounts of lower molecular weight PEOs. Desirably, such compositions contain about 60% or greater levels of the lower molecular weight PEO in the PEO-blend polymer component.

To balance the properties of adhesion prevention, fast dissolution rate, and good tear resistance, desirable film compositions may include about 50% to 75% low molecular weight PEO, optionally combined with a small amount of a higher molecular weight PEO, with the remainder of the polymer component containing a hydrophilic cellulosic polymer (HPC or HPMC).

Controlled Release Films

The term "controlled release" is intended to mean the release of active at a pre-selected or desired rate. This rate will vary depending upon the application. Desirable rates include fast or immediate release profiles as well as delayed, sustained or sequential release. Combinations of release patterns, such as initial spiked release followed by lower levels of sustained release of active are contemplated. Pulsed drug releases are also contemplated.

The polymers that are chosen for the films of the present invention may also be chosen to allow for controlled disintegration of the active. This may be achieved by providing a substantially water insoluble film that incorporates an active that will be released from the film over time. This may be accomplished by incorporating a variety of different soluble or insoluble polymers and may also include biodegradable polymers in combination. Alternatively, coated controlled release active particles may be incorporated into a readily soluble film matrix to achieve the controlled release property of the active inside the digestive system upon consumption.

Films that provide a controlled release of the active are particularly useful for buccal, gingival, sublingual and vaginal applications. The films of the present invention are particularly useful where mucosal membranes or mucosal fluid is present due to their ability to readily wet and adhere to these areas.

The convenience of administering a single dose of a medication which releases active ingredients in a controlled fashion over an extended period of time as opposed to the administration of a number of single doses at regular intervals has long been recognized in the pharmaceutical arts. The advantage to the patient and clinician in having consistent and uniform blood levels of medication over an extended period of time are likewise recognized. The advantages of a variety of sustained release dosage forms are well known. However,

the preparation of a film that provides the controlled release of an active has advantages in addition to those well-known for controlled release tablets. For example, thin films are difficult to inadvertently aspirate and provide an increased patient compliance because they need not be swallowed like a tablet. Moreover, certain embodiments of the inventive films are designed to adhere to the buccal cavity and tongue, where they controllably dissolve. Furthermore, thin films may not be crushed in the manner of controlled release tablets which is a problem leading to abuse of drugs such as Oxycontin.

The actives employed in the present invention may be incorporated into the film compositions of the present invention in a controlled release form. For example, particles of drug may be coated with polymers such as ethyl cellulose or polymethacrylate, commercially available under brand names such as Aquacoat ECD and Eudragit E-100, respectively. Solutions of drug may also be absorbed on such polymer materials and incorporated into the inventive film compositions. Other components such as fats and waxes, as well as sweeteners and/or flavors may also be employed in such controlled release compositions.

The actives may be taste-masked prior to incorporation into the film composition, as set forth in co-pending PCT application titled, Uniform Films For Rapid Dissolve Dosage Form Incorporating Taste-Masking Compositions, (based on U.S. Provisional Application No. Express Mail Label No.: EU552991605 US of the same title, filed Sep. 27, 2003, Ser. No. 60/414,276 the entire subject matter of which is incorporated by reference herein.

Actives

When an active is introduced to the film, the amount of active per unit area is determined by the uniform distribution of the film. For example, when the films are cut into individual dosage forms, the amount of the active in the dosage form can be known with a great deal of accuracy. This is achieved because the amount of the active in a given area is substantially identical to the amount of active in an area of the same dimensions in another part of the film. The accuracy in dosage is particularly advantageous when the active is a medicament, i.e. a drug.

The active components that may be incorporated into the films of the present invention include, without limitation pharmaceutical and cosmetic actives, drugs, medicaments, proteins, antigens or allergens such as ragweed pollen, spores, microorganisms, seeds, mouthwash components, flavors, fragrances, enzymes, preservatives, sweetening agents, colorants, spices, vitamins and combinations thereof.

A wide variety of medicaments, bioactive active substances and pharmaceutical compositions may be included in the dosage forms of the present invention. Examples of useful drugs include ace-inhibitors, antianginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, biological response modifiers, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, anti-tumor drugs, anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, anti-convulsants, neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, terine relaxants, anti-obesity drugs, erythropoietic drugs, anti-asthmatics, cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

Examples of medicating active ingredients contemplated for use in the present invention include antacids, H_2-antagonists, and analgesics. For example, antacid dosages can be prepared using the ingredients calcium carbonate alone or in combination with magnesium hydroxide, and/or aluminum hydroxide. Moreover, antacids can be used in combination with H_2-antagonists.

Analgesics include opiates and opiate derivatives, such as oxycodone (available as Oxycontin®), ibuprofen, aspirin, acetaminophen, and combinations thereof that may optionally include caffeine.

Other preferred drugs for other preferred active ingredients for use in the present invention include anti-diarrheals such as immodium AD, anti-histamines, anti-tussives, decongestants, vitamins, and breath fresheners. Common drugs used alone or in combination for colds, pain, fever, cough, congestion, runny nose and allergies, such as acetaminophen, chlorpheniramine maleate, dextromethorphan, pseudoephedrine HCl and diphenhydramine may be included in the film compositions of the present invention.

Also contemplated for use herein are anxiolytics such as alprazolam (available as Xanax®); anti-psychotics such as clozopin (available as Clozaril®) and haloperidol (available as Haldol®); non-steroidal anti-inflammatories (NSAID's) such as dicyclofenacs (available as Voltaren®) and etodolac (available as Lodine®), anti-histamines such as loratadine (available as Claritin®), astemizole (available as Hismanal™), nabumetone (available as Relafen®), and Clemastine (available as Tavist®); anti-emetics such as granisetron hydrochloride (available as Kytril®) and nabilone (available as Cesamet™); bronchodilators such as Bentolin®, albuterol sulfate (available as Proventil®); anti-depressants such as fluoxetine hydrochloride (available as Prozac®), sertraline hydrochloride (available as Zoloft®), and paroxetine hydrochloride (available as Paxil®); anti-migraines such as Imigra®, ACE-inhibitors such as enelaprilat (available as Vasotec®), captopril (available as Capoten®) and lisinopril (available as Zestril®); anti-Alzheimer's agents, such as nicergoline; and Ca^H-antagonists such as nifedipine (available as Procardia® and Adalat®), and verapamil hydrochloride (available as Calan®).

Erectile dysfunction therapies include, but are not limited to, drugs for facilitating blood flow to the penis, and for effecting autonomic nervous activities, such as increasing

parasympathetic (cholinergic) and decreasing sympathetic (adrenersic) activities. Useful non-limiting drugs include sildenafils, such as Viagra®, tadalafils, such as Cialis®, vardenafils, apomorphines, such as Uprima®, yohimbine hydrochlorides such as Aphrodyne®, and alprostadils such as Caverject®.

The popular H_2-antagonists which are contemplated for use in the present invention include cimetidine, ranitidine hydrochloride, famotidine, nizatidine, ebrotidine, mifentidine, roxatidine, pisatidine and aceroxatidine.

Active antacid ingredients include, but are not limited to, the following: aluminum hydroxide, dihydroxyaluminum aminoacetate, aminoacetic acid, aluminum phosphate, dihydroxyaluminum sodium carbonate, bicarbonate, bismuth aluminate, bismuth carbonate, bismuth subcarbonate, bismuth subgallate, bismuth subnitrate, bismuth subsilysilate, calcium carbonate, calcium phosphate, citrate ion (acid or salt), amino acetic acid, hydrate magnesium aluminate sulfate, magaldrate, magnesium aluminosilicate, magnesium carbonate, magnesium glycinate, magnesium hydroxide, magnesium oxide, magnesium trisilicate, milk solids, aluminum mono- or di-basic calcium phosphate, tricalcium phosphate, potassium bicarbonate, sodium tartrate, sodium bicarbonate, magnesium aluminosilicates, tartaric acids and salts.

The pharmaceutically active agents employed in the present invention may include allergens or antigens, such as, but not limited to, plant pollens from grasses, trees, or ragweed; animal danders, which are tiny scales shed from the skin and hair of cats and other furred animals; insects, such as house dust mites, bees, and wasps; and drugs, such as penicillin.

An anti-oxidant may also be added to the film to prevent the degradation of an active, especially where the active is photosensitive.

Cosmetic active agents may include breath freshening compounds like menthol, other flavors or fragrances, especially those used for oral hygiene, as well as actives used in dental and oral cleansing such as quaternary ammonium bases. The effect of flavors may be enhanced using flavor enhancers like tartaric acid, citric acid, vanillin, or the like.

Also color additives can be used in preparing the films. Such color additives include food, drug and cosmetic colors (FD&C), drug and cosmetic colors (D&C), or external drug and cosmetic colors (Ext. D&C). These colors are dyes, their corresponding lakes, and certain natural and derived colorants. Lakes are dyes absorbed on aluminum hydroxide.

Other examples of coloring agents include known azo dyes, organic or inorganic pigments, or coloring agents of natural origin. Inorganic pigments are preferred, such as the oxides or iron or titanium, these oxides, being added in concentrations ranging from about 0.001 to about 10%, and preferably about 0.5 to about 3%, based on the weight of all the components.

Flavors may be chosen from natural and synthetic flavoring liquids. An illustrative list of such agents includes volatile oils, synthetic flavor oils, flavoring aromatics, oils, liquids, oleoresins or extracts derived from plants, leaves, flowers, fruits, stems and combinations thereof. A non-limiting representative list of examples includes mint oils, cocoa, and citrus oils such as lemon, orange, grape, lime and grapefruit and fruit essences including apple, pear, peach, grape, strawberry, raspberry, cherry, plum, pineapple, apricot or other fruit flavors.

The films containing flavorings may be added to provide a hot or cold flavored drink or soup. These flavorings include, without limitation, tea and soup flavorings such as beef and chicken.

Other useful flavorings include aldehydes and esters such as benzaldehyde (cherry, almond), citral i.e., alphacitral (lemon, lime), neral, i.e., beta-citral (lemon, lime), decanal (orange, lemon), aldehyde C-8 (citrus fruits), aldehyde C-9 (citrus fruits), aldehyde C-12 (citrus fruits), tolyl aldehyde (cherry, almond), 2,6-dimethyloctanol (green fruit), and 2-dodecenal (citrus, mandarin), combinations thereof and the like.

The sweeteners may be chosen from the following non-limiting list: glucose (corn syrup), dextrose, invert sugar, fructose, and combinations thereof saccharin and its various salts such as the sodium salt; dipeptide sweeteners such as aspartame; dihydrochalcone compounds, glycyrrhizin; Stevia Rebaudiana (Stevioside); chloro derivatives of sucrose such as sucralose; sugar alcohols such as sorbitol, mannitol, xylitol, and the like. Also contemplated are hydrogenated starch hydrolysates and the synthetic sweetener 3,6-dihydro-6-methy-1-1-1-1,2,3-oxathiazin-4-one-2,2-dioxide, particularly the potassium salt (acesulfame-K), and sodium and calcium salts thereof, and natural intensive sweeteners, such as Lo Han Kuo. Other sweeteners may also be used.

When the active is combined with the polymer in the solvent, the type of matrix that is formed depends on the solubilities of the active and the polymer. If the active and/or polymer are soluble in the selected solvent, this may form a solution. However, if the components are not soluble, the matrix may be classified as an emulsion, a colloid, or a suspension.

Dosages

The film products of the present invention are capable of accommodating a wide range of amounts of the active ingredient. The films are capable of providing an accurate dosage amount (determined by the size of the film and concentration of the active in the original polymer/water combination) regardless of whether the required dosage is high or extremely low. Therefore, depending on the type of active or pharmaceutical composition that is incorporated into the film, the active amount may be as high as about 300 mg, desirably up to about 150 mg or as low as the microgram range, or any amount therebetween.

The film products and methods of the present invention are well suited for high potency, low dosage drugs. This is accomplished through the high degree of uniformity of the films. Therefore, low dosage drugs, particularly more potent racemic mixtures of actives are desirable.

Anti-Foaming and De-Foaming Compositions

Anti-foaming and/or de-foaming components may also be used with the films of the present invention. These components aid in the removal of air, such as entrapped air, from the film-forming compositions. As described above, such entrapped air may lead to non-uniform films. Simethicone is one particularly useful anti-foaming and/or de-foaming agent. The present invention, however, is not so limited and other anti-foam and/or de-foaming agents may suitable be used.

As a related matter, simethicone and related agents may be employed for densification purposes. More specifically, such agents may facilitate the removal of voids, air, moisture, and similar undesired components, thereby providing denser, and thus more uniform films. Agents or components which perform this function can be referred to as densification or densifying agents. As described above, entrapped air or undesired components may lead to non-uniform films.

Simethicone is generally used in the medical field as a treatment for gas or colic in babies. Simethicone is a mixture of fully methylated linear siloxane polymers containing

repeating units of polydimethylsiloxane which is stabilized with trimethylsiloxy end-blocking unites, and silicon dioxide. It usually contains 90.5-99% polymethylsiloxane and 4-7% silicon dioxide. The mixture is a gray, translucent, viscous fluid which is insoluble in water.

When dispersed in water, simethicone will spread across the surface, forming a thin film of low surface tension. In this way, simethicone reduces the surface tension of bubbles air located in the solution, such as foam bubbles, causing their collapse. The function of simethicone mimics the dual action of oil and alcohol in water. For example, in an oily solution any trapped air bubbles will ascend to the surface and dissipate more quickly and easily, because an oily liquid has a lighter density compared to a water solution. On the other hand, an alcohol/water mixture is known to lower water density as well as lower the water's surface tension. So, any air bubbles trapped inside this mixture solution will also be easily dissipated. Simethicone solution provides both of these advantages. It lowers the surface energy of any air bubbles that trapped inside the aqueous solution, as well as lowering the surface tension of the aqueous solution. As the result of this unique functionality, simethicone has an excellent anti-foaming property that can be used for physiological processes (anti-gas in stomach) as well as any for external processes that require the removal of air bubbles from a product.

In order to prevent the formation of air bubbles in the films of the present invention, the mixing step can be performed under vacuum. However, as soon as the mixing step is completed, and the film solution is returned to the normal atmosphere condition, air will be re-introduced into or contacted with the mixture. In many cases, tiny air bubbles will be again trapped inside this polymeric viscous solution. The incorporation of simethicone into the film-forming composition either substantially reduces or eliminates the formation of air bubbles.

Simethicone may be added to the film-forming mixture as an anti-foaming agent in an amount from about 0.01 weight percent to about 5.0 weight percent, more desirably from about 0.05 weight percent to about 2.5 weight percent, and most desirably from about 0.1 weight percent to about 1.0 weight percent.

Optional Components

A variety of other components and fillers may also be added to the films of the present invention. These may include, without limitation, surfactants; plasticizers which assist in compatibilizing the components within the mixture; polyalcohols; anti-foaming agents, such as silicone-containing compounds, which promote a smoother film surface by releasing oxygen from the film; thermo-setting gels such as pectin, carageenan, and gelatin, which help in maintaining the dispersion of components; and inclusion compounds, such as cyclodextrins and caged molecules, which improve the solubility and/or stability of certain active components.

The variety of additives that can be incorporated into the inventive compositions may provide a variety of different functions. Examples of classes of additives include excipients, lubricants, buffering agents, stabilizers, blowing agents, pigments, coloring agents, fillers, bulking agents, sweetening agents, flavoring agents, fragrances, release modifiers, adjuvants, plasticizers, flow accelerators, mold release agents, polyols, granulating agents, diluents, binders, buffers, absorbents, glidants, adhesives, anti-adherents, acidulants, softeners, resins, demulcents, solvents, surfactants, emulsifiers, elastomers and mixtures thereof. These additives may be added with the active ingredient(s).

Useful additives include, for example, gelatin, vegetable proteins such as sunflower protein, soybean proteins, cotton seed proteins, peanut proteins, grape seed proteins, whey proteins, whey protein isolates, blood proteins, egg proteins, acrylated proteins, water-soluble polysaccharides such as alginates, carrageenans, guar gum, agar-agar, xanthan gum, gellan gum, gum arabic and related gums (gum ghatti, gum karaya, gum tragacanth), pectin, water-soluble derivatives of cellulose: alkylcelluloses hydroxyalkylcelluloses and hydroxyalkylalkylcelluloses, such as methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxyethylmethylcellulose, hydroxypropylmethylcellulose, hydroxybutylmethylcellulose, cellulose esters and hydroxyalkylcellulose esters such as cellulose acetate phthalate (CAP), hydroxypropylmethylcellulose (HPMC); carboxyalkylcelluloses, carboxyalkylalkylcelluloses, carboxyalkylcellulose esters such as carboxymethylcellulose and their alkali metal salts; water-soluble synthetic polymers such as polyacrylic acids and polyacrylic acid esters, polymethacrylic acids and polymethacrylic acid esters, polyvinylacetates, polyvinylalcohols, polyvinylacetatephthalates (PVAP), polyvinylpyrrolidone (PVP), PVY/vinyl acetate copolymer, and polycrotonic acids; also suitable are phthalated gelatin, gelatin succinate, crosslinked gelatin, shellac, water soluble chemical derivatives of starch, cationically modified acrylates and methacrylates possessing, for example, a tertiary or quaternary amino group, such as the diethylaminoethyl group, which may be quaternized if desired; and other similar polymers.

Such extenders may optionally be added in any desired amount desirably within the range of up to about 80%, desirably about 3% to 50% and more desirably within the range of 3% to 20% based on the weight of all components.

Further additives may be inorganic fillers, such as the oxides of magnesium aluminum, silicon, titanium, etc. desirably in a concentration range of about 0.02% to about 3% by weight and desirably about 0.02% to about 1% based on the weight of all components.

Further examples of additives are plasticizers which include polyalkylene oxides, such as polyethylene glycols, polypropylene glycols, polyethylene-propylene glycols, organic plasticizers with low molecular weights, such as glycerol, glycerol monoacetate, diacetate or triacetate, triacetin, polysorbate, cetyl alcohol, propylene glycol, sorbitol, sodium diethylsulfosuccinate, triethyl citrate, tributyl citrate, and the like, added in concentrations ranging from about 0.5% to about 30%, and desirably ranging from about 0.5% to about 20% based on the weight of the polymer.

There may further be added compounds to improve the flow properties of the starch material such as animal or vegetable fats, desirably in their hydrogenated form, especially those which are solid at room temperature. These fats desirably have a melting point of 50° C. or higher. Preferred are tri-glycerides with C_{12}-, C_{14}-, C_{16}-, C_{18}-, C_{20}- and C_{22}-fatty acids. These fats can be added alone without adding extenders or plasticizers and can be advantageously added alone or together with mono- and/or di-glycerides or phosphatides, especially lecithin. The mono- and di-glycerides are desirably derived from the types of fats described above, i.e. with C_{12}-, C_{14}-, C_{16}-, C_{18}-, C_{20}- and C_{22}-fatty acids.

The total amounts used of the fats, mono-, di-glycerides and/or lecithins are up to about 5% and preferably within the range of about 0.5% to about 2% by weight of the total composition

It is further useful to add silicon dioxide, calcium silicate, or titanium dioxide in a concentration of about 0.02% to about 1% by weight of the total composition. These compounds act as texturizing agents.

These additives are to be used in amounts sufficient to achieve their intended purpose. Generally, the combination of certain of these additives will alter the overall release profile of the active ingredient and can be used to modify, i.e. impede or accelerate the release.

Lecithin is one surface active agent for use in the present invention. Lecithin can be included in the feedstock in an amount of from about 0.25% to about 2.00% by weight. Other surface active agents, i.e. surfactants, include, but are not limited to, cetyl alcohol, sodium lauryl sulfate, the Spans™ and Tweens™ which are commercially available from ICI Americas, Inc. Ethoxylated oils, including ethoxylated castor oils, such as Cremophor® EL which is commercially available from BASF, are also useful. Carbowax™ is yet another modifier which is very useful in the present invention. Tweens™ or combinations of surface active agents may be used to achieve the desired hydrophilic-lipophilic balance ("HLB"). The present invention, however, does not require the use of a surfactant and films or film-forming compositions of the present invention may be essentially free of a surfactant while still providing the desirable uniformity features of the present invention.

As additional modifiers which enhance the procedure and product of the present invention are identified, Applicants intend to include all such additional modifiers within the scope of the invention claimed herein.

Other ingredients include binders which contribute to the ease of formation and general quality of the films. Non-limiting examples of binders include starches, pregelatinize starches, gelatin, polyvinylpyrrolidone, methylcellulose, sodium carboxymethylcellulose, ethylcellulose, polyacrylamides, polyvinyloxoazolidone, and polyvinylalcohols.

Further potential additives include solubility enhancing agents, such as substances that form inclusion compounds with active components. Such agents may be useful in improving the properties of very insoluble and/or unstable actives. In general, these substances are doughnut-shaped molecules with hydrophobic internal cavities and hydrophilic exteriors. Insoluble and/or instable actives may fit within the hydrophobic cavity, thereby producing an inclusion complex, which is soluble in water. Accordingly, the formation of the inclusion complex permits very insoluble and/or instable actives to be dissolved in water. A particularly desirable example of such agents are cyclodextrins, which are cyclic carbohydrates derived from starch. Other similar substances, however, are considered well within the scope of the present invention.

Forming the Film

The films of the present invention must be formed into a sheet prior to drying. After the desired components are combined to form a multi-component matrix, including the polymer, water, and an active or other components as desired, the combination is formed into a sheet or film, by any method known in the art such as extrusion, coating, spreading, casting or drawing the multi-component matrix. If a multi-layered film is desired, this may be accomplished by co-extruding more than one combination of components which may be of the same or different composition. A multi-layered film may also be achieved by coating, spreading, or casting a combination onto an already formed film layer.

Although a variety of different film-forming techniques may be used, it is desirable to select a method that will provide a flexible film, such as reverse roll coating. The flexibility of the film allows for the sheets of film to be rolled and transported for storage or prior to being cut into individual dosage forms. Desirably, the films will also be self-supporting or in other words able to maintain their integrity and structure in the absence of a separate support. Furthermore, the films of the present invention may be selected of materials that are edible or ingestible.

Coating or casting methods are particularly useful for the purpose of forming the films of the present invention. Specific examples include reverse roll coating, gravure coating, immersion or dip coating, metering rod or meyer bar coating, slot die or extrusion coating, gap or knife over roll coating, air knife coating, curtain coating, or combinations thereof, especially when a multi-layered film is desired.

Roll coating, or more specifically reverse roll coating, is particularly desired when forming films in accordance with the present invention. This procedure provides excellent control and uniformity of the resulting films, which is desired in the present invention. In this procedure, the coating material is measured onto the applicator roller by the precision setting of the gap between the upper metering roller and the application roller below it. The coating is transferred from the application roller to the substrate as it passes around the support roller adjacent to the application roller. Both three roll and four roll processes are common.

The gravure coating process relies on an engraved roller running in a coating bath, which fills the engraved dots or lines of the roller with the coating material. The excess coating on the roller is wiped off by a doctor blade and the coating is then deposited onto the substrate as it passes between the engraved roller and a pressure roller.

Offset Gravure is common, where the coating is deposited on an intermediate roller before transfer to the substrate.

In the simple process of immersion or dip coating, the substrate is dipped into a bath of the coating, which is normally of a low viscosity to enable the coating to run back into the bath as the substrate emerges.

In the metering rod coating process, an excess of the coating is deposited onto the substrate as it passes over the bath roller. The wire-wound metering rod, sometimes known as a Meyer Bar, allows the desired quantity of the coating to remain on the substrate. The quantity is determined by the diameter of the wire used on the rod.

In the slot die process, the coating is squeezed out by gravity or under pressure through a slot and onto the substrate. If the coating is 100% solids, the process is termed "Extrusion" and in this case, the line speed is frequently much faster than the speed of the extrusion. This enables coatings to be considerably thinner than the width of the slot.

It may be particularly desirable to employ extrusion methods for forming film compositions containing PEO polymer components. These compositions contain PEO or PEO blends in the polymer component, and may be essentially free of added plasticizers, and/or surfactants, and polyalcohols. The compositions may be extruded as a sheet at processing temperatures of less than about 90° C. Extrusion may proceed by squeezing the film composition through rollers or a die to obtain a uniform matrix. The extruded film composition then is cooled by any mechanism known to those of ordinary skill in the art. For example, chill rollers, air cooling beds, or water cooling beds may be employed. The cooling step is particularly desirable for these film compositions because PEO tends to hold heat.

The gap or knife over roll process relies on a coating being applied to the substrate which then passes through a "gap"

between a "knife" and a support roller. As the coating and substrate pass through, the excess is scraped off.

Air knife coating is where the coating is applied to the substrate and the excess is "blown off" by a powerful jet from the air knife. This procedure is useful for aqueous coatings.

In the curtain coating process, a bath with a slot in the base allows a continuous curtain of the coating to fall into the gap between two conveyors. The object to be coated is passed along the conveyor at a controlled speed and so receives the coating on its upper face.

Drying the Film

The drying step is also a contributing factor with regard to maintaining the uniformity of the film composition. A controlled drying process is particularly important when, in the absence of a viscosity increasing composition or a composition in which the viscosity is controlled, for example by the selection of the polymer, the components within the film may have an increased tendency to aggregate or conglomerate. An alternative method of forming a film with an accurate dosage, that would not necessitate the controlled drying process, would be to cast the films on a predetermined well. With this method, although the components may aggregate, this will not result in the migration of the active to an adjacent dosage form, since each well may define the dosage unit per se.

When a controlled or rapid drying process is desired, this may be through a variety of methods. A variety of methods may be used including those that require the application of heat. The liquid carriers are removed from the film in a manner such that the uniformity, or more specifically, the non-self-aggregating uniform heterogeneity, that is obtained in the wet film is maintained.

Desirably, the film is dried from the bottom of the film to the top of the film. Desirably, substantially no air flow is present across the top of the film during its initial setting period, during which a solid, visco-elastic structure is formed. This can take place within the first few minutes, e.g. about the first 0.5 to about 4.0 minutes of the drying process. Controlling the drying in this manner, prevents the destruction and reformation of the film's top surface, which results from conventional drying methods. This is accomplished by forming the film and placing it on the top side of a surface having top and bottom sides. Then, heat is initially applied to the bottom side of the film to provide the necessary energy to evaporate or otherwise remove the liquid carrier. The films dried in this manner dry more quickly and evenly as compared to air-dried films, or those dried by conventional drying means. In contrast to an air-dried film that dries first at the top and edges, the films dried by applying heat to the bottom dry simultaneously at the center as well as at the edges. This also prevents settling of ingredients that occurs with films dried by conventional means.

The temperature at which the films are dried is about 100° C. or less, desirably about 90° C. or less, and most desirably about 80° C. or less.

Another method of controlling the drying process, which may be used alone or in combination with other controlled methods as disclosed above includes controlling and modifying the humidity within the drying apparatus where the film is being dried. In this manner, the premature drying of the top surface of the film is avoided.

Additionally, it has also been discovered that the length of drying time can be properly controlled, i.e. balanced with the heat sensitivity and volatility of the components, and particularly the flavor oils and drugs. The amount of energy, temperature and length and speed of the conveyor can be balanced to accommodate such actives and to minimize loss, degradation or ineffectiveness in the final film.

A specific example of an appropriate drying method is that disclosed by Magoon. Magoon is specifically directed toward a method of drying fruit pulp. However, the present inventors have adapted this process toward the preparation of thin films.

The method and apparatus of Magoon are based on an interesting property of water. Although water transmits energy by conduction and convection both within and to its surroundings, water only radiates energy within and to water. Therefore, the apparatus of Magoon includes a surface onto which the fruit pulp is placed that is transparent to infrared radiation. The underside of the surface is in contact with a temperature controlled water bath. The water bath temperature is desirably controlled at a temperature slightly below the boiling temperature of water. When the wet fruit pulp is placed on the surface of the apparatus, this creates a "refractance window." This means that infrared energy is permitted to radiate through the surface only to the area on the surface occupied by the fruit pulp, and only until the fruit pulp is dry. The apparatus of Magoon provides the films of the present invention with an efficient drying time reducing the instance of aggregation of the components of the film.

Another method of controlling the drying process involves a zone drying procedure. A zone drying apparatus may include a continuous belt drying tunnel having one or more drying zones located within. The conditions of each drying zone may vary, for example, temperature and humidity may be selectively chosen. It may be desirable to sequentially order the zones to provide a stepped up drying effect.

The speed of the zone drying conveyor desirably is continuous. Alternatively, the speed may be altered at a particular stage of the drying procedure to increase or decrease exposure of the film to the conditions of the desired zone. Whether continuous or modified, the zone drying dries the film without surface skinning.

According to an embodiment of the zone drying apparatus **100**, shown in FIG. **35**, the film **110** may be fed onto the continuous belt **120**, which carries the film through the different drying zones. The first drying zone that the film travels through **101** may be a warm and humid zone. The second zone **102** may be hotter and drier, and the third zone **103** may also be hot and dry. These different zones may be continuous, or alternatively, they may be separated, as depicted by the zone drying apparatus **200** in FIG. **36**. The zone drying apparatus, in accordance with the present invention, is not limited to three drying zones. The film may travel through lesser or additional drying zones of varying heat and humidity levels, if desired, to produce the controlled drying effect of the present invention.

To further control temperature and humidity, the drying zones may include additional atmospheric conditions, such as inert gases. The zone drying apparatus further may be adapted to include additional processes during the zone drying procedure, such as, for example, spraying and laminating processes, so long as controlled drying is maintained in accordance with the invention.

The films may initially have a thickness of about 500 μm to about 1,500 μm, or about 20 mils to about 60 mils, and when dried have a thickness from about 3 μm to about 250 μm, or about 0.1 mils to about 10 mils. Desirably, the dried films will have a thickness of about 2 mils to about 8 mils, and more desirably, from about 3 mils to about 6 mils.

Testing Films for Uniformity

It may be desirable to test the films of the present invention for chemical and physical uniformity during the film manu-

facturing process. In particular, samples of the film may be removed and tested for uniformity in film components between various samples. Film thickness and over all appearance may also be checked for uniformity. Uniform films are desired, particularly for films containing pharmaceutical active components for safety and efficacy reasons.

A method for testing uniformity in accordance with the present invention includes conveying a film through a manufacturing process. This process may include subjecting the film to drying processes, dividing the film into individual dosage units, and/or packaging the dosages, among others. As the film is conveyed through the manufacturing process, for example on a conveyor belt apparatus, it is cut widthwise into at least one portion. The at least one portion has opposing ends that are separate from any other film portion. For instance, if the film is a roll, it may be cut into separate sub-rolls. Cutting the film may be accomplished by a variety of methods, such as with a knife, razor, laser, or any other suitable means for cutting a film.

The cut film then may be sampled by removing small pieces from each of the opposed ends of the portion(s), without disrupting the middle of the portion(s). Leaving the middle section intact permits the predominant portion of the film to proceed through the manufacturing process without interrupting the conformity of the film and creating sample-inducted gaps in the film. Accordingly, the concern of missing doses is alleviated as the film is further processed, e.g., packaged. Moreover, maintaining the completeness of cut portions or sub-rolls throughout the process will help to alleviate the possibility of interruptions in further film processing or packaging due to guilty control issues, for example, alarm stoppage due to notice of missing pieces.

After the end pieces, or sampling sections, are removed from the film portion(s), they may be tested for uniformity in the content of components between samples. Any conventional means for examining and testing the film pieces may be employed, such as, for example, visual inspection, use of analytical equipment, and any other suitable means known to those skilled in the art. If the testing results show non-uniformity between film samples, the manufacturing process may be altered. This can save time and expense because the process may be altered prior to completing an entire manufacturing run. For example, the drying conditions, mixing conditions, compositional components and/or film viscosity may be changed. Altering the drying conditions may involve changing the temperature, drying time, moisture level, and dryer positioning, among others.

Moreover, it may be desirable to repeat the steps of sampling and testing throughout the manufacturing process. Testing at multiple intervals may ensure that uniform film dosages are continuously produced. Alterations to the process can be implemented at any stage to minimize non-uniformity between samples.

Uses of Thin Films

The thin films of the present invention are well suited for many uses. The high degree of uniformity of the components of the film makes them particularly well suited for incorporating pharmaceuticals. Furthermore, the polymers used in construction of the films may be chosen to allow for a range of disintegration times for the films. A variation or extension in the time over which a film will disintegrate may achieve control over the rate that the active is released, which may allow for a sustained release delivery system. In addition, the films may be used for the administration of an active to any of several body surfaces, especially those including mucous membranes, such as oral, anal, vaginal, opthalmological, the surface of a wound, either on a skin surface or within a body such as during surgery, and similar surfaces.

The films may be used to orally administer an active. This is accomplished by preparing the films as described above and introducing them to the oral cavity of a mammal. This film may be prepared and adhered to a second or support layer from which it is removed prior to use, i.e. introduction to the oral cavity. An adhesive may be used to attach the film to the support or backing material which may be any of those known in the art, and is preferably not water soluble. If an adhesive is used, it will desirably be a food grade adhesive that is ingestible and does not alter the properties of the active. Mucoadhesive compositions are particularly useful. The film compositions in many cases serve as mucoadhesives themselves.

The films may be applied under or to the tongue of the mammal. When this is desired, a specific film shape, corresponding to the shape of the tongue may be preferred. Therefore the film may be cut to a shape where the side of the film corresponding to the back of the tongue will be longer than the side corresponding to the front of the tongue. Specifically, the desired shape may be that of a triangle or trapezoid. Desirably, the film will adhere to the oral cavity preventing it from being ejected from the oral cavity and permitting more of the active to be introduced to the oral cavity as the film dissolves.

Another use for the films of the present invention takes advantage of the films' tendency to dissolve quickly when introduce to a liquid. An active may be introduced to a liquid by preparing a film in accordance with the present invention, introducing it to a liquid, and allowing it to dissolve. This may be used either to prepare a liquid dosage form of an active, or to flavor a beverage.

The films of the present invention are desirably packaged in sealed, air and moisture resistant packages to protect the active from exposure oxidation, hydrolysis, volatilization and interaction with the environment. Referring to FIG. **1**, a packaged pharmaceutical dosage unit **10**, includes each film **12** individually wrapped in a pouch or between foil and/or plastic laminate sheets **14**. As depicted in FIG. **2**, the pouches **10**, **10'** can be linked together with tearable or perforated joints **16**. The pouches **10**, **10'** may be packaged in a roll as depicted in FIG. **5** or stacked as shown in FIG. **3** and sold in a dispenser **18** as shown in FIG. **4**. The dispenser may contain a full supply of the medication typically prescribed for the intended therapy, but due to the thinness of the film and package, is smaller and more convenient than traditional bottles used for tablets, capsules and liquids. Moreover, the films of the present invention dissolve instantly upon contact with saliva or mucosal membrane areas, eliminating the need to wash the dose down with water.

Desirably, a series of such unit doses are packaged together in accordance with the prescribed regimen or treatment, e.g., a 10-90 day supply, depending on the particular therapy. The individual films can be packaged on a backing and peeled off for use.

The features and advantages of the present invention are more fully shown by the following examples which are provided for purposes of illustration, and are not to be construed as limiting the invention in any way.

EXAMPLES

Examples A-I

Water soluble thin film compositions of the present invention are prepared using the amounts described in Table 1.

TABLE 1

Component	Weight (g) A	B	C	D	E	F	G	H	I
Hydroxypropylmethyl cellulose		1.76		1.63	32.00		3.67		32.00
Peppermint oil		0.90	1.0	1.05		8.0	2.67		
Sweetener	0.15	0.15	0.22	0.10		4.6	1.53	0.15	
Polyvinylpyrrolidone		0.94		1.05		7.0	2.33		
Tween 80[1]	0.5	0.5	2.0	0.65	11.80		1.35	0.5	11.80
Simethicone[2]	0.2	0.2	0.15	0.30	1.80		0.21	0.2	1.80
Listerine[3]	83.35							83.35	
Methylcellulose	6.0								
Cornstarch[4]			1.75						
Agar			1.25						
Water		42.24	93.63	39.22	768.0	280.0	88.24		768.0
Loratadine[5]					19.2				19.2
Pullulan[6]								6.0	
Ibuprofen									38.4

[1]Available from ICI Americas

[2]Available from OSI

[3]Available from Pfizer, Inc. including thymol (0.064%), eucalyptol (0.092%), methyl salicylate (0.060%), menthol (0.042%), water (up to 72.8%), alcohol (26.9%), benzoic acid, poloxamer 407, sodium benzoate, and caramel color

[4]Available from Grain Processing Corporation as Pure Cote B792

[5]Available from Schering Corporation as Claritin

[6]Available from Hayashibara Biochemical Laboratories, Inc., Japan

The ingredients of inventive compositions A-I were combined by mixing until a uniform mixture was achieved. The compositions were then formed into a film by reverse roll coating. These films were then dried on the top side of an infrared transparent surface, the bottom side of which was in contact with a heated water bath at approximately 99° C. No external thermal air currents were present above the film. The films were dried to less than about 6% by weight water in about 4 to 6 minutes. The films were flexible, self-supporting and provided a uniform distribution of the components within the film.

The uniform distribution of the components within the film was apparent by examination by either the naked eye or under slight magnification. By viewing the films it was apparent that they were substantially free of aggregation, i.e. the carrier and the actives remained substantially in place and did not move substantially from one portion of the film to another. Therefore, there was substantially no disparity among the amount of active found in any portion of the film.

Uniformity was also measured by first cutting the film into individual dosage forms. Twenty-five dosage forms of substantially identical size were cut from the film of inventive composition (E) above from random locations throughout the film. Then eight of these dosage forms were randomly selected and additively weighed. The additive weights of eight randomly selected dosage forms, are as shown in Table 2 below:

TABLE 2

Sample	Additive Weight (g) Trial 1	Trial 2
1	0.04	0.04
2	0.08	0.08
3	0.12	0.12
4	0.16	0.16
5	0.20	0.20
6	0.24	0.24
7	0.28	0.28
8	0.32	0.32

The individual dosages were consistently 0.04 gm, which shows that the distribution of the components within the film was consistent and uniform. This is based on the simple principal that each component has a unique density. Therefore, when the components of different densities are combined in a uniform manner in a film, as in the present invention, individual dosages forms from the same film of substantially equal dimensions, will contain the same mass.

An alternative method of determining the uniformity of the active is to cut the film into individual doses. The individual doses may then be dissolved and tested for the amount of active in films of particular size. This demonstrates that films of substantially similar size cut from different locations on the same film contain substantially the same amount of active.

When the films formed from inventive compositions A-H are placed on the tongue, they rapidly dissolve, releasing the active ingredient. Similarly, when they are placed in water, the films rapidly dissolve which provides a flavored drink when the active is chosen to be a flavoring.

Examples J-L

Thin films that have a controlled degradation time and include combinations of water soluble and water insoluble polymers and water soluble films that allow controlled release of an active are prepared using approximately the amounts described in Table 3.

TABLE 3

Component	Weight (g) J	K	L
Hydroxypropylmethyl cellulose		1.0	1.0
Tween 80[1]	0.7	0.7	0.7
Water			5.0
Aquacoat ECD[2]	17.0	17.0	17.5
Peppermint oil	1.0	0.4	1.1

[1]Available from ICI Americas

[2]A 30% by weight aqueous dispersion of ethyl cellulose available from FMC

The components of inventive compositions J-L were combined and formed into films using the methods for preparing

inventive compositions A-I above. These films were also flexible, self-supporting and provided a uniform distribution of active which permits accuracy in dosing.

The uniformity of the films prepared from inventive compositions J-L may also be tested by either visual means measuring the weights of individual dosage films, or by dissolving the films and testing for the amount of active as described above.

Examples M-O

An alternative method of preparing films which provides an accurate dosing may be used for any of inventive compositions A-I. The method begins with first combining the ingredients with mixing. The combination of ingredients is then divided among individual wells or molds. In such a method, aggregation of the components during drying is prevented by the individual wells.

TABLE 4

	Weight %		
Component	M	N	O
5% Methylcellulose Solution[1]	73.22	44.22	74.22
Raspberry Flavor	3.28	3.28	3.28
Sweetener Blends	1.07	1.07	1.07
Tween-80[2]	2.47	2.47	2.47
Polyvinylpyrrolidone	3.30	3.30	3.30
Ethanol 95%	8.24	8.24	8.24
Propylene Glycol	1.65	1.65	1.65
Calcium Carbonate	4.12	4.12	4.12
Cornstarch[3]	1.65	1.65	1.65
Red Dye[4]	1.00		
Corn Syrup[5]		30.00	

[1]Available from Dow Chemical Co. as Methocel K35
[2]Available from ICI Americas
[3]Available from Grain Processing Corporation as Pure Cote B792
[4]Available from McCormick
[5]Available from Bestfoods, Inc. as Karo Syrup

The ingredients in the above Table 4 were combined and formed into a film by casting the combination of ingredients onto the glass surface and applying heat to the bottom side of the glass. This provided inventive compositions M-O.

The film of composition M was examined both prior to and after drying for variations in the shading provided by the red dye. The film was examined both under sunlight and by incandescent bulb light. No variations in shade or intensity of color were observed.

Further testing of the films of composition M included testing of absorption which is directly related to concentration. The film was cut into segments each measuring 1.0 in. by 0.75 in., which were consecutively assigned numbers. Approximately 40 mg of the scrap material from which the segments were cut was dissolved in about 10 ml of distilled water and then quantitatively transferred to a 25 ml volumetric flask and brought to volume. The solution was centrifuged and scanned at 3 nm intervals from 203-1200 nm. The frequency of maximum absorption was found to be 530 nm. The solution was then re-centrifuged at a higher RPM (for the same length of time) and re-scanned, which demonstrated no change in the % transmission or frequency.

Each of the segments were weighed to 0.1 mg and then dissolved in 10 ml distilled water and transferred quantitatively to a 25 ml volumetric flask and brought to volume with distilled water. Each segment solution was then centrifuged as above, and then scanned, at first from 203-1200 nm and later from only 500 nm to 550 nm at a 1 nm scanning speed. The value recorded was the % transmission at the lowest wave length, which was most frequently 530 nm.

The absorption values are shown in Table 5 below:

TABLE 5

Segment	mg/% A
1-2	1.717
3-4	1.700
5-6	1.774
7*	1.701
9-10	1.721
11-12	1.729
13-14	1.725
15-16	1.713

*segment 8 was lost

The overall average absorption was 1.724. Of the 15 segments tested, the difference between the highest and lowest values was 0.073 units, or 4% based on the average. This shows excellent control over the uniformity of the dye within the composition because the absorption is directly proportional to the concentration of the dye within each segment.

The film of inventive composition N provided a very flexible film. This film was able to be stretched and exhibited a very high tensile strength.

After forming the film of inventive composition O, the film was removed from the glass by very rapidly stripping the length of the glass with a razor. This provided very tightly wound "toothpick-like" dosage forms. Each dosage form consistently weighed 0.02 g. This demonstrates the uniformity of the dosage forms as well as the superior self-supporting properties of the films.

Examples P-W

Compositions P-W were prepared to demonstrate the interaction among various conditions in production of films as they relate to the present invention. The ingredients in the below Table 6 were combined and formed into a film using the process parameters listed in Table 7 below, prepared in a 6 m drying tunnel designed to incorporate bottom drying of the films. Each of the examples shows the effect of different ingredient formulations and processing techniques on the resultant film products.

TABLE 6

	Weight (g)							
Component	P	Q	R	S	T	U	V	W
Hydroxy propylmethyl cellulose	320	320	320	320	320	320	345	345
Water	1440	1440	1440	1440		1440	999	999
Sweetener						60	60	45
Mint Flavor						80	80	
Propylene Glycol	50	50	50	100	100	100	100	69.3
Xanthan	22		11	11.23	10	10	10	6.9
Water/ Ethanol (60/40)					1440			
Orange Flavor								42

TABLE 7

	Film Thickness (Micron)	Top[1] v (m/sec)	Bot.[1] v (m/sec)	T[1] (° C.)	Top[2] v (m/sec)
P1	100	0	22	75	0
P2	350	0	22	75	0
P3	350	0	40	75	0
P4	350	0	40	75	0
P5	350	10	40	75	10
Q	350	0	40	75	10
R	350	0	40	85	10
S1	250	0	40	100	0
S2	300	0	40	100	0
S3	350	0	40	100	0
T1	250	0	40	100	0
T2	350	0	40	100	0
U1	300	0	40	100	0
U2	250	0	40	100	0
U3	300	0	40	100	0
V1	300	0	40	100	0
V2	300	0	40	100	0
V3	300	0	40	100	0
W1	300	0	40	93	0
W2	250	0	40	90	0
W3	200	0	40	90	0

	Bot.[2] v (m/sec)	T[2] (° C.)	Film Weight (g)	Coater Speed m/min	% Moisture
P1	23	60	109	5	>20
P2	23	60	n/a	5	>20
P3	40	60	161	3	>20
P4	40	75	191	3	>20
P5	40	75	253	3	>20
Q	40	75	n/a	3	>20
R	0	85		2.5	>20
S1	40	90	163	1.5	<5
S2	40	90	193	1.5	<5
S3	40	90	225	1.5	<5
T1	40	90	64	1.5	<5
T2	40	90	83	1.5	<5
U1	40	90	208	1.5	20
U2	40	90	177	1.5	20
U3	40	90	212	1.3	20
V1	40	90	237	1.3	20
V2	40	100	242	1.3	20
V3	40	100	221	1	6
W1	40	90	220	1.3	5
W2	40	90	199	1.3	5
W3	40	90	169	1.3	5

[1]First Heater Section (3 m)
[2]Second Heater Section (3 m)

In Table 7, each of the process parameters contributes to different properties of the films. Film thickness refers to the distance between the blade and the roller in the reverse roll coating apparatus. Bottom velocity and top velocity refer to the speed of air current on the bottom and top sides of the film, respectively. The film weight is a measure of the weight of a circular section of the substrate and the film of 100 cm^2.

Compositions P-R show the effects of visco-elastic properties on the ability to coat the film composition mixture onto the substrate for film formation. Composition P displayed a stringy elastic property. The wet film would not stay level, the coating was uneven, and the film did not dry. In Composition Q, substantially the same formulation as P was used however the xanthan was not included. This product coated the substrate but would not stay level due to the change in the visco-elastic properties of the wet foam. Composition R was prepared using substantially the same formulation, but incorporated one-half of the amount of xanthan of Composition P. This formulation provided a composition that could be evenly coated. Compositions P-Q demonstrate the importance of proper formulation on the ability of the film matrix to conform to a particular coating technique.

The films produced from Composition S contained a large amount of air in the films. This is shown by the dried film thickness which was the same despite that variation in the coated thickness as in Table 7. Microscopic examination of the film revealed a large number of air bubbles in the film. In order to correct for the addition of air in the films, care must be taken in the mixing process to avoid air inclusion.

Composition T included a change in the solvent to 60/40 water ethanol. Composition T was stirred slowly for 45 min. to deaerate the mixture. The dried weight film products T1 and T2 were consistent with the increase in solids from T1 to T2. The films dried much faster with less than 5% moisture. With the particular combination of ingredients in Composition T, the substitution of part ethanol for part water allowed the film to dry more quickly. The elimination of air from the film as a result of the slow stirring also contributed to the uniformity of the final film product and the faster drying time.

Only water was used as a solvent in Composition U. The dried weight of the U1-U3 changed consistently in accordance with the change in coating thickness indicating that no air bubbles were present. However, these films contained 20% moisture upon exit from the oven, unlike the films of Composition T, which included part ethanol and dried completely.

The amount of solids was increased and the amount of water was decreased in Compositions V1 and V2. The dried weight was greater than U1-U3 due to the increase in solids, however the films still contained 20% moisture upon exit from the oven, similar to Composition U.

The coating line speed was reduced for Composition V3, to prevent premature drying of the exposed top film surface. This film product dried to 6% moisture.

While increasing the amount of solids improved the film weight, longer drying times were required. This was due to the surface of the film sealing preventing easy removal of the water. Therefore, for Compositions W1-W3, the temperature in the first 3 m section of the dryer was decreased. This prevented the premature drying of the top surface of the films. Even at greater film thicknesses, the films were dried to 5% moisture even at faster coater line speeds.

Examples X-AA

TABLE 8

	Weight (g)			
Component	X	Y	Z	AA
Loratadine	104.69			
Zomig		52.35		
Paxil			104.69	
Hydroxypropyl methylcellulose	320	320	320	150
Sweetener blend	60	60	60	0.4
Simethicone	1.5	1.5	1.5	1.5
Propylene glycol	100	100	100	
Water	1440	1440	1440	790
Cream essence				0.4
Polyvinyl pyrrolidinone				4
Ethanol				40
Cocoa				55.2
Polyoxyl-40-stearate				7

Compositions X, Y and Z of Table 8 were taste mask coated using a Glatt coater and Eudragit E-100 polymethacrylate

polymer as the coating. The coating was spray coated at a 20% level. Therefore 10 mg of drug 12.5 mg of the final dry product must be weighed.

The base formula which excluded the drug additive was mixed with care to not incorporate air. After initial mixing the formula was slowly mixed to deaerate over 30 min. During this time the drug was weighed and prepared for addition to the base mix.

For Composition X, the Loratadine (80% drug) was added slowly to the mix with stirring. After 5 min. of stirring, the total mix was added to the pan of a three roll coater set (reverse roll coater) at 30 micron coating thickness.

The process bottom temperature was set at 90° C. with no top heat or air, the bottom air velocity was set at 40 m/sec., and the line speed was set at 1.3 m/min. Total drying time for the film was 4.6 min.

The liquid was coated at 30 microns and dried in the oven in less than 5 min. The film was flexible and a 1"×0.75" piece weighed 70 mg and contained 10 mg of Loratadine.

The experiment was repeated for Compositions Y and Z, Zomig and Paxil, respectively. Both produced flexible films with the target weight of 70 mg containing 5 mg of Zomig and 70 mg containing 10 mg of Paxil, respectively.

The products were sweet without any noticeable drug aftertaste.

Examples BA-BI

The incorporation of the anti-foaming/de-foaming agent (i.e., simethicone) provided a film that not only provided a uniform film that substantially reduced or eliminated air bubbles in the film product, but also provided other benefits. The films displayed more desirable organoleptic properties. The films had an improved texture that was less "paper-like" provided a better mouth-feel to the consumer.

The compositions in Table 9 were prepared (including the addition of simethicone in inventive compositions BA-BG) and mixed under vacuum to remove air bubbles.

The resultant uncut films of inventive compositions BA-BG exhibited uniformity in content particularly with respect to the insoluble active, as well as unit doses of ¾" by 1" by 5 mils cut therefrom. The inventive compositions also were observed to have a smooth surface, absent of air bubbles. The significantly higher amounts of simethicone present in inventive compositions BF-BG also provided a very uniform film, but not significantly improved from that of inventive compositions BA-BE.

By contrast, comparative examples BH-BI were observed to have a rougher surface, exhibiting the inclusion of air bubbles in the resultant film which provided a less uniform texture and distribution of the ingredients.

TABLE 9

Component	BA	BB	BC	BD	BE	BF	BG	BH	BI
Hydroxypropylmethyl cellulose	0	3.77	3.70	3.84	0	3.67	0	0	3.84
Peppermint oil	2.94	1.93	2.39	0	0	2.67	2.94	2.67	0
Sweetener	2.20	0.32	0.23	0	0.17	1.53	2.20	1.54	0
Polyvinylpyrrolidone	2.68	2.01	2.39	0	0	2.33	2.68	2.34	0
Tween 80[1]	2.24	1.07	1.48	1.42	0.55	1.35	2.24	0	1.42
Simethicone[2]	0.66	0.42	0.68	0.22	0.22	5.00	2.00	0	0
Listerine[3]	0	0	0	0	92.41	0	0	0	0
Methylcellulose	4.03	0	0	0	0	0	4.03	0	0
Cornstarch[4]	2.68	0	0	0	0	0	2.68	0	0
Water	73.53	90.47	89.14	92.22	0	83.45	72.19	93.46	92.44
Loratadine[5]	4.29	0	0	2.31	0	0	4.29	0	2.31
Pullulan[6]	0	0	0	0	6.65	0	0	0	0
Calcium Carbonate	1.43	0	0	0	0	0	1.43	0	0
Xanthan Gum	0.30	0	0	0	0	0	0.30	0	0
Propylene Glycol	3.02	0	0	0	0	0	3.02	0	0

[1]Available from ICI Americas

[2]Available from OSI

[3]Available from Pfizer, Inc. including thymol (0.064%), eucalyptol (0.092%), methyl salicylate (0.060%), menthol (0.042%), water (up to 72.8%), alcohol (26.9%), benzoic acid, poloxamer 407, sodium benzoate, and caramel color

[4]Available from Grain Processing Corporation as Pure Cote B792

[5]Available from Schering Corporation as Claritin

[6]Available from Hayashibara Biochemical Laboratories, Inc., Japan

The ingredients of Composition AA were mixed in order to reduce air captured in the fluid matrix. After mixing 45 g of loratadine coated at a 80% active level and 20% coating using Eudragit E-100, this mixture was added slowing with mixing until the drug was evenly dispersed, approximately 5 min. The liquid was then deposited into the 3 roll coater (reverse roll coater) and coated at 30 microns at a line speed of 1.3 m/min. The oven temperature was set at 90° C. to apply air and heat to the bottom only, with an air velocity set at 40 m/sec. The dried film was 0.005 inch. thick (5 mil) and was cut into 1 in.×0.75 in. pieces weighing 70 mg+/−0.7 mg, demonstrating the uniformity of the composition of the film. The film was flexible with 5% moisture, free of air bubbles, and had uniform drug distribution as seen under the light microscope, as well as shown by the substantially identical weight measurements of the film pieces.

Examples CA-CC

The following examples of the present invention describe films and film-forming compositions that use an ethoxylated caster oil as a surfactant, or alternatively are free of surfactants, plasticizers and/or polyalcohols. Desirably, the films or film-forming compositions of the present invention are essentially free of surfactants. Moreover, the films or film-forming compositions of the present invention are desirably formulated to be essentially free of surfactants. Furthermore, the films or film-forming compositions of the present invention are desirably formulated to be essentially free of plasticizers. Still furthermore, the films or film-forming compositions of the present invention are desirably formulated to be essentially free of polyalcohols. Moreover, the films or film-form-

ing compositions of the present invention are desirably formulated to be essentially free of surfactants and plasticizers. Furthermore, the films or film-forming compositions of the present invention are desirably formulated to be essentially free of surfactants, plasticizers and polyalcohols.

TABLE 10

Component	(parts by wt.) CA
POLYMERS:	
Hydroxypropylmethyl cellulose	15.6
Cornstarch[1]	10.41
Polyvinylpyrrolidone	10.41
Xanthan Gum	1.14
SURFACTANT[2]:	2.0
PLASTICIZER[3]:	11.67
ANTI-FOAM AGENT[4]	2.44
OTHER	
Spearmint Flavor	10.43
Loratadine (drug)	16.62
Calcium Carbonate	5.54
Sweetener	9.36

[1]Available from Grain Processing Corporation as Pure Cote B792
[2]Ethoxylated caster oil, Cremophor ® EL available from BASF
[3]Propylene Glycol
[4]Silicone Emulsion

The above ingredients were added at 30% to 70% water and stirred until polymers were fully hydrated which took 45 min. The mix was then put under vacuum to eliminate entrapped air. Vacuum was added in a steady manner starting at 500 mm and progressing up to 760 mm over 45 min.

After release of the vacuum, 6 grams of the liquid was added to a coating paper using a 200 micron spiral wound rod and a K Control Coater Model 101 (RK Print Coat Inst. Ltd.). The paper substrate onto which the coating was added was a silicone coated paper. The coated paper was then dried at 90° C. until about 5% moisture remained. The formula coated and dried to a film thickness of approx. 60 microns and quickly dissolved in the mouth.

TABLE 11

Component	(parts by wt.) CB
POLYMERS:	
Hydroxypropylmethyl cellulose	15.6
Cornstarch[1]	10.41
Polyvinylpyrrolidone	10.41
PLASTICIZER/SOLVENT[2]:	22.1
ANTI-FOAM AGENT[3]	2.44
OTHER	
Raspberry Flavor	0.3
Calcium Carbonate[4]	30.38
Sweetener	8.36

[1]Available from Grain Processing Corporation as Pure Cote B792
[2]Propylene Glycol
[3]Polydimethyl Siloxane Emulsion
[4]Functioned to mimic drug loading

The above ingredients were added to water at 40% until a homogeneous suspension was made. Vacuum was added over 20 min. starting at 500 mm Hg. and ending at 660 mm Hg. until all air was removed from suspension. Film was made as described in prior experiments. The liquid coated the silicone release substrate and dried to a uniform flexible film. The film passed the 180° bend test without cracking and dissolved in the mouth.

TABLE 12

Component	(parts by wt.) CC
POLYMERS:	
Hydroxypropylmethyl cellulose	7.8
Hydroxypropyl cellulose	7.8
ANTI-FOAM AGENT[1]	0.75
OTHER	
Peppermint & Bittermint Flavor	2.25
Tastemasking Flavor[2]	0.3
Calcium Carbonate[3]	15.2
Sweeteners	0.9

[1]Polydimethyl Siloxane Emulsion
[2]Prosweet from Virginia Dare
[3]Functioned to mimic drug loading

The above ingredients were added at 30% to 70% water and stirred until polymers were fully hydrated which took 20 min. The mix was then put under vacuum to eliminate entrapped air. Vacuum was added in a steady manner up to 760 mm over 35 min.

After release of the vacuum, the liquid was added to a coating paper using a 350 micron smooth bar and a K Control Coater Model 101 (RK Print Coat Inst. Ltd.). The paper substrate onto which the coating was added was a silicone coated paper. The coated paper was then dried at 90° C. until about 4% moisture remained. The formula coated and dried to a film. The film had an acceptable taste and quickly dissolved in the mouth. The taste-masking flavor is an ingredient that affects the taste receptors to mask the receptors from registering a different, typical undesirable, taste. The film passed the 180° bend test without cracking and dissolved in the mouth.

Example CD

The following example of the present invention describes films and film-forming compositions that use a taste-masked, pharmaceutically active agent which also contains flavors and taste-masking aids. A taste-masking flavor is an ingredient that effects taste receptors to mask the receptors from registering a different, typically undesirable, taste.

TABLE 13

Component	(grams) CD
Hydroxypropylmethyl cellulose	4.26
Hydroxypropyl cellulose	1.42
Precipitated calcium Carbonate	1.22
Sweetner[1]	0.6
Taste-Masking flavor[2]	0.08
Taste-masked Acetaminophen[3]	5.86
Cinnamon Flavor	0.9
Spearmint Flavor	0.43
Polydimethylsiloxane emulsion	0.23

[1]Sucralose, available from McNeil Nutritionals
[2]Magna Sweet, available from Mafco Worldwide Corp.
[3]Gutte Enteric, coated acetaminophen, Gatte, LLC

The above ingredients, except for the pharmaceutically active agent and flavors, were added at 35 grams water and stirred until polymers were fully hydrated which took about 20 min. Food coloring (7 drops of red food coloring and 1

drop of yellow fool coloring) was also added. The mix was then put under vacuum to eliminate entrapped air. Vacuum was added in a steady manner starting at 500 mm and progressing up to 760 mm over about 10 to 20 minutes. The taste-masked Acetaminophen was added to the mix in about 4 minutes was stirring under vacuum. The flavors were then added to the mix in about 4 minutes was stirring under vacuum.

After release of the vacuum, the liquid solution was added to a coating paper using a 350 micron smooth bar. The paper substrate onto which the coating was added was a silicone coated paper. The coated paper was then dried at 90° C. for about 11 minutes until about 3% moisture remained.

The formula coated and dried to a film. The film had an acceptable taste and moderately quickly dissolved in the mouth. The film did not curl on standing. The film passed the 180° bend test without cracking and dissolved in the mouth.

Examples CE-CF

Thin film compositions of the present invention were prepared using the amounts described in Table 14.

TABLE 14

Component	Weight (g)
Hydroxypropylmethyl cellulose	3.92
Pullulan	3.92
Trehalose[1]	3.5
Precipitated Calcium Carbonate	3.85
Propylene Glycol	1.96
Simethicone[2]	0.35
Bovine Extract[3]	32.5
Water	q.s.

[1]Available from Cargill Inc.
[2]Available from Sentry
[3]Available from Amarillo Biosciences Inc.

The above ingredients were combined by mixing until a uniform mixture was achieved. A sufficient amount of water was present in the film compositions prior to drying, i.e., q.s., which may range between about 200 g to about 1000 g. The bovine extract protein contained in the compositions is a heat sensitive protein. After mixing, the compositions were cast into films on release paper using a K-Control Coater with a 250 micron smooth bar.

In Example CE, the films subsequently were dried in an oven at approximately 80° C. for about 6 minutes. The films were dried to about 4.3 percent moisture. In Example CF, the films were dried in an oven at approximately 60° C. for about 10 minutes. The films were dried to about 5.06 percent moisture. After drying, the protein derived from bovine extract, which was contained in the films, was tested to determine whether or not it remained substantially active. To test the activity, a film dosage unit of this example was administered to a human. After ingesting the dosage, a microarray on the human's blood was conducted. The results, listed in Appendix A which is incorporated by reference herein, and graphically represented in FIG. **32**, demonstrate that the protein was approximately 100 percent active in the final, dried film products of both Examples CE and CF. Therefore, the heat sensitive active did not substantially degrade or denaturize during the drying process.

Example CG

Thin film compositions of the present invention were prepared using the amounts described in Table 15.

TABLE 15

Component	Weight (g unless otherwise indicated) CG	CH
Hydroxypropylmethyl cellulose	4.59	9.18
Hydroxypropyl cellulose	1.53	3.06
Sucralose[1]	0.7	1.4
Magna Sweet[2]	0.09	0.18
Precipitated calcium carbonate	2.0	4
Fat-coated dextromethorphan hydrobromide	5.96	11.93
Orange concentrate flavor	1.05	2.1
Prosweet MM24[3]	0.18	0.35
Propylene glycol	1.22	2.45
Simethicone[4]	0.18	0.35
Water	32.5	65
Red food color		4 drops
Yellow food color		6 drops

[1]Available from McNeil Nutritional
[2]Taste-masking flavor, available from Mafco Worldwide Corp.
[3]Taste-masking flavor, available from Virginia Dare
[4]Available from Sentry

The above ingredients in the amounts listed for CG were combined by mixing, and then cast into two films on release paper using a K-Control Coater with a 350 micron smooth bar. The films were subsequently dried according to conventional drying techniques, rather than via the uniform drying process of the present invention. One film was dried in an oven at 80° C. for 9 minutes on a wire rack. The second film was dried in an oven at 80° C. for 9 minutes on a wire screen. Both films were dried to about 2.4 percent moisture.

The resulting dried films showed imprints of the wire rack and screen after drying. These configurations comprise imprints of wire supports typically used in the drying process. Without uniform heat diffusion, the wire supports conducted heat more intensely at the points of contact with the substrate, leading to increased evaporation at these points. This caused more vigorous mixing, thereby pulling more particles to the contact points. The result is increased particle density seen as aggregations at the contact points.

The solution was cast into two more films on release paper using the K-Control Coater with a 350 micron smooth bar. These films were dried by the process of the present invention, under the same time and temperature conditions as above. In particular, the films were dried in an 80° C. air oven for 9 minutes on trays lined with furnace filters, which uniformly disperse heat. The films were dried to about 1.89 percent moisture. The resulting films had no streaks, and were homogenous. Due to uniform heat diffusion throughout the film, no particle aggregations developed.

Example CH

The ingredients in Table 15, in the amounts listed for CH, were combined by mixing, and then cast into three films on release paper using a K-Control Coater with a 350 micron smooth bar. The films were dried for 9 minutes in an 80° C. air oven on trays lined with furnace filters, which uniformly distribute heat. The films were dried to about 2.20 percent moisture. As depicted in FIG. **17**, the dried films **200** had no streaks, and were homogenous, i.e., no particle aggregations developed. The active particles appeared intact in the dried films. The films exhibited adequate strength and passed the 180° bend test without cracking, in which the films are bent in half with pressure.

The mixed solution was cast into three more films on release paper using a K-Control Coater with a 350 micron smooth bar. These films similarly were dried for 9 minutes in

an 80° C. air oven, but by conventional top and bottom drying means. Two of the films were dried on wire racks, while the third was dried on a wire screen. All three films were dried to about 2.65 percent moisture. The dried films showed the imprints of the wire racks and screen, for the reasons described above in Example CG.

More particularly, the dried films **100** exhibited aggregations **110** of particles in both line and diamond configurations, as shown in FIGS. **9-16**. These configurations comprise imprints of wire supports used in the drying process to display the disuniformity in heat transfer which occurs in conventional top and bottom drying. As discussed above, the wire supports conducted heat more intensely at the points of contact with the substrate, leading to increased evaporation at these points. This caused more vigorous mixing, thereby pulling more particles to the contact points. The resulting increased particle density at the contact points is depicted in FIGS. **9-16**.

Moreover, the fat-coated dextromethorphan particles contained within the films of this example were not destroyed by the drying processes. FIGS. **28-31** depict fat-coated dextromethorphan particles **500** prior to any processing, and particularly, their substantially spherical shape. After exposure to drying conditions of 80° C. for 9 minutes, the fat-coated drug particles **500** were found to have remained intact within the films, i.e., maintained their spherical shape, as shown in FIGS. **18-25**. Although the active particles were exposed to potentially deleterious temperatures, they did not degrade. In contrast, fat-coated dextromethorphan particles placed in an evaporating dish and heated in an air oven at 80° C. for 9 minutes substantially degrade. As seen in FIGS. **26** and **27**, the fat-coated dextromethorphan particles appear completely melted after the exposure.

Example CI

Thin film compositions of the present invention were prepared using the amounts described in Table 16.

TABLE 16

Component	Weight (g unless otherwise indicated)
Hydroxypropylcellulose	6.00
Polyethylene oxide	2.00
Sucralose[1]	0.84
Magna sweet[2]	0.09
Mixture of microcrystalline cellulose and sodium carboxymethylcellulose[3]	0.18
Precipitated calcium carbonate	1.55
Sildenafil[4]	2.91
Peppermint & bittermint flavor	1.75
Prosweet[5]	0.44
Masking flavor[6]	1.31
N,2,3-trimethyl-2-isopropylbutanamide[7]	0.075
Simethicone[8]	0.035
Water	32.5
Blue food coloring	3 drops

[1]Available from McNeil Nutritional
[2]Taste-masking flavor, available from Mafco Worldwide Corp.
[3]Avicel CL-611, available from FMC Biopolymer
[4]Available from Pfizer, Inc. as Viagra ®
[5]Taste-masking flavor, available from Virginia Dare
[6]Available from Ungerer and Co.
[7]Cooling agent
[8]Available from Sentry

The above ingredients were combined by mixing until a uniform mixture was achieved, and then cast into two films on release paper using a K-Control Coater with a 350 micron smooth bar. One film was dried for 10 minutes in an 80° C. air oven to a moisture level of 3.52%, while the second film was dried for 10 minutes in an 80° C. air oven to a moisture level of 3.95%. The dried films had adequate strength and tear resistance. The films passed the 180° bend test without breaking. The films also dissolved at a moderately fast rate in the mouth and exhibited an acceptable flavor.

As mentioned above, the controlled drying process of the present invention allows for uniform drying to occur, whereby evaporative cooling and thermal mixing contribute to the rapid formation of viscoelastic film and the "locking-in" of uniformity of content throughout the film. One of the additional advantages of the present invention is that the film composition reaches its viscoelastic state, and even the fully dried state, without exposing the components of the composition to temperatures which will cause them to be altered or unusable for their intended purpose. For example, heat sensitive drugs, proteins, flavors, sweeteners, volatile components, antigens, antibodies and the like, readily decompose at certain temperatures become inactive or denature, making them ineffective for their intended use. In the present invention, due to the combination of a short heat history required to dry, and the controlled non-top-skinning drying process, the film composition never need to attain the oven temperature (or other heat source) to reach the dried state. To demonstrate this, films were made in accordance with the present invention and dried as discussed below. A first thermocouple was placed within the film and a second thermocouple was suspended in the oven in order to measure the temperature differential between the oven environment and the film composition during the drying process.

To measure the temperature differentials, a thermocouple, which was connected to a Microtherma 1 thermometer, was placed within the films, and another thermocouple was suspended in the drying oven. Temperature readings in the films and oven were recorded every 30 seconds during the drying of the films.

The thermocouple results for the first film are listed in Table 17 below, and graphically represented in FIG. **33**. The results for the second film are listed in Table 18 below, and graphically represented in FIG. **34**. The results show that even after 10 minutes of drying, the temperatures of the film were substantially below (at least about 5° C.) the oven environment. Films dried for less than 10 minutes may experience significantly greater temperature differentials. For example, drying for 4 to 6 minutes, which is a particularly desirable time frame for many films of the present invention, produces differentials of about 25° C. to about 30° C. Accordingly, films may be dried at high, potentially deleterious temperatures without harming heat sensitive actives contained within the films.

TABLE 17

Time (Min.)	Probe Temp (° C.)	Oven Temp (° C.)
0	42.7	78
1	48.1	80
2	48.8	81
3	50	80
4	51.6	80
5	53.6	80
6	56.8	80
7	61.4	80
8	66.8	80
9	72.7	80
10	76.1	80

TABLE 18

Time (Min.)	Probe Temp (° C.)	Oven Temp (° C.)
0	44.4	77
1	49.8	81
2	49.2	81
3	49.4	80
4	51	80
5	52	80
6	55	80
7	58.9	80
8	64.5	80
9	69.8	80
10	74.4	80

Examples CJ-DB

The following examples describe film compositions of the present invention, which contain water-soluble polymers including polyethylene oxide (PEO) alone or in combination with hydroxypropyl cellulose (HPC) or hydroxypropylmethyl cellulose (HPMC). Thin film compositions were prepared using the polymer amounts listed in Table 19.

TABLE 19

Composition	PEO (g)	HPC (g)	HPMC (g)
CJ		32	8
CK		24	16
CL		16	24
CM		8	32
CN			40
CO	8		32
CP	16		24
CQ	24		16
CR	32		8
CS	40		
CT	4		36
CV	6		34
CV	32	8	
CW	24	16	
CX	16	24	
CY	8	32	
CZ		40	
DA	4	36	
DB	6	34	

The above polymer components were combined with equal amounts of precipitated calcium carbonate (mimics drug loading), simethicone emulsion, and water to form the film compositions. The components were combined by mixing until a uniform mixture was achieved, and then cast into films on release paper using a K-Control Coater with a 350 micron smooth bar. The films then were dried for about 9 minutes at 80° C. in accordance with the present invention. The film compositions were tested for various properties, the results of which are described in Table 20 below.

TABLE 20

Composition	Composition of Polymer in Film	Solution Coating Rating	Solution Leveling Rating	% Moisture in Film	180° Bend Test	Dissolution Test (seconds)	Curl Test
CJ	20% HPMC/ 80% HPC	well	well	2.9	Failed at crease	12, 15	Curl
CK	40% HPMC/ 60% HPC	well	well	1.70	Failed at crease	21, 22	Curl
CL	60% HPMC/ 40% HPC	well	well	2.40	Failed at crease	24, 27	Curl
CM	80% HPMC/ 20% HPC	well	well	2.76	Failed at crease	31, 31	Curl
CN	100% HPMC	reasonably well	well	2.66	Failed at crease	35, 38	Curl
CO	10% PEO/ 90% HPMC	some streaking	well	2.27	Failed at crease	31, 32	Curl
CP	15% PEO/ 85% HPMC	well	well	3.31	Failed	24, 27	Curl
CQ	20% PEO/ 80% HPMC	well	well	2.06	Passed	22, 31	Slight curl
CR	40% PEO/ 60% HPMC	well	well	2.01	Passed	13, 12	Slight curl
CS	60% PEO/ 40% HPMC	well	well	1.40	Passed	5, 6	Very slight curl
CT	80% PEO/ 20% HPMC	well	well	1.35	Passed	5, 6	Very slight curl
CU	100% PEO	well	well	0.98	Passed	5, 5	No curl
CV	20% HPC/ 80% PEO	well	well	1.01	Passed	5, 5	No curl
CW	40% HPC/ 60% PEO	well	well	2.00	Passed	6, 6	No curl
CX	60% HPC/ 40% PEO	well	well	0.97	Passed	7, 7	Slight curl
CY	80% HPC/ 20% PEO	well	well	1.41	Passed	12, 12	Very slight curl
CZ	85% HPC/ 15% PEO	well	well	1.86	Failed at crease	13, 14	Curl
DA	90% HPC/ 10% PEO	well	well	1.62	Failed at crease	14, 13	Curl

TABLE 20-continued

Composition	Composition of Polymer in Film	Solution Coating Rating	Solution Leveling Rating	% Moisture in Film	180° Bend Test	Dissolution Test (seconds)	Curl Test
DB	100% HPC	well	well	2.01	Failed at crease	16, 17	Curl

The solution coating rating and solution leveling rating were both based upon panel observations made during casting of the film compositions.

For the 180° bend test, the dried films were placed in a moisture analyzer (HR73 Moisture Analyzer from Mettler Toledo) to obtain percent moisture and to remove any solvent (e.g. water) remaining in the films after drying at 80° C. in accordance with the present invention. The films then were creased to about 180° and observed for break. Films that broke during creasing were considered a failure. If the film did not break during creasing, a 200 g weight was dropped onto the creased film from a height of about 8.5 mm. Films that broke were considered a failure, and those that did not break were considered a pass. It should be noted, however, that this flexibility test is an extreme test. Films that failed this test are still considered operable within the scope of the present invention. More specifically, there may be certain applications that do not require such extreme flexibility properties.

The films also were tested for dissolution rate. An approximately 20 mm by 100 mm piece of film, having a 2.85 g weight attached, was lowered into a 32.5° C. water bath to a depth of about 50 mm. The time required for the film to dissolve and separate into two pieces was determined (in seconds).

For the curl test, samples of film (about 35 mm by 35 mm) were placed on a glass plate in a laboratory window ledge. The film samples were allowed to stand in the window ledge at room conditions for two to three days and then were observed for curling.

In accordance with the present invention, desirable film compositions are flexible, fast dissolving, and not likely to substantially curl. As indicated by the results in Table 20, Compositions CQ-CY performed best, exhibiting good flexibility, dissolution, and curling properties. In particular, Compositions CQ-CY passed the 180° bend test and dissolved at moderate to fast rates. These compositions also exhibited no or only slight curl. Accordingly, it may be desirable to employ polymer components as in Compositions CQ-CY, particularly about 20% to 100% PEO in the polymer component optionally combined with about 0% to 80% HPC or HPMC.

Examples DC-DG

The following examples of the present invention describe films that include PEO or PEO-polymeric blends and an active component. Thin film compositions with these components were prepared using the amounts described in Table 21.

TABLE 21

Component	Weight (g unless otherwise indicated) DC	DD	DE	DF	DG
PEO[1]	8.75	7	1.75	7	1.75
Sucralose	0.7	0.7	0.7	0.7	0.7
Precipitated calcium carbonate	3.65	3.65	3.65	3.65	3.65
Orange concentrate flavor	1.05	1.05	1.05	1.05	1.05
Vanilla	0.5	0.5	0.5	0.5	0.5
HPMC		1.75	7.0		
HPC				1.75	7.0
Simethicone[2]	0.35	0.35	0.35	0.35	0.35
Water	32.5	32.5	32.5	32.5	32.5
Loratadine[3]	2.5	2.5	2.5	2.5	2.5
Yellow food coloring	3 drops	3 drops	3 drops	3 drops	3 drops
Red food coloring	2 drops	2 drops	2 drops	2 drops	2 drops

[1]Available from the Dow Chemical Company
[2]Available from Sentry
[3]Available from Schering Corporation as Claritin

The above components for each of Compositions DC through DG were combined by mixing until a uniform mixture was achieved, and then cast into films on release paper using a K-Control Coater with a 350 micron smooth bar. The films were dried for about 9 minutes at 80° C. in accordance with the method of the present invention to varying moisture levels.

After drying, the films were tested for various properties, including the 180° bend test, dissolution test, and curl test, as described above in Examples CJ-DB. The films also were tested for resistance to tearing. Tear resistance was measured by a panel test in which members tried to tear the film apart by pulling on opposing ends of the film. Films that tore cleanly received a low grade. Films that stretched a little and began to break received a moderate grade, and films that stretched and were difficult to tear received a high grade.

Composition DC, which included a 100% PEO film base, was dried in accordance with the method of the present invention to about 1.30 percent moisture. The dried film had good strength, and passed the 180° bend test. The film also exhibited good resistance to tearing (high grade). The film dissolved at a fast rate on the tongue, and had a dissolution testing rate of about 3.5 to 4 seconds. The film exhibited no curling.

Composition DD, which included an 80%/20% PEO/HPMC film base, was dried in accordance with the method of the present invention to about 2.30 percent moisture. The dried film exhibited adequate strength, and passed the 180° bend test. The film also exhibited good resistance to tearing. It dissolved at a moderate to fast rate on the tongue, and had a dissolution testing rate of about 5 seconds. The film exhibited slight curling.

Composition DE, which included a 20%/80% PEO/HPMC film base, was dried in accordance with the method of the present invention to about 3.0 percent moisture. The film had good strength, and passed the 180° bend test. The film exhib-

ited moderate tear resistance, dissolved on the tongue at a slow rate, and had a dissolution testing rate of 16 seconds. The film exhibited some curling.

Composition DF, which included an 80%/20% PEO/HPC film base, was dried in accordance with the method of the present invention to about 2.52 percent moisture. The film exhibited good strength, passed the 180° bend test, and exhibited high tear resistance. The film also dissolved at a fast rate on the tongue, and had a dissolution rating of 4 seconds. The film exhibited very slight curling.

Composition DG, which included a 20%/80% PEO/HPC film base, was dried in accordance with the method of the present invention to about 2.81 percent moisture. The film had adequate strength, passed the 180° bend test, and exhibited moderate tear resistance. The film dissolved on the tongue at a fast rate, and had a 10 second dissolution testing rate. The film exhibited no curling.

As indicated above, each of Compositions DC-DG contained about 20% to 100% PEO in the polymer component, optionally in combination with varying levels of HPC or HPMC. The results indicate that varying the polymer component achieved different film properties.

Examples DH-DZ

The following examples of the present invention describe films that include PEO or PEO-HPC polymer blends. The film compositions include PEO of varying molecular weights. Thin film compositions with these components were prepared using the amounts described in Table 22 (listed by weight percent of the polymer component).

TABLE 22

Composition	100,000 PEO (wt. %)	200,000 PEO (wt. %)	300,000 PEO (wt. %)	900,000 PEO (wt. %)	HPC (wt. %)
DH			20		80
DI			50		50
DJ			80		20
DK		50			50
DL		67.5			32.5
DM		70			30
DN		75			25
DO		100			
DP	50				50
DQ	100				
DR				10	90
DS				20	80
DT		40		10	50
DU	25			15	60
DV	20	80			
DW		80		20	
DX		80	20		
DY		50	50		
DZ		20	80		

The above polymer components were combined with sucralose, precipitated calcium carbonate (mimics drug loading), orange concentrate flavor, Tween 80 (available from ICI Americas), vanilla flavor, simethicone emulsion, water, and yellow and red food coloring to form the film compositions. The components were combined by mixing until a uniform mixture was achieved, and then cast into films on release paper using a K-Control Coater with a 350 micron smooth bar. The solution coating and leveling properties were observed. The films then were dried for about 9 minutes at 80° C. in accordance with the method of the present invention. The film compositions were tested for various properties to determine the effect of varying the PEO molecular weight and level in the polymer component, the results of which are described in Table 23 below.

TABLE 23

Composition	Film thickness (mils)	% Moisture	Roof of Mouth Tendency	180° Bend Test	Dissolution Test (seconds)	Tear Resistance
DH	3.5	2.5	low	passed	8	poor
DI	3.8	2.01	low	passed	7	moderate
DJ	2.6	2.63	high	passed	3	excellent
DK	3.4	2.35	low	passed	4	poor
DL	3.5	1.74	low	passed	4	good to excellent
DM	3.5	1.68	low	passed	4	good to excellent
DN	3.3	2.33	moderate	passed	3	good to excellent
DO	3.1	2.14	high	passed	4	excellent
DP	4.1	1.33	high	passed	3.5	poor
DQ	3.2	2.07	high	passed	4	good
DR	3.4	1.90	low	passed	10	poor
DS	3.5	2.04	low	passed	10	poor
DT	3.3	2.25	moderate	passed	5	good
DU	3.6	2.84	low to moderate	passed	6	moderate
DV	2.5	3.45	high	passed	2	excellent
DW	2.5	2.83/1.68	high	passed	3-4	excellent
DX	3.5	2.08	high	passed	5	excellent
DY	2.8	1.67	high	passed	3	excellent
DZ	2.5	1.89/0.93	high	passed	3	excellent

The films were tested for various properties, including the 180° bend test, dissolution test, and tear resistance, as described above. The films also were tested for adhesion, i.e., tendency to go to the roof of the mouth. Adhesion was rated by a panel test in which films that did not stick to the roof of the mouth received a low grade, films that stuck somewhat received a moderate grade, and films that stuck completely received a high grade.

As indicated above, the level and molecular weight of PEO in the polymer component were varied to achieve different film properties. In general, the higher the level of PEO in the polymer component, the greater the adhesiveness and tear resistance exhibited by the film. Film compositions containing about 50% or greater levels of PEO attained higher tear resistance ratings than those with less than 50% PEO. The tear resistance of lower levels of PEO, however, was shown to be improved by combining small amounts of higher molecular weight PEOs with the lower molecular weight PEOs (e.g. Compositions DT and DU).

Compositions containing about 20% to 75% PEO performed best with respect to adhesion prevention (lower tendencies to go to the roof of the mouth). Compositions containing higher levels of PEO performed well when adhesion was desired.

As regards dissolution rate, polymer components containing about 50% or higher levels of PEO performed best, providing faster dissolving film compositions. In those films containing combinations of varying molecular weight PEOs, those with about 60% or higher of the lower molecular weight PEOs (100,000 to 300,000) in the PEO combination dissolved faster.

Example EA

The following example of the present invention describes films that include PEO and polyvinyl pyrrolidone (PVP) polymeric blends. Thin film compositions with these components were prepared using the amounts described in Table 24. In particular, the polymer component of the films contained about 80% PEO and 20% PVP, or a ratio of 4:1 PEO to PVP.

TABLE 24

Component	Weight (g unless otherwise noted)
PVP	3.75
PEO	15
Sucralose[1]	1.5
Precipitated calcium carbonate	14.57
Orange concentrate flavor	2.25
Tween 80[2]	0.056
Simethicone[3]	0.38
Water	62.5
Yellow food color	6 drops
Red food color	4 drops

[1]Available from McNeil Nutritionals
[2]Available from Fisher
[3]Available from Sentry

The above components were combined by mixing until a uniform mixture was achieved, and then cast into films on release paper using a K-Control Coater with a 350 micron smooth bar. The films were dried for about 9 minutes at 80° C. in accordance with the method of the present invention to a moisture level of about 2.19%. The films exhibited good strength, dissolved in the mouth at a moderate to fast rate, had high tear resistance, a thickness of about 4 mils, good flavor, low tendency to adhere to the roof of the mouth, and passed the 180° bend test. The film had a dissolution rate of 4 seconds, according to the test described above. In addition, the film easily released from the release paper.

Example EB-ED

The following examples of the present invention describe extruded films that include PEO-based polymer components. Film compositions were prepared using the amounts described in Table 25 for Example EC and Table 26 for Example ED.

TABLE 25

COMPONENT	WEIGHT (g unless otherwise noted)
HPC	73.78
Polyethylene oxide	153.22
Sucralose	18.16
Precipitated calcium carbonate	176.38
Orange concentrated flavor	27.24
Tween 80	0.68
Simethicone	4.54
Yellow food coloring	27 drops
Red food coloring	18 drops

TABLE 26

COMPONENT	WEIGHT (g unless otherwise noted)
Polyethylene oxide	227
Sucralose	18.16
Precipitated calcium carbonate	176.38
Orange concentrated flavor	27.24
Tween 80	0.68
Simethicone	4.54
Yellow food coloring	27 drops
Red food coloring	18 drops

The films of Examples EB-ED were extruded using a single screw extruder in accordance with the specifications provided in Table 27 below (temperatures are in ° F.).

TABLE 27

		Temp. Barrel	Temp. Barrel	Temp. Barrel	Temp.	Temp.	Temp.	PSI Pressure		
Composition	RPM	Zn. 1	Zn. 2	Zn. 3	Zn. 4	Die	Melt	P1	P2	Amps
EB	73	175	181	185	190	190	194	600	1250	12
EB	153	177	181	199	211	210	217	175	1070	7.8
ED	253	175	181	200	211	210	222	0	761	6.3

TABLE 27-continued

Composition	RPM	Temp. Barrel Zn. 1	Temp. Barrel Zn. 2	Temp. Barrel Zn. 3	Temp. Zn. 4	Temp. Die	Temp. Melt	PSI Pressure P1	PSI Pressure P2	Amps
ED	109	175	181	200	211	210	207	0	1000	6.0
EC	109	175	181	200	211	210	217	0	875	12.1
EC	149	175	200	226	248	239	258	0	583	7.3

More specifically, for Example EB, two pounds of PEO having a molecular weight of about 200,000 were weighed and placed in a polyethylene plastic bag. This PEO flush was then extruded according to the specifications in Table 27.

For Example EC, a blend of the components listed in Table 25 was prepared. The HPC, PEO, sucralose, and precipitated calcium carbonate were placed in a large electric blender and allowed to mix. A solution of orange concentrate flavor and Tween 80 was added to the blender while mixing, after which a solution of simethicone and the food colors was added to the blender while mixing. The blended composition was extruded in accordance with the specifications in Table 27.

For Example ED, a blend of the components listed in Table 26 was prepared. The PEO, sucralose, and precipitated calcium carbonate were placed in a large electric blender and allowed to mix. A solution of orange concentrate flavor and Tween 80 was added to the blender while mixing, after which a solution of simethicone and the food colors was added to the blender while mixing. The blended composition was extruded in accordance with the specifications in Table 27.

The extruded films did not exhibit stickiness to each other during processing. As such, the resulting film could be rolled or wound onto itself without the need for a backing material.

Examples EE-EH

The following examples of the present invention describe films that include a densifying agent. A thin film composition including PEO-polymeric blends and a densifying agent (simethicone) were prepared using the amounts described in Table 28.

TABLE 28

Component	Weight (g unless otherwise indicated) EE	EF	EG	EH
Hydroxypropylcellulose	3.05	3.05	3.05	3.05
Polyethylene oxide	6.33	6.33	6.33	6.33
Sucralose	0.75	0.75	0.75	0.75
Precipitated calcium carbonate	7.47	7.47	7.09	7.09
Orange concentrate flavor	1.12	1.12	1.12	1.12
Tween 80	0.028	0.028	0.028	0.028
Simethicone	0	0	0.38	0.38
Water	31.25	31.25	31.25	31.25
Yellow food coloring	3 drops	3 drops	3 drops	3 drops
Red food coloring	2 drops	2 drops	2 drops	2 drops

The densities of these thin film compositions were measured, the results of which are shown in Table 29.

TABLE 29

Composition	Average Weight of Film/Density
EE	146.5 mg/1.123
EF	126.5 mg/0.969
EG	137 mg/1.057
EH	146 mg/1.119

Vacuum conditions were added to two of the film compositions (EE and EH). Composition EE contained 0% simethicone and vacuum was applied. Composition EF contained 0% simethicone and no vacuum applied. As shown in Table 29 above, the density increased with the addition of vacuum conditions from 0.969 (EF) to 1.123 (EE). Composition EG contained 2% simethicone and no vacuum applied. Composition EH contained 2% simethicone and vacuum was applied. Again, density increased from 1.057 (EG) to 1.119 (EH). Overall, the density of the films increased from 0.969 (EF: no simethicone and no vacuum) to 1.057 (EG: simethicone but no vacuum) to 1.119 (EH: simethicone and vacuum).

Examples EI-EW

The following examples of the present invention describe films that include PEO or PEO-polymeric blends. In particular, PEO was combined with polyvinylpyrrolidone (PVP), starch (pregelatinized modified corn starch), sodium carboxymethyl cellulose (CMC), hydroxypropylcellulose (HPC), hydroxypropylmethyl cellulose (HPMC) or polyvinyl alcohol (PVA) to form the polymer components of the films. Thin film compositions with these components were prepared in accordance with the method of the present invention using the amounts described in FIG. **38**.

In addition to the polymer components listed in FIG. **38**, each of these film compositions included: about 4% sucralose, about 38.85% calcium carbonate, about 6% orange flavor, about 0.15% Tween 80, about 1% simethicone, and food coloring. The PEO included in the polymer component of these examples had a molecular weight of about 200,000.

FIG. **38** also displays certain properties of these films, including: percent solids of solution; viscosity; percent moisture; film thickness; film strength; tear resistance of the film; tendency of the film to go to the roof of the mouth; the 180° bend test; whether molding, or aggregations, are present in the film; dissolution times of the film; rating of dissolution in the mouth; and time in drying oven. Each of these film property tests is described in detail above. The results of these various tests are indicated in FIG. **38**.

Examples EX-FK

The following examples of the present invention describe films that include PEO or PEO-polymeric blends (with HPC)

and different active components. Thin film compositions with these components were prepared in accordance with the method of the present invention using the amounts described in Tables 30 and 31.

TABLE 30

	Weight (in g, unless otherwise indicated)						
Component	EX	EY	EZ	FA	FB	FC	FD
HPC	5.68	5.64	6	6.73	6.22	6.22	
PEO	1.89	1.88	2	2.25	1.78	1.78	9.04
Sucralose	0.84	0.84	0.44	0.66	0.84	0.84	0.44
Magna Sweet	0.08	0.08	0.09	0.10	0.09	0.09	
Avicel CL 611[1]	0.18	0.18	0.18	0.20	0.18	0.18	
Precipitated calcium carbonate	0.67		2.2		0.71	3.07	
Dextromethorphan	5.83	6.94					
Caffeine			3.28				
Tadalafil[2]				4.92			
Sildenafil[3]					4.38		
Loperamide[4]						2.8	
Prosweet	0.18	0.18		0.20	0.61	0.18	
Taste Masking Flavor			0.87		1.31	0.89	
Peppermint			0.87				
Peppermint Bittermask flavor			1.07				
Vanilla flavor				0.56			
Watermelon artificial flavor	1.23	1.23			1.22		
Orange flavor				1.18			
Hawaiian punch flavor						1.22	
Strawberry & cream flavor							1.11
WS-23[5]	0.075	0.075	0.075	0.084	0.075	0.075	
WS-3[6]							0.025
Simethicone	0.08	0.08	0.18	0.39	0.09	0.18	46.43
Propylene glycol	0.76	0.38	0.25	0.22			
Water	32.5	32.5	32.5	32.5	32.5	32.5	
Green color	5 drop	5 drop			5 drop		
Red color				2 drop		5 drop	7 drop
Blue color			3 drop				
Yellow color				3 drop			

[1]Mixture of microcrystalline cellulose and sodium carboxymethylcellulose, available from FMC Biopolymer
[2]Available from Lilly ICOS, LLC, as Cialis ®
[3]Available from Pfizer, Inc. as Viagra ®
[4]Available as Imodium
[5]N-2,3-trimethyl-2-isopropyl butanamide
[6]N-Ethyl-p-menthane-3-carboxamide

TABLE 31

	Weight (in g, unless otherwise indicated)						
Component	FE	FF	FG	FH	FI	FJ	FK
HPC	1.28	3.05	4.5	3.29	2.6	2.92	3.29
PEO	2.66	6.33	3	6.83	5.4	6.08	6.83
Sucralose	0.31	0.9	0.6		0.64		
Magna Sweet		0.09					
Avicel CL 611[1]		0.56	0.45				
Precipitated calcium carbonate	1.07	2.02	0.99	6.05	0.90	2.67	1.39
Meloxicam[2]	1.97						
Risperidone[3]		0.62					
Zyrtec ®[4]			3.75				
Five Grass Powder[5]				2.207			
Tea Tree Oil[6]					4		
Antibacterial concentrate[7]						6.12	
Mite extract[8]							6.87
Prosweet		0.66					
Taste Masking Flavor		1.41					
Peppermint Bittermask flavor		2.81			2.24		
Orange flavor	0.47						
Strawberry & cream flavor			1.5				

TABLE 31-continued

Component	Weight (in g, unless otherwise indicated)						
	FE	FF	FG	FH	FI	FJ	FK
WS-3[9]	0.020	0.081	0.038		0.04		
Tween 80	0.012	0.028	0.022		0.024	0.027	
Simethicone	0.08	0.19	0.15	0.37	0.16	0.18	0.37
Water	14.63	31.25	25	31.25	24	22	31.25
Red color	2 drop		5 drop				
Blue color		3 drop			3 drop		
Yellow color	3 drop						

[1]Mixture of microcrystalline cellulose and sodium carboxymethylcellulose, available from FMC Biopolymer
[2]Available as Mobic ®
[3]Available as Risperdal ®
[4]Available from Pfizer, Inc.
[5]Allergy treatment
[6]Antibiotic
[7]MegaBac ™, available from Nicrosol Technologies
[8]Allergy treatment
[9]N-Ethyl-p-menthane-3-carboxamide

The above components were combined by mixing until a uniform mixture was achieved, and then cast into films on release paper using a K-Control Coater with a 250 or 350 micron smooth bar. The films were dried for about 9 to 10 minutes at 80° C. in accordance with the method of the present invention resulting in dried films having adequate to good strength.

While there have been described what are presently believed to be the preferred embodiments of the invention, those skilled in the art will realize that changes and modifications may be made thereto without departing from the spirit of the invention, and it is intended to include all such changes and modifications as fall within the true scope of the invention.

What is claimed is:

1. A process for making a film having a substantially uniform distribution of components, comprising the steps of:

(a) forming a masterbatch pre-mix comprising a solvent and a polymer selected from the group consisting of water-soluble polymers, water-swellable polymers and combinations thereof;

(b) adding an active to a pre-determined amount of said masterbatch pre-mix to form a flowable polymer matrix, said matrix having a substantially uniform distribution of said active;

(c) casting said flowable polymer matrix;

(d) evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film within about 10 minutes or fewer to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film; and

(e) forming a resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained.

2. The process of claim **1**, wherein said pre-determined amount of master batch pre-mix is controllably fed via a first metering pump and a control valve to a first mixer and a second mixer.

3. The process of claim **2**, wherein said first mixer and said second mixer are arranged in parallel, series or a combination thereof.

4. The process of claim **1**, wherein said water-soluble polymer comprises polyethylene oxide.

5. The process of claim **1**, wherein said polymer comprises a polymer selected from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.

6. The process of claim **5**, wherein said polymer further comprises a water insoluble polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone and combinations thereof.

7. The process of claim **5**, wherein said polymer further comprises a polymer selected from the group consisting of methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(α-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof.

8. The process of claim **5**, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

9. The process of claim **5**, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate,

polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(d-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

10. The process of claim **1**, wherein said solvent is selected from the group consisting of water, polar organic solvent, and combinations thereof.

11. The process of claim **10**, wherein said solvent is selected from the group consisting of ethanol, isopropanol, acetone, and combinations thereof.

12. The process of claim **1**, wherein said active is selected from the group consisting of bioactive active, pharmaceutical actives, drugs, medicaments and combinations thereof.

13. The process of claim **1**, wherein said active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, anti-tumor drugs, anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, anti-convulsants, neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, anti-asthmatics, cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

14. The process of claim **1**, wherein said active is selected from the group consisting of cosmetic actives, antigens, allergens, spores, microorganisms, seeds, mouthwash components, flavors, fragrances, enzymes, preservatives, sweetening agents, colorants, spices, vitamins and combinations thereof.

15. The process of claim **1**, wherein said active is a bioactive active.

16. The process of claim **1**, wherein said active is a biological response modifier.

17. The process of claim **1**, wherein said active is an opiate or opiate-derivative.

18. The process of claim **1**, wherein said active is an anti-emetic.

19. The process of claim **1**, wherein said active is an amino acid preparation.

20. The process of claim **1**, wherein said active is selected from the group consisting of sildenafils, tadalafils, vardenafils, apomorphines, yohimbine hydrochlorides, alprostadils and combinations thereof.

21. The process of claim **1**, wherein said active is a protein.

22. The process of claim **1**, wherein said active is insulin.

23. The process of claim **1**, wherein said active is an anti-diabetic.

24. The process of claim **1**, wherein said active is an anti-histamine.

25. The process of claim **1**, wherein said active is an anti-tussive.

26. The process of claim **1**, wherein said active is a non-steroidal anti-inflammatory.

27. The process of claim **1**, wherein said active is an anti-asthmatics.

28. The process of claim **1**, wherein said active is an anti-diarrhea.

29. The process of claim **1**, wherein said active is an alkaloid.

30. The process of claim **1**, wherein said active is an anti-psychotic.

31. The process of claim **1**, wherein said active is an anti-spasmodic.

32. The process of claim **1**, wherein said active is a biological response modifier.

33. The process of claim **1**, wherein said active is an anti-obesity drug.

34. The process of claim **1**, wherein said active is an H_2-antagonist.

35. The process of claim **34**, wherein said H_2-antagonist is selected from the group consisting of cimetidine, ranitidine hydrochloride, famotidine, nizatidine, ebrotidine, mifentidine, roxatidine, pisatidine, aceroxatidine and combinations thereof.

36. The process of claim **1**, wherein said active is a smoking cessation aid.

37. The process of claim **1**, wherein said active is an anti-parkinsonian agent.

38. The process of claim **1**, wherein said active is an anti-depressant.

39. The process of claim **1**, wherein said active is an anti-migraine.

40. The process of claim **1**, wherein said active is an anti-Alzheimer's agents.

41. The process of claim **1**, wherein said active is a dopamine receptor agonist.

42. The process of claim **1**, wherein said active is a cerebral dilator.

43. The process of claim **1**, wherein said active is a psychotherapeutic agent.

44. The process of claim **1**, wherein said active is an antibiotic.

45. The process of claim 1, wherein said active is an anesthetic.

46. The process of claim 1, wherein said active is a contraceptive.

47. The process of claim 1, wherein said active is an antithrombotic drug.

48. The process of claim 1, wherein said active is diphenhydramine.

49. The process of claim 1, wherein said active is nabilone.

50. The process of claim 1, wherein said active is albuterol sulfate.

51. The process of claim 1, wherein said active is an antitumor drug.

52. The process of claim 1, wherein said active is a glycoprotein.

53. The process of claim 1, wherein said active is an analgesic.

54. The process of claim 1, wherein said active is a hormone.

55. The process of claim 1, wherein said active is a decongestant.

56. The process of claim 1, wherein said active is a loratadine.

57. The process of claim 1, wherein said active is dextromethorphan.

58. The process of claim 1, wherein said active is chlorpheniramine maleate.

59. The process of claim 1, wherein said active is selected from the group consisting of an analgesic, an anti-inflammatory, an antihistamine, a decongestant, a cough suppressant and combinations thereof.

60. The process of claim 1, wherein said active is an appetite stimulant.

61. The process of claim 1, wherein said active is a gastrointestinal agent.

62. The process of claim 1, wherein said active is a hypnotic.

63. The process of claim 1, wherein said active is taste-masked.

64. The process of claim 1, wherein said active is taste-masked using a flavor.

65. The process of claim 1, wherein said active is coated with a controlled release composition.

66. The process of claim 65, wherein said controlled release composition provides an immediate release.

67. The process of claim 65, wherein said controlled release composition provides a delayed release.

68. The process of claim 65, wherein said controlled release composition provides a sustained release.

69. The process of claim 65, wherein said controlled release composition provides a sequential release.

70. The process of claim 1, wherein said active is a particulate.

71. The process of claim 1, further comprising adding a degassing agent to said masterbatch premix.

72. The process of claim 1, further comprising a step of providing a second film layer.

73. The process of claim 72, wherein said second film layer is coated onto said resulting film.

74. The process of claim 72, wherein said second film layer is spread onto said resulting film.

75. The process of claim 72, wherein said second film layer is cast onto said resulting film.

76. The process of claim 72, wherein said second film layer is extruded onto said resulting film.

77. The process of claim 72, wherein said second film layer is sprayed onto said resulting film.

78. The process of claim 72, wherein said second film layer is laminated onto said resulting film.

79. The process of claim 72, further comprising laminating said resulting film to another film.

80. The process of claim 72, wherein said second film comprises an active.

81. The process of claim 72, wherein said active in said second film is different than said active in said resulting film.

82. A process for making a film having a substantially uniform distribution of components, comprising the steps of:

(a) forming a flowable polymer matrix comprising a polymer selected from the group consisting of a water-soluble polymer, a water swellable polymer and combinations thereof, a solvent and an active selected from the group consisting of bioactive actives, pharmaceutical actives, drugs, medicaments and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix;

(c) evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film within about 10 minutes or fewer to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film; and

(d) forming a resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained.

83. The process of claim 82, wherein said water-soluble polymer comprises polyethylene oxide.

84. The process of claim 82, wherein said polymer comprises a polymer selected from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.

85. The process of claim 84, wherein said polymer further comprises a water insoluble polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone and combinations thereof.

86. The process of claim 84, wherein said polymer further comprises a polymer selected from the group consisting of methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(α-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof.

87. The process of claim 84, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

88. The process of claim 84, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(α-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

89. The process of claim 82, wherein said solvent is selected from the group consisting of water, polar organic solvent, and combinations thereof.

90. The process of claim 89, wherein said solvent is selected from the group consisting of ethanol, isopropanol, acetone, and combinations thereof.

91. The process of claim 82, wherein said active is selected from the group consisting of bioactive active, pharmaceutical actives, drugs, medicaments and combinations thereof.

92. The process of claim 82, wherein the active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, anti-tumor drugs, anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, anti-convulsants, neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, anti-asthmatics, cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

93. The process of claim 82, wherein said active is selected from the group consisting of cosmetic actives, antigens, allergens, spores, microorganisms, seeds, mouthwash components, flavors, fragrances, enzymes, preservatives, sweetening agents, colorants, spices, vitamins and combinations thereof.

94. The process of claim 82, wherein said active is a bioactive active.

95. The process of claim 82, wherein said active is a biological response modifier.

96. The process of claim 82, wherein said active is an opiate or opiate-derivative.

97. The process of claim 82, wherein said active is an anti-emetic.

98. The process of claim 82, wherein said active is an amino acid preparation.

99. The process of claim 82, wherein said active is selected from the group consisting of sildenafils, tadalafils, vardenafils, apomorphines, yohimbine hydrochlorides, alprostadils and combinations thereof.

100. The process of claim 82, wherein said active is a protein.

101. The process of claim 82, wherein said active is insulin.

102. The process of claim 82, wherein said active is an anti-diabetic.

103. The process of claim 82, wherein said active is an antihistamine.

104. The process of claim 82, wherein said active is an anti-tussive.

105. The process of claim 82, wherein said active is a non-steroidal anti-inflammatory.

106. The process of claim 82, wherein said active is an anti-asthmatics.

107. The process of claim 82, wherein said active is an anti-diarrhea.

108. The process of claim 82, wherein said active is an alkaloid.

109. The process of claim 82, wherein said active is an anti-psychotic.

110. The process of claim 82, wherein said active is an anti-spasmodic.

111. The process of claim 82, wherein said active is a biological response modifier.

112. The process of claim 82, wherein said active is an anti-obesity drug.

113. The process of claim 82, wherein said active is an H_2-antagonist.

114. The process of claim 82, wherein said H_2-antagonist is selected from the group consisting of cimetidine, ranitidine hydrochloride, famotidine, nizatidine, ebrotidine, mifentidine, roxatidine, pisatidine, aceroxatidine and combinations thereof.

115. The process of claim 82, wherein said active is a smoking cessation aid.

116. The process of claim 82, wherein said active is an anti-parkinsonian agent.

117. The process of claim 82, wherein said active is an anti-depressant.

118. The process of claim 82, wherein said active is an anti-migraine.

119. The process of claim 82, wherein said active is an anti-Alzheimer's agents.

120. The process of claim 82, wherein said active is a dopamine receptor agonist.

121. The process of claim 82, wherein said active is a cerebral dilator.

122. The process of claim 82, wherein said active is a psychotherapeutic agent.

123. The process of claim 82, wherein said active is an antibiotic.

124. The process of claim 82, wherein said active is an anesthetic.

125. The process of claim 82, wherein said active is a contraceptive.

126. The process of claim, 82, wherein said active is an anti-thrombotic drug.

127. The process of claim 82, wherein said active is diphenhydramine.

128. The process of claim 82, wherein said active is nabilone.

129. The process of claim 82, wherein said active is albuterol sulfate.

130. The process of claim 82, wherein said active is an anti-tumor drug.

131. The process of claim 82, wherein said active is a glycoprotein.

132. The process of claim 82, wherein said active is an analgesic.

133. The process of claim 82, wherein said active is a hormone.

134. The process of claim 82, wherein said active is a decongestant.

135. The process of claim 82, wherein said active is a loratadine.

136. The process of claim 82, wherein said active is dextromethorphan.

137. The process of claim 82, wherein said active is chlorpheniramine maleate.

138. The process of claim 82, wherein said active is selected from the group consisting of an analgesic, an anti-inflammatory, an antihistamine, a decongestant, a cough suppressant and combinations thereof.

139. The process of claim 82, wherein said active is an appetite stimulant.

140. The process of claim 82, wherein said active is a gastrointestinal agent.

141. The process of claim 82, wherein said active is a hypnotic.

142. The process of claim 82, wherein said active is taste-masked.

143. The process of claim 82, wherein said active is taste-masked using a flavor.

144. The process of claim 82, wherein said active is coated with a controlled release composition.

145. The process of claim 144, wherein said controlled release composition provides an immediate release.

146. The process of claim 144, wherein said controlled release composition provides a delayed release.

147. The process of claim 144, wherein said controlled release composition provides a sustained release.

148. The process of claim 144, wherein said controlled release composition provides a sequential release.

149. The process of claim 82, wherein said active is a particulate.

150. The process of claim 82, further comprising adding a degassing agent to said flowable polymer matrix.

151. The process of claim 82, further comprising a step of providing a second film layer.

152. The process of claim 151, wherein said second film layer is coated onto said resulting film.

153. The process of claim 151, wherein said second film layer is spread onto said resulting film.

154. The process of claim 151, wherein said second film layer is cast onto said resulting film.

155. The process of claim 151, wherein said second film layer is extruded onto said resulting film.

156. The process of claim 151, wherein said second film layer is sprayed onto said resulting film.

157. The process of claim 151, wherein said second film layer is laminated onto said resulting film.

158. The process of claim 151, further comprising laminating said resulting film to another film.

159. The process of claim 151, wherein said second film comprises an active.

160. The process of claim 151, wherein said active in said second film is different than said active in said resulting film.

161. A process for making a film capable of being administered to a body surface having a substantially uniform distribution of components, comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and an active, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix;

(c) evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film within about 10 minutes or fewer to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film;

(d) forming a resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained; and

(e) administering said resulting film to a body surface.

162. The process of claim 161, wherein said body surface is a mucous membrane.

163. The process of claim 162, wherein said mucous membrane is oral, anal, vaginal or ophthalmological.

164. The process of claim 161, wherein said body surface is the surface of a wound.

165. The process of claim 161, wherein said water-soluble polymer comprises polyethylene oxide.

166. The process of claim 161, wherein said polymer comprises a polymer selected from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.

167. The process of claim 166, wherein said polymer further comprises a water insoluble polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone and combinations thereof.

168. The process of claim 166, wherein said polymer further comprises a polymer selected from the group consisting of methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(α-esters), polyanhy-

drides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof.

169. The process of claim **166**, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

170. The process of claim **166**, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(α-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

171. The process of claim **161**, wherein said solvent is selected from the group consisting of water, polar organic solvent, and combinations thereof.

172. The process of claim **161**, wherein said solvent is selected from the group consisting of ethanol, isopropanol, acetone, and combinations thereof.

173. The process of claim **161**, wherein said active is selected from the group consisting of bioactive active, pharmaceutical actives, drugs, medicaments and combinations thereof.

174. The process of claim **161**, wherein said active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, anti-tumor drugs, anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, anti-convulsants, neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, anti-asthmatics, cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

175. The process of claim **161**, wherein said active is selected from the group consisting of cosmetic actives, antigens, allergens, spores, microorganisms, seeds, mouthwash components, flavors, fragrances, enzymes, preservatives, sweetening agents, colorants, spices, vitamins and combinations thereof.

176. The process of claim **161**, wherein said active is a bioactive active.

177. The process of claim **161**, wherein said active is a biological response modifier.

178. The process of claim **161**, wherein said active is an opiate or opiate-derivative.

179. The process of claim **161**, wherein said active is an anti-emetic.

180. The process of claim **161** wherein said active is an amino acid preparation.

181. The process of claim **161**, wherein said active is selected from the group consisting of sildenafils, tadalafils, vardenafils, apomorphines, yohimbine hydrochlorides, alprostadils and combinations thereof.

182. The process of claim **161**, wherein said active is a protein.

183. The process of claim **161**, wherein said active is insulin.

184. The process of claim **161**, wherein said active is an anti-diabetic.

185. The process of claim **161**, wherein said active is an antihistamine.

186. The process of claim **161**, wherein said active is an anti-tussive.

187. The process of claim **161**, wherein said active is a non-steroidal anti-inflammatory.

188. The process of claim **161**, wherein said active is an anti-asthmatics.

189. The process of claim **161**, wherein said active is an anti-diarrhea.

190. The process of claim **161**, wherein said active is an alkaloid.

191. The process of claim **161**, wherein said active is an anti-psychotic.

192. The process of claim **161**, wherein said active is an anti-spasmodic.

193. The process of claim **161**, wherein said active is a biological response modifier.

194. The process of claim **161**, wherein said active is an anti-obesity drug.

195. The process of claim **161**, wherein said active is an H_2-antagonist.

196. The process of claim **195**, wherein said H_2-antagonist is selected from the group consisting of cimetidine, ranitidine hydrochloride, famotidine, nizatidine, ebrotidine, mifentidine, roxatidine, pisatidine, aceroxatidine and combinations thereof.

197. The process of claim **161**, wherein said active is a smoking cessation aid.

198. The process of claim **161**, wherein said active is an anti-parkinsonian agent.

199. The process of claim 161, wherein said active is an anti-depressant.

200. The process of claim 161, wherein said active is an anti-migraine.

201. The process of claim 161, wherein said active is an anti-Alzheimer's agents.

202. The process of claim 161, wherein said active is a dopamine receptor agonist.

203. The process of claim 161, wherein said active is a cerebral dilator.

204. The process of claim 161, wherein said active is a psychotherapeutic agent.

205. The process of claim 161, wherein said active is an antibiotic.

206. The process of claim 161, wherein said active is an anesthetic.

207. The process of claim 161, wherein said active is a contraceptive.

208. The process of claim 161, wherein said active is an anti-thrombotic drug.

209. The process of claim 161, wherein said active is diphenhydramine.

210. The process of claim 161, wherein said active is nabilone.

211. The process of claim 161, wherein said active is albuterol sulfate.

212. The process of claim 161, wherein said active is an anti-tumor drug.

213. The process of claim 161, wherein said active is a glycoprotein.

214. The process of claim 161, wherein said active is an analgesic.

215. The process of claim 161, wherein said active is a hormone.

216. The process of claim 161, wherein said active is a decongestant.

217. The process of claim 161, wherein said active is a loratadine.

218. The process of claim 161, wherein said active is dextromethorphan.

219. The process of claim 161, wherein said active is chlorpheniramine maleate.

220. The process of claim 161, wherein said active is selected from the group consisting of an analgesic, an anti-inflammatory, an antihistamine, a decongestant, a cough suppressant and combinations thereof.

221. The process of claim 161, wherein said active is an appetite stimulant.

222. The process of claim 161, wherein said active is a gastrointestinal agent.

223. The process of claim 161, wherein said active is a hypnotic.

224. The process of claim 161, wherein said active is taste-masked.

225. The process of claim 161, wherein said active is taste-masked using a flavor.

226. The process of claim 161, wherein said active is coated with a controlled release composition.

227. The process of claim 226, wherein said controlled release composition provides an immediate release.

228. The process of 226, wherein said controlled release composition provides a delayed release.

229. The process of claim 226, wherein said controlled release composition provides a sustained release.

230. The process of claim 226, wherein said controlled release composition provides a sequential release.

231. The process of claim 161, wherein said active is a particulate.

232. The process of claim 161, further comprising adding a degassing agent to said flowable polymer matrix.

233. The process of claim 161, further comprising a step of providing a second film layer.

234. The process of claim 233, wherein said second film layer is coated onto said resulting film.

235. The process of claim 233, wherein said second film layer is spread onto said resulting film.

236. The process of claim 233, wherein said second film layer is cast onto said resulting film.

237. The process of claim 233, wherein said second film layer is extruded onto said resulting film.

238. The process of claim 233, wherein said second film layer is sprayed onto said resulting film.

239. The process of claim 233, wherein said second film layer is laminated onto said resulting film.

240. The process of claim 233, further comprising laminating said resulting film to another film.

241. The process of claim 233, wherein said second film comprises an active.

242. The process of claim 233, wherein said active in said second film is different than said active in said resulting film.

243. The process of claim 1, said active is an anti-nauseant.

244. The process of claim 1, said active is an erectile dysfunction.

245. The process of claim 1, said active is a vasoconstrictor.

246. The process of claim 1, said active is a stimulant.

247. The process of claim 1, said active is a migraine treatment.

248. The process of claim 1, said active is granisetron hydrochloride.

249. The process of claim 1, wherein said resulting film provides administration of said active to an individual through the buccal cavity of said individual.

250. The process of claim 1, wherein said resulting film provides administration of said active through gingival application of said individual.

251. The process of claim 1, wherein said resulting film provides administration of said active through sublingual application of said individual.

252. The process of claim 1, wherein said resulting film provides administration of said active to an individual through a mucosal membrane of said individual.

253. The process of claim 1, wherein said resulting film provides administration of said active to an individual by administration within the body of the individual during surgery.

254. The process of claim 1, wherein said resulting film has a variation of active content of less than 10% per film unit.

255. The process of claim 1, further comprising the step of forming a plurality of individual dosage units of substantially the same size, wherein the active content of individual dosage units has a variance of no more than 10%.

256. The method of claim 1, wherein said resulting film contains less than about 6% by weight solvent.

257. The method of claim 1, wherein said at least one edible polymer, said active, and said at least one polar solvent are each ingestible materials.

258. The method of claim 1, wherein said resulting film is orally administrable.

259. The method of claim 1, wherein said active is in the form of a particle.

260. The method of claim 1, wherein said matrix comprises a dispersion.

261. The process of claim **82**, said active is an anti-nauseant.

262. The process of claim **82**, said active is an erectile dysfunction.

263. The process of claim **82**, said active is a vasoconstrictor.

264. The process of claim **82**, said active is a stimulant.

265. The process of claim **82**, said active is a migraine treatment.

266. The process of claim **82**, said active is granisetron hydrochloride.

267. The process of claim **82**, wherein said resulting film provides administration of said active to an individual through the buccal cavity of said individual.

268. The process of claim **82**, wherein said resulting film provides administration of said active through gingival application of said individual.

269. The process of claim **82**, wherein said resulting film provides administration of said active through sublingual application of said individual.

270. The process of claim **82**, wherein said resulting film provides administration of said active to an individual through a mucosal membrane of said individual.

271. The process of claim **82**, wherein said resulting film provides administration of said active to an individual by administration within the body of the individual during surgery.

272. The process of claim **82**, wherein said resulting film has a variation of active content of less than 10% per film unit.

273. The process of claim **82**, further comprising the step of forming a plurality of individual dosage units of substantially the same size, wherein the active content of individual dosage units has a variance of no more than 10%.

274. The method of claim **82**, wherein said resulting film contains less than about 6% by weight solvent.

275. The method of claim **82**, wherein said at least one edible polymer, said active, and said at least one polar solvent are each ingestible materials.

276. The method of claim **82**, wherein said resulting film is orally administrable.

277. The method of claim **82**, wherein said active is in the form of a particle.

278. The method of claim **82**, wherein said matrix comprises a dispersion.

279. The process of claim **161**, said active is an anti-nauseant.

280. The process of claim **161**, said active is an erectile dysfunction.

281. The process of claim **161**, said active is a vasoconstrictor.

282. The process of claim **161**, said active is a stimulant.

283. The process of claim **161**, said active is a migraine treatment.

284. The process of claim **161**, said active is granisetron hydrochloride.

285. The process of claim **161**, wherein said resulting film provides administration of said active to an individual through the buccal cavity of said individual.

286. The process of claim **161**, wherein said resulting film provides administration of said active through gingival application of said individual.

287. The process of claim **161**, wherein said resulting film provides administration of said active through sublingual application of said individual.

288. The process of claim **161**, wherein said resulting film provides administration of said active to an individual through a mucosal membrane of said individual.

289. The process of claim **161**, wherein said resulting film provides administration of said active to an individual by administration within the body of the individual during surgery.

290. The process of claim **161**, wherein said resulting film has a variation of active content of less than 10% per film unit.

291. The process of claim **161**, further comprising the step of forming a plurality of individual dosage units of substantially the same size, wherein the active content of individual dosage units has a variance of no more than 10%.

292. The method of claim **161**, wherein said resulting film contains less than about 6% by weight solvent.

293. The method of claim **161**, wherein said at least one edible polymer, said active, and said at least one polar solvent are each ingestible materials.

294. The method of claim **161**, wherein said resulting film is orally administrable.

295. The method of claim **161**, wherein said active is in the form of a particle.

296. The method of claim **161**, wherein said matrix comprises a dispersion.

297. The method of claim **1**, wherein said matrix comprises an emulsion, a colloid or a suspension.

298. The method of claim **82**, wherein said matrix comprises an emulsion, a colloid or a suspension.

299. The method of claim **161**, wherein said matrix comprises an emulsion, a colloid or a suspension.

* * * * *

EXHIBIT 3

Docket No.: 117744-00023
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Inter Partes Reexamination of:	)	
	)	
US Patent No. 7,897,080	)	
	)	
Issued: March 1, 2011	)	Confirmation No.: 6418
	)	
Named Inventor: Robert K. Yang et al.	)	Group Art Unit: 3991
	)	
Control No.: 95/002,170	)	Examiner: Diamond, Alan D.
	)	
Filed: September 10, 2012	)	M&E Docket: 117744-00023
	)	
Title: Polyethylene-oxide based RCE/CON/REX films and Drug delivery systems made therefrom	)	H&B Docket: 1199-26
	)	

Mail Stop Inter Partes Reexam
Attn: Central Reexamination Unit
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Declaration of Jason O. Clevenger under 37 C.F.R. § 1.132

I, Jason O. Clevenger, Ph.D., declare:

1. I am a Principal Scientist at Exponent, a science and engineering consulting firm. My expertise focuses on materials characterization and process engineering for specialty manufacturing, including regulated products such as medical devices and pharmaceuticals. Specifically with regard to pharmaceuticals, my experience includes process engineering and method development for transdermal and solid oral formulations, regulatory compliance and CMC (Chemistry, Manufacturing, and Controls) related issues including root cause analysis, corrective and preventive action plans, and regulatory submissions. Attached is my *curriculum vitae*.

2. While Exponent is being paid for my time, I am not an employee of, nor do I have any financial interest in, BioDelivery Sciences International, Inc.

3. I have carefully reviewed U.S. Patent No. 7,897,080 ("the '080 Patent"), International Publication No. WO 00/42992 ("Chen"), the Declaration of B. Arlie Bogue, Ph.D. submitted to the U.S. Patent Office on March 13, 2013 ("Bogue Declaration") and the Declaration of David T. Lin, Ph.D. submitted to the U.S. Patent Office on March 13, 2013 ("Lin Declaration").

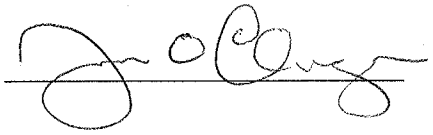
4. In my experience, the route to regulatory approval is an ongoing negotiation with the FDA through the New Drug Application (NDA) process. In this negotiation process, analytical testing and standards are determined for each product depending on its particular properties and characteristics. Different active agents and dosage forms have different properties, and would thus generally have different standards and testing requirements. Also, standardized test methods can change over time (e.g., USP <905> was revised in 2007 and 2011), so regulations from 2000 will not provide adequate information for present approval processes.

5. An FDA New Drug Application ("NDA") is a long and very detailed document. The CMC Section alone is often many hundreds to thousands of pages long. Patents are not intended to be part of an NDA and would not be expected to have the same disclosure, at least because the two documents have different requirements and very different purposes. To the extent that Chen does not provide sufficient information to comply with all of the information required in an NDA, neither does the '080 Patent.

6. The analysis in the Bogue Declaration is not consistent with the currently adopted definition of content uniformity as described in USP <905> Uniformity of Dosage Units. The calculation in paragraphs 9 and 10 of the Bogue Declaration are not included within the definition of content uniformity as described in USP <905> Uniformity of Dosage Units.

All statements herein of my own knowledge are true and all statements made on information and belief are believed to be true; and further these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon

Dated: 12 April 2013

Signature: 

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Professional Profile

Dr. Jason O. Clevenger is a Principal Scientist in Exponent's Polymer Science and Materials Chemistry practice. His expertise focuses on materials characterization and process engineering for specialty manufacturing, with a particular emphasis on regulated products such as medical devices and pharmaceuticals.

Dr. Clevenger's physical chemistry experience is applicable to problems involving materials such as semiconductors, MEMS, metal films, dielectrics, polymers, materials processing, materials characterization, pharmaceutical process chemistry, identification of trace contaminants including organics and particulates, and corrosion processes.

His pharmaceutical experience includes process engineering and optimization for transdermal and solid oral formulations, regulatory compliance and CMC (Chemistry, Manufacturing, and Controls) related issues involving root cause analysis, corrective and preventive action plans, quality assurance, and Quality by Design initiatives. His medical device experience includes method development for regulatory submissions, product development and manufacturing support, and technology due diligence assessment.

His characterization background encompasses a broad range of advanced technologies and techniques including laser spectroscopy, X-ray photoelectron spectroscopy (XPS), Auger spectroscopy, Raman, FTIR, solid/liquid-NMR, optical emission/absorption spectroscopy, energy dispersive spectroscopy (EDS), white-light interferometry, spectroscopic ellipsometry, atomic force microscopy (AFM), and secondary ion mass spectrometry (SIMS). In addition, he has extensive experience with plasma chemistry and spectroscopy, thin film metrology and reliability, high vacuum technology and semiconductor processing.

Academic Credentials and Professional Honors

Ph.D., Physical Chemistry, Massachusetts Institute of Technology, 2002
B.A., Chemistry, Vanderbilt University (*magna cum laude* with *high honors*), 1995

Phi Beta Kappa and Omicron Delta Kappa

High Honors in Chemistry for Undergraduate Thesis, 1995; Outstanding Senior in Chemistry Award, 1995; T.W. Martin Award and D.E. Pearson Award for Excellence in Undergraduate Research and Study of Physical Chemistry, 1995; J.M. Breckenridge Scholarship, 1994; Barry M. Goldwater Foundation Scholarship, Goldwater Excellence in Education Foundation, 1994;

Stephen H. Cook Summer Research Fellowship, 1994; Top-Tennessee Scholars Tuition Scholarship, 1993; Eastman Kodak National Merit Scholarship, 1991

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Prior Experience

Process Technologist (Etch and CVD), Applied Materials, Inc., 2002–2004

Professional Affiliations

- American Association of Pharmaceutical Scientists—AAPS
- American Chemical Society—ACS
- Society of Photo-Optical Instrumentation Engineers—SPIE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re *Inter Partes* Reexamination of:	)	
	)	
US Patent No. 7,897,080	)	Confirmation No.: 6418
	)	
Named Inventor: Robert K. Yang *et al.*	)	Group Art Unit: 3991
	)	
Control No.: 95/002,170	)	Examiner: Alan D. Diamond
	)	
Request Filed: September 10, 2012	)	M&E Docket: 117744-00023
	)	
Title: POLYETHYLENE OXIDE-BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM	)	H&B Docket: 1199-26 RCE/CON/REX
	)	
Mailing Date: March 10, 2014	)	

Mail Stop *Inter Partes* Reexam
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Alexandria, VA 22313-1450

BDSI'S APPEAL BRIEF IN *INTER PARTES* REEXAMINATION

All claims of the instant patent stand finally rejected by the reexamination panel. BioDelivery Sciences International, Inc. ("BDSI") appeals the decision of the examining panel to not adopt the proposed rejections of all claims under 35 USC §112.

Certificate Regarding Word Count Pursuant to 37 CFR 1.943(c)

I hereby certify that, pursuant to 37 CFR 1.943(c), based on the Word version word count of 10,217 words total, including 8,598 words in the instant brief and 1,619 words in the cited paragraphs of the expert declarations, which does not exceed 14,000 words in length.

Signed: Danielle L. Herritt /Danielle L. Herritt / Reg. No. 43,670 Dated: March 10, 2014

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I. REAL PARTY IN INTEREST

Appellant, BioDelivery Sciences International, Inc. ("BDSI") is the real party in interest for this brief.

II. RELATED APPEALS, INTERFERENCES, AND TRIALS

BDSI is not aware of any related appeals, interferences or judicial proceedings.

III. STATUS OF CLAIMS

Reexamination was initiated with respect to all of the 299 original claims in the '080 patent. But MonoSol cancelled claims 12, 16, 91, 95, 173, 177, 254-255, 257, 272-273, 275, 290-291, and 293. The reexamination now involves 303 claims total—claims 1-11, 13-15, 17-90, 92-94, 96-172, 174-176, 178-253, 256, 258-271, 274, 276-289, 292, 294-299, and new claims 300-318. All of the new and original claims that were not cancelled by MonoSol were finally rejected in the Right of Appeal Notice.

IV. STATUS OF AMENDMENTS

Only one of the three sets of amendments MonoSol proposed was entered. Both the first proposed amendment filed January 29, 2013, and the third proposed amendment filed September 3, 2013, were not entered. See Notice Regarding Defective Paper mailed February 26, 2013 at 3; RAN at 3. A second proposed amendment filed March 13, 2013 was entered. The claims, as amended in the March 13, 2013 filing, are listed in the Claims Appendix.

V. SUMMARY OF CLAIMED SUBJECT MATTER

There are 7 independent claims[1] (*i.e.*, claims 1, 82, 161, 315, 316, 317, and 318) and 296 dependent claims finally rejected in this proceeding. In the RAN, the reexamination panel identified a representative claim (claim 1) and a summary of claimed subject matter. See RAN at 4-9. Because of the substantial similarity of the independent claims, we will address claim 1 as a representative claim, and then address each independent claim separately, to the extent each differs. Referring to claim 1, the rejected claims are directed to a method of making a film with three basic steps: (i) forming a polymer matrix; (ii) casting the matrix; and (iii) drying the matrix to form a film. BDSI could find no disclosure of such a general method, but it did find a description that required specific polymers and excluded plasticizers. See '080 patent at 4:51-58.

The independent claims divide drying into two drying steps (i.e., "controlling drying … to form a visco-elastic film" and then "forming said resulting film from said visco-elastic film"). BDSI could find no conditions that differentiate these two "steps." *Compare* steps (d) and (e) of claim 1 and/or steps

[1] Exhibit A of the April 12, 2013 Comments is a comparison of the independent claims.

(c) and (d) of any of the other independent claims. Accordingly, BDSI cannot provide any support for two distinct drying steps. The "controlled drying" of step (c)/(d) is described as possible "through a variety of methods." Id. at 27:26-27. This variety of methods is described in the section entitled "Drying of Films." Id. at 27:11-28:64. For example, the "Drying of Films" section disclosed a drying method involving an underside water bath, which is admitted to be in the prior art. Id. at 28:2-6. The claims appear to encompass all of the drying methods, including the admitted prior art, disclosed in the "Drying of Films" section. Id.

The independent claims also recite a step—added to each independent claim during reexamination—of "*performing analytical chemical tests*" for uniformity of content of active. See step (f) of claim 1 and step (e) of all other independent claims. The panel correctly found that the term "analytical chemical tests" is neither used nor defined in the '080 patent. See RAN at 7. In the section entitled "Testing Films for Uniformity," uniformity is confirmed by visual inspection and, alternatively, by use of analytical equipment. See '080 patent at 28:65-29:53. Uniformity testing is then exemplified in Examples A-I where visual inspection (use of magnification) and weight testing (a scale for additive weights) are employed as alternatives for confirming uniformity of distribution of the

components within the film. Id. at 31:38-32:45. Dissolution testing is also generally described, as a third alternative for determining the uniformity of active, but not exemplified. Id. at 32:35-39.

Various independent claims add other steps listed here for the sake of completeness. Claim 1 adds the steps of forming a masterbatch pre-mix prior to adding the active to the polymer matrix. See Claim 1, steps (a-b); see id. at 9:64-10:49. Claims 82 and 315 add a step of repeating steps already recited to make and compare "further resulting films." See Claims 82 and 315, step (f); see id. at 29:47-53. Claim 161 oddly adds a step of administering a film to a body surface, even though the claim is recited to be a process for manufacturing a film. See Claim 161, step (f); see id. at 19:6-9.

The other independent claims do not recite any new steps. Claim 315 shifts a desired uniformity result, added to claim 82 in both steps (c) and (e), to steps (d) and (e). Claim 316 is virtually identical to claim 315, except in claim 316, apparently the uniformity is only required in intermediate step (d). Claim 317 is also virtually identical except now the uniformity is only required in intermediate step (c). BDSI found no support in the '080 patent for any methods where

uniformity is transient and/or measured during specific intermediate steps or combination of steps.

Finally, claim 318, as the ACP and RAN has already stated, combines disparate elements unconnected in the specification. See ACP at 26-27; RAN at 27-29.

The independent claims also recite a number of desired results relating to suitability for commercial and regulatory approval and uniformity of the active. These recitations are found in the preamble, and throughout the various claim steps. These recitations are alleged to be supported by nine lines in the '080 patent's background, in a passage disparaging a prior art reference, Fuchs:

> For this reason, dosage forms formed by processes such as Fuchs, would not likely meet the stringent standards of governmental or regulatory agencies, such as the U.S. Federal Drug Administration ("FDA"), relating to the variation of active in dosage forms. Currently, as required by various world regulatory authorities, dosage forms may not vary more than 10% in the amount of active present. When applied to dosage units based on films, this virtually mandates that uniformity in the film be present.
>
> Id. at 2:38-46.

But interestingly, despite Fuchs' disclosure of "uniform" films, and methods and materials for making uniform films—MonoSol argues that Fuchs' films were "inherently non-uniform." Compare id. at 2:10-13 to id. at 2:18-21. In particular,

MonoSol claims to have examined films made in accordance with the process disclosed in Fuchs. Id. at 2:18-19. MonoSol argues the non-uniformity in the examined films "can be attributed to *Fuchs' process parameters*, which although *not disclosed* likely include the use of relatively long drying times." Id. at 2:21-26 (emphasis added). And, MonoSol argues that Fuchs's films are inherently non-uniform due to "relatively long drying times" admittedly not disclosed by Fuchs. Rather than the newly added recitations, the language quoted above appears to support anticipation by Fuchs.

VI. ISSUES TO BE REVIEWED ON APPEAL

A. Whether the panel erred by not holding MonoSol to its interpretation of the new recitation "*suitable for commercialization and regulatory approval…*" as lacking written description and enablement, and by not rejecting the claim as indefinite for being susceptible to at least two interpretations – the PTO's and MonoSol's.

B. Whether the panel erred in declining to adopt the proposed rejections for the term "*analytical chemical tests*" even though the term is not used, not described, not defined, and not exemplified in the '080 patent.

C. Whether the panel erred in declining to adopt the proposed rejections for the step of performing analytical tests to verify specific levels of uniformity, even though this step is not used, not described, not defined, and not exemplified in the '080 patent.

D. Whether the panel erred in declining to adopt the proposed rejections based on limited variation between films even though such limitation is not described, not defined, and not exemplified in the '080 patent.

E. Whether the panel erred in failing to conclude that the scope of the claims cannot be determined because the newly-added "*rapidly increasing the viscosity of said flowable polymer matrix*" includes terms of degree both lacking a reference point and standards for comparison.

F. Whether the panel erred in determining that the "*100 °C or less*" in the "*controlling drying*" step clearly applies throughout the step.

G. (Adopted)

H. Whether the panel erred in declining to adopt the proposed 112 rejections for the newly-added uniformity requirements added to different steps and combinations of steps even though these requirements are not described, not defined, and not exemplified in the '080 patent..

VII. ARGUMENT

Summary

All 300+ claims in this reexamination appeal are directed to methods of making films for delivery of an active. They each recite the same three general steps for making a film: (i) forming a polymer-solvent matrix that includes a bioactive and/or pharmaceutical active; (ii) casting the matrix; and (iii) evaporating at least a portion of the solvent to form a film. But the prior art teaches the same materials and the same film-making process steps. See ACP at 35:12-16; 35-39 (referring to *Chen*[2]); 95:5-8 (referring to *Staab*[3]); RAN at 82 . And, despite multiple opportunities during reexamination, MonoSol has never explained why performing all the claimed process steps with the claimed materials—as the prior art does—would not necessarily produce a film that has the claimed desired results, e.g., the newly recited uniformity results. See RAN at 82.

Instead, MonoSol relies on its new limitations of uniformity—without explaining how the claimed methods differ from those disclosed in the cited prior art. MonoSol never took on its burden to rebut the inherency rejections by

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[2] International Patent Publication No. WO 00/42992 to Chen *et al.*

[3] US Patent No. 5,393,528 to Staab.

reproducing any examples from, e.g., *Chen* or *Staab*. And it has failed to rebut the obviousness of merely reciting desired results—results MonoSol does not dispute were well known long before its earliest claimed priority date. MonoSol certainly does not recite any new or non-obvious methods of achieving them in its claims. As such, the panel correctly found that all of the new recitations are anticipated and/or obvious in view of the cited prior art.

But in addition to failing to patentably distinguish over the cited prior art, the '080 patent also fails to disclose or enable the new recitations, particularly when MonoSol is held to its own interpretation of these recitations. For example, although iterative sampling and testing throughout one film manufacturing run is briefly mentioned (see the '080 patent at 29:48-53), the '080 patent neither discloses nor exemplifies repetition of steps to satisfy a certain uniformity standard between films, as recited in step (f) of claims 82 and 315. Thus, the '080 patent fails to provide the disclosure that MonoSol itself argues is required of the prior art. In short, in addition to lack of novelty and obviousness over the prior art, the recitation of this new matter is entirely without basis in the specification and has only resulted in invalid claims, the scope of which is unclear.

BDSI files this appeal because, although the non-adopted rejections under 35

USC § 112 might be considered redundant to the final rejections, BDSI wants to make clear that, even if these new recitations did somehow distinguish the methods over the prior art methods (which they do not), the claims are still invalid under 35 USC § 112 for the reasons MonoSol itself advances.

A. Whether the panel erred by not holding MonoSol to its interpretation of the new recitation "*suitable for commercialization and regulatory approval…*" as lacking written description and enablement, and by not rejecting the claim as indefinite for being susceptible to at least two interpretations – the PTO's and MonoSol's.[4]

MonoSol added a new recitation to each of its methods for making a film requiring a resulting film "*suitable for commercialization and regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units*." See Claims Appendix or Reply by Patentee to a Non-Final Office Action Pursuant to 37 CFR 1.111 filed March 13, 2013 (hereinafter "Reply-2") at 2-41. This recitation is in the preamble and is also referred to in the body of the claims in the step requiring performing analytical chemical tests. See step (f) for claim 1, step (e) for all other independent claims. The examining panel correctly

[4] The lettering of the headings is consistent with the lettering of the proposed rejections, the ACP, and the RAN.

determined that this new recitation fails to distinguish the claimed methods over the prior art teachings of the same method steps and the same levels of uniformity. See e.g., ACP at 36-37 (*Chen*) and 56 (*Staab*); RAN at 36-37 (*Chen*) at 57-59 (*Staab*). The panel concluded that the new recitation was satisfied by performing the rest of the step in which the "suitability" language appears:

> The claims do not require commercialization or regulatory approval, they set forth suitability for commercialization and regulatory approval. The bright line test for such suitability is based on performing analytical chemical tests for uniformity of content active, said tests showing a particular variation of active, for example, not more than 10%.
>
> ACP at 13; RAN at 14.

In other words, the examining panel read the new recitation (indicated in bold type below) as satisfied by the rest of the step (indicated with underlining below) in which it appears in the body of the claim.

Exemplary Claim 82: preamble and step (e)
82. A process for manufacturing resulting films **suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units**, said films having a substantially uniform distribution of components, comprising a substantially uniform distribution of a desired amount of said active in individual dosage units of said resulting films, comprising the steps of: …. (e) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units sampled from different locations of said resulting film, said tests indicating that uniformity of content in the amount of the active varies by no more than 10% and said resulting film is **suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration**; and

This is one interpretation. But MonoSol argued a different interpretation of this recitation—an interpretation that lacks written description and enablement in the '080 patent by MonoSol's own proposed standards.

To be clear, there is no error in the outstanding final prior art rejections because, where a claim is indefinite because it is subject to multiple interpretations, it is appropriate to make a prior art rejection applying an interpretation of the claims that renders the prior art applicable. See MPEP 2173.06; see also *Ex Parte Mesher*, No. 2012-009669, 2013 WL 6122669 at 3 (PTAB Nov. 25, 2013); *Ex parte Miyazaki*, No. 2007-3300, 2008 WL 5105055 at 5 (BPAI Nov. 19, 2008).

But, in addition, the claims should also have been rejected as lacking clarity with respect to claim scope, and lacking written description and enablement according to the interpretation advanced by MonoSol.

1. *Lack of Enablement*

MonoSol argued that, for the cited art to anticipate this new recitation, it must disclose films meeting all of the requirements for FDA approval. See, e.g., Reply-2 at 66:16-20; 78:6-8; Lin at ¶¶ 17-20. MonoSol's expert states that *Chen* lacked an enabling disclosure because it lacked "sufficient information contained within to allow FDA regulatory approval" of its films. Lin Decl. at ¶ 17. Application of MonoSol's proclaimed standard for determining whether the *prior art* is sufficiently enabled, demonstrates that its own claims are not enabled:

MonoSol argued the following deficiencies in the cited prior art:	**But MonoSol's '080 Patent is similarly deficient:**
"[T]here is insufficient disclosure to allow FDA to determine that a drug product as described can be manufactured for commercial distribution, manufactured in a consistent manner and meet specifications that will ensure the identity, strength, quality, purity, and potency of the drug product." Lin Decl. ¶ 17.	The '080 patent does not qualify as an FDA CMC submission, which is the bar set by MonoSol and its expert, Dr. Lin.

MonoSol argued the following deficiencies in the cited prior art:	**But MonoSol's '080 Patent is similarly deficient:**
"Chen lacks any disclosure which would necessarily lead to the manufacture of films with uniformity of content (strength) of drug active required for FDA approval." Lin Decl. ¶ 17.	Although the '080 patent discloses some uniformity data from physical tests (see '080 patent at 31:38-45 (disclosing data from visual inspection tests) and at 31:46-32:34 (disclosing weight variation tests)), MonoSol argues that these tests are insufficient (see Reply-2 at 58-59). Thus, applying MonoSol's standards, there is no uniformity data in the '080 patent that can be relied upon to satisfy this claim limitation.
"Chen does not disclose sufficient information that the films containing drug can be produced consistently with respect to uniformity of content of the drug." Lin Decl. ¶ 18.	The '080 patent does not include any data or other information regarding the reproducibility of films made according to the methods described.
"No information was disclosed that demonstrated uniformity of content in the amounts of drug in individual dosage units." Lin Decl. ¶ 18.	Again, applying MonoSol's standards, there is no uniformity data that can be relied upon in the '080 patent. See Reply-2 at 58-59.
"Chen discloses no specific test methods, and hence no test results, that could allow for the determination of the actual amount of drug (active) in individual dosage units." Lin Decl. ¶ 18.	While disclosing that a dose may be dissolved and tested for the amount of active (see '080 patent at 32:36-38), the '080 patent specification fails to disclose any specific test methods or exemplify any results that could allow for the determination of the actual amount of drug (active) in individual dosage units.

MonoSol argued the following deficiencies in the cited prior art:	**But MonoSol's '080 Patent is similarly deficient:**
"Chen's patent did not disclose sufficient information regarding the manufacturing process and process controls. The information disclosed by Chen would not ensure that films containing drug could be manufactured to meet specifications that ensure consistent strength." Lin Decl. ¶ 19.	Like *Chen*, the '080 patent fails to disclose or claim any information about manufacturing processes or controls to ensure consistent strength. To the extent that *Chen* is lacking, the '080 patent is also lacking.
"[T]here is no information regarding the test methods that are necessary to determine the amount of drug in individual dosage units." Lin Decl. ¶ 20.	Beyond its so-called physical tests (which MonoSol argues are insufficient in its Reply-2 at 58-59), the '080 patent is devoid of any information regarding "test methods that are necessary to determine the amount of drug in individual dosage units." For example, while disclosing that a dose may be dissolved and tested for the amount of active (see '080 patent at 32:36-38), the '080 patent discloses no such test methods or results.

In short, to the extent that *Chen* lacks an enabling disclosure with respect to this newly added recitation, the '080 patent also lacks an enabling disclosure. See *Inter Partes* Reexamination Comments Under 37 CFR § 1.947 filed April 12, 2013 ("Comments-2") at 11-13.

2. *Lack of Written Description*

In addition, because the new recitation in the pending claims extends beyond what is disclosed in the specification, the amended claims lack written description. See Comments-2 at 14. For example, the '080 patent does not qualify as an FDA CMC submission, which is the bar set by MonoSol and its expert, Dr. Lin, for the prior art to anticipate. See Lin Decl. ¶ 17; Reply-2 at 66:16-20, 78:6-8.

3. *Lack of Clarity*

The claims are indefinite because they subject to at least two very different interpretations—the examining panel's and MonoSol's. The panel interpreted this recitation to only require satisfaction of one uniformity parameter. MonoSol argued that this interpretation requires disclosure equivalent to an FDA submission for a regulatory approval of a new drug product.

In addition, the "suitable for commercial and regulatory approval…." recitation is ambiguous and unclear because there are no set tests or standards that can be applied to determine whether the recitation is satisfied. Indeed, not only do the regulatory standards change over time, but they may differ for each drug

product. As Dr. Clevenger explains, suitability for approval can only be determined through negotiation with the FDA:

> In my experience, the route to regulatory approval is an ongoing negotiation with the FDA through the New Drug Application (NDA) process. In this negotiation process, analytical testing and standards are determined for each product depending on its particular properties and characteristics. Different active agents and dosage forms have different properties, and would thus generally have different standards and testing requirements. Also, standardized test methods can change over time…so regulations from 2000 will not provide adequate information for present approval processes.
>
> Clevenger Decl. ¶ 4.

Without the test methods or standards, it is impossible to understand what is required by the amended claims, particularly when the standards and test methods may differ for each active and the claims potentially cover thousands of actives. And, even with respect to one active, the tests and standards may change over time as the FDA requires.

B. Whether the panel erred in declining to adopt the proposed rejections for the term "*analytical chemical tests*" even though the term is not used, not described, not defined, and not exemplified in the '080 patent.

MonoSol added the step of performing "*analytical chemical tests*" to every independent claim, and took the position that in order for the cited art to anticipate

this new recitation, the cited art must be "supported" by proof that it verified its active uniformity by performing analytical testing. See Reply-2 at 51; Lin Decl. ¶¶ 17-22. The examining panel correctly found the step of performing analytical chemical tests to verify properties does not patentably distinguish the claims. See ACP at 38 (*Chen*) and at 57 (*Staab*); RAN at 39 and 58-59, respectively.

1. *Lack of Written Description*

The examining panel should also have rejected the claims for lacking written description. Nowhere in the '080 patent is the term "analytical chemical testing" employed. And nowhere in the '080 patent is any "analytical chemical test" described or employed to verify the amount of active in any sample. MonoSol's citation of support to an example (Example M) testing a dye—not a bioactive and/or pharmaceutical active—was soundly rejected as evidence of verification of active uniformity by analytical chemical tests. See RAN at 86-87; see also ACP at 6, last two lines (concluding that the '080 patent does not disclose any analytical chemical tests used to verify the amount of active in a sample). In addition, MonoSol proposes the following standard, which the '080 patent fails to meet:

> In the cited prior art, terms such as uniformity, substantial uniformity, and homogeneity are all accepted without real support. They cannot

> be relied upon. What is missing is the support for the statements–that is, having had the amount of active tested by analytical chemical testing, including assaying.
>
> Reply-2 at 51 (citing Lin Decl. ¶¶ 17-22).

Again, MonoSol argues that Example M of the '080 patent includes exemplary analytical chemical testing to verify uniformity. See Reply-2 at 59. But Example M does not verify or even test uniformity of bioactive and/or pharmaceutical active. Indeed, MonoSol admits Example M includes a dye—not the claimed bioactive and/or pharmaceutical actives. See Response by Patentee to Action Closing Prosecution filed September 3, 2013 (hereinafter "Reply-3") at 66. Finally, MonoSol does not explain how the light absorption reading employed in Example M is a "chemical based" test. See generally Reply-2 and Reply-3.

2. *Lack of Clarity*

In addition to the lack of written description, this new recitation renders the scope of the claims unclear. MonoSol's arguments about how uniformity may be appropriately measured contradict the '080 patent. For example, the '080 patent specification provides three alternative tests for confirming uniformity of components (i) visual inspection, (ii) weight measurement, and (iii) dissolution testing. See '080 patent at 31:37-32:39. Weight measurement is even confirmed

as one of several valid methods of confirming active content for the FDA. See Comments-2 at 14-15 and Exhibits J-K (FDA Chapter <905> Uniformity of Dosage Units). But MonoSol now argues that weight measurement is not an acceptable alternative to analytical chemical tests. See Reply-2 at 56-59. So, what exactly is claimed? MonoSol points to the dissolution test, a "chemical based test," as the only type of test that can directly establish the same amount of active. See Reply-2 at 59. But MonoSol does not explain what this dissolution test is or how it differs from that exemplified in, for example, *Chen*.[5]

While an applicant is allowed to be its own lexicographer, it must do so within the patent disclosure (*i.e.*, not after grant), and it must define terms clearly. See MPEP 2111.01(IV) citing *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994) (inventor may define specific terms used to describe invention, but must do so "with reasonable clarity, deliberateness, and precision" and, if done, must "'set out

[5] Although MonoSol contradicts itself in questioning whether the results in *Chen* verify uniformity (see *Inter Partes* Reexamination Comments Under 37 CFR § 1.947 filed October 3, 2013 ("Comments-3") at 18), Dr. Reitman's reproduction of *Chen* verifies that the claimed uniformity was inherently met (see id. at 19-20; Reitman Decl. ¶ 7).

his uncommon definition in some manner within the patent disclosure so as to give one of ordinary skill in the art notice of the change" in meaning). MonoSol seeks to create a new and undefined category of analytical chemical testing—post grant—in an attempt to avoid the cited prior art. See Reply-2 at 53, last ¶, to 59, last full ¶. But the cited prior art employs the same methods that the '080 patent employs to verify uniformity. See *Chen* at 17:15-16 (disclosing visual inspection), Table 4 (disclosing weight measurement), and Figure 5 (disclosing dissolution testing). While MonoSol clearly argues that the term "analytical chemical tests" does not include the tests described in the prior art, but is superior to those prior tests (in direct contradiction to the teachings of its own specification)—MonoSol has not identified a single test in the '080 patent that meets its newly-invented criteria.

C. Whether the panel erred in declining to adopt the proposed rejections for the step of performing analytical tests to verify specific levels of uniformity, even though this step is not used, not described, not defined, and not exemplified in the '080 patent.

MonoSol added the step of "performing analytical chemical tests…indicating…the amount of active varies by no more than 10%" to every

independent claim, except claim 318.[6] See step (f) of claim 1 and step (e) of all other independent claims. Various new dependent claims recite that "the amount of active varies by no more than 2%, 1% and 0.5%." See e.g., Claims Appendix or Reply-2 at 34-35 (new claims 300-311). MonoSol argued that neither *Chen* nor *Staab* expressly or inherently disclosed this newly-recited desired result. But both references expressly disclose films that satisfy the claimed variation percentages using the '080 patent's own criteria—*i.e.*, weight variation of 0% demonstrated by weight per dosage unit. *Compare* '080 patent at 31:46-66 (reporting consistent 0.04 g, *i.e.,* 40 mg, dosage unit weights) *to Chen* at Table 4 (reporting consistent 28 mg dosage weights rounded to the same decimal place as the '080 patent), and *to Staab* at 11:35-12:3 (reporting consistent 19 mg dosage unit weights).

Indeed, correctly applying the variation/uniformity criteria disclosed in the '080 patent, the examining panel found that all of the claims anticipated and/or obvious in view of the cited art. See, e.g., ACP at 36 and 58-59; RAN at 36-37 and 57. And where a claim is indefinite, it is appropriate to make a prior art rejection over an interpretation of the claims which renders the prior art applicable. See MPEP 2173.06; see also *Ex parte Mesher*, No. 2012-009669, 2013 WL 6122669 at

[6] Claim 318 recites "the amount of active varies by no more than 5%."

3 (PTAB Nov. 25, 2013); *Ex parte Miyazaki*, No. 2007-3300, 2008 WL 5105055 at 5 (BPAI Nov. 19, 2008).

But in addition to the prior art rejections, correctly made and maintained, the examining panel should have also found that the new recitation—explicitly recited in the claims and argued extensively by MonoSol—not only failed to patentably distinguish the claims, but also failed to meet the requirements of 35 USC §112.

1. *Lack of Enablement*

MonoSol argued a different interpretation of its new language—and one that directly contradicts its own specification. MonoSol argued that the prior art does not demonstrate its claimed variation/uniformity because the prior art uniformity has not been verified in accordance with MonoSol's interpretation of its new recitation. MonoSol now insists—post grant—that "physically observable properties of the resulting film product, for example, its appearance and weight … do not indicate that the amount of active in individual dosage units varies by no more than 10%." Reply-2 at 54-55. "Even if the film appears uniform, analytical chemical tests must then be conducted to verify uniformity of content at the prescribed level." Reply-2 at 59. In short, MonoSol argues that to satisfy its new

"variation" recitation, uniformity must be verified by analytical chemical testing of film, not merely by physically observable properties of film.

But there is no evidence in the '080 patent that the disclosed methods result in a film with the claimed variation/uniformity as verified by analytical chemical testing. Despite over 100 examples and 150 pages of specification, the '080 patent discloses no method that results in a film that it states satisfies the new variation/uniformity recitation or which is actually verified by analytical chemical testing as doing so. Indeed, the '080 patent does not even disclose analytical chemical testing. See Section VII.B, *supra*.

MonoSol attempted to remediate its enablement problem by providing new data in the first Bogue Declaration dated March 13, 2013 ("Bogue Declaration"). This is problematic. First, MonoSol asserts that the data supports all 300+ claims, including the 7 independent claims. MonoSol presumably believes that all 300+ claims are not identical methods —yet the data in the Bogue Declaration describes one method—and that method fails to match a single claim. It also fails to disclose the underlying facts that could allow the panel or the Board to independently evaluate if the data is commensurate in scope with the claims. For example, the Bogue Declaration does not identify which polymer or polymers were used—and it

is impossible to tell if these polymers are interchangeable such that the claimed results are achieved with the dozens of other polymers classes claimed or the thousands of polymers covered by the claims.

Second, according to Bogue, "[t]he results shown in the appendices establish … the amount of active varies by no more than 10% between individual dosage units sampled from a particular lot of resulting film." Bogue Decl. at ¶ 11. Thus, it appears that a lot may be a subset of a "resulting film." But there is no certainty as to how a "resulting film" or "resulting films" may relate to one or more "lots." Neither MonoSol nor Bogue equates a "lot" to any recited claim element.

Third, even if the Bogue process were commensurate with a single recited claim, which has not been demonstrated, the results presented in the Bogue Declaration does not fall within the recited desired maximum variance in active content. As can be clearly seen from the data presented in Appendix B, the amount of pharmaceutical active varies between individual dosage units from less than 94% on the far left of the figure, to nearly 106% on the upper right. That is, the amount of pharmaceutical active varies by more than 10%.

Finally, because MonoSol chose only to provide the results of its calculations and not the underlying data, the Office has no way of determining if

the data, analyzed in Appendix A, supports the claims. Unsupported expert testimony may be given little or no weight. See e.g., Rohm & Haas Co. v. Brotech Corp., 127 F.3d 1089, 1092 (Fed. Cir. 1997).

With respect to the recited active variation of 5% or less, Bogue's data does not support these claims. Specifically, for example, Bogue's data demonstrates active variation greater than 5% in 27 of the 73 allegedly relevant lots. See Bogue Decl. ¶ 11; see also id. at Appendices A and C. In other words, 37% have active variation greater than 5%. Bogue's data demonstrates that only one allegedly relevant lot (*i.e.*, 1%) has active variation of 2%. See id. at ¶ 11; see also id. at Appendices A and C. In other words, the active in 99% of the Bogue lots varies by more than 2%. None of the Bogue lots has active variation less than 2%, 1%, or 0.5%. See Bogue Decl. at Appendices A and C.

2. *Lack of Written Description*

Again, despite over 100 examples and 150 total original pages of specification, the '080 patent discloses no method that results in a film that satisfies the new variation/uniformity recitations as verified by analytical chemical testing.

In short, the '080 patent neither describes nor enables verification of any of the recited variation/uniformity levels as verified by so-called "analytical chemical tests." And, by MonoSol's own admission, without verification, there is no indication that the claimed methods meet the newly recited requirements. See Reply-2 at 67, lines 10-15. The physical tests provided in the '080 patent are not enough, according to MonoSol. See id.

3. *Lack of Clarity*

This recitation also lacks clarity. MonoSol's position is that the prior art methods—which are the same as its own disclosed verification methods—are inferior and so somehow not credible. It is not clear how the newly claimed tests may differ from those in the cited prior art.

MonoSol, for example, acknowledges that *Staab* explicitly discloses dosage forms where the amount of active varies by no more than 0%, but dismisses this explicit anticipation of the claims as "suspect." See ACP at 69 citing *Staab* at 11:35-12:3 (reporting consistent 19 mg dosage unit weights). MonoSol's sole reason for its suspicion is that any result with consistent amount of active (in *Staab*, the active is consistently 10% of the total weight) "must always be

considered suspect." Reply-2 at 69. MonoSol dismisses the evidence of Dr. Reitman who recreated an example in *Chen* and reports 0% variation by so-called analytical chemical tests, but could provide no credible reason for doing so. Reply-2 at 66 (referring to the Reitman Decl. ¶ 6 (reporting consistent weights of 34 mg)).[7] In short, MonoSol's overall position with respect to the cited art—art that explicitly anticipates this new recitation—can be summarized as follows: any result that anticipates the '080 patent claims is suspect because it anticipates the '080 patent claims. MonoSol's new recitation lacks disclosure and enablement, and only serves to muddy the waters with respect to claim scope.

D. Whether the panel erred in declining to adopt the proposed rejections based on limited variation between films even though such limitation is not described, not defined, and not exemplified in the '080 patent.

Independent claims 82 and 315, include a new step (f) of "repeating steps (a) through (e) to form additional resulting films, such that … the amount of said active in said resulting film and said additional resulting films varies no more than 10% from the desired amount of the active." Dependent claims 83-90, 92-94, 96-

[7] Although MonoSol implies that Dr. Reitman failed to follow the example exactly, it could provide no example of how Dr. Reitman did not faithfully reproduce the example. See ACP at 66.

160, 261-271, 274, 276-278, 298, 304-307, and 313 each recite a similar "repeating" step.

1. *Lack of Written Description and Enablement*

MonoSol argues there were numerous problems with manufacturing a uniform film in the prior art. Reply-2 at 60 ("Recognition of the Problem"). It asserts that it discovered how to maintain uniformity by "controlling polymer matrix viscosity" and "controlling the drying processes" in order to maintain a lot-to-lot consistency. Reply-2 at 61 ("Solving the Problem"). But, notably, MonoSol does not tell us what step or method condition or conditions are required to "solve the problem." And nowhere does the '080 patent disclose "repeating" these steps, much less verification of resulting variation/uniformity. Logically, repeating a set of steps should produce more of the same film, but not change the quality of the film.

Asserting that there is no requirement to disclose working examples, the examining panel concluded that Example E demonstrates uniformity, by so-called "physical tests", equivalent to the recited variation. See ACP at 18, RAN at 19. But MonoSol argues that assumptions based on the so-called "physical tests," such

as described in Example E, cannot be used as the basis for the claimed variation percentage between films. See Reply-2 at 61. According to MonoSol's proposed standards, the '080 patent does not disclose or enable repeatability of a method to obtain the claimed variation/uniformity. The '080 patent discloses no method involving a "repeating" step and verification of a resulting variation/uniformity.

Accordingly, while the claims were properly rejected as anticipated and/or obvious in view of the cited prior art, the examining panel should also have rejected the claims as lacking written description and enablement. There is simply no support in the '080 patent for a method that achieves one variation percentage within a resulting film, and a second variation percentage between resulting films. This new step is a post-grant idea. "If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from…the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application." MPEP 2163.02.

2. *Lack of Clarity*

With respect to clarity, the new and amended claims indicate that "repeating" produces a variation of up to 20% (± 10% around a target) in active content. This is a much larger variation than the claims indicate are produced each individual time the method is carried out ("varies by no more than 10%, 5%, etc."). The claims suggest and MonoSol argues that its methods do not produce consistent films, *i.e.,* that the method is not repeatable such that each time there is less than 10% variation each time. In sum, it is unclear what uniformity is required and how such uniformity is achieved since the claim only recites known methods and materials.

E. Whether the panel erred in failing to conclude that the scope of the claims cannot be determined because the newly-added "*rapidly increasing the viscosity of said flowable polymer matrix*" includes terms of degree both lacking a reference point and standards for comparison.

Step (d) of claim 1 and step (c) of claims 82 and 161 have been amended to include the relative phrase "*rapidly increasing the viscosity of said flowable polymer matrix*." Each new independent claim recites the same language. MonoSol states its inventive methods avoids the prior art problems by "controlling polymer matrix viscosity" and "controlling the drying processes" to maintain the

recited uniformity. Reply-2 at 61. Both phrases are ambiguous and lacking in any specificity or new teaching not found in the art. Although MonoSol attempts to use this new recitation to overcome the cited prior art, it is unclear how the recitation may do so because no actual method step is recited. The examining panel correctly found the recitation anticipated and/or obvious over the cited prior art. See RAN at 22. *Chen's* method, for example, produces film having less than 10% moisture in 4 minutes and meets the claimed uniformity requirements. See Reitman Decl. ¶¶ 5-8.

But the examining panel should also have rejected these claims for failure to clearly define any process step or condition with the new recitation. First, the term "rapidly" is a relative term with no benchmark for assessment provided in the '080 patent. The term "rapidly" only refers to the timing at which a desired result is obtained, but not how it is achieved. In other words, "rapidly" is a term of degree that requires a standard for measuring the degree; otherwise its scope cannot be determined. See *Sony Corporation v. Network-1 Security Solutions, Inc.*, IPR2013-00092 at 8 (PTAB May 24, 2013) citing *Playtex Prods., Inc. v. Procter & Gamble, Co.*, 400 F.3d 901, 908 (Fed. Cir. 2010). Second, there is no indication of the degree to which the viscosity must be increased. By its very nature, any drying process increases viscosity to some extent and may be deemed to do so

"rapidly" by some benchmark. In short, introduction of this phrase into every independent claim creates ambiguity and indefiniteness and provides no way of determining if the claims is infringed or how it differs from the methods in the cited art. See, e.g., *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 927 F.2d 1200, 1217-18 (Fed. Cir. 1991).

F. Whether the panel erred in determining that the "*100 °C or less*" in the "*controlling drying*" step clearly applies throughout the step.

During reexamination, the "controlling drying" step of each independent claim was amended to recite "controlling drying…to form a visco-elastic film…wherein during said drying said flowable polymer matrix temperature is 100 °C or less." See Claims Appendix or Reply-2 at 2-42 (at step (d) in claim 1 and step (c) of every other independent claim). It is unclear whether this new temperature limit applies only to the beginning or throughout the "controlling drying" step. The examining panel concluded that the temperature limitation applied to the entire drying step until the matrix is no longer a flowable polymer matrix, as determined by its viscosity exceeding the range recited in the previous step. See ACP at 22-23; RAN at 23.

The examining panel erred by concluding that the viscosity range recited in the previous casting step clearly defines the metes and bounds of the flowable polymer matrix in the later drying step. The viscosity range recited in a casting step identifies a requirement of the flowable polymer matrix during that step. The upper limit of the viscosity range recited in a casting step does not define when a flowable polymer matrix becomes a visco-elastic film. The '080 patent describes the flowable polymer matrix as already visco-elastic. See, e.g., '080 patent at 9:9-20; 9:31-40; 35:55-57; and 35:61-63. That is, once cast, the flowable polymer matrix is a visco-elastic film—even before drying begins. In short, it is unclear when the 100°C or less temperature limit no longer applies.

G. (Adopted)

H. Whether the panel erred in declining to adopt the proposed 112 rejections for the newly-added uniformity requirements added to different steps and combinations of steps even though these requirements are not described, not defined, and not exemplified in the '080 patent.

Again, MonoSol adds multiple new expressions of its desired variation/uniformity, without reciting what new and non-obvious method steps achieve them. In MonoSol's words, there are numerous factors that can destroy uniformity:

> Even when a wet film matrix is properly formed so as to have a substantially uniform distribution of active within it, there are numerous factors which can destroy that uniformity of content during later processing such as casting and drying.
>
> Reply-2 at 61.

But the claims still recite the same general method steps disclosed in the cited prior art. Although the claimed methods differ in that they require uniformity at different steps, it is impossible to discern any process differences. While MonoSol argues that uniformity can be "destroyed" by "numerous factors," it has not identified any reasonable rationale that supports its assertion that the cited prior art failed to achieve the claimed uniformity.

1. *Lack of clarity*

MonoSol adds so many new and different recitations regarding variation limitations to its independent claims, with multiple uniformity variation levels, even within the same claim, that the claims are mired in ambiguity and uncertainty. For example, if "there are numerous factors which can destroy that uniformity of content during later processing such as casting and drying" (Reply-2 at 61), then what method steps are required to maintain this uniformity that are not already disclosed in the prior art?

In addition, it is unclear where or when analytical tests are required with respect to the various intermediate steps with new recitations regarding uniformity.

In yet another example, to add more confusion, analytical chemical tests are required in a different part of step (e) to "indicate" that the active varies by no more than 10% in individual dosage units. First, this is not the FDA standard for approval. As discussed above, the standard is defined in USP General Chapter <905>. See Exhibit J to Comment-2. Second, what does it mean to "indicate" that the active varies by no more than 10%?

Yet, there is one more layer of confusion. New step (f) of claim 82 also recites "said resulting film and said additional resulting films." How does a "resulting film" differ from "additional resulting films"? Where is that described in the specification? Or demonstrated for that matter? There is simply no discussion of ±10% from a target amount of active anywhere in the specification with respect to a comparison of "resulting films." And why is the amount of variation for merely repeating the method so large compared with the smaller variation required each time a film is made? This new claim amendment, and the data presented in the Bogue Declaration, only serve to demonstrate that repeating the claimed method does not produce consistent films.

Every single independent claim is similarly confusing, each with their own combination of the many shades of "uniformity" that individually and collectively create a hopeless morass of confusion as to the meaning of the claims, the scope of the claims, and what is required by the claims.

Claim 82 is reproduced here with all its varied uniformity requirements underlined:

> 82. (Amended) A process for manufacturing resulting films <u>suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units said film having a substantially uniform distribution of components comprising a substantially uniform distribution of a desired amount of said active in individual dosage units of said resulting films</u>, comprising the steps of:
>
> (a) forming a flowable polymer matrix comprising a polymer selected from the group consisting of a water-soluble polymer, a water swellable polymer and combinations thereof, a solvent and said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, said matrix having a substantially uniform distribution of said active;
>
> (b) casting said flowable polymer matrix. said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus and evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film, having said active substantially uniformly distributed throughout within about the first 4 minutes by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, wherein during said drying said flowable polymer matrix temperature is 100°C or less, and wherein uniformity of content of said active in substantially equal sized individual dosage units of said visco-elastic film is such that the amount of the active varies by no more than 10%;

(d) forming said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained;

(e) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units sampled from different locations of said resulting film, said tests indicating that uniformity of content in the amount of said active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration; and

(f) repeating steps (a) through (e) to form additional resulting films, such that uniformity of content in the amount of said active in said resulting

film and said additional resulting films varies no more than 10% from the desired amount of the active as indicated by said analytical chemical tests.

The vast majority of this claim is dedicated to varied expressions of desired uniformity at intermediate steps, as final desired result of the method, and then in comparing films with additional results films, but with no recitation the actual method step or combination of steps required to achieve them. Not only are the claimed methods unclear, but it is unclear even as to the requirements with respect to various desired uniformity limitations.

2. *Lack of written description.*

MonoSol argues post-grant that uniformity has to be verified by analytical chemical tests. But there is no evidence in the '080 patent that MonoSol verified uniformity at any step, including the intermediate steps where its new recitations require a specific variation/uniformity. See, e.g., '080 patent at 29:10-54 (only referencing uniformity testing of finished film samples). MonoSol has never explained how its methods actually differ from those of the prior art and thereby achieve this allegedly inventive variation/uniformity. No new method step is recited in the claims.

In addition, as discussed above, there is absolutely no support for the recitation of "varying by no more 10% from a desired target" in connection with any inventive method, or film resulting from the method. And certainly none for the claimed variation between "resulting films" and "additional resulting films." And while the '080 patent denigrates the prior art methods in its Background as not meeting this target (see discussion of Fuchs in '080 patent at 2:7-46)—it fails to tell us why and how its own methods achieve what it alleges others could not, apparently with the same methods.

3. *Lack of enablement*

Nowhere in any of the over 100 examples in the '080 Patent is any film demonstrated to meet any of the newly recited "uniformity" limitations. No analytical chemical tests are performed with respect to an active. No results of analytical chemical tests of active are provided. No demonstration is made that the active varies by no more than 10% in individual dosage units. No demonstration is made that "resulting films" and "additional resulting films" vary by no more than 10% from a desired target. In short, the '080 patent cannot withstand application of MonoSol's own proposed statements for written description and enablement.

Conclusion

In a failed attempt to overcome the cited prior art, MonoSol added a variety of recitations to every claim. The new recitations are confusing and unsupported. BDSI files this appeal because although the non-adopted rejections under 35 USC § 112 might be considered redundant to the final rejections, BDSI wants to make clear that, even if these new recitations did somehow distinguish the methods over the cited prior art methods (which they do not), the claims are still invalid under 35 USC § 112 for the reasons MonoSol itself advances.

Respectfully submitted,
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Dated: March 10, 2014

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VIII. CLAIMS APPENDIX

1. (Amended) A process for manufacturing a resulting film suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said [making a]film having a substantially uniform distribution of components comprising a substantially uniform distribution of said active in individual dosage units of said resulting film, comprising the steps of:

(a) forming a masterbatch pre-mix comprising a solvent and a polymer selected from the group consisting of water-soluble polymers, water-swellable polymers and combinations thereof;

(b) adding [an]said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, to a pre-determined amount of said masterbatch pre-mix to form a flowable polymer matrix, said matrix having a substantially uniform distribution of said active;

(c) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(d) controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus and evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first [10]4 minutes [or fewer]by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, wherein during said drying said flowable polymer matrix temperature is 100 °C or less; [and]

(e) forming [a]said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained; and

(f) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units sampled from different locations of said resulting film, said tests indicating that uniformity of content in the amount of the active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration.

2. (Original) The process of claim 1, wherein said pre-determined amount of master batch pre-mix is controllably fed via a first metering pump and a control valve to a first mixer and a second mixer.

3. (Original) The process of claim 2, wherein said first mixer and said second mixer are arranged in parallel, series or a combination thereof.

4. (Original) The process of claim 1, wherein said water-soluble polymer comprises polyethylene oxide.

5. (Original) The process of claim 1, wherein said polymer comprises a polymer selected from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.

6. (Original) The process of claim 5, wherein said polymer further comprises a water insoluble polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl

cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone and combinations thereof.

7. (Original) The process of claim 5, wherein said polymer further comprises a polymer selected from the group consisting of methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(ά-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof.

8. (Original) The process of claim 5, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

9. (Original) The process of claim 5, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(d-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

10. (Original) The process of claim 1, wherein said solvent is selected from the group

consisting of water, polar organic solvent, and combinations thereof.

11. (Original) The process of claim 10, wherein said solvent is selected from the group consisting of ethanol, isopropanol, acetone, and combinations thereof.

12. (Cancelled)

13. (Amended) The process of claim 1, wherein said active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, [anti-tumor drugs,]anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, [anti-convulsants,]neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-

spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, [anti-asthmatics,]cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

14. (Amended) The process of claim 1, wherein said active is selected from the group consisting of [cosmetic actives,]antigens, allergens, spores, microorganisms, seeds, [mouthwash components, flavors, fragrances,]enzymes, [preservatives, sweetening agents, colorants, spices,]vitamins and combinations thereof.

15. (Original) The process of claim 1, wherein said active is a bioactive active.

16. (Cancelled)

17. (Original) The process of claim 1, wherein said active is an opiate or opiate-derivative.

18. (Original) The process of claim 1, wherein said active is an anti-emetic.

19. (Original) The process of claim 1, wherein said active is an amino acid preparation.

20. (Original) The process of claim 1, wherein said active is selected from the group consisting of sildenafils, tadalafils, vardenafils, apomorphines, yohimbine hydrochlorides, alprostadils and combinations thereof.

21. (Original) The process of claim 1, wherein said active is a protein.

22. (Original) The process of claim 1, wherein said active is insulin.

23. (Original) The process of claim 1, wherein said active is an anti-diabetic.

24. (Original) The process of claim 1, wherein said active is an antihistamine.

25. (Original) The process of claim 1, wherein said active is an anti-tussive.

26. (Original) The process of claim 1, wherein said active is a non-steroidal anti-inflammatory.

27. (Original) The process of claim 1, wherein said active is an anti-asthmatics.

28. (Amended) The process of claim 1, wherein said active is an anti-diarrhea preparation.

29. (Original) The process of claim 1, wherein said active is an alkaloid.

30. (Original) The process of claim 1, wherein said active is an anti-psychotic.

31. (Original) The process of claim 1, wherein said active is an anti-spasmodic.

32. (Original) The process of claim 1, wherein said active is a biological response modifier.

33. (Original) The process of claim 1, wherein said active is an anti-obesity drug.

34. (Original) The process of claim 1, wherein said active is an H_2-antagonist.

35. (Original) The process of claim 34, wherein said H_2-antagonist is selected from the group consisting of cimetidine, ranitidine hydrochloride, famotidine, nizatidine, ebrotidine, mifentidine, roxatidine, pisatidine, aceroxatidine and combinations thereof.

36. (Original) The process of claim 1, wherein said active is a smoking cessation aid.

37. (Original) The process of claim 1, wherein said active is an anti-parkinsonian agent.

38. (Original) The process of claim 1, wherein said active is an anti-depressant.

39. (Original) The process of claim 1, wherein said active is an anti-migraine.

40. (Original) The process of claim 1, wherein said active is an anti-Alzheimer's agents.

41. (Original) The process of claim 1, wherein said active is a dopamine receptor agonist.

42. (Original) The process of claim 1, wherein said active is a cerebral dilator.

43. (Original) The process of claim 1, wherein said active is a psychotherapeutic agent.

44. (Original) The process of claim 1, wherein said active is an antibiotic.

45. (Original) The process of claim 1, wherein said active is an anesthetic.

46. (Original) The process of claim 1, wherein said active is a contraceptive.

47. (Original) The process of claim 1, wherein said active is an anti-thrombotic drug.

48. (Original) The process of claim 1, wherein said active is diphenhydramine.

49. (Original) The process of claim 1, wherein said active is nabilone.

50. (Original) The process of claim 1, wherein said active is albuterol sulfate.

51. (Original) The process of claim 1, wherein said active is an anti-tumor drug.

52. (Original) The process of claim 1, wherein said active is a glycoprotein.

53. (Original) The process of claim 1, wherein said active is an analgesic.

54. (Original) The process of claim 1, wherein said active is a hormone.

55. (Original) The process of claim 1, wherein said active is a decongestant.

56. (Original) The process of claim 1, wherein said active is a loratadine.

57. (Original) The process of claim 1, wherein said active is dextromethorphan.

58. (Original) The process of claim 1, wherein said active is chlorpheniramine maleate.

59. (Original) The process of claim 1, wherein said active is selected from the group consisting of an analgesic, an anti-inflammatory, an antihistamine, a decongestant, a cough suppressant and combinations thereof.

60. (Original) The process of claim 1, wherein said active is an appetite stimulant.

61. (Original) The process of claim 1, wherein said active is a gastrointestinal agent.

62. (Original) The process of claim 1, wherein said active is a hypnotic.

63. (Original) The process of claim 1, wherein said active is taste-masked.

64. (Original) The process of claim 1, wherein said active is taste-masked using a flavor.

65. (Original) The process of claim 1, wherein said active is coated with a controlled release composition.

66. (Original) The process of claim 65, wherein said controlled release composition provides an immediate release.

67. (Original) The process of claim 65, wherein said controlled release composition provides a delayed release.

68. (Original) The process of claim 65, wherein said controlled release composition provides a sustained release.

69. (Original) The process of claim 65, wherein said controlled release composition provides a sequential release.

70. (Original) The process of claim 1, wherein said active is a particulate.

71. (Original) The process of claim 1, further comprising adding a degassing agent to said masterbatch premix.

72. (Original) The process of claim 1, further comprising a step of providing a second film layer.

73. (Original) The process of claim 72, wherein said second film layer is coated onto said resulting film.

74. (Original) The process of claim 72, wherein said second film layer is spread onto said resulting film.

75. (Original) The process of claim 72, wherein said second film layer is cast onto said resulting film.

76. (Original) The process of claim 72, wherein said second film layer is extruded onto said resulting film.

77. (Original) The process of claim 72, wherein said second film layer is sprayed onto said resulting film.

78. (Original) The process of claim 72, wherein said second film is laminated onto said resulting film.

79. (Original) The process of claim 72, further comprising laminating said resulting film to another film.

80. (Original) The process of claim 72, wherein said second film layer comprises an active.

81. (Amended) The process of claim [72]80, wherein said active in said second film is different than said active in said resulting film.

82. (Amended) A process for manufacturing resulting films suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said [making a]films having a substantially uniform distribution of components comprising a substantially uniform distribution of a desired amount of said active in individual dosage units of said resulting films, comprising the steps of:

(a) forming a flowable polymer matrix comprising a polymer selected from the group consisting of a water-soluble polymer, a water swellable polymer and combinations thereof, a solvent and [an]said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives[, drugs, medicaments] and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus and evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first [10]4 minutes [or fewer]by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, wherein during said drying said flowable polymer matrix temperature is 100 °C or less, and wherein uniformity of content of said active in substantially equal sized individual dosage units of said visco-elastic film is such that the amount of the active varies by no more than 10%; [and]

(d) forming [a]said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained;

(e) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units sampled from different locations of said resulting film, said tests indicating that uniformity of content in the amount of said active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration; and

(f) repeating steps (a) through (e) to form additional resulting films, such that uniformity of content in the amount of said active in said resulting film and said additional resulting films varies no more than 10% from the desired amount of the active as indicated by said analytical chemical tests.

83. (Original) The process of claim 82, wherein said water-soluble polymer comprises polyethylene oxide.

84. (Original) The process of claim 82, wherein said polymer comprises a polymer selected

from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.

85. (Original) The process of claim 84, wherein said polymer further comprises a water insoluble polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone and combinations thereof.

86. (Original) The process of claim 84, wherein said polymer further comprises a polymer selected from the group consisting of methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(ά-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof.

87. (Original) The process of claim 84, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

88. (Original) The process of claim 84, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol

copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(ά-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

89. (Original) The process of claim 82, wherein said solvent is selected from the group consisting of water, polar organic solvent, and combinations thereof.

90. (Original) The process of claim 89, wherein said solvent is selected from the group consisting of ethanol, isopropanol, acetone, and combinations thereof.

91. (Cancelled)

92. (Amended) The process of claim 82, wherein the active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management

agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, [anti-tumor drugs,]anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, [anti-convulsants,]neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, [anti-asthmatics,]cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

93. (Amended) The process of claim 82, wherein said active is selected from the group consisting of [cosmetic actives,]antigens, allergens, spores, microorganisms, seeds, [mouthwash components, flavors, fragrances,]enzymes, [preservatives, sweetening agents, colorants, spices,]vitamins and combinations thereof.

94. (Original) The process of claim 82, wherein said active is a bioactive active.

95. (Cancelled)

96. (Original) The process of claim 82, wherein said active is an opiate or opiate-derivative.

97. (Original) The process of claim 82, wherein said active is an anti-emetic.

98. (Original) The process of claim 82, wherein said active is an amino acid preparation.

99. (Original) The process of claim 82, wherein said active is selected from the group consisting of sildenafils, tadalafils, vardenafils, apomorphines, yohimbine hydrochlorides, alprostadils and combinations thereof.

100. (Original) The process of claim 82, wherein said active is a protein.

101. (Original) The process of claim 82, wherein said active is insulin.

102. (Original) The process of claim 82, wherein said active is an anti-diabetic.

103. (Original) The process of claim 82, wherein said active is an antihistamine.

104. (Original) The process of claim 82, wherein said active is an anti-tussive.

105. (Original) The process of claim 82, wherein said active is a non-steroidal anti-inflammatory.

106. (Original) The process of claim 82, wherein said active is an anti-asthmatics.

107. (Amended) The process of claim 82, wherein said active is an anti-diarrhea preparation.

108. (Original) The process of claim 82, wherein said active is an alkaloid.

109. (Original) The process of claim 82, wherein said active is an anti-psychotic.

110. (Original) The process of claim 82, wherein said active is an anti-spasmodic.

111. (Original) The process of claim 82, wherein said active is a biological response modifier.

112. (Original) The process of claim 82, wherein said active is an anti-obesity drug.

113. (Original) The process of claim 82, wherein said active is an H_2-antagonist.

114. (Amended) The process of claim [82]113, wherein said H_2-antagonist is selected from the group consisting of cimetidine, ranitidine hydrochloride, famotidine, nizatidine, ebrotidine, mifentidine, roxatidine, pisatidine, aceroxatidine and combinations thereof.

115. (Original) The process of claim 82, wherein said active is a smoking cessation aid.

116. (Original) The process of claim 82, wherein said active is an anti-parkinsonian agent.

117. (Original) The process of claim 82, wherein said active is an anti-depressant.

118. (Original) The process of claim 82, wherein said active is an anti-migraine.

119. (Original) The process of claim 82, wherein said active is an anti-Alzheimer's agents.

120. (Original) The process of claim 82, wherein said active is a dopamine receptor agonist.

121. (Original) The process of claim 82, wherein said active is a cerebral dilator.

122. (Original) The process of claim 82, wherein said active is a psychotherapeutic agent.

123. (Original) The process of claim 82, wherein said active is an antibiotic.

124. (Original) The process of claim 82, wherein said active is an anesthetic.

125. (Original) The process of claim 82, wherein said active is a contraceptive.

126. (Original) The process of claim 82, wherein said active is an anti-thrombotic drug.

127. (Original) The process of claim 82, wherein said active is diphenhydramine.

128. (Original) The process of claim 82, wherein said active is nabilone.

129. (Original) The process of claim 82, wherein said active is albuterol sulfate.

130. (Original) The process of claim 82, wherein said active is an anti-tumor drug.

131. (Original) The process of claim 82, wherein said active is a glycoprotein.

132. (Original) The process of claim 82, wherein said active is an analgesic.

133. (Original) The process of claim 82, wherein said active is a hormone.

134. (Original) The process of claim 82, wherein said active is a decongestant.

135. (Original) The process of claim 82, wherein said active is a loratadine.

136. (Original) The process of claim 82, wherein said active is dextromethorphan.

137. (Original) The process of claim 82, wherein said active is chlorpheniramine maleate.

138. (Original) The process of claim 82, wherein said active is selected from the group consisting of an analgesic, an anti-inflammatory, an antihistamine, a decongestant, a cough suppressant and combinations thereof.

139. (Original) The process of claim 82, wherein said active is an appetite stimulant.

140. (Original) The process of claim 82, wherein said active is a gastrointestinal agent.

141. (Original) The process of claim 82, wherein said active is a hypnotic.

142. (Original) The process of claim 82, wherein said active is taste-masked.

143. (Original) The process of claim 82, wherein said active is taste-masked using a flavor.

144. (Original) The process of claim 82, wherein said active is coated with a controlled release composition.

145. (Original) The process of claim 144, wherein said controlled release composition provides an immediate release.

146. (Original) The process of claim 144, wherein said controlled release composition provides a delayed release.

147. (Original) The process of claim 144, wherein said controlled release composition provides a sustained release.

148. (Original) The process of claim 144, wherein said controlled release composition provides a sequential release.

149. (Original) The process of claim 82, wherein said active is a particulate.

150. (Original) The process of claim 82, further comprising adding a degassing agent to said flowable polymer matrix.

151. (Original) The process of claim 82, further comprising a step of providing a second film layer.

152. (Original) The process of claim 151, wherein said second film layer is coated onto said resulting film.

153. (Original) The process of claim 151, wherein said second film layer is spread onto said resulting film.

154. (Original) The process of claim 151, wherein said second film layer is cast onto said resulting film.

155. (Original) The process of claim 151, wherein said second film layer is extruded onto said resulting film.

156. (Original) The process of claim 151, wherein said second film layer is sprayed onto said resulting film.

157. (Original) The process of claim 151, wherein said second film layer is laminated onto said resulting film.

158. (Original) The process of claim 151, further comprising laminating said resulting film to another film.

159. (Original) The process of claim 151, wherein said second film comprises an active.

160. (Amended) The process of claim [151]159, wherein said active in said second film is different than said active in said resulting film.

161. (Amended) A process for manufacturing a resulting film suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said[making a] film capable of being administered to a body surface and having a substantially uniform distribution of components comprising a substantially uniform distribution of said active in individual dosage units of said resulting film, comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and [an]said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus and evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first [10]4 minutes [or fewer]by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, wherein during said drying said flowable polymer matrix temperature is 100 °C or less, and wherein uniformity of content of said active in substantially equal sized individual dosage units of said visco-elastic film is such that the amount of the active varies by no more than 10%;

(d) forming [a]said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained; [and]

(e) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units sampled from different locations of said resulting film, said tests indicating that uniformity of content in the amount of said active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration, and

[(e)](f) administering said resulting film to a body surface.

162. (Original) The process of claim 161, wherein said body surface is a mucous membrane.

163. (Original) The process of claim 162, wherein said mucous membrane is oral, anal, vaginal or ophthalmological.

164. (Original) The process of claim 161, wherein said body surface is the surface of a wound.

165. (Original) The process of claim 161, wherein said water-soluble polymer comprises polyethylene oxide.

166. (Original) The process of claim 161, wherein said polymer comprises a polymer selected from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.

167. (Original) The process of claim 166, wherein said polymer further comprises a water insoluble polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone and combinations thereof.

168. (Original) The process of claim 166, wherein said polymer further comprises a polymer selected from the group consisting of methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic

acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(ά-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof.

169. (Original) The process of claim 166, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, caragcenan, locust bean gum, dextran, gellan gum and combinations thereof.

170. (Original) The process of claim 166, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(ά-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

171. (Original) The process of claim 161, wherein said solvent is selected from the group consisting of water, polar organic solvent, and combinations thereof.

172. (Original) The process of claim 161, wherein said solvent is selected from the group consisting of ethanol, isopropanol, acetone, and combinations thereof.

173. (Cancelled)

174. (Amended) The process of claim 161, wherein said active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, [anti-tumor drugs,]anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, [anti-convulsants,]neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, [anti-asthmatics,]cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

175. (Amended) The process of claim 161, wherein said active is selected from the group consisting of [cosmetic actives,]antigens, allergens, spores, microorganisms, seeds, [mouthwash components, flavors, fragrances,]enzymes, [preservatives, sweetening agents, colorants, spices,

]vitamins and combinations thereof.

176. (Original) The process of claim 161, wherein said active is a bioactive active.

177. (Cancelled)

178. (Original) The process of claim 161, wherein said active is an opiate or opiate-derivative.

179. (Original) The process of claim 161, wherein said active is an anti-emetic.

180. (Original) The process of claim 161 wherein said active is an amino acid preparation.

181. (Original) The process of claim 161, wherein said active is selected from the group consisting of sildenafils, tadalafils, vardenafils, apomorphines, yohimbine hydrochlorides, alprostadils and combinations thereof.

182. (Original) The process of claim 161, wherein said active is a protein.

183. (Original) The process of claim 161, wherein said active is insulin.

184. (Original) The process of claim 161, wherein said active is an anti-diabetic.

185. (Original) The process of claim 161, wherein said active is an antihistamine.

186. (Original) The process of claim 161, wherein said active is an anti-tussive.

187. (Original) The process of claim 161, wherein said active is a non-steroidal anti-inflammatory.

188. (Original) The process of claim 161, wherein said active is an anti-asthmatics.

189. (Amended) The process of claim 161, wherein said active is an anti-diarrhea preparation.

190. (Original) The process of claim 161, wherein said active is an alkaloid.

191. (Original) The process of claim 161, wherein said active is an anti-psychotic.

192. (Original) The process of claim 161, wherein said active is an anti-spasmodic.

193. (Original) The process of claim 161, wherein said active is a biological response modifier.

194. (Original) The process of claim 161, wherein said active is an anti-obesity drug.

195. (Original) The process of claim 161, wherein said active is an H_2-antagonist.

196. (Original) The process of claim 195, wherein said H_2-antagonist is selected from the group consisting of cimetidine, ranitidine hydrochloride, famotidine, nizatidine, ebrotidine, mifentidine, roxatidine, pisatidine, aceroxatidine and combinations thereof.

197. (Original) The process of claim 161, wherein said active is a smoking cessation aid.

198. (Original) The process of claim 161, wherein said active is an anti-parkinsonian agent.

199. (Original) The process of claim 161, wherein said active is an anti-depressant.

200. (Original) The process of claim 161, wherein said active is an anti-migraine.

201. (Original) The process of claim 161, wherein said active is an anti-Alzheimer's agents.

202. (Original) The process of claim 161, wherein said active is a dopamine receptor agonist.

203. (Original) The process of claim 161, wherein said active is a cerebral dilator.

204. (Original) The process of claim 161, wherein said active is a psychotherapeutic agent.

205. (Original) The process of claim 161, wherein said active is an antibiotic.

206. (Original) The process of claim 161, wherein said active is an anesthetic.

207. (Original) The process of claim 161, wherein said active is a contraceptive.

208. (Original) The process of claim 161, wherein said active is an anti-thrombotic drug.

209. (Original) The process of claim 161, wherein said active is diphenhydramine.

210. (Original) The process of claim 161, wherein said active is nabilone.

211. (Original) The process of claim 161, wherein said active is albuterol sulfate.

212. (Original) The process of claim 161, wherein said active is an anti-tumor drug.

213. (Original) The process of claim 161, wherein said active is a glycoprotein.

214. (Original) The process of claim 161, wherein said active is an analgesic.

215. (Original) The process of claim 161, wherein said active is a hormone.

216. (Original) The process of claim 161, wherein said active is a decongestant.

217. (Original) The process of claim 161, wherein said active is a loratadine.

218. (Original) The process of claim 161, wherein said active is dextromethorphan.

219. (Original) The process of claim 161, wherein said active is chlorpheniramine maleate.

220. (Original) The process of claim 161, wherein said active is selected from the group consisting of an analgesic, an anti-inflammatory, an antihistamine, a decongestant, a cough suppressant and combinations thereof.

221. (Original) The process of claim 161, wherein said active is an appetite stimulant.

222. (Original) The process of claim 161, wherein said active is a gastrointestinal agent.

223. (Original) The process of claim 161, wherein said active is a hypnotic.

224. (Original) The process of claim 161, wherein said active is taste-masked.

225. (Original) The process of claim 161, wherein said active is taste-masked using a flavor.

226. (Original) The process of claim 161, wherein said active is coated with a controlled release composition.

227. (Original) The process of claim 226, wherein said controlled release composition provides an immediate release.

228. (Original) The process of 226, wherein said controlled release composition provides a delayed release.

229. (Original) The process of claim 226, wherein said controlled release composition

provides a sustained release.

230. (Original) The process of claim 226, wherein said controlled release composition provides a sequential release.

231. (Original) The process of claim 161, wherein said active is a particulate.

232. (Original) The process of claim 161, further comprising adding a degassing agent to said flowable polymer matrix.

233. (Original) The process of claim 161, further comprising a step of providing a second film layer.

234. (Original) The process of claim 233, wherein said second film layer is coated onto said resulting film.

235. (Original) The process of claim 233, wherein said second film layer is spread onto said resulting film.

236. (Original) The process of claim 233, wherein said second film layer is cast onto said resulting film.

237. (Original) The process of claim 233, wherein said second film layer is extruded onto said resulting film.

238. (Original) The process of claim 233, wherein said second film layer is sprayed onto said resulting film.

239. (Original) The process of claim 233, wherein said second film layer is laminated onto said resulting film.

240. (Original) The process of claim 233, further comprising laminating said resulting film to another film.

241. (Original) The process of claim 233, wherein said second film comprises an active.

242. (Amended) The process of claim [233]241, wherein said active in said second film is different than said active in said resulting film.

243. (Original) The process of claim 1, said active is an anti-nauseant.

244. (Amended) The process of claim 1, said active is an erectile dysfunction drug.

245. (Original) The process of claim 1, said active is a vasoconstrictor.

246. (Original) The process of claim 1, said active is a stimulant.

247. (Original) The process of claim 1, said active is a migraine treatment.

248. (Original) The process of claim 1, said active is granisetron hydrochloride.

249. (Original) The process of claim 1, wherein said resulting film provides administration of said active to an individual through the buccal cavity of said individual.

250. (Original) The process of claim 1, wherein said resulting film provides administration of said active through gingival application of said individual.

251. (Original) The process of claim 1, wherein said resulting film provides administration of said active through sublingual application of said individual.

252. (Original) The process of claim 1, wherein said resulting film provides administration of said active to an individual through a mucosal membrane of said individual.

253. (Original) The process of claim 1, wherein said resulting film provides administration of said active to an individual by administration within the body of the individual during surgery.

254. (Cancelled)

255. (Cancelled)

256. (Original) The method of claim 1, wherein said resulting film contains less than about 6% by weight solvent.

257. (Cancelled)

258. (Original) The method of claim 1, wherein said resulting film is orally administrable.

259. (Original) The method of claim 1, wherein said active is in the form of a particle.

260. (Original) The method of claim 1, wherein said matrix comprises a dispersion.

261. (Original) The process of claim 82, said active is an anti-nauseant.

262. (Amended) The process of claim 82, said active is an erectile dysfunction drug.

263. (Original) The process of claim 82, said active is a vasoconstrictor.

264. (Original) The process of claim 82, said active is a stimulant.

265. (Original) The process of claim 82, said active is a migraine treatment.

266. (Original) The process of claim 82, said active is granisetron hydrochloride.

267. (Original) The process of claim 82, wherein said resulting film provides administration of said active to an individual through the buccal cavity of said individual.

268. (Original) The process of claim 82, wherein said resulting film provides administration of said active through gingival application of said individual.

269. (Original) The process of claim 82, wherein said resulting film provides administration of said active through sublingual application of said individual.

270. (Original) The process of claim 82, wherein said resulting film provides administration of said active to an individual through a mucosal membrane of said individual.

271. (Original) The process of claim 82, wherein said resulting film provides administration of said active to an individual by administration within the body of the individual during surgery.

272. (Cancelled)

273. (Cancelled)

274. (Original) The method of claim 82, wherein said resulting film contains less than about 6% by weight solvent.

275. (Cancelled)

276. (Original) The method of claim 82, wherein said resulting film is orally administrable.

277. (Original) The method of claim 82, wherein said active is in the form of a particle.

278. (Original) The method of claim 82, wherein said matrix comprises a dispersion.

279. (Original) The process of claim 161, said active is an anti-nauseant.

280. (Amended) The process of claim 161, said active is an erectile dysfunction drug.

281. (Original) The process of claim 161, said active is a vasoconstrictor.

282. (Original) The process of claim 161, said active is a stimulant.

283. (Original) The process of claim 161, said active is a migraine treatment.

284. (Original) The process of claim 161, said active is granisetron hydrochloride.

285. (Original) The process of claim 161, wherein said resulting film provides administration of said active to an individual through the buccal cavity of said individual.

286. (Original) The process of claim 161, wherein said resulting film provides administration of said active through gingival application of said individual.

287. (Original) The process of claim 161, wherein said resulting film provides administration of said active through sublingual application of said individual.

288. (Original) The process of claim 161, wherein said resulting film provides administration of said active to an individual through a mucosal membrane of said individual.

289. (Original) The process of claim 161, wherein said resulting film provides administration of said active to an individual by administration within the body of the individual during surgery.

290. (Cancelled)

291. (Cancelled)

292. (Original) The method of claim 161, wherein said resulting film contains less than about 6% by weight solvent.

293. (Cancelled)

294. (Original) The method of claim 161, wherein said resulting film is orally administrable.

295. (Original) The method of claim 161, wherein said active is in the form of a particle.

296. (Original) The method of claim 161, wherein said matrix comprises a dispersion.

297. (Original) The method of claim 1, wherein said matrix comprises an emulsion, a colloid or a suspension.

298. (Original) The method of claim 82, wherein said matrix comprises an emulsion, a colloid or a suspension.

299. (Original) The method of claim 161, wherein said matrix comprises an emulsion, a colloid or a suspension.

300. (New) The process of claim 1, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 5%.

301. (New) The process of claim 1, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 2%.

302. (New) The process of claim 1, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 1%.

303. (New) The process of claim 1, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 0.5%.

304. (New) The process of claim 82, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 5%.

305. (New) The process of claim 82, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 2%.

306. (New) The process of claim 82, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 1%.

307. (New) The process of claim 82, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 0.5%.

308. (New) The process of claim 161, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 5%.

309. (New) The process of claim 161, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 2%.

310. (New) The process of claim 161, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 1%.

311. (New) The process of claim 161, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 0.5%.

312. (New) The process of claim 1, wherein said evaporating is conducted by applying radiant energy selected from the group consisting of hot air currents, heat, infrared radiation, radio frequency radiation and combinations thereof.

313. (New) The process of claim 82, wherein said evaporating is conducted by applying radiant energy selected from the group consisting of hot air currents, heat, infrared radiation, radio frequency radiation and combinations thereof.

314. (New) The process of claim 161, wherein said evaporating is conducted by applying radiant energy selected from the group consisting of hot air currents, heat, infrared radiation, radio frequency radiation and combinations thereof.

315. (New) A process for manufacturing resulting films suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said films having a substantially uniform distribution of components comprising a substantially uniform distribution of a desired amount of said active in individual dosage units of said resulting films, comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said polymer matrix through a drying apparatus and evaporating at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes

by rapidly increasing the viscosity of said polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, wherein during said drying said flowable polymer matrix temperature is 100 °C or less;

(d) forming said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of said active by said locking-in or substantially preventing migration of said active is maintained, such that uniformity of content in the amount of the active in substantially equal sized individual dosage units, sampled from different locations of said resulting film, varies by no more than 10%;

(e) performing analytical chemical tests for uniformity of content of said active in said substantially equal sized individual dosage units of said sampled resulting film, said tests indicating that uniformity of content in the amount of the active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration; and

(f) repeating steps (a) through (e) to form additional resulting films, such that uniformity of content in the amount of said active in said resulting film and said additional resulting films varies no more than 10% from the desired amount of said active as indicated by said analytical chemical tests.

316. (New) A process for manufacturing a resulting film suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said film having a substantially uniform distribution of components comprising a substantially uniform distribution of said active in individual dosage units of said resulting film, comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said polymer matrix through a drying apparatus and evaporating at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, wherein during said drying said flowable polymer matrix temperature is 100 °C or less;

(d) forming said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said resulting film, varies by no more than 10%; and

(e) performing analytical chemical tests for uniformity of content of said active in said substantially equal sized individual dosage units of said sampled resulting film, said tests indicating that uniformity of content in the amount of said active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration.

317. (New) A process for manufacturing a resulting film suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said film having a substantially uniform distribution of components comprising a substantially uniform distribution of said active in individual dosage units of said resulting film, comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus using air currents, which have forces below a yield value of said flowable polymer matrix during drying, to evaporate at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said visco-elastic film, varies by no more than 10%, and wherein during said drying said flowable polymer matrix temperature is 100 °C or less;

(d) forming said resulting film from said visco-elastic film by further controlling drying by continuing evaporation to a water content of said resulting film of 10% or less and wherein said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained, such that uniformity of content in the amount of said

active in substantially equal sized individual dosage units, sampled from different locations of said resulting film, varies by no more than 10%; and

(e) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units of said sampled resulting film, said tests indicating that uniformity of content in the amount of said active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration.

318. (New) A process for manufacturing a resulting film suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said film having a substantially uniform distribution of components comprising a substantially uniform distribution of said active in individual dosage units of said resulting film, comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus at a temperature of about 60 °C and using air currents, which have forces below a yield value of the polymer matrix during drying, to evaporate at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-

elastic film, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said visco-elastic film, varies by less than 5%, and wherein during said drying said flowable polymer matrix temperature is 100 °C or less;

(d) forming said resulting film from said visco-elastic film by further controlling by continuing evaporation to a water content of said resulting film of 10% or less and wherein said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said resulting film, varies by less than 5%; and

(e) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units of said sampled resulting film, said tests indicating that uniformity of content in the amount of said active varies by less than 5% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration.

IX. EVIDENCE APPENDIX

Exhibit 1: US Patent No. 7,897,080

Exhibit 2: Reitman Declaration filed April 12, 2013

Exhibit 3: Clevenger Declaration filed April 12, 2013

Exhibit 4: Bogue and Lin Declarations filed March 13, 2013

X. RELATED PROCEEDINGS APPENDIX

None.

XI. CERTIFICATE OF SERVICE

CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of the foregoing Appellant's Brief was served on March 10, 2014, by first class mail, directed to the patent owner at the correspondence address of record for the subject patent at the following address:

Daniel A. Scola, Jr.

HOFFMANN & BARON, LLP

6900 JERICHO TURNPIKE

SYOSSET, NY 11791,

By: /Danielle L. Herritt/
Danielle L. Herritt
Registration No. 43,670
Attorney for Respondent

EXHIBIT 2

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re *Inter Partes* Reexamination of:	)
US Patent No. 7,897,080	)
Issued: March 1, 2011	) Confirmation No.: 6418
Named Inventor: Robert K. Yang *et al.*	) Group Art Unit: 3991
Control No.: 95/002,170	) Examiner: Diamond, Alan D.
Filed: September 10, 2012	) M&E Docket: 117744-00023
Title: POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM	) H&B Docket: 1199-26 RCE/CON/REX

Mail Stop *Inter Partes* Reexam
Attn: Central Reexamination Unit
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION BY MAUREEN REITMAN, SC.D.
UNDER 37 CFR § 1.132

Sir/Madam:

I, Maureen Reitman, do hereby make the following declaration:

I. Technical Background

1. I am a Principal and the Director of the Polymer Science and Materials Chemistry Practice at Exponent. I hold two academic degrees: (1) a Bachelor of Science in Materials Science and Engineering from the Massachusetts Institute of Technology (MIT), and (2) a Doctor of Science in Materials Science and Engineering, with a thesis in the field of polymers, from MIT. I have been practicing in the field of polymer science and engineering for more than 20 years as a researcher at MIT, in a variety of technical roles at the 3M Company, and as a consultant with Exponent. I provide consulting engineering services in all aspects of polymer science and engineering including, but not limited to material selection, product design and development, mechanical and chemical testing, failure analysis, polymer chemistry, polymer

physics, and polymer processing. My specialties include formulation, processing and performance evaluation of polymeric materials, including films, coatings, adhesives and transdermal drug delivery systems. I have been directly involved in product development, product line extensions, transfer of new products to manufacturing, qualification of alternative materials and manufacturing equipment, evaluating field performance, and assessing intellectual property. I am a past chairman and continue to serve as a member of the board of directors of the Medical Plastics Division of the Society of Plastics Engineers. My *curriculum vitae* is provided in Appendix A.

2. While Exponent is being paid for my time, I am not an employee of, nor do I have any financial interest in, BioDelivery Sciences International, Inc.

3. I have been asked to carefully review International Publication No. WO 00/42992 ("*Chen*"), and manufacture a film as described in *Chen*. I carefully reviewed *Chen*. Under my direction, my team manufactured a film in accordance with Example 7 of *Chen*. I have also been asked to take samples and perform various analytical tests to confirm the uniform distribution of the pharmaceutical active in substantially equal sized individual dosage units of the film, which we did.

4. Manufacturing Example 7 of *Chen*

Chen states: "According to Examples 1-8, the hydrocolloid [Methocel E5(HPMC)] was dissolved in water under agitated mixing to form a uniform and viscous solution." Chen 17:7-8.

- Methocel E5(HPMC) was dissolved in water under agitated mixing to form a uniform and viscous solution, by my team.

Chen states: "Additional ingredients were then added sequentially to the viscous solution such as peppermint, aspartame, propyl[ene] glycol, benzoic acid and citric acid under agitated mixing until they were uniformly dispersed or dissolved in the hydrocolloid." Chen 17:8-11.

- Additional ingredients were then added sequentially to the viscous solution including peppermint oil, aspartame, propylene glycol, benzoic acid and citric acid under agitated mixing until they were uniformly dispersed or dissolved in the hydrocolloid, by my team.

- Kolliphor EL was also added to the viscous solution.

Chen states: "Therapeutic agents were added to the homogeneous mixture (coating solution) prior to forming the film." *Chen* 20:19-20.

- Oxybutynin chloride (the therapeutic agent of Example 7) was added to the homogeneous mixture (coating solution) prior to forming the film, by my team.

Chen's Table 5 specifies the composition for Example 7.

- We used the ingredients in the amounts identified in *Chen*'s Table 5. *See* Table 1.

Table 1			
Formulation, Ex. 7, Table 5, *Chen*	% Weight	Formulation, Prepared by Maureen Reitman Team	% Weight
Oxybutynin	3.71	Oxybutynin chloride	3.71
Methocel E5 (HPMC)	21.06	Methocel E5 Premium LV	21.06
Water	70.72	Water, distilled	70.72
Cremophor EL40	1	Kolliphor EL[1]	1
Propylene glycol	1	Propylene glycol	1
Peppermint	1	Peppermint oil	1
Aspartame	0.8	Aspartame	0.8
Benzoic acid	0.013	Benzoic acid	0.013
Citric acid	0.7	Citric acid, monohydrate	0.7

Chen states: "The resultant mixture was degassed in a vacuum chamber until trapped air bubbles were removed." Chen 17:11-12.

- The resultant mixture was degassed in a vacuum chamber until trapped air bubbles were removed, by my team.

Chen states: "The formulation was then coated on the non-siliconized side of a polyester film at a wet thickness of 10 mil and dried in a hot air circulating oven at 50°C for 9 minutes." Chen 17:13-15.

- The formulation was then coated on a non-siliconized side of a polyester film at a wet thickness of 10 mil and dried in a hot air circulating oven at 50°C for up to 9 minutes, on commercial manufacturing equipment by my team.

Chen states: "Methods for manufacturing the dosage unit include the solvent casting methods as shown in Figure 2." Chen 15:13-14. "The manufacturing process for forming the dosage unit is illustrated in Figure 2. The dry film formed by this process is a glossy, stand alone, self supporting, non-tacky and flexible film (12)." Chen 15:29-31.

- A solvent casting manufacturing process for forming the dosage unit as illustrated in Figure 2 was used[2], by my team.

[1] The Cremophor line of products now owned by BASF and renamed Kolliphor. Based on the naming convention of the Cremophor/ Kolliphor products, EL40 is Polyoxyl 40 Castor Oil and EL is Polyoxyl 35 Castor Oil (*i.e.*, they are based on a 1:40 and 1:35 ratio, respectively, of castor oil:ethylene oxide). They are different materials. However, one of skill in the art would recognize Kolliphor EL as an appropriate substitute, as Cremophor EL40 is no longer available.

- The film was manufactured using a controlled drying process.
- As illustrated in Figure 2, the drying oven featured aeration controller with 3 zones set such that in each successive zone air impingement on the surface of the film increased.
- The dry film formed by the process is a glossy, stand alone, self-supporting, non-tacky and flexible film.

Chen states: "A glossy, substantially transparent, stand alone, self-supporting, non-tacky and flexible film was obtained after drying." Chen 17:15-16.

- A glossy, substantially transparent, stand alone, self-supporting, non-tacky and flexible film was obtained after drying, by my team.

5. Verification of Content Uniformity – Visual Inspection

- By examination with the naked eye, uniformity was verified by my team.

6. Verification of Content Uniformity – Unit Dose Weight

- By weighing individual dosage units of substantially identical size, uniformity was verified by my team. *See* Table 2.

Table 2	
Sample	Weight of 5 cm^2 dosage unit (grams)
1	0.034
2	0.034
3	0.034
4	0.034
5	0.034
6	0.034
7	0.034

7. Verification of Content Uniformity – Dissolution Test (HPLC)

- By dissolution of individual dosage units of substantially identical size and analysis by High Performance Liquid Chromatography (HPLC) active content uniformity was verified by my team. *See* Table 3.

[2] Our backing was not looped and we did not die cut in line, but the solvent casting and drying under aeration is matched.

Table 3	
Sample	Oxybutynin weight (mg)
A	4.4
B	4.4
C	4.3
D	4.4
E	4.1

- As can be seen in Table 3, the active varies by less than 10%.

8. Additional Observations

   - The components of the formulation, including the active component, were uniformly distributed in the viscous solution, which was used to cast the film, as was verified by my team.

   - The viscous solution, which was used to cast the film, exhibited the flow properties of honey (around 10,000 cps), as observed by my team.

   - Water content of the film was less than 10%, as verified by my team.

   - Within about 4 minutes after initiation of drying, the film was self-supporting, non-tacky, flexible and viscoelastic, as verified by my team.

9. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine, or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful statements may jeopardize the validity of the application or any patents issued thereon.

Dated: February 28, 2013

Maureen Reitman, Sc.D.

Appendix A

Exponent
Failure Analysis Associates

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Maureen T. F. Reitman, Sc.D.
Principal and Practice Director

Professional Profile

Dr. Maureen Reitman is a Principal and the Director of Exponent's Polymer Science and Material Chemistry practice. Her expertise includes polymer and composite technology, mechanics of materials, adhesion science, fiber mechanics, history and technology of plastics, and material failure analysis. She is skilled in the development and use of testing tools and methods and has applied them to plastic, rubber, textile, metal, glass, ceramic, and composite materials and systems. She is experienced in major aspects of product development, including materials selection, formulation, scale-up, end-use testing, failure analysis, certification procedures and issues related to intellectual property.

Dr. Reitman has conducted research in the areas of packaging and barrier materials; paints and coatings; plastic pipes; transdermal drug delivery; adhesives, sealants, and encapsulants; molding compounds; high temperature resins; nanoparticles; fibers and textiles; protective coatings and finishes; polymer chemical resistance; plastic insulation; connectors and splices; plastic packaging; medical devices; environmental effects on durability; and product aging. She has used her expertise to solve a broad range of problems related to coatings, fibers, films, and extruded and molded products, and their use in the telecom, electronics, electrical, transportation, construction, fire protection, medical, and consumer products markets.

Dr. Reitman is a member of the Board of Directors of the Medical Plastics Division of the Society of Plastics Engineers and an active member of two Underwriters Laboratories Standard Technical Panels, addressing Polymeric Materials (UL 94, UL 746, UL 1694) and Appliance Wiring (UL758).

Prior to joining Exponent, Dr. Reitman worked for the 3M Company in both research and management roles. Her activities included technology identification, materials selection and qualification, product development, customer support, program management, acquisition integration, intellectual property analysis, and patent litigation support.

Academic Credentials and Professional Honors

Sc.D., Materials Science and Engineering/ Program in Polymer Science and Technology, Massachusetts Institute of Technology, 1993
B.S., Materials Science and Engineering, Massachusetts Institute of Technology, 1990

National Academy of Engineering Frontiers of Engineering, 2009; Tau Beta Pi; Sigma Xi
John Wulff Award; Carl Loeb Fellowship; NCAA Postgraduate Scholarship;
Malcolm G. Kispert Award; GTE Academic All-American

Patents

Patent 6,311,524: Accelerated Method for Increasing the Photosensitivity of a Glassy Material, issued November 6, 2001.

European Patent EP0830428: Tackified Polydiorganosiloxane Polyurea Segmented Copolymers and a Process for Making Same, published March 25, 1998.

Patent 5,371,051: Fiber Optic Fusion Splice Protector Sleeve, issued March 24, 1998.

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Kurtz S, Siskey R, Reitman M. Accelerated aging, natural aging, and small punch testing of gamma-air sterilized polycarbonate urethane acetabular components. Journal of Biomedical Materials Research Part B: Applied Biomaterials 2010 May; 93B(2):422–447.

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Fahey MT. Nonlinear and anisotropic properties of high performance fibers. MIT Thesis, 1993.

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Book Contributions

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Reitman M, Jaekel D, Siskey R, Kurtz S. Morphology and crystalline architecture of polyarylketones, pp. 49-60. In: PEEK Biomaterials Handbook. Kurtz SM (ed), Elsevier William Andrews, Kidlington, Oxford, UK, 2012. ISBN 13:978-1-4377-4463-7

Tsuji JS, Mowat FS, Donthu S, Reitman M. Application of toxicology studies in assessing the health risks of nanomaterials in consumer products, pp. 543-580. In: Nanotoxicity: From In Vivo and In Vitro Models to Health Risks. Sahu S, and Casciano D. (eds), John Wiley & Sons, Chicester, West Sussex, UK, 2009. ISBN 978-0-470-74137-5.

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Selected Invited Presentations

Reitman MTF. Failure analysis tools. Workshop on Future Needs for Service Life Prediction of Polymeric Materials. NIST and Underwriters Laboratories, Gaithersburg, MD, October 2012.

Hoffman J, MacLean S, Ralston B, Reitman M, Ledwith P. Fractography of unfilled thermoplastic materials experiencing common mechanical failure modes. Materials Science & Technology 2012 Conference, Pittsburgh PA, October 2012.

Hoffman J, Reitman M, Ledwith P. Microscopic characterization of CPVC failure. Materials Science & Technology 2012 Conference, Pittsburgh PA, October 2012.

Reitman MTF. Polymer material properties for next generation medical devices. Invited Speaker: MedTech Polymers, UBM Canon, Chicago, IL, September 2012.

Reitman MTF. Polymers for medical applications. Fundamentals and Fellows Forum, ANTEC 2012, Orlando FL, April 2012.

Reitman MTF. Plastic and composite product failures. Invited lecture in Failure Analysis of Emerging Technologies. Stanford University Department of Materials Science and Engineering, Menlo Park, CA October 2009.

Reitman MTF. Factors for success: Plastics in injection molded medical devices. Part of *Injection Molding Works for Medical Design*, Design News Webcast, October 2008.

Reitman MTF. Plastic and composite product failures. Keynote Speaker: Third International Conference on Engineering Failure Analysis (ICEFA III), Elsevier, Sitges Spain, July 2008.

Reitman MTF. Multiphase materials for medical device applications, an overview. Medical Device and Manufacturing (MDM), Canon Communications, various locations, January- June 2008.

Reitman MTF. Nanotechnology and plastics for medical devices. Capitalizing on Nanoplastics, Intertek PIRA San Antonio TX, February 2008.

Reitman MTF. Nano additives in composites and coatings for medical device applications. Medical Device and Manufacturing Minneapolis, Canon Communications, Minneapolis MN, October 2007.

Reitman MTF, Swanger LA. Practical tips on how to manage your technical expert in patent disputes. Ropes & Gray IP Master Class, Live Teleconference, June 2007.

Reitman MTF, Kennedy E. Root cause failure analysis and accident investigation. Lorman Educational Services, Live Teleconference, November 2007.

Reitman MTF. Plastics failure analysis: Case studies. Baltimore/ Washington Chapter of SAMPE, October 2006.

Reitman MTF. Plastics failure analysis. Baxter Global Plastics Processing Conference 2005, Schaumburg IL, 2005.

Fahey MT. Fiber mechanics, corrosion, sealants: Tales of a 3M materials scientist. Class of 1960's Scholars Program, Williams College, 1999.

Fahey MT. Adhesives and sealants for the telecommunications industry. Riverwood V Conference, St. Paul MN, 1998.

Current Professional Appointments

- Underwriter's Laboratory Standards Technical Panel STP 746 (Polymeric Materials, includes UL94, UL 746 and UL1694)
- Underwriter's Laboratory Standards Technical Panel STP 758 (Appliance Wires/ UL758)
- Medical Plastics Division Board of Directors, Society of Plastics Engineers

Committee and Review Activities

- UL Forum on Initiatives to Improve the Long Term Aging Program, LTTA Tools Working Groups, Underwriters Laboratories
- Research and Engineering Technology Award Committee, Society of Plastics Engineers
- Reviewer, Medical Plastics Technical Program Committee, Society of Plastics Engineers
- Reviewer, Failure Analysis and Prevention Technical Program Committee, Society of Plastics Engineers
- Reviewer, various book proposals and submissions related to polymer science, ASM International, Elsevier, John Wiley

Professional Affiliations

- American Association for the Advancement of Science (member)
- American Association of Textile Chemists and Colorists—AATCC (senior member)
- American Chemical Society (member)
- ASTM International (member)
- Society for the Advancement of Material and Process Engineering (member)
- Society of Plastics Engineers (senior member)

EXHIBIT 4

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patentee:	Yang et al.	Examiner:	Diamond, Alan D.
Patent No.:	U.S. 7,897,080	Group Art Unit:	3991
Reexamination Control No.:	95/002,170	Confirmation No.	6418
Filed:	September 10, 2012	H&B Docket:	1199-26 RCE/CON/REX
Dated:	March 13, 2013	M&E Docket:	117744-00023

Mail Stop Inter Partes Reexam
Central Reexamination Unit
Commissioner for Patents
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

Certificate of EFS-Web Transmission
I hereby certify that this correspondence is being transmitted via the U.S. Patent and Trademark Office electronic filing system (EFS-Web) to the USPTO on
March 13, 2013.
Signed: Michael I. Chakansky /Michael I Chakansky/

DECLARATION OF B. ARLIE BOGUE, PH.D. UNDER 37 C.F.R. § 1.132

Madame:

I, B. Arlie Bogue, Ph.D., do hereby make the following declaration:

I. Technical Background

1. I have worked in the field of pharmaceutical development, and particularly oral dosage form development, for 22 years. I am employed by MonoSol Rx, LLC. ("Patentee" and/or "MonoSol"), the assignee of issued patent U.S. 7,897,080 ("the '080 Patent"), as Senior Director for Manufacturing Strategy and Innovation.

2. I have a BS in Physical Chemistry from Colorado State University and a Ph.D. in Chemical and BioEngineering from Arizona State University. I have participated in postdoctoral studies in Biochemical Engineering at the University of Virginia. During my career, I have been named as an inventor on over 23 U.S. patents and numerous foreign patents directed to the formulation,

processing and/or packaging of pharmaceutical oral disintegrating unit doses (tablets and film strips). I have direct experience with the commercial scale processing of pharmaceutical film systems as well as an understanding of the uniformity of content of active and methods for testing the same.

3. I have read the '080 Patent and the Office Action issued on November 29, 2012 in the reexamination of the '080 Patent ("Office Action") and the references cited therein, and I have also reviewed the amendment as to the independent claims set forth in Patentee's Reply to the Office Action concurrently filed herewith.

II. Producing resulting films in accordance with the '080 Patent

4. Each of the 73 lots of resulting films (Lots 1-73) containing approximately 2,000,000 individual dosage units per lot discussed herein were manufactured: (i) for commercial use and regulatory approval; (ii) in compliance with U.S Food and Drug Administration ("FDA") standards and regulations, including those relating to analytical chemical testing for variation in active in individual dosage units; and (iii) in accordance with the invention disclosed in the '080 Patent, and as claimed by the '080 Patent both as issued and as amended in the Patentee's Reply to the Office Action; by:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and a pharmaceutical active, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said polymer matrix through a drying apparatus and evaporating at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film wherein the polymer matrix temperature is 100 °C or less;

(d) forming the resulting pharmaceutical film from said visco-elastic film, wherein said resulting pharmaceutical film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained, such that uniformity of content in the amount of the active in substantially equal sized individual dosage units, sampled from different locations of said resulting pharmaceutical film, varies by no more than 10%; and

(e) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units of said sampled resulting pharmaceutical film, said tests indicating that uniformity of content in the amount of the active varies by no more than 10%, [see Appendix A] said resulting pharmaceutical film suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration.

5. Additionally, the uniformity of content in the amount of active as sampled from the 73 lots of resulting film varies no more than 10% from the desired amount of the active as indicated by said analytical chemical tests from 4(e) above. [See Appendix B]

III. Analytical Chemical Testing for Uniformity of Content of Patentee's Resulting Films

6. To demonstrate the uniformity of individual dosage unit films, I compiled individual dosage unit assay data for individual Lots 1- 73, all of which were disclosed in MonoSol's 2012 Annual Product Review to the FDA.

7. Ten (10) individual dosage units all having the same dimensions were cut out from different locations of each of the 73 lots of resulting films using a commercial packaging machine, thus providing 730 randomly sampled individual dosage units, ten each from the 73 separate lots. All samples were analyzed by a validated method, in compliance with FDA guidelines and regulations regarding same, using analytical chemical testing, in which the pharmaceutical active

was extracted and analyzed by High Performance Liquid Chromatography (HPLC) against an external standard to quantify the amount of active present in each individual dosage unit.

8. According to the inventive process set forth and claimed in the '080 Patent, and in accordance with FDA nomenclature, I have prepared tables shown as Appendices A, B and C, reflecting the uniformity of content of active of individual dosage units within particular lots and across different lots.

9. First, the uniformity of content of active in a lot is determined through establishing the amount of active ($A_{N(I)}$) actually present in each sampled individual dosage unit from the same lot (N) as determined by taking the difference between the amount of active in the sample with the most active ($Max_{LOT(N)}$) minus the amount of active in the sample with the least amount of active ($Min_{LOT(N)}$) and dividing the difference by the average amount of active in the lot samples ($Lot_{(N)}$ Sample Average). That is: $(Max_{LOT(N} - Min_{LOT(N)}) / ((A_{N(1)} + A_{N(2)} + + + A_{N(10)})/10)$. The results are shown in Appendix A.

10. Second, the uniformity of content across different lots is determined through establishing the amount of active actually present in each sampled individual dosage unit from all 73 lots and comparing that amount of active with a "target" or "desired" amount of active contained therein. The target amount of active, when it is a pharmaceutical, is referred to as the "Label Claim", thus identifying the amount of pharmaceutical active in the film to a user. The desired amount is 100% of the target amount. Each individual dosage unit film cut from any individual lot must have the desired content of pharmaceutical active, varying no more that 10% from the target or desired amount. See Appendix B.

IV. '080 Patent Process Produces Films With Required Uniformity of Content of Active

11. The results shown in the appendices establish that the resulting films produced by the inventive method of the '080 Patent as disclosed and claimed have the required uniformity of content based on analytical chemical testing. First, the amount of active varies by no more than 10% between individual dosage units sampled from a particular lot of resulting film. See Appendix A.

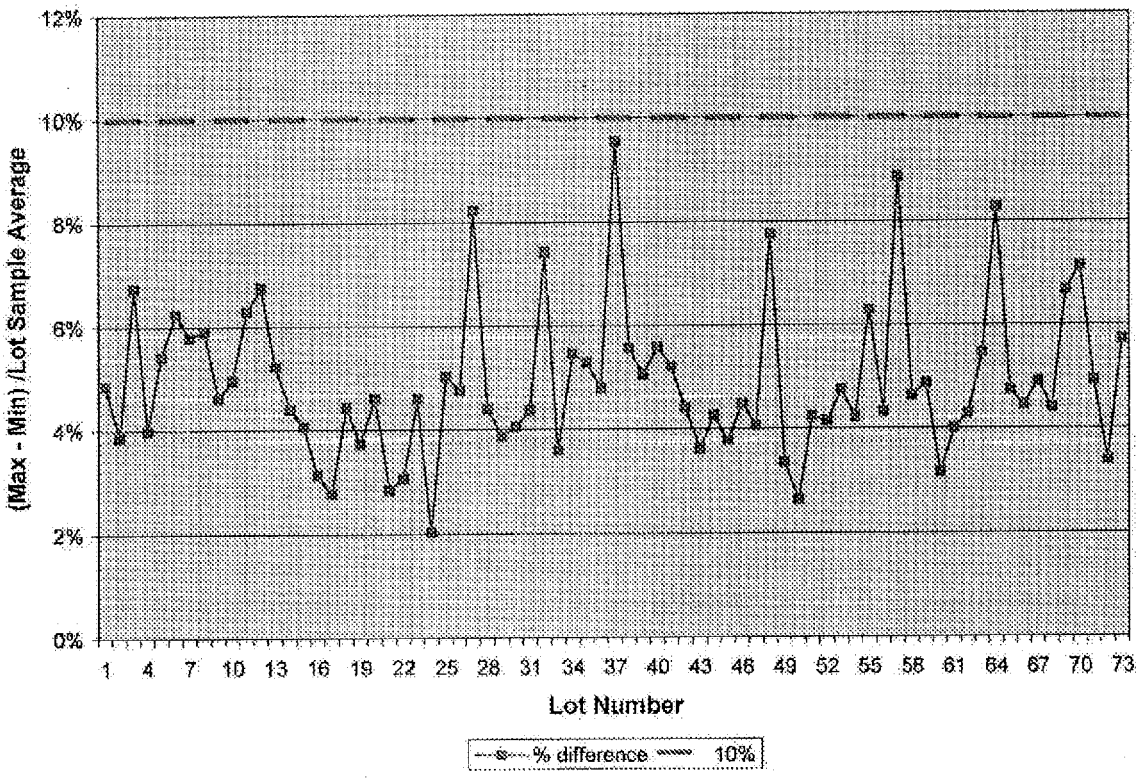
Second, the amount of active across different lots of resulting film varies no more than 10% from the desired amount of the active. See Appendix B. Finally, the uniformity of content of the 73 lots of resulting film meets even more stringent standards, for example, the data shows: (i) 46 lots of resulting film wherein the uniformity of content of active is shown with the amount of active varying by less than 5%; (ii) 15 lots of resulting film wherein the uniformity of content of active is shown with the amount of active varying by less than 4%; 4 lots of resulting film wherein the uniformity of content of active is shown with the amount of active varying by less than 3%; and 1 lot of resulting film wherein the uniformity of content of active is shown with the amount of active varying by only 2%. See Appendix C.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and. that such statements may jeopardize the validity of the application or any patents issued thereon.

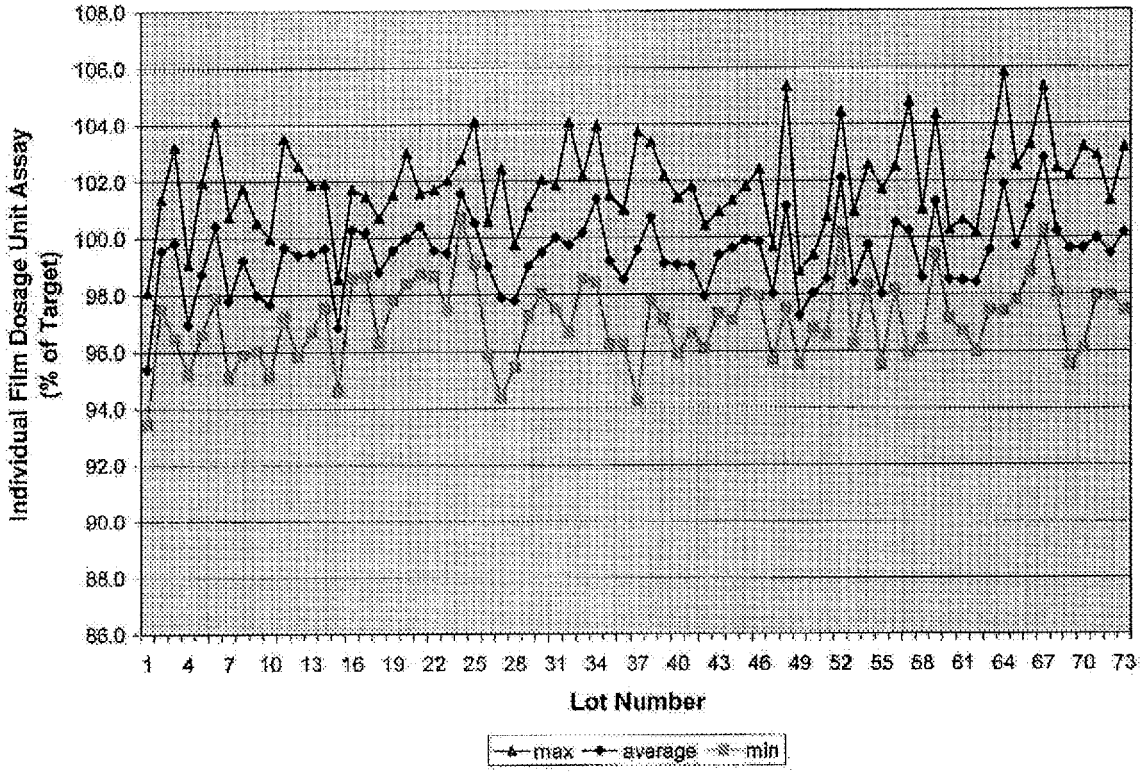
Dated this 13th day of March, 2013

B. Arlie Bogue

APPENDIX A


12%
10%
8%
6%
4%
2%
0%
(Max - Min) /Lot Sample Average
1 4 7 10 13 16 19 22 25 28 31 34 37 40 43 46 49 52 55 58 61 64 67 70 73
Lot Number
% difference
10%

APPENDIX B



APPENDIX C

Lots less than 5%			lots 5% to 10%	
Lot #	% Difference		Lot #	% Difference
24	2.0%		10	5.0%
45	2.6%		25	5.0%
17	2.8%		39	5.0%
21	2.8%		41	5.2%
22	3.1%		13	5.2%
16	3.1%		35	5.3%
60	3.2%		5	5.4%
50	3.4%		63	5.5%
72	3.4%		34	5.5%
33	3.6%		38	5.6%
43	3.6%		40	5.6%
19	3.7%		73	5.7%
46	3.8%		7	5.8%
29	3.9%		8	5.9%
2	3.9%		6	6.2%
4	4.0%		11	6.3%
61	4.0%		55	6.3%
30	4.0%		69	6.7%
48	4.1%		3	6.7%
15	4.1%		12	6.7%
52	4.2%		70	7.1%
54	4.2%		32	7.4%
51	4.2%		49	7.8%
44	4.3%		27	8.2%
62	4.3%		64	8.3%
56	4.3%		57	8.9%
31	4.4%		37	9.5%
28	4.4%			
14	4.4%			
68	4.4%			
42	4.4%			
18	4.4%			
66	4.5%			
47	4.5%			
23	4.6%			
20	4.6%			
9	4.6%			
58	4.6%			
65	4.7%			
26	4.8%			
53	4.8%			
36	4.8%			
1	4.9%			
59	4.9%			
67	4.9%			
71	4.9%			
total	46		total	27

CERTIFICATE OF FIRST CLASS SERVICE

It is certified that a copy of this **DECLARATION OF B. ARLIE BOGUE, PH.D. UNDER 37 C.F.R. § 1.132** has been served, by first class mail, on March 13, 2013, in its entirety on the third party requester as provided in 37 CFR § 1.903 and 37 CFR § 1.248 at the addess below.

DANIELLE L. HERRITT
McCARTER & ENGLISH LLP
265 FRANKLIN STREET
BOSTON, MASSACHUSETTS 02110

/Daniel A. Scola, Jr./
Daniel A. Scola, Jr.
Registration No.: 29,855
Attorney for the Patentee

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patentee:	Yang et al.	Examiner:	Diamond, Alan D.
Patent No.:	U.S. 7,897,080	Group Art Unit:	3991
Reexamination Control No.:	95/002,170	Confirmation No.	6418
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Dated:	March 13, 2013	M&E Docket:	117744-00023

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Central Reexamination Unit
Commissioner for Patents
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

Certificate of EFS-Web Transmission
I hereby certify that this correspondence is being transmitted via the U.S. Patent and Trademark Office electronic filing system (EFS-Web) to the USPTO on
March 13, 2013.
Signed: Michael I. Chakansky /Michael I Chakansky/

DECLARATION OF DAVID T. LIN, PH.D. UNDER 37 C.F.R. § 1.132

Madame:

I, David T. Lin, Ph.D. do hereby make the following declaration:

I. SUMMARY OF CREDENTIALS AND EXPERIENCE

1. Since January 2005, I have served as a Senior Consultant to Biologics Consulting Group, Inc. ("BCG"), a team of consultants who provide national and international regulatory and product development advice on the development and commercial production of small molecular weight synthetic drug, biotechnological and biological products.

2. While BCG is being paid for my time, I am not an employee of, nor do I have any financial interest in, MonoSol Rx, LLC ("Patentee" and/or "MonoSol").

3. Before joining BCG, I held various positions with the United States Food and Drug Administration ("FDA"). From 1997-2001, I was a Chemistry Reviewer in the Division of Reproductive and Urologic Drug Products, Center for Drug Evaluation and Research ("CDER"). In 2001, I became the Team Leader in the same Division and served in that role until 2003 when I was promoted to the position of acting Deputy Division Director in the Division of New Drug Chemistry III, Office of New Drug Chemistry (currently referred to as Office of New Drug Quality Assessment). In 2004, I was promoted to the position of acting Division Director.

4. As a Chemistry Reviewer at CDER, I was responsible for the comprehensive review of Chemistry, Manufacturing and Controls ("CMC") data for drugs being investigated during Phase 1, 2, and 3 clinical studies. I was also responsible for the review of CMC data in New Drug Applications and provided regulatory input to CMC reviewers responsible for review of Abbreviated New Drug Applications. This included providing scientific and regulatory guidance during development of small molecular weight drugs and biotechnological/biological drugs across a wide variety of dosage forms. I have reviewed CMC data submitted with respect to over 100 Investigational New Drug Applications and New Drug Applications (original and supplemental) as a chemistry reviewer, contributed to decisions regarding the approval of drugs, made presentations before scientific and regulatory conferences and participated in a variety of special FDA projects and committees, including serving as the co-Chair of the CMC Good Review Practices Committee.

5. As Team Leader, acting Deputy Division Director and acting Division Director in the Office of New Drug Chemistry, I was actively involved in directing the content of FDA guidances that pertained to CMC topics. As acting Deputy Division Director and Division Director, I was directly involved in discussions, regarding the content of the 2003 FDA draft guidance on Drug Product-Chemistry, Manufacturing, and Controls Information, with the committee responsible for writing this guidance. I had signatory authority for this draft guidance prior to public issuance by FDA. As acting Deputy Division Director and Division Director, I was involved in regular meetings with the supervisory staff in the Office of Generic Drugs to discuss regulatory and review policy issues that are common to both New Drug Applications and Abbreviated New Drug Applications.

6. I consider myself an expert in the fields of FDA practice and procedure as applicable to the testing requirements for drugs and review of Investigational New Drug Applications (INDs) and New Drug Applications (NDAs).

7. I received my B.A. in Biochemistry from the University of Pennsylvania in 1984, my Ph.D. in Organic Chemistry from the University of Maryland in 1989 and my M.B.A. from the University of Maryland's RH Smith School of Business in 2002. Attached hereto as Exhibit A is my curriculum vitae, including a list of my publications for the past ten years.

8. I have carefully reviewed Chen (WO 00/42992) ("Chen").

II. U.S. STATUTORY AND REGULATORY BACKGROUND FOR TESTING DRUGS FOR POTENCY AND DOSAGE UNITS FOR UNIFORMITY

9. From a US regulatory perspective, for a drug to be approved for commercial marketing and distribution, specifications necessary to ensure the identity, strength, quality, purity, potency, and bioavailability of the drug product must be provided in a New Drug Application.[1] In addition, reference to the current U.S. Pharmacopeia (USP) may satisfy these requirements.

10. Section 501(b) of the Food, Drug, and Cosmetic Act (the Act) deems an official drug (i.e., a drug represented as a drug which is recognized in the U.S. Pharmacopeia) to be adulterated if it fails to conform to compendial standards of quality, strength or purity. Compendial tests or assay methods are used when determining such conformance under 501(b); the standards are stated in individual monographs as well as portions of the General Notices section of the USP/NF. Standards and test methods have been established for such characteristics as potency and content uniformity.

11. Section 501(c) of the Act deems a drug that is not recognized in the USP to be adulterated if it fails to meet the strength, purity or quality which it is represented to possess.

[1] 21 CFR 314.50(d)(1)(ii)(a)

The applicable quality standards for a drug not recognized in the USP can be determined from such sources as the labeling of the drug (or drug product), the manufacturer's written specifications, and new drug applications.

12. The current good manufacturing practice (cGMP) regulations include the minimum requirements for the preparation of drug product for administration to humans. One of the requirements is that the strength[2] of the drug (active ingredient) in the drug product must be determined for each batch of drug product manufactured for commercial distribution.[3] Strength is taken to mean content or assay of the drug.

13. Batch uniformity of the drug products is ensured with procedures that describe the in-process controls, and tests, or examinations to be conducted on appropriate samples of in-process materials of each batch.[4] FDA also describes in guidance that it is expected the sampling plan for drug product is representative of the batch.[5]

14. Controls include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that the drug product conform to appropriate standards of identity, strength, quality, and purity.[6]

15. Regulatory specifications must be established to ensure that the dosage form will meet acceptable therapeutic and physicochemical standards throughout the shelf-life of the marketed product.[5] These specifications include tests for strength (content or assay) and uniformity of dosage units.

---

[2] 21 CFR 210.3(b)(16)

[3] 21 CFR 211.165(a)

[4] 21 CFR 211.110(a)

[5] FDA Guideline for Submitting Documentation for the Manufacture and Controls for Drug Products, February 1987

[6] 21 CFR 211.160(b)

16. Testing to establish uniformity of dosage units is defined in the USP under the USP general chapter <905>.[7]

III. CHEN'S DISCLOSURE IS INSUFFICIENT

17. I have been asked to review Chen and render an opinion as to whether there is sufficient information contained within to allow regulatory FDA approval and commercialization of a drug product that is manufactured as described. After review of the patent in light of FDA practice and procedure, it is my opinion that there is insufficient disclosure to allow FDA to determine that a drug product as described can be manufactured for commercial distribution, manufactured in a consistent manner and meet specifications that will ensure the identity, strength, quality, purity, and potency of the drug product. In particular, Chen lacks any disclosure which would necessarily lead to the manufacture of films with uniformity of content (strength) of drug active required for FDA approval.

18. As would be required for FDA approval Chen does not disclose sufficient information that films containing drug can be produced consistently with respect to uniformity of content of the drug. No information was disclosed that demonstrated uniformity of content in the amounts of drug in individual dosage units. Chen discloses no specific test methods, and hence no test results, that could allow for the determination of the actual amount of drug (active) in individual dosage units.

19. As required for FDA approval, Chen's patent did not disclose sufficient information regarding the manufacturing process and process controls. The information disclosed by Chen would not ensure that films containing drug could be manufactured to meet specifications that ensure consistent strength.

20. Even if the information disclosed in Chen could be utilized to develop a manufacturing process for films containing drug, there is no information regarding the test methods that are necessary to determine the amount of drug in individual dosage units.

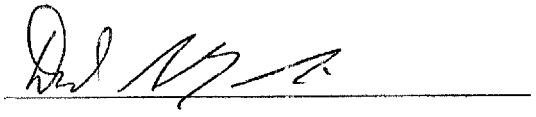
[7] USP General Chapter <905> Uniformity of Dosage Units

21. Therefore, Chen's disclosure is lacking, both explicitly and inherently, the disclosure necessary to provide for the manufacture of drug-containing films with the uniformity of content in amount of drug (active) in individual dosage units to make FDA approvable film products. It is my understanding that an inherent disclosure may not be established by probabilities or possibilities and that the mere fact that a certain thing may result from a given set of circumstances is not sufficient and that to be inherent requires that the missing disclosure is necessarily present.

22. Finally, Chen's patent discloses the release profiles of four active agents from films. See Chen, Figure 5. The release profile data presented in Figure 5 show a high degree of variability at each data point. For example, the release profile for nicotine containing film product show that the amount of nicotine released at the 5 minute and 8 minute time point can be as high as approximately 115-120%. This level of active agent is greater than the 110% level (from an expected amount of 100%) that is considered acceptable to FDA for regulatory approval of a product that purports to be manufactured consistently with acceptable content uniformity. These data indicate that the test method used in the analysis is not reproducible and/or there is a lack of active agent content uniformity between individual dosage units. These deficiencies demonstrate the lack of manufacturing consistency and lack of active agent content uniformity in the film.

23. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and. that such statements may jeopardize the validity of the application or any patents issued thereon.

Dated this 13th day of March, 2013



David T. Lin

CERTIFICATE OF FIRST CLASS SERVICE

It is certified that a copy of this **DECLARATION OF DAVID T. LIN, PH.D. UNDER 37 C.F.R. § 1.132** has been served, by first class mail, on March 13, 2013, in its entirety on the third party requester as provided in 37 CFR § 1.903 and 37 CFR § 1.248 at the addess below.

DANIELLE L. HERRITT
McCARTER & ENGLISH LLP
265 FRANKLIN STREET
BOSTON, MASSACHUSETTS 02110

/Daniel A. Scola, Jr./
Daniel A. Scola, Jr.
Registration No.: 29,855
Attorney for the Patentee

EXHIBIT A

DAVID TSOCHUNG LIN

9121 Fall River Lane, Potomac, MD 20854 (301) 299-2853 dlin@bcg-usa.com

EXPERTISE

- 18+ years pharmaceutical regulatory experience.
  - 7+ years regulatory chemistry, manufacturing and controls (CMC) experience at CDER/FDA on small molecular-weight drugs, botanical drugs, peptide drugs, and protein drugs formulated in a broad range of sterile and non-sterile dosage forms.
  - 3+ years research experience at CBER/FDA.
  - 8+ years experience as regulatory CMC consultant.
- Unique combination of biologic/biotechnological and small molecular-weight drug regulatory experience, including device/drug and device/biologics combination products.
- Understanding of FDA regulatory requirements and expectations for drug development and marketing approval.
- Performed primary CMC review and assessment of drug products for treatment of reproductive and urologic disorders and diseases.
- Supervised CMC review activities in 7 CDER medical reviewing divisions including Reproductive/Urologic, Anti-viral, Dermatologic/Dental, Anti-inflammatory/ Analgesic/Ophthalmologic, Anti-infective, Special Pathogen/Immunologic, and Over-the-Counter drug products.
- Understanding of drug substance and drug product analytical method development and validation.
- Understanding of drug substance and drug product stability protocol development and stability data analysis.
- Understanding of current Good Manufacturing Practices (cGMPs)
- Experienced in chemical synthesis, small-scale and pilot-scale fermentation, biologics/ biotechnology, and protein chemistry.
- Experienced working in cross-functional teams (i.e., Pharmacology/toxicology, Clinical, Biostatistics, Biopharmaceutics, and Analytical).
- Ph.D. in Organic Chemistry; M.B.A. degree and training for managers.

EXPERIENCE

BIOLOGICS CONSULTING GROUP, INC. Alexandria, VA
January 2005 – Present
Senior Consultant

- Evaluate and provide advice on client CMC scientific and regulatory strategies for a wide range of therapeutic drug products (biologic and non-biologic) in dosage forms that include tablets, topicals, injectables, transdermals, implants, sprays, and inhalation, at all stages of product development, from pre-IND through post-NDA/BLA approval.
- Review and provide advice on IND and NDA/BLA submissions for suitability relative to FDA expectations for CMC data.
- Perform gap analysis audits for deficiencies relative to FDA expectations.
- Conduct regulatory and scientific due diligence audits for business acquisitions and licensing partnerships. Provide assessment of strengths and deficiencies.
- Represent clients in interactions with FDA.
- Prepare and write submissions to FDA, with focus on CMC sections.
- Represent client as FDA regulatory expert in legal proceedings.
- Advise clients on manufacturing contractor and vendor evaluation and selection.
- Provide management and technical oversight of contract manufacturing organizations (CMOs).
- Involved in business development to increase client base.
- Provide scientific and regulatory training and presentations at pharmaceutical/biopharmaceutical conferences.

FOOD & DRUG ADMINISTRATION, CENTER FOR DRUG EVALUATION AND RESEARCH, OFFICE OF NEW DRUG CHEMISTRY, DIVISION OF NEW DRUG CHEMISTRY III. Rockville, MD
July 2003 – December 2004
Division Director (acting) *March 2004 – December 2004*
Deputy Division Director (acting) *July 2003 – March 2004*

- Supervised 34 employees in 9 therapeutic product classes, includes 6 Team Leaders, review chemists and administrative staff. Responsible for employee work performance review and career development.
- Planned and set long-range plans and schedules for Division work. Directed and coordinated workload, and assured implementation of Division policies, goals and objectives.
- Evaluated budget and fiscal controls to manage Division functions.
- Made critical decisions and provided expert advice concerning regulatory, scientific and compliance approaches and options consistent with Office policies and objectives.
- Represented FDA in dealing and negotiating with the regulated industry, and professional and industry organizations.
- Participated as invited speaker at regulatory and scientific conferences on behalf of FDA.
- Served as the Chair of the Stability Guidance Technical Committee, Co-chair of the Conjugated Estrogens Working Group and Co-chair of the Good Review Practices Working Group.

FOOD & DRUG ADMINISTRATION, CENTER FOR DRUG EVALUATION AND RESEARCH, DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS. Rockville, MD
October 2001-July 2003
Lead Chemist (Team Leader)

- Managed a team of 4 review chemists in 2 therapeutic product classes.
- Responsible for secondary review, consistency of CMC reviews and adherence to FDA/ONDC policies and guidances.
- Coordinated reviewers' workload of IND and NDA submissions to ensure that reviews were conducted in timely manner.
- Interacted extensively with the regulated industry to provide regulatory direction during IND drug development and NDA post-approval activities.
- Active in the development of FDA guidances for industry and internal good review practices. Served as the Chair of the Stability Guidance Technical Committee, Co-chair of the Conjugated Estrogens Working Group and Co-chair of the Good Review Practices Working Group.

FOOD & DRUG ADMINISTRATION, CENTER FOR DRUG EVALUATION AND RESEARCH, DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS. Rockville, MD
April 1997-October 2001
Chemistry Reviewer

- Evaluated the quality of new drug products submitted to the FDA for approval.
- Integral part of a cross-functional review team responsible for evaluating the quality and effectiveness of reproductive and urologic drug products being investigated in clinical studies.
- Major contributor to committees responsible for establishing drug product quality standards and publishing guidances for pharmaceutical companies.
- Provided regulatory guidance to pharmaceutical company representatives during drug development.
- Mentored new reviewers.
- Served as computer focal point to facilitate and troubleshoot computer issues.

FOOD & DRUG ADMINISTRATION, CENTER FOR BIOLOGICS EVALUATION AND RESEARCH, LABORATORY OF PARASITIC BIOLOGY AND BIOCHEMISTRY. Bethesda, MD
February 1994-April 1997
National Research Council Fellow

- Investigated the biological role of specific proteins in the sexual differentiation of the malaria parasite. Published three research papers in peer-reviewed journals.
- Presented research data at three separate scientific conferences.
- Supervised the research projects of college students.
- Responsible for the coordination of instrument repairs and the ordering of laboratory supplies.

GENERAL ELECTRIC CO., CORPORATE RESEARCH & DEVELOPMENT, BIOLOGICAL SCIENCES LABORATORY. Schenectady, NY
July 1989-January 1994
Staff Scientist

- Developed recombinant biphenyl-metabolizing microorganisms capable of degrading environmental contaminants. Marketed this technology to the GE business units and government agencies responsible for environmental clean-up.
- Investigated the factors affecting aerobic biodegradation of indigenous PCBs in Hudson River sediment by various bacterial strains.
- Isolated and conducted mechanistic studies of the dioxygenase enzymes involved in biodegradation.
- Investigated the scientific and economic feasibility of biologically synthesizing aromatic monomers for use as a feedstock to produce biodegradable polymers.
- Supervised research projects of summer interns.
- Published research in peer-reviewed journals.
- Recruited at major East Coast universities. Interviewed and screened graduating science Ph.D. students for second round interviews at the Research Center.

UNIVERSITY OF MARYLAND, Dept. of Chemistry/Biochemistry. College Park, MD
May 1985-May 1989
Research Assistant

- Investigated mechanism of action of two bacterial enzymes, mandelate racemase and D-amino acid oxidase.
- Synthesized and tested novel halogenated aromatic hydroxy- and amino- acid analogs as potential irreversible inhibitors.
- Published research in peer-reviewed journals and co-authored one chapter in a biotechnology book. In addition, the research data was presented at two national scientific conferences.
- Served as the computer expert for the laboratory group.

EDUCATION

ROBERT H. SMITH SCHOOL OF BUSINESS. College Park, MD
University of Maryland
Master of Business Administration (MBA), *2002*
Concentration: Finance

UNIVERSITY OF MARYLAND. College Park, MD
Department of Chemistry and Biochemistry
Ph. D. -- Organic Chemistry, *1989*
Research Advisor -- Dr. John W. Kozarich

UNIVERSITY OF PENNSYLVANIA. Philadelphia, PA
Bachelor of Arts with Honors – Biochemistry, *1984*
Dean's List, Phi Lambda Upsilon Chemical Honor Society

TRAINING

- Facilitation Skills, CDER/FDA (Fall 2002)
- Six Sigma Strategy and Methods, Univ. of MD (Summer 2002)
- Group Decision-Making Techniques, CDER/FDA (Feb. 2002)
- Managing Written Communications for Team Leaders, CDER/FDA (Spring 2002)
- Organizational Behavior and Human Resources, Univ. of MD (Fall 1999)
- Management of Human Resources, Univ. of MD (Fall 1999)
- Introduction to Drug Law and Regulation, CDER/FDA (Nov. 1998)
- Basic Statistical Methods, CDER/FDA (Fall 1998)

HONORS/AWARDS

- CDER's Team Excellence Award (Nov 2004)
- FDA's Group Recognition Award (May 2004)
- CDER's Special Recognition Award (Nov 2002)
- CDER's Team Excellence Award (Nov 2002)
- OPS/ONDC Special Recognition Award (Dec 2001)
- CDER's Team Excellence Award (Nov 2000)
- OPS/ONDC Special Recognition Award (Jun 2000)
- CDER's Excellence in Mentoring Award (Nov 1999)

PRESENTATIONS

- Conducting Effective & Compliant Stability Programs for Pharmaceuticals & Biologics, "Stability Studies During Development", "Stability of Biopharmaceuticals", "Development of Specifications for Biopharmaceuticals", and "Extractables, Leachables, and Particulates – Safety Concern for Biotechnology Products", Dubai, UAE (Sep 2012).
- 4th DIA China Annual Meeting, "ICH Guidelines Q1D, Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products", and "Q1E, Evaluation of Stability Data", Shanghai, China (May 2012).
- IPA's Current Trends and Practices in Stability Testing, "Stability Testing Requirements for Biopharmaceutical Products", Montreal, Canada (Oct 2011)
- IPA's Current Trends and Practices in Stability Testing, "Stability Program for Combination Products", Montreal, Canada (Oct 2011)
- 3rd DIA China Annual Meeting, "Thinking About Comparability for Biosimilar Proteins", Beijing, China (May 2011).
- IPA's Current Trends and Practices in Stability Testing, "Stability Challenges for Combination Products", Boston, MA (May 2011).
- IPA's Current Trends and Practices in Stability Testing, "Country Specific Stability Requirements", Boston, MA (May 2011).
- Stability Programs Forum, "Stability Testing for Biotechnology/Biologic Products", Philadelphia, PA (Dec 2010).
- 11th Annual EuroTIDES/EuroPEPTIDES Conference, "Stability Considerations and Testing for Peptide-and Oligo-Based Therapeutics", Barcelona, Spain (Nov 2010).
- International Summit of China Pharmaceutical Industry, "FDA Requirements for Peptide Product Development: Considerations from Small Molecule and Biological Products", Hangzhou, China (Oct 2010).

- 7th Annual Method Validation Conference, "Ensure Method Validation Compliance through a Review of FDA Warning Letters", San Francisco, CA (Jul 2010).
- 6th Annual BioProcess International European Conference, "Extractables, Leachables and Particulates – Safety Concern for Biotechnology Products," Vienna, Austria (May 2010)
- ISPE-CSAC Meeting, "Biotechnological Drug Development and Interactions with CDER," Raleigh, NC (Oct 2009).
- Seminar on China International Bio-medicine Outsourcing Service, "Product Quality Issues with GLPs and GCPs," Hangzhou, China (Sep 2009).
- Informa Stability Testing for Biologics Conference, "Understanding Product Expiry and Shelf-Life," Prague, Czech Republic (Sep 2009).
- Informa Stability Testing for Biologics Conference Workshop, "Stability Testing Performed Over a Product Lifecycle," Prague, Czech Republic (Sep 2009).
- IVT Lab Compliance Conference, "Implement a Comprehensive and Compliant Stability Program," Philadelphia, PA (Aug 2009).
- OKBio ACCELERATE Workshop, "Product Development – Regulatory CMC Considerations," Oklahoma City, OK (Jun 2009).
- IVT Method Validation Conference, "Challenges in Understanding Impurities and Degradants for Biological/Biotechnological Products," San Francisco, CA (Oct 2008).
- IVT Method Validation Conference, "Strategies for Setting Biological Product Specifications," San Francisco, CA (Oct 2008).
- CBI 3rd Annual Stability Programs Conference, "Complex Stability Programs for Biologics," Philadelphia, PA (Jun 2008).
- IVT Lab Compliance Conference, "Stability Testing Fundamentals and Considerations in the Current Regulatory Environment," Baltimore, MD (Apr 2008).
- R&D Direction's 5th Annual Drug Development Summit, "Looking Forward in 2008: Regulatory Priorities and Considerations," Amelia Island, FL (Feb 2008).
- 2007 AAPS Annual Meeting, "Critical Stability Evaluation of Biopharmaceuticals During Clinical Development Stages," San Diego, CA (Nov 2007).
- 2007 DIA Annual Meeting, "The Impact of FDA's Quality by Design Initiative on Biologics Development," Atlanta, GA (Jun 2007).
- Institute for International Research: Formulation and Forced Degradation Strategies for Biomolecules, "Regulatory Requirements for Successful Product Development," San Diego, CA (Mar 2007).
- International Pharmaceutical Academy: Effective Management of Stability Programs, "Stability Design Considerations for Global Regulatory Filings," Toronto, Canada (Feb 2007).
- Cambridge Healthtech Institute's PepTalk: Optimizing Protein and Antibody Therapeutics, "Regulatory Considerations for the Development of Protein Therapeutic Products," San Diego, CA (Jan 2007).
- 2006 AAPS Annual Meeting, "The Impact of FDA Initiatives on the Development of Biological Products," San Antonio, TX (Nov 2006).
- SWE Enterprises: Stability Testing for the FDA Regulated Industry, "In-Use Testing of Biotechnological and Biologic Products," Boston, MA (Oct 2006).
- SWE Enterprises: Stability Testing for the FDA Regulated Industry, "Cost Efficient Design of Stability Studies," Boston, MA (Oct 2006).
- Institute for International Research: Chemistry Manufacturing & Controls, "Clarifying and Understanding ICH Guidance to Help Meet International Requirements for Submissions," Philadelphia, PA (July 2006).
- IVT Stability Testing: Implementing Effective Processes for Stability Program Development, "Cost Efficient Design of Stability Studies," San Diego, CA (June 2006).
- IVT Stability Testing: Implementing Effective Processes for Stability Program Development, "Stability Requirements for Global Regulatory Filings," San Diego, CA (June 2006).

- CBI Stability Programs: New Approaches to Test, Analyze and Document Data for Improved Program Design and Global Compliance, "In Use Testing of Biotechnological and Biological Products," Princeton, NJ (June 2006).
- IBC/TIDES: Oligonucleotide and Peptide Technology and Product Development, "Stability Considerations and Testing for Oligo- and Peptide-Based Therapeutics," Carlsbad, CA (May 2006).
- IBC Biopharm Manufacturing and Distribution Summit: Logistics for Biopharmaceutics, "Stability Studies to Support the Chain of Custody of Biotechnology Products," Reston, VA (Dec 2005).
- 2005 AAPS Annual Meeting: AAPS Short Course on Degradation and Stability in Small Molecule Active Pharmaceutical Ingredients/Stability Testing for Global Filings, "Stability Requirements for Global Regulatory Filings," Nashville, TN (Nov 2005).
- Therapeutic Strategies Against Neurodegenerative Conditions, "The Regulatory Product Development Process," Burlington, MA (Oct 2005).
- International Pharmaceutical Federation (FIP) Workshop: Harmonizing Clinical Trial GMP and Quality Requirements Across the EU and Beyond, "The US Investigational New Drug (IND) System," Noordwijk Zee, The Netherlands (Mar 2005).
- 2004 AAPS Annual Meeting, "Phase 2 and 3 IND CMC Guidance: FDA Perspective," Baltimore, MD (Nov 2004).
- 64th Annual World FIP Congress, "Clinical Trial Application Process – CMC: US FDA Perspective," New Orleans, LA (Sep 2004).
- AAPS Pharmaceutical Technologies 3rd Summer Conference: Optimizing the Global Clinical Trial Process, "IND Applications – FDA Perspective," Cherry Hill, NJ (Aug 2004).
- 2004 DIA Annual Meeting, "FDA Stability Guidance Update," Washington, DC (Jun 2004).
- DIA Meeting on CM&C/Regulatory and Technical Strategies, "Challenges and Opportunities in CMC Requirements for Phase 2-3," Bethesda, MD (Mar 2004).
- 2003 PDA Annual Meeting, "Draft FDA Stability Guidance," Atlanta, GA (Nov 2003).
- 2003 DIA Annual Meeting, "Product Quality of Non-clinical and Clinical Trial Materials," San Antonio, TX (Jun 2003).
- PARCS Meeting, "Managing CMC Requirements during IND," Irvine, CA (Apr 2003).
- PARCS Meeting, "Use of SUPAC Guidances during IND Development," Irvine, CA (Apr 2003).
- DIA Meeting on Global Chemistry, Manufacturing and Controls: Pre IND/CTX and IND/CTX Development Challenges, "FDA Perspective on Stability Testing during IND Development," Philadelphia, PA (Feb 2003).

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- C. Syin, D. Parzy, F. Traincard, I. Boccaccio, M.G. Joshi, D.T. Lin, X.-M. Yang, K. Assemat, C. Doerig, and G. Langeley, "The H89 cAMP-dependent protein kinase inhibitor blocks *Plasmodium falciparum* development in infected erythrocytes," *Eur. J. Biochem. 268*, 4842 (2001).
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- D.T. Lin, V.M. Powers, L.J. Reynolds, C.P. Whitman, G.L. Kenyon and J.W. Kozarich, "Evidence for the generation of α-carboxy-α-hydroxy-*p*-xylylene from *p*-(bromomethyl)mandelate by mandelate racemase," *J. Am. Chem. Soc. 110*, 323 (1988).

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- N.R. Schmuff and D.T. Lin, "Contents of Module 3 for an Electronic Common Technical Document Investigational New Drug Application," in Preparation and Maintenance of the IND Application in eCTD Format, W.K. Sietsema (ed.), FDAnews, Falls Church, VA, 117-134 (2008).
- N.R. Schmuff and D.T. Lin, "Chemistry, Manufacturing and Controls (CMC)," in Wiley Encyclopedia of Clinical Trials, (2008).
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- D.T. Lin, N.D. Goldman, and C. Syin, "*Plasmodium falciparum* mitogen-activated protein kinase homologue contains an unusually large carboxyl terminal domain which is highly charged and homologous to merozoite surface antigens," Molecular Parasitology Meeting, Woods Hole, MA (1995).
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- J. H. Lobos, M. J. Brennan, J. T. Jackman and D. T. Lin, "*In situ* stimulation of PCB biodegradation in Hudson River sediment: III. enumeration and characterization of aerobic bacteria," ASM Meeting, New Orleans (1992).
- G.L. Kenyon, D.T. Lin, V.M. Powers, L.J. Reynolds, C.P. Whitman and J.W. Kozarich, "Generation of α-carboxy-α-hydroxy-*p*-xylylene from *p*-bromomethyl-mandelate by mandelate racemase– further evidence for a carbanion mechanism," *FASEB J.* 2, 1329 (1988).
- D.T. Lin, V.M. Powers, L.J. Reynolds, C.P. Whitman, G.L. Kenyon and J.W. Kozarich, "Formation of *p*-xylylene species in the mandelate racemase catalyzed reaction of *p*-(bromomethyl)mandelate," *Fed. Proc. 46*, 2042 (1987)

Electronic Acknowledgement Receipt

EFS ID:	18425655
Application Number:	95002170
International Application Number:	
Confirmation Number:	6418
Title of Invention:	POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM
First Named Inventor/Applicant Name:	7897080
Customer Number:	23869
Filer:	Danielle L. Herritt/Maureen Tierney
Filer Authorized By:	Danielle L. Herritt
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1	Reexam - Affidavit/Decl/Exhibit Filed by 3rd Party	Exhibit_1_US7897080.pdf	11515802 553039d87d2a837a52d99a7fa4116e1f506f040c	no	73

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2	Reexam - Affidavit/Decl/Exhibit Filed by 3rd Party	Exhibit_3_Clevenger_Decl.pdf	515093 ee77a994060c8bec1a3614b7786897b4f759a2ac	no	7
Warnings:					
Information:					
3	Appeal Brief - Third Party Requester	117744_00023_Appeal_Brief_FINAL_2014MAR10.pdf	2634267 e4c2ae2fb9c3f9b3d8cb438e0fc5df9e269f1cef	no	91
Warnings:					
Information:					
4	Reexam - Affidavit/Decl/Exhibit Filed by 3rd Party	Exhibit_2_Reitman_Decl--.pdf	712304 9fa5e8f0d31e6e606d68abf4e411f152545ea96a	no	11
Warnings:					
Information:					
5	Reexam - Affidavit/Decl/Exhibit Filed by 3rd Party	Exhibit_4_Bogue_Lin_Decls--.pdf	2317521 54427f6e1c4b137dd028b061e1ca94efc5d0ccc3	no	25
Warnings:					
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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inter Partes Reexamination of Yang et al.	Examiner: Alan D. Diamond
U.S. Patent No. 7,897,080	Group Art Unit: 3991
Reexamination Control No. 95/002,170	Confirmation No. 6418
Filed: September 10, 2012	H&B Docket: 1199-26 RCE/CON/REX M&E Docket: 117744-00023

For: POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM

APPELLANT'S APPEAL BRIEF

Mail Stop *Inter Partes* Reexam
Central Reexamination Unit
Commissioner for Patents
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

Certificate of EFS-Web Transmission
I hereby certify that this correspondence is being transmitted via the U.S. Patent and Trademark Office electronic filing system (EFS-Web) to the USPTO on March 10, 2014.

Signed: Michael I. Chakansky /Michael I Chakansky/Reg. No. 31,600

I hereby certify that, pursuant to 37 CFR § 1.943(c), based on the WordPerfect word count of 13,976 words, Appellant's brief, counting the words on those pages beginning at page 1 (entitled Appellant's Appeal Brief) and continuing through and including all words of the signature page (entitled Conclusion), does not exceed 14,000 words in length.

Signed: Michael I. Chakansky /Michael I Chakansky/Reg. No. 31,600

Dear Madame:

On December 26, 2013, patent owner MonoSol Rx, LLC ("Appellant") filed its Notice of Appeal to the Patent Trial and Appeal Board (PTAB), appealing all of the Examiner's rejections of all claims delineated as rejected in the Right of Appeal Notice mailed December 6, 2013 ("RAN"), in the above-identified *inter partes* reexamination. On January 9, 2014, Third Party Requester BioDelivery Sciences International, Inc. ("Third Party Requester") filed a Notice of

Cross Appeal regarding certain claims rejections not adopted by the Examiner in the RAN. As March 9, 2014 is a Sunday, this Appeal Brief, filed Monday March 10, 2014 is timely.

Appellant submits this Appeal Brief in support of it appeal, and authorizes the Commissioner to charge all fees associated therewith, including, without limitation, the $2,000.00 fee for filing this brief in support of an appeal in an *inter partes* reexamination proceeding, pursuant to 37 C.F.R. § 41.20(b)(2)(i), to Deposit Account No. 08-2461.

TABLE OF CONTENTS

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CASES

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RULES & MPEP

APPELLANT'S APPEAL BRIEF

I. Statement of the Real Party in Interest

MonoSol Rx, LLC, owner of U.S. Patent No. 7,897,080 (the " '080 Patent"), is the real party in interest for Appellant.

II. Related Appeals and Interferences

Other than as noted below, Appellant is not aware of any related appeals, interferences or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

On November 2, 2010, Appellant commenced an action, for patent infringement of several patents it owns, namely, U.S. 7,824,588 (the " '588 Patent"), U.S. 7,357,891 (the " '891 Patent") and U.S. 7,425,292 (the " '292 Patent"), against Third Party Requestor, *inter alia*, in the U.S. District Court for the District of New Jersey, captioned *MonoSol Rx, LLC v. BioDelivery Sciences International, Inc., MEDA Pharmaceuticals, Inc. and Aveva Drug Delivery Systems, Inc.*, 10-cv-5695 ("the Litigation").

While the Litigation was ongoing, Third Party Requester first requested *inter partes* reexamination of the '588 Patent (95/001,753, filed September 12, 2011); and then requested *ex parte* reexamination of the remaining patents in the Litigation, the '891 Patent (90/012,098, filed January 20, 2012) and the '292 Patent (90/012,097, filed January 20, 2012). After filing all of its reexamination requests, Third Party Requestor, *inter alia*, moved the District Court to stay the

Litigation and on March 7, 2012, the Court stayed the Litigation and the stay is still in effect. The '891 Patent and the '292 Patent successfully exited reexamination with reexamination certificates, leaving the '588 Patent *inter partes* reexamination pending and currently on appeal to the PTAB.

On June 12, 2013, Third-Party Requestor, improperly petitioned for *Inter Partes* Review of the '891 Patent (IPR2013-00316) and the '292 Patent (IPR2013-00315) which had recently successfully exited reexamination. The PTAB denied both petitions on November 13, 2013, as untimely.

Third-Party Requester has also requested *inter partes* reexamination of two additional patents of Appellant, namely, the '080 Patent and U.S. 7,666,337 (the " '337 Patent") (Control No. 95/002,171). The '337 Patent reexamination is currently on appeal to the PTAB. All five (5) reexaminations were assigned to the same examiner, Alan D. Diamond.

Several ANDA-based actions have been recently commenced for patent infringement arising from the submission of ANDAs regarding '150 Patent, *inter alia*., in the U.S. District Court for the District of Delaware. The '150 Patent is a divisional of the application for the '337 Patent, of which the '080 Patent is a continuation. On August 20, 2013, Reckitt Benckiser Pharmaceuticals, Inc. ("RBP"), RB Pharmaceuticals Limited ("RBP UK") and Appellant commenced their patent action against Par Pharmaceutical, Inc., IntelGenX Technologies Corp., and LTS Lohmann Therapy Systems Corp., captioned *Reckitt Benckiser Pharmaceuticals, Inc., et al. v. Par Pharmaceutical, Inc. , et al.*, 1:13-cv-01461. On October 8, 2013, RBP, RBP UK and Appellant commenced their patent action against Watson Laboratories, Inc. and Actavis,

Inc., captioned *Reckitt Benckiser Pharmaceuticals, Inc., et al. v. Watson Laboratories, Inc. , et al.*, 1:13-cv-01674. On December 6, 2013, RBP, RBP UK and Appellant commenced their patent action against Alvogen Pine Brook, Inc. and Alvogen Group, Inc., captioned *Reckitt Benckiser Pharmaceuticals, Inc., et al. v. Alvogen Pine Brook, Inc. , et al.*, 1:13-cv-02003.

III. Status of Claims

Claims 1-299 were issued in the '080 Patent; these claims, subject to reexamination, were rejected in the Office Action dated November 29, 2012 ("Office Action"). In Patentee's Response to Office Action dated March 13, 2013 ("Patentee's ROA"), claims 12, 16, 91, 95, 173, 177, 254, 255, 257, 272, 273, 275, 290, 291, and 293 were canceled and claims 300 through 318 were added.

In Appellant's Response to Action Closing Prosecution dated September 3, 2013, Appellant attempted to amend claims 1, 82, 161 and 315-318 in an effort to advance the prosecution of the reexamination and to address rejections made by the Examiner based on new references. See Action Closing Prosecution ("ACP"), pp. 3, 48-51. In the RAN, the Examiner refused to enter the claim amendments, *see infra*.

After the RAN, the following claims are pending and currently stand rejected: claims: 1-11, 13-15, 17-90, 92-94, 96-172, 174-176, 178-253, 256, 258-271, 274, 276-289, 292 and 294-318. Appellant is appealing each and every claim rejected and all the grounds therefor.

IV. Status of Amendments

In the RAN, the Examiner, in connection with Appellant's September 3, 2013 Reply to the July 31, 2013 Action Closing Prosecution ("ACP"), refused entry of Appellant's amendment to claims 1, 82, 161 and 315-318 (see attached CA-Not Entered).

V. Summary of Claimed Subject Matter

The present invention is directed to novel and non-obvious processes for manufacturing pharmaceutical and bioactive active containing films, suitable for commercialization and U.S. Food and Drug Administration ("FDA") approval (i) where the degree of uniformity of content of active throughout a particular lot of resulting films, as well as (ii) where the degree of uniformity of content of active in dosage units taken from different lots of resulting films can also be strictly maintained through the claimed processes. Processes for such control of content uniformity are not present in the prior art.

A. The Pending Independent Claims[1]

There are seven independent claims on appeal, *i.e.*, claims 1, 82, 161, 315, 316, 317 and 318.

Claims 1, 82, 161, 315, 316, 317 and 318 are *generally* directed to:

> A process for **manufacturing resulting films suitable for commercialization and regulatory approval,** said regulatory approval including analytical chemical testing which meets the **standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units**, said films having **a substantially uniform distribution of components comprising a substantially uniform distribution of [a desired amount of] said active in individual dosage units of said resulting films**, comprising the steps of:
> *[Preamble - Claims 82 and 315 included bracketed limitation; claim 161 adds "film capable of being administered to a body surface".]*

[1] The support provided herein for the claimed subject matter is by way of example only. Additional support for the claimed subject matter may be found throughout the issued '080 Patent, including in the Tables, Figures, Examples, and claims of the issued '080 Patent. Moreover, as stated in MPEP 2258.II, "[c]onsideration of 35 U.S.C. 112 issues should . . . be limited to the amendatory (*e.g.*, new language) matter."

(a) **forming a flowable polymer matrix** comprising a water-soluble polymer, a solvent and said active, said active selected from the group consisting **of bioactive actives, pharmaceutical actives and combinations thereof**, said matrix having a substantially uniform distribution of said active;
[(a) - Claim 1 does step (a) in 2 steps (a) and (b), generally by adding active last.]

(b) **casting said flowable polymer matrix**, said flowable polymer matrix having a **viscosity from about 400 to about 100,000 cps;**
[(b) - Claim 1's version is denoted step (b).]

(c) **controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus** [at a temperature of about **60 °C** and **using air currents,** which have **forces below a yield value of the polymer matrix during drying**,] to evaporate at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, **within about the first 4 minutes by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying** to **maintain said substantially uniform distribution** of said active **by locking-in** or substantially preventing migration of said active within said visco-elastic film[[, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said visco-elastic film, **varies by less than 5%,**]] and wherein during said drying said flowable **polymer matrix temperature is 100 °C or less**;
[(c) - Claim 1 does not have the bracketed limitations and it is denoted as step (d); in claims 82 and 161 the double bracketed percent is 10%; only claim 318 has single bracketed limitation of 60 °C .]

(d) **forming said resulting film from said visco-elastic film by further controlling drying** by continuing evaporation to a **water content of said resulting film of 10% or less** and wherein said **substantially uniform distribution of active by said locking-in** or substantially preventing migration of said active **is maintained**[, such that **uniformity of content** in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said resulting film**, varies by no more than 10%**];
[(d) - Claim 1 denotes this as step (e); claims 1, 82 and 161 do not have bracketed limitation; claim 318 replaces bracketed "varies by no more than 10%" with "varies by less than 5%".]

(e) **performing analytical chemical tests for uniformity of content of said active** in said substantially equal sized individual dosage units of said sampled resulting film, said tests indicating that uniformity of content in the amount of said **active varies by no more**

than 10% and said **resulting film is suitable for commercial and regulatory approval**, wherein said regulatory approval is provided by the U.S. Food and Drug Administration.
[(e) - Claim 1 denotes this as step (f); claim 318 replaces "varies by no more than 10%" with "varies by less than 5%".]

(f) **repeating steps (a) through (e)** to form additional resulting films, such that **uniformity of content** in the amount of said active in said resulting film and said additional resulting films **varies no more than 10%** from **the desired amount** of said active as indicated by said analytical chemical tests.
[(f) - only claims 82 and 315 have this step.]

(f) **administering said resulting film to a body surface**.
[(f) - only claim 161 has this step.]

B. Examples of claim elements as referenced in the ‘080 Patent

Support for claims may be found throughout the '080 Patent, including, the Abstract, Specification, Figures and Claims, for example, at:

***Preamble and Step (e); step (f) for claim 1*:** col. 3, ll. 58-60 ("the manufacture of a pharmaceutical film suitable for commercialization and regulatory approval").

***Step ((a); steps (a) and (b) for claim 1*:** col. 19, l. 30 through col. 21, l. 31 (actives including pharmaceutical actives, bioactive actives, and combinations thereof).

***Steps (b) and (c); steps (c) and (d) for claim 1*:** col. 6, ll. 49-52 ("These films provide a non-self-aggregating uniform heterogeneity of the components within them by utilizing a selected casting or deposition method and a controlled drying process."); Figures 6, 7, 8, 35 and 36 and col. 14, ll. 20-25 ("drying" and "drying apparatus"); col. 11, ll. 17-19 (“Any top fluid flow, such as air, also must not overcome the inherent viscosity of the film-forming composition”); col. 11, ll. 21-23 (“yield values . . . force”); col. 12, ll. 20-36, col. 13, ll. 37-38 ("After mechanical mixing, the film may be placed on a conveyor"); col. 29, ll. 11-13 ("As the film is conveyed through the manufacturing process, for example on a conveyor belt apparatus"); col. 33, l. 10 through col. 34, l. 24 (example M); col. 44, 11. 9-13 ("the controlled drying process of the present invention allows for uniform drying to occur, whereby evaporative cooling and thermal mixing contribute to the rapid formation of viscoelastic film and the 'locking-in' of

uniformity of content throughout the film"); col. 6, ll. 52-60 ("Examples of controlled drying processes include . . . hot air impingement across the bottom substrate and bottom heating plates . . . controlled radiation drying . . . such as infrared and radio frequency radiation . . . ."); col. 7, lines 5 through 16 ("This may be achieved by applying heat to the bottom surface of the film . . . or alternatively by the introduction of controlled microwaves to evaporate the water . . . . air currents directed at the bottom of the film should desirably be controlled"); col. 27, ll. 53-55 ("The temperature at which the films are dried is about 100°C. or less"); col. 41, ll. 49-50 ("films were dried in an oven at approximately 60° C."); col. 13, ll. 23-36 ("For instance, the films of the present invention desirably are dried for 10 minutes or less. Drying the films at 80° C. for 10 minutes produces a temperature differential of about 5° C. This means that after 10 minutes of drying, the temperature of the inside of the film is 5° C. less than the outside exposure temperature. In many cases, however, drying times of less than 10 minutes are sufficient, such as 4 to 6 minutes. Drying for 4 minutes may be accompanied by a temperature differential of about 30° C., and drying for 6 minutes may be accompanied by a differential of about 25° C. Due to such large temperature differentials, the films may be dried at efficient, high temperatures without causing heat sensitive actives to degrade."); col. 16, l. 62 through col. 17, l. 3 ("The polymer plays an important role in affecting the viscosity of the film. Viscosity is one property of a liquid that controls the stability of the active in an emulsion, a colloid or a suspension. Generally the viscosity of the matrix will vary from about 400 cps to about 100,000 cps, preferably from about 800 cps to about 60,000 cps, and most preferably from about 1,000 cps to

about 40,000 cps. Desirably, the viscosity of the film-forming matrix will rapidly increase upon initiation of the drying process.").

Step ((e); step (f) for claim 1: col. 28, l. 66 through col. 29, l. 6 ("It may be desirable to test the films of the present invention for chemical and physical uniformity during the film manufacturing process. In particular, samples of the film may be removed and tested for uniformity in film components between various samples. Film thickness and overall appearance may also be checked for uniformity. Uniform films are desired, particularly for films containing pharmaceutical active components for safety and efficacy reasons."); col. 29, ll. 20 through 35 ("The cut film then may be sampled by removing small pieces from each of the opposed ends of the portion(s), without disrupting the middle of the portion(s). . . . After the end pieces, or sampling sections, are removed from the film portion(s), they may be tested for uniformity in the content of components between samples."); col. 32, ll. 34-41 ("An alternative method of determining the uniformity of the active is to cut the film into individual doses. The individual doses may then be dissolved and tested for the amount of active in films of particular size. This demonstrates that films of substantially similar size cut from different locations on the same film contain substantially the same amount of active."); col. 33, l. 10 through col. 34, l. 24 (example M); col. 15, ll. 28-43 (emphasis supplied) ("Consideration of the above discussed parameters, such as but not limited to rheology properties, viscosity, mixing method, casting method and drying method, also impact material selection for the different components of the present invention. *Furthermore, such consideration with proper material selection provides the*

compositions of the present invention, including a pharmaceutical and/or cosmetic dosage form or film product having no more than a 10% variance of a pharmaceutical and/or cosmetic active per unit area. In other words, the uniformity of the present invention is determined by the ***presence of no more than a 10% by weight of pharmaceutical and/or cosmetic variance throughout the matrix. Desirably, the variance is less than 5% by weight, less than 2% by weight, less than 1% by weight, or less than 0.5% by weight.*** *")(this is the substantial uniformity of film as measured by percent difference in amount between samples where the samples differ in amount of active by 10% or less claim claim limitation a more exacting degree of uniformity than that required by, e.g., the FDA).*

Step (f), only claims 82 and 315**:** col. 2, ll. 27-46 (emphasis supplied) ("The formation of agglomerates randomly distributes the film components and any active present as well. When large dosages are involved, a small change in the dimensions of the film would lead to a large difference in the amount of active per film. If such films were to include low dosages of active, it is possible that portions of the film may be substantially devoid of any active. Since sheets of film are usually cut into unit doses, certain doses may therefore be devoid of or contain an insufficient amount of active for the recommended treatment. Failure to achieve a high degree of accuracy with respect to the amount of active ingredient in the cut film can be harmful to the patient. *For this reason, dosage forms formed by processes such as Fuchs, would not likely meet the stringent standards of governmental or regulatory agencies, such as the U.S. Federal Drug Administration ("FDA"), relating to the variation of active in dosage forms.* ***Currently, as***

required by various world regulatory authorities, dosage forms may not vary more than 10% in the amount of active present. *When applied to dosage units based on films, this virtually mandates that uniformity in the film be present."*) (this is the substantial uniformity within 10% of desired amount of active claim limitation).

***Step (f), only claim 161*:** col. 29, l. 64 to col. 30., l.2 ("In addition, the films may be used for the administration of an active to any of several body surfaces, especially those including mucous membranes, such as oral, anal, vaginal, opthalmological, the surface of a wound, either on a skin surface or within a body such as during surgery, and similar surfaces.")

VI. Issues to be Reviewed on Appeal

A. Claim Rejections based on 35 U.S.C. § 112.

1. Was the rejection of **Claim 318** under 35 U.S.C. § 112(a) or 35 U.S.C. § 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement (RAN, pp. 27-28) proper?

2. Was the rejection of **Claim 318** under 35 U.S.C. § 112(b) or 35 U.S.C. § 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention (RAN, p. 28) proper?

B. Claim Rejections based on 35 U.S.C. §§ 102 & 103.

1. Were the rejections of Claims 1-11, 13-15, 17-71, 82-90, 92-94, 96-150, 161-172, 174-176, 178-232, 243-253, 256, 258-271, 274, 276-289, 292 and 294-318 under **35 U.S.C. § 103(a)** as being unpatentable over **Chen** (RAN, pp. 29-44) proper?

2. Were the rejections of Claims 2, 3, 32, 55, 72-81, 111, 134, 151-160, 193, 216 and 233-242 under **35 U.S.C. §103(a)** as being unpatentable over the combined teaching of **Chen and Staab** (RAN, pp. 45-48) proper?

3. Were the rejections of Claims 317 and 318 under **35 U.S.C. § 103(a)** as being unpatentable over the combined teachings of **Chen and Arter** are improper (RAN, pp. 48-50).

4. Were the rejections of Claims 317 and 318 under **35 U.S.C. § 103(a)** as being unpatentable over the combined teachings of **Chen and Strobush** (RAN, pp. 50-52) proper?

5. Were the rejections of Claims 1-5, 10, 13-15, 21, 24, 25, 32, 44-46, 54, 55, 59, 63-70, 72-75, 78-84, 89, 92-94,100,103,104,111,123-125,133,134,138, 142-149, 151-154, 157-166,171, 174-176, 182, 185, 186, 193, 205-207, 215, 216, 220, 224-231, 233-236, 239-242, 249-252, 258-260, 267-270, 276-278, 285-288 and 294-318 under **35 U.S.C. § 102(b)** as anticipated by or, in the alternative under **35 U.S.C. § 103(a)** as being obvious over **Staab** (RAN, pp. 52-62) proper?

6. Were the rejections of Claims 8, 9, 76, 77, 87, 88, 155, 156, 169, 170, 237 and 238 under **35 U.S.C. § 103(a)** as being unpatentable over **Staab** are (RAN, pp. 62-63) proper?

7. Were the rejections of Claims 82, 89, 90, 92, 161, 171, 172, 174, 274, 292, 304-311 and 313-318 under **35 U.S.C. § 103(a)** as being unpatentable over **Le Person** (RAN, pp. 63-71) proper?

VII. Prior art cited by Examiner in rejecting '080 Patent Claims

The Examiner cited the following against Appellant's claims in the RAN:

Chen (WO 00/42992) ("Chen");

Staab (U.S. 5,393,528) ("Staab");

Le Person (*"Near infrared drying of pharmaceutical thin films: experimental analysis of internal mass transport,"* Chemical Engineering and Processing, Vol. 37, pp. 257-263 (1998)) ("Le Person");

Arter (U.S. 4,365,423) ("Arter"); and

Strobush (U.S. 5,881,476) ("Strobush").

VIII. ARGUMENT

A. Preliminary Statement

Prior to the present invention, commercial, FDA approved, prescription pharmaceutical sublingual and lingual films for systemic delivery did not exist. Patent Owner/Appellant MonoSol Rx is the uniquely successful pioneer in prescriptive film manufacturing. Success can be measured in part by the fact that the retail sales of MonoSol Rx's drug delivery films sold in 2012 was almost US $1,000,000,000 (One Billion US Dollars), due to their new dosage form. The '080 Patent discloses methods for the manufacture of a pharmaceutical film suitable for commercialization and regulatory approval, including FDA approval. These methods are used by Appellant in the manufacture of its highly successful film products.

None of the prior art drug delivery films disclose, recognize or suggest the problem of uniformity of content as recited in the claims. The prior art mentioned problems of such things as release characteristics, residence times, mechanical characteristics or adhesion characteristics, but these problems are completely different than the problem of maintaining the uniformity of content of active. The prior art incorrectly presumed that uniformity was essentially a "given" and achievable simply by providing a uniform mix of active in a carrier and forming this mixture into resultant film product. This presumption is completely erroneous. The '080 Patent describes in great detail that this is not the case and offers the means to address this problem in order to produce a film with the claimed degree of uniformity.

Some prior art references, *e.g.* Chen, refer to physical measurements and the glossy appearance of the film, which the Examiner misconstrues as indicative of uniformity of content of active. Uniformity of weight and uniformity of appearance are insufficient measurements for purposes of the present claims. The information provided in such measurements cannot be relied on to determine whether the uniformity of active content has been preserved from the original mixture through film formation and processing to arrive at a resultant film product with the desired degree of uniformity. These measurements, while helpful (Appellant's own specification discuss these) are by no means dispositive as to the existence of uniformity of active content in the final film product. Only by analytical chemical testing is it possible to determine the actual amount of active present and hence whether uniformity of active content has been maintained during processing. This is the essence of the '080 Patent claims.

It should be mentioned that the Le Person reference raised the question as to whether uniformity of films was a problem. To begin with, Le Person's films did not contain active. His inquiry was a general investigation as to what problems may exist in the film making process. Le Person posited that uniformity was a complex issue which needed addressing, but failed to fully recognize the problem articulated by Appellant's invention, and certainly failed to suggest any potential causes and solutions. At best, Le Person stands for the proposition that uniformity in non-active-containing film forming had not been achieved.

The '080 Patent claims clearly recite, for the first time, those steps necessary for maintaining the recited uniformity of active content throughout the film-making process, in order to obtain exceptionally high degrees of uniformity of active content in the resultant film product.

These high degrees of uniformity of active content as recited in the '080 claims exceed even the stringent requirements placed on pharmaceutical products by the FDA.

B. Bogue Declarations (EA-1 & EA-2) Demonstrate Uniformity of Content and Locking-In in 4 Minutes[2]

The inventive methods and processes of the '080 Patent maintain the desired uniformity of content of active by, *inter alia*, controlling polymer matrix viscosity and controlling the drying processes so as to form a visco-elastic film that locks-in the substantially uniform distribution of active(s) during the first about 4 minutes of drying. This ability to lock-in the substantially uniform distribution of active(s) provides the novel and non-obvious processes for manufacturing pharmaceutical and bioactive active containing films, suitable for commercialization and FDA approval. As noted in Bogue Declaration I, EA-1, ¶ 4, one manufactured lot of resulting film can contain 2,000,000 individual dosage units. The claimed processes accomplish this feat while providing the necessary narrow ranges in variation of the amount of active in individual dosage units across all lots and even narrower ranges of uniformity of content in variation of active within a single lot of resulting film. Thus, as claimed, the '080 Patent requires a uniformity of content in amount of active (i) in individual dosage units sampled from a single lot of resulting film of 10% or less (independent claims 1, 161 and 316-318, see Appendix A, Bogue Declaration

[2] Importantly, the Examiner did not give the appropriate weight to Appellant's declarations which dealt, in part, with the non-obvious uniformity obtained by practicing the '080 Patent in manufacturing the extremely successful commercial Suboxone® sublingual unit dose film products. *See Institut Pasteur & Universite Pierre et Marie Curie V. Focarino*, Nos. 2012-1485, 2012-1486, 2012-1487 (Fed. Cir. December 30, 2013) ("*Institut Pasteur* "), *e.g.*, at pp. 19-21.

I, EA-1), and (ii) in individual dosage units sampled from two or more lots of resulting films of +/-10% of the pre-determined desired amount (independent claims 82 and 315, see Appendix B, Bogue Declaration I, EA-1).

None of Chen, Staab, Le Person, Arter and/or Strobush separately or together disclose or inherently possess the novel, non-obvious claimed degrees of uniformity of distribution of active in (1) dosage units from a single lot of resulting film and (2) dosage units from different lots of resulting film; or the novel, non-obvious degree of uniformity of content obtained by within about the first 4 minutes of initiation of drying locking-in migration of the active within said visco-elastic film.

There are many types of tests for film uniformity, weight, size, appearance and content. However, the only type of test which will provide the degree of accuracy in the actual amount of active content in a sample is an analytical chemical test. The '080 Patent claims all require at least a 10% degree of content uniformity of active, and the only way to establish that degree of uniformity of content is by an analytical test of samples. It is Appellant's contention that mere statements of uniformity are insufficient to meet this claim limitation.

The patent law axiom of "that which infringes, if later, would anticipate, if earlier"[3] is pertinent here. Surely, if the Third Party Requester was in the role of a defendant they would surely demand that patent owner prove infringement by analytical chemical testing and not by bald statements that the ingredients were uniformly mixed or that the the alleged infringing product looked "glossy" or that substantially equally sized samples weighed the same.

---

[3] *Peters v. Active Mfg. Co.*, 129 US 530, 537 (1889).

As set forth in Bogue Declaration I, ¶ 4, EA-1 (emphasis supplied).

> 4. Each of the 73 lots of resulting films (Lots 1-73) containing approximately 2,000,000 individual dosage units per lot discussed herein were manufactured: (i) for commercial use and regulatory approval; (ii) in compliance with U.S. Food and Drug Administration ("FDA") standards and regulations, including those relating to analytical chemical testing for variation in active in individual dosage units; and (iii) in accordance with the invention disclosed in the '080 Patent, and as claimed by the '080 Patent both as issued and as amended in the Patentee's Reply to the Office Action; by:
>
> (a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and a pharmaceutical active, said matrix having a substantially uniform distribution of said active;
>
> (b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;
>
> (c) **controlling drying through a process comprising conveying said polymer matrix through a drying apparatus and evaporating at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film** wherein the polymer matrix temperature is 100 °C or less;
>
> (d) forming the resulting pharmaceutical film from said visco-elastic film, wherein said resulting pharmaceutical film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained, such that uniformity of content in the amount of the active in substantially equal sized individual dosage units, sampled from different locations of said resulting pharmaceutical film, varies by no more than 10%; and
>
> (e) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units of said sampled resulting pharmaceutical film, **said tests indicating that**

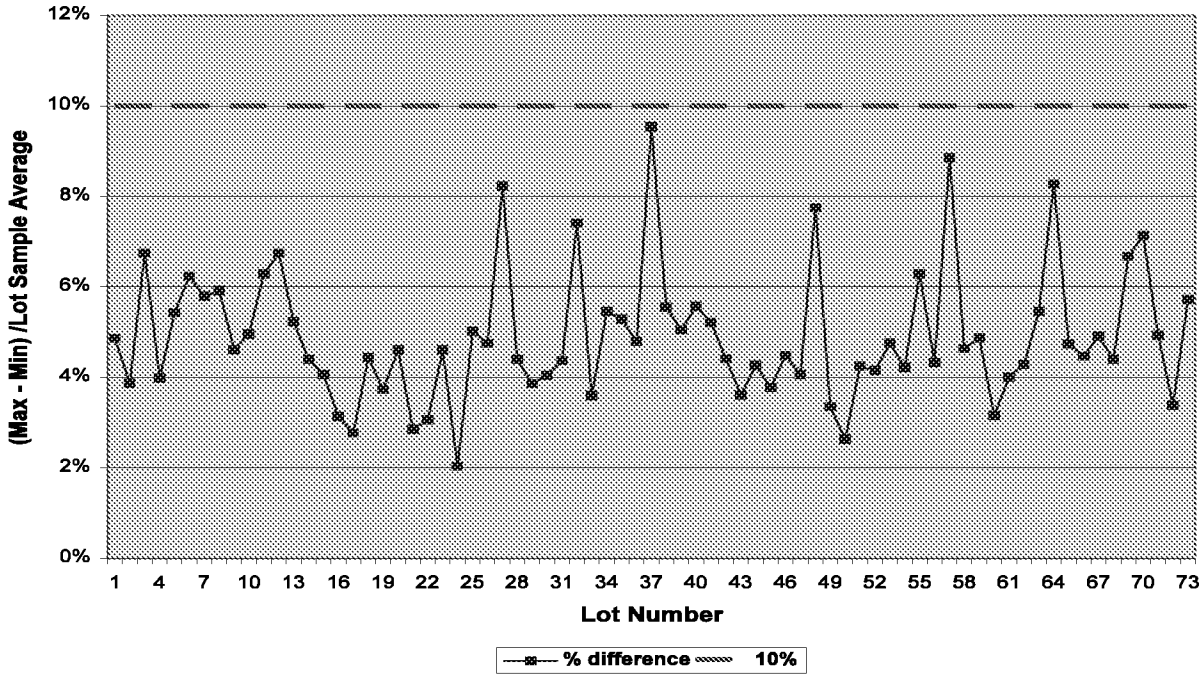
uniformity of content in the amount of the active varies by no more than 10%, [see Appendix A] said resulting pharmaceutical film suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration.

Bogue Declaration I, ¶ 4, EA-1 (emphasis supplied).

1. 10% Degree of Uniformity within a Lot of Resulting Films

The '080 Patent's variation in uniformity of content of the active 10% or less between samples from individual lots of resulting films is achieved by rapidly increasing the viscosity of said polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic films is clearly demonstrated in the Appendices to the Bogue Declaration I, EA-1.

APPENDIX A (Bogue Declaration I, EA-1)



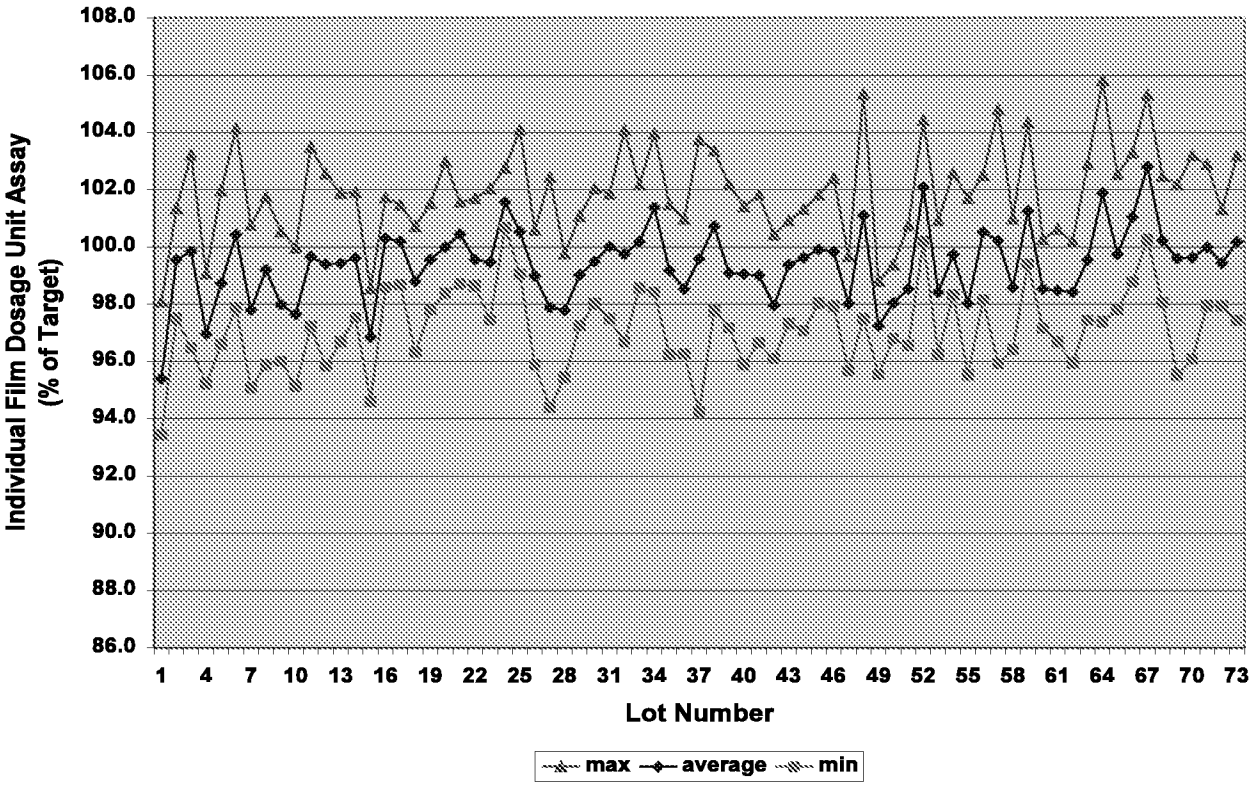
Appendix A from Bogue Declaration I, EA-1 copied above and Bogue Declaration I, ¶ 9, EA-1, show the results of analytical chemical tests unequivocally demonstrating that uniformity of content in the amount of the active in substantially equal sized individual dosage units sampled from the individual lots of resulting film varies by no more than 10%. This degree of

uniformity was maintained for the 73 separately manufactured lots (lots 1-73) of resulting film -- all manufactured by Appellant in accordance with the claimed invention.

2. Within 10% of Desired Amount Degree of Uniformity Across Different Lots of Resulting Films

The '080 Patent's degree of uniformity of content of the active which varies by no more than 10% from a desired amount between samples taken from different lots of resulting films is also achieved by rapidly increasing the viscosity of said polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic films is also clearly demonstrated in the Appendices to the Bogue Declaration I, EA-1.

APPENDIX B (Bogue Declaration I)



In the case of resulting films from different manufacturing lots the substantially uniform distribution of the active is indicated through analytical chemical tests which indicate that uniformity of content in the amount of the active varies by no more than 10% from a desired amount. See Appendix B (EA-1) from Bogue Declaration I copied above and Bogue Declaration I, ¶ 10, where this is shown to be true across all 73 separately manufactured lots of film --- all manufactured by Appellant in accordance with the claimed invention. For each lot the lowest, mean and highest results are shown, and as is demonstrated the when comparing the lowest or any lot with the highest of any lot, the amount of active remains within the +/-10% of desired amount as required by the FDA range in the '080 Patent. The "100.0% of Target" line on Appendix B above is the desired amount.

3. Example M from the '080 Patent - Degree of Uniformity 4%

Example M of the '080 Patent exemplifies the use of analytical chemical testing demonstrating that active-containing films manufactured in accordance with the invention obtain **degrees of uniformity of content in the amount of active approaching 4%**. '080 Patent, col. 33, l. 10 through col. 34, l. 24. The uniformity of content was measured using a spectrophotometer (analytical chemical testing), which measures light absorption and is directly related to the amount of active present.

Example M used percent difference of active concentration
as measured by light absorption found in equally sized samples.

Highest minus lowest = 1.774 – 1.700 = .074

Average of 8 samples = 1.725

0.074 divided by 1.725 = 0.043

4.3%

Appellant obtains even better degrees of uniformity of content with its commercial manufacturing production runs. As the Examiner stated in the RAN, pp. 19-20.

> Patent Owner's Bogue Declaration I is not part of the '080 patent specification, but supports non-adoption of the proposed lack of enablement and clarity rejections. ¶ 4 of Bogue Declaration I states that each of 73 lots containing 2,000,000 individual dosage units per lot were manufactured according to the steps set forth in ¶ 4, which

include forming a resulting pharmaceutical film and performing chemical analytical tests for uniformity of content of the active in substantially equally sized dosage units of the sampled resulting pharmaceutical film. **As seen in Appendices A and C of Bogue Declaration I, a variation as low as 2% was obtained. The variation was calculated by taking the maximum active content of a lot minus the minimum active content of that lot, divided by the average active content of that lot (see ¶ 9).** While the red dye of the '080 Patent's Example M is not a pharmaceutical active or bioactive active, a similar calculation is made in Example M at col. 34, lines 18-20 based on absorbance measurements, which are directly related to concentration of the red dye (see also col. 33, lines 49-51). Further, ¶¶ 10-11 of Bogue Declaration I, citing Appendix B, allege that "the amount of active across different lots of resulting film varies no more than 10% from the desired amount of the active."

RAN, pp. 19-20 (emphasis supplied).

In the RAN, the Examiner refused to use Example M to support non-obviousness based on analytical chemical testing (*see* RAN, at pp. 84, 86, 87, *etc.*). This is clearly wrong. The Examiner distinguished Example M for the sole reason that "this testing is done for content of McCormick red dye, which is not a pharmaceutical active or bioactive active." RAN, p. 84.

On the contrary, as set forth in the '080 Patent, in the section entitled Actives, *no distinction is made between pharmaceutical actives and colorants actives, such as red dye.* "The active components that may be incorporated into the films of the present invention include, without limitation pharmaceutical and cosmetic actives, . . . [and] colorants." '080 Patent, col. 19, ll. 40-48. There is no legal requirement that a patent disclose examples for each embodiment

(active) claimed. The '080 Patent clearly used analytical chemical testing in demonstrating its novel and non-obvious results. Appellant's Example M should have been properly considered.

Importantly, the film manufactured by Appellant and described in Bogue Declaration I (EA-1) is the commercial, FDA approved, Suboxone® sublingual unit dose film product, which Appellant manufactures exclusively for Reckitt Benckiser Pharmaceuticals Inc ("Reckitt Benckiser"). Bogue Declaration II, EA-2, ¶¶ 5-7. As noted earlier, in 2012, Reckitt Benckiser had **nearly one billion dollars in sales** of its Suboxone® sublingual unit dose film products manufactured in accordance with the claims of the '080 Patent.

C. *Leo* - a relevant, analogous situation

In *Leo Pharmaceutical Products, Ltd. v. Rea*, 726 F. 3d 1346 (Fed. Cir. 2013) (*Leo*) the CFAC clarified obviousness determinations in cases similar to the present reexamination. The case strongly supports the patentability of the claims of the '080 Patent.

In *Leo* the invention is directed to pharmaceutical compositions for the topical treatment of psoriasis. The prior art disclosed that psoriasis could be treated through a combination of a Vitamin D analog and a corticosteroid. The *Leo* patent teaches that the simultaneous treatment with vitamin D and corticosteroids heals psoriasis faster and more effectively. It also taught that previous combination formulas were not storage stable because vitamin D and corticosteroids have different pH requirements. In an analogous manner, the '080 Patent teaches that the prior art did not obtain the required level of uniformity of content of active in drug delivery films because of many unrecognized problems in their manufacture.

After being the first to recognize the problem, the patentee in *Leo* discovered that a selection of solvents solved the stability problem by allowing the Vitamin D and corticosteroid to coexist in a single product. Similarly, Appellant was first to (i) recognize the problems associated with obtaining the necessary degree of uniformity, (ii) disclose many factors impacting on maintaining the initial uniformity in the resulting film, and (iii) provide solutions addressing those factors so as to obtain extremely high degrees of uniformity-- including by drying the film so as to rapidly increase the viscosity to lock-in the required uniformity.

1. The '080 Patent's Recognition of the Problem with Uniformity of Content is an Invention in itself

Appellant's recognition that there was a problem with uniformity of content is a situation where the identification of the problem is itself the invention.

> **As an initial matter, an invention can often be the recognition of a problem itself.** *See Cardiac Pacemakers, Inc. v. St. Jude Med., Inc.*, 381 F.3d 1371, 1377 (Fed. Cir. 2004) ("There can of course arise situations wherein identification of the problem is itself the invention."). Here, the prior art either discouraged combining vitamin D analogs and corticosteroids in a single formulation, or attempted the combination without recognizing or solving the storage stability problems associated with the combination.
>
> *Leo*, 726 F.3d at 1353 (emphasis supplied).

> Moreover, because neither Dikstein nor Serup [2 of the three prior art references cited against the *Leo* patent] recognized or disclosed the stability problem, the record shows no reason for one of ordinary skill in the art to attempt to improve upon either Dikstein or Serup using Turi. The ordinary artisan would first have needed to recognize the problem, i.e., that the formulations disclosed in Dikstein and Serup were not storage stable. To discover this problem, the ordinary artisan would have needed to spend several months running storage stability tests.
>
> *Leo*, 726 F.3d at 1354.

Except for Le Person (and Le Person merely raised the question as to whether uniformity was a problem in making non-active containing film (Le Person, *see e.g.*, p. 257)), none of the other prior art references Chen, Staab, Strobush and/or Arter recognized the problems with obtaining the '080 Patent's degrees of uniformity of content of active. Since there was no recognition of the problem, there was no attempt to solve it.

2. The Examiner's use of "optimizing" the Chen, Staab, Strobush, Le Person and/or Arter disclosures, in the case where the problem is not recognized, is like throwing darts at a board and does not demonstrate obviousness

The Examiner relies on "optimizing" the Chen, Staab, Strobush, Le Person and/or Arter disclosures, to establish obviousness. RAN, pp. 39, 59, 60, 96, etc. Such reliance is misplaced, because even if the individual prior art disclosures inadvertently disclosed some of the process parameters that would assist uniformity, the record shows there is no reason for one of ordinary skill in the art to attempt to improve upon the prior art by combining their disclosures. This situation was also directly addressed in *Leo*.

Leo discusses the concept of undue experimentation associated with optimizing the prior art in connection with "unknown problems" and concluded that <u>there could be no optimization, because those skilled in the art would not have known to even try to solve it.</u>

> The problem was not known, the possible approaches to solving the problem were not known or finite, and the solution was not predictable. Therefore, the claimed invention would not have been obvious to try to one of ordinary skill in the art. **Indeed ordinary artisans would not have thought to try at all because they would not have recognized the problem.**
>
> *Leo*, 726 F.3d at 1356-1357 (emphasis supplied).

> **Because the problem was not known, the possible approaches to solving the problem were not known or finite, and the solution was not predictable, it would not have been obvious for a person of ordinary skill to make the claimed invention.**
>
> *Leo*, 726 F.3d at 1357 (emphasis supplied).

In the same way the claims of the '080 Patent are not made obvious by "optimizing" Chen, Staab, Strobush, Le Person and/or Arter .

Finally the *Leo* court affirmed that relying on prior art "optimization" can be comparable to throwing metaphorical darts at a board, and without direction as to where on the board the darts should go such "optimization" may not be used to demonstrate obviousness.

> This court and obviousness law in general recognizes an important distinction between combining known options into "a finite number of identified, predictable solutions," *KSR*, 550 U.S. at 421, and "'merely throwing metaphorical darts at a board' in hopes of arriving at a successful result," *Cyclobenzaprine,* 676 F.3d at 1071 (quoting *In re Kubin*, 561 F.3d at 1359). While the record shows that, as early as 1995, the prior art indicated that both vitamin D analogs and corticosteroids were effective treatments for psoriasis, see J.A. 610, 6237, that same prior art gave no direction as to which of the many possible combination choices were likely to be successful.
>
> *Leo*, 726 F.3d at 1357.

3. The '080 Patent's Commercial Success Supports Non-Obviousness

The Federal Circuit went further in its obviousness discussion to hold that objective indicia of non-obviousness must always be given its proper weight and place and not treated as an afterthought.

> Whether before the Board or a court, this court has emphasized that consideration of the objective indicia is *part of* the whole obviousness analysis, not just an afterthought. *See Cyclobenzaprine*, 676 F.3d at 1075–76 (A fact finder "may not defer examination of the objective considerations until after

> the fact finder makes an obviousness finding." (quoting *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530 (Fed. Cir. 1983))).
>
> *Leo*, 726 F.3d at 1357-1358.

> Objective indicia of nonobviousness play a critical role in the obviousness analysis. They are "not just a cumulative or confirmatory part of the obviousness calculus but constitute[] independent evidence of nonobviousness." *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1365 (Fed. Cir. 2008). This case illustrates a good reason for considering objective indicia as a critical piece of the obviousness analysis: Objective indicia "can be the most probative evidence of nonobviousness in the record, and enables the court to avert the trap of hindsight." *Crocs, Inc. v. Int'l Trade Comm'n*, 598 F.3d 1294, 1310 (Fed. Cir. 2010) (internal quotation marks omitted). Here, the objective indicia of nonobviousness are crucial in avoiding the trap of hindsight when reviewing, what otherwise seems like, a combination of known elements.
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> *Leo*, 726 F.3d at 1358.
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> Leo Pharmaceuticals provided other objective indicia of nonobviousness. For example, the commercial success of Leo Pharmaceutical's Taclonex® ointment is a testament to the improved properties of the '013 patent's claimed invention. Taclonex® is the first FDA-approved drug to combine vitamin D and corticosteroids into a single formulation for topical application. While FDA approval is not determinative of nonobviousness, it can be relevant in evaluating the objective indicia of nonobviousness. *See Knoll Pharm. Co., Inc. v. Teva. Pharm. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004). Here, FDA approval highlights that Leo Pharmaceutical's formulation is truly storage stable, something that the prior art formulations did not achieve. *Leo*, 726 F.3d at 1358.

Appellant's '080 Patent follows a path very similar to that in *Leo*. The inventors recognized the problem, explored the possible causes and solved the problem of how to achieve a high degree of uniformity of content of active. Appellant's/Patentee's commercial success story and the long felt need are equally as compelling as *Leo*'s. The FDA approval of the various Suboxone® sublingual unit dose film products highlights the success of Appellant's films that

prior art formulations did not achieve. Appellant is not aware of any of the prior art references resulting in a commercial product.

Currently, Patentee manufactures (among other products produced in accordance with the '080 Patent) Suboxone® sublingual unit dose film products. These FDA approved unit dose film drug products are manufactured for Reckitt Benckiser Pharmaceuticals Inc. ("Reckitt Benckiser") in accordance with the '080 Patent. *See* Bogue Declaration II, ¶¶ 5-7, EA-2.

As to the extraordinary commercial success of these products, by the end of 2012 Reckitt Benckiser's Suboxone® sublingual unit dose film products **manufactured by Patentee in accordance with the '080 Patent approached sales reached almost one billion dollars in 2012.**[4] Without the ability to make the Suboxone® unit dose film products using processes which achieve the uniformity of content as claimed, these products would not have been approved by the FDA, and no sales would be possible.

In light of the obvious commercial value, for example, of Suboxone® sublingual unit dose film products, if Chen, Staab, Le Person, Arter and/or Strobush made the process of manufacturing such film products inherent or obvious, why didn't anyone come out with the product before Appellant? The answer is simple, it was **not obvious to do so.** Thus, objective secondary indicia firmly establish that the '080 Patent is neither inherent nor made obvious by any of the cited prior art.

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[4] By the end of 2012 Reckitt Benckiser's Suboxone® sublingual unit dose film products had 64% market share of the total Suboxone® drug products market which included Suboxone® tablets. In 2012 , sales in this market totaled $1,491,597,000. *See* Exhibits 5&6 to Applicant's Response to ACP. Thus, assuming a 64% share of the $1,491,597,000 market or $954,622,000, sales of the Reckitt Benckiser's Suboxone® sublingual unit dose film products manufactured by Patentee in accordance with the '080 Patent approached almost one billion dollars in 2012.

D. Claim Rejections based on 35 U.S.C. § 112.

1. The rejection of Claim 318 under § 112(a) or § 112 (pre-AIA), first paragraph (RAN, pp. 27-28) is improper.

Claim 318 is rejected under 35 U.S.C. § 112(a) or 35 U.S.C. § 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement was improper and should be withdrawn. The Examiner stating that: "Claim 318 requires that the controlled drying is through a drying apparatus at a temperature of 'about 60°C', and also requires uniformity of active varies by less than 5%. This combination of elements is found in unconnected passages of the specification and lacks adequate written description." RAN, p.27.

In its Appellant's Response to ACP, p. 75, Appellant attempted to address this concern of the Examiner stating "While Patentee does not agree with the reasoning or the rejections, and expressly disagrees with Third Party Requester's comments relied on by the Examiner, in order to advance prosecution, Patentee has amended paragraph (c) of claim 318 from that submitted in Patentee's ROA by deleting reference to "at a temperature of about 60 °C and". " Unfortunately, the Examiner did not admit any of the post-ACP claims amendments, including this extremely reasonable one. Appellant requests that this amendment be entered and the rejection withdrawn.

2. The rejection of Claim 318 under § 112(b) or § 112 (pre-AIA), second paragraph (RAN, p. 28) is improper.

Claim 318 is rejected under 35 U.S.C. § 112(b) or 35 U.S.C. § 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention was improper and should be withdrawn. The Examiner stated that: "Claim 318 recites

'during said drying said flowable polymer matrix temperature is 100°C or less'. This is at odds with another requirement of claim 318 that the controlled drying is through a drying apparatus at a temperature of about 60°C. It is not clear how the matrix would ever reach a temperature that is 40° hotter than the drying apparatus."

Appellant's response is the same as given above for the § 112 first paragraph rejection above. Appellant requests that this amendment be entered and the rejection withdrawn.

E. Claim Rejections based on 35 U.S.C. §§ 102 & 103.

Patentee hereby incorporates the foregoing discussions into each of the following discussions of the improper rejection of claims below.

1. Rejections under 35 U.S.C. § 103(a) as being unpatentable over Chen (RAN, pp. 29-44) are improper.

Claims 1-11, 13-15, 17-71, 82-90, 92-94, 96-150, 161-172, 174-176, 178-232, 243-253, 256, 258-271, 274, 276-289, 292 and 294-318 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Chen. These rejections are improper and should be withdrawn.

To establish prima facie obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F 2d 981, 180 USPQ 580 (CCPA 1974). In this case, the Examiner has not even considered all of the elements of step (d) of Claim 1 or step (c) of Claims 82, 161 and 315-318, as required by MPEP § 2143.03.

The Examiner asserts that Chen teaches a dosage unit that includes a water-soluble hydrocolloid, mucosal surface-coat-forming film that includes an effective dose of a pharmaceutical or bioactive agent. The Examiner further asserts that the water-soluble polymer, solvent, and actives exemplified in Chen are the same as those exemplified in the `080 patent.

Still further, the Examiner asserts that, in the method of preparation of the film, Chen discloses that a hydrocolloid is dissolved in water under agitated mixing to form a uniform and viscous solution, and the additional ingredients are added under agitated mixing until they are uniformly dispersed or dissolved in a hydrocolloid. The resultant mixture is degassed in a vacuum chamber and then cast on a polyester film. Thus according to the Examiner the resulting film, *i.e.* subsequent to drying, is uniform in the distribution of active and concludes the'080 Patent claims are obvious. *See* RAN, pp. 33-34.

With respect to steps (c) and (d) of Claims 82, 161 and 315-318, and with respect to steps (d) and (e) of Claim 1, the Examiner states that Chen controls drying and evaporates water from the cast matrix in 9 minutes of drying in a hot air circulating oven at 50°C (citing page 17, lines 13-15 and Figure 2). Moreover, "it is the Specialist's position that Chen's mixture before drying is viscoelastic." RAN, p. 34. The Examiner goes on to note that Chen adds the same hydrocolloid as in the `080 Patent and Chen's wet matrix before drying has a viscosity of 500-15000 cps which is within the instantly claimed range. The Examiner concludes, "Chen's films in Examples 1, 2 and 5-8 and the Example in Tables 7 and 8 are inherently viscoelastic before drying. Within 4 minutes of the 9 minutes of drying in Chen's Examples 1, 2, and 5-8 and Example in Tables 7 and 8, a more dry viscoelastic film is obtained." RAN, p. 35. Thus, the Examiner makes an impermissible leap here and improperly concludes that steps (c) and (d) of Claims 82, 161 and 315-318 and steps (d) and (e) of Claim 1 are disclosed or suggested.

However, in making this blind leap, the Examiner ignores key aspects of the elements set forth in step (d) of Claim 1 (and step (c) of Claims 82, 161 and 315-318). Step (d) of Claim 1 does not simply require that a visco-elastic state be formed. Rather, step (d) of Claim 1 also

requires a visco-elastic film be formed "having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said viscoelastic film…." '080 Patent, claim 1. Thus, step (d) requires not only the creation of a **viscoelastic film** within the first 4 minutes of drying, but also rapidly increasing the viscosity upon the initiation of the drying process **such that the active is locked-in** or substantially prevented from migrating within the film. Chen does not teach, suggest or disclose this element. These important aspects of the claims cannot be ignored.

As indicated above, the Examiner cites page 17 and Figure 2 for the disclosure of the drying process in Chen. Figure 2 merely discloses the apparatus utilized in Chen's drying process and contains no disclosure whatsoever regarding "locking-in" or substantially preventing the migration of the active within the viscoelastic film within the first 4 minutes. Figure 2 is devoid of any details and is at best conventional in its set up. The nozzles are directed to cover the maximum surface coverage of the film. The figure is simply too general to teach anything specific. Chen merely discloses on page 17, lines 13-15, "the formulation was then coated on the non-siliconized side of a polyester film at a wet thickness of 10 mil and dried in a hot air circulating oven at 50°C for 9 minutes". Thus, there is no disclosure at all in Chen of the "locking-in" element within the first 4 minutes necessary to achieve the recited the desired degree of uniformity of content of pharmaceutical active as verified by the only methods capable of actually ascertaining the amount of active present– analytical chemical testing.

Similarly, the Examiner cites Examples 1, 2 and 5-8 and the Example in Tables 7 and 8 to argue that the films disclosed therein are inherently viscoelastic before drying. However, even if this assertion were to be true (and there is no evidence in Chen that it is), it fails to satisfy the disclosure of the elements of step (d) of Claim 1. In other words, even if Chen disclosed a **viscoelastic film** before the end of the 9 minute drying period disclosed therein, there is no disclosure of the formation of a viscoelastic film within the first 4 minutes **such that the active is** substantially uniformly distributed throughout and **locked-in to prevent subsequent migration of the active and achieve the desired level of uniformity of content of the active**.

On page 35 of the RAN, the Examiner asserts that, "Alternatively, to the extent that Chen's wet film in Examples 1, 2, and 5-8 and the Example in Tables 7 and 8 before drying are not viscoelastic, then within about 4 minutes in the hot air circulating oven at 50°C, a viscoelastic film is inherently formed." Again, as indicated above, even assuming a viscoelastic state of one form or another is inherently formed, there is no disclosure or teaching in Chen that the active is "locked-in" within the first about 4 minutes by forming a viscoelastic film so as to substantially prevent the active from migrating within the film.

a. Figure 5 of Chen Shows Active Distribution above 10% of Desired Amount.

Importantly, Figure 5 of Chen discloses various points of percentage release of active. This figure shows the amounts of pharmaceutical active released from the drug dosage units as compared with a desired amount of drug released from the drug dosage units over time. Many of the points plotted for each of the actives, i.e., hydromorphone, estradiol, nicotine and oxybutynin; show ranges of pharmaceutical active release from the drug dosage forms well above 110% of the label/desired amount of drug active. That is, there was more than 10% above the desired amount of active in the samples. What happens during Chen's drying process, for example, is undisclosed and she fails to include any discussion or suggestions whatsoever on this point.

The Chen reference teaches a homogeneous mixture of ingredients (i.e., "a coating solution") that is then cast and dried to form a film. Chen, p. 15, ll. 19-30. However, the films of Chen do not achieve the uniformity of pharmaceutical active of +/- 10% of the desired/label amount claimed in the '080 Patent. As shown in Figure 5 of Chen, see below, which shows the amount of pharmaceutical active content of four different actives released from and therefore present in Chen's exemplary films, in six instances the amount of pharmaceutical active released from Chen's unit dose films is greater than 110% of the expected/desired amount of pharmaceutical active for that drug and thus outside the '080 Patent's claim limitations.

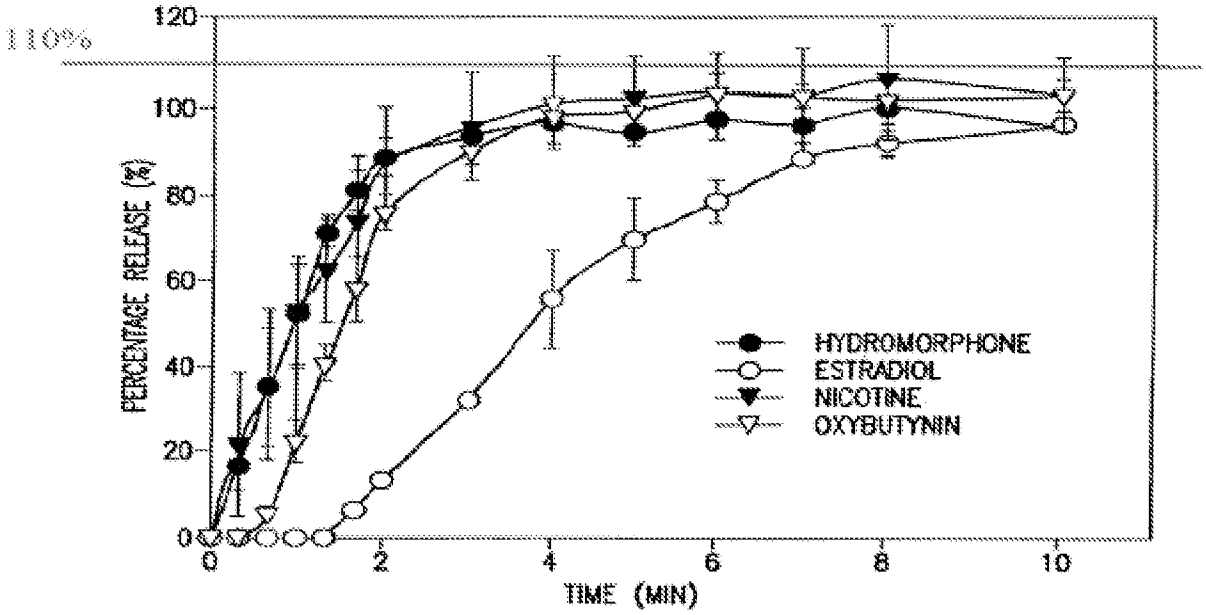

FIG.5

Chen, Figure 5 (110% line added by Patentee for clarity).

This additional amount of pharmaceutical active over the label/desired amount of drug active, clearly demonstrates the non-uniform distribution of the pharmaceutical active in these Chen films. *See* discussion *supra*. By Chen acknowledging in Figure 5 a lack of uniformity content of pharmaceutical active of greater than 10% as demonstrated by Figure 5, Chen admittedly fails to lock-in or substantially prevent migration of the active within the first 4 minutes of drying so as to provided the '080 Patent claimed +/- 10 uniformity of content in amount of pharmaceutical active.

It is well settled that, "to establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a

given set of circumstances it not sufficient." *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999); MPEP § 2112 IV.

b. Chen cannot be realistically "optimized" so as to make the '080 Patent obvious

The Examiner also bases his Chen obviousness rejections on the concept that one ordinarily skilled in the art would have "optimized" Chen.

> A skilled artisan would minimize active content variation by optimizing the available parameters in Chen's process, which are the same as or similar to those in the '337 patent specification. These include, [1]mixing/[2]degassing, [3]casting of the wet film, [4]viscosity of the wet film, [5]drying temperature, [6]drying time, [7]control of air flow in Chen's Fig. 2, [8]selection of appropriate colloid material, [9]etc. RAN, p. 38 (numbers in brackets added).
>
> It further would have been obvious to a skilled artisan at the time the invention was made to have prepared the multiple films such that the active content in each film does not vary by more than 10% from the amount of active the dosages are supposed to contain as required by various world regulatory authorities, in order to minimize dosage variation and commercialize the product. A skilled artisan would obtain the variation of no [more] than 10% from the desired amount by optimizing said available parameters in Chen's process. RAN, p. 39.

Thus, the Examiner is basing his rejections on an argument that a "skilled artisan" could optimize at least nine (9) parameters to get the desired '080 Patent process and could do it without the teachings of the '080 Patent. But as held in *Leo*:

> In addition, the Board found that a person of ordinary skill in the art would have been capable of selecting the correct formulation from available alternatives. J.A. 12. Specifically, the Board found more than eight different classes of additives (e.g., diluents, buffers, thickeners, lubricants). J.A. 12; Serup col. 19, ll. 10–15. The Board also found more than ten different categories of composition forms (e.g., liniments, lotions, applicants, oil-in-water or water-in-oil emulsions such as creams, ointments, pastes, or gels). J.A. 12; Serup col. 19, ll. 5–9. "Based on these

> broad and general disclosures," the Board reasoned that an artisan would have been able to "mak[e] choices about what ingredients to include, and which to exclude" in formulating a composition with a vitamin D analog and steroid. J.A. 12. **To the contrary, the breadth of these choices and the numerous combinations indicate that these disclosures would not have rendered the claimed invention obvious to try.** *See Rolls-Royce PLC v. United Techs. Corp.*, 603 F.3d 1325, 1339 (Fed. Cir. 2010)(claimed invention was not obvious to try because the prior art disclosed a "broad selection of choices for further investigation").

Leo, 726 F.3d at 1357 (emphasis supplied).

Just consider a few of the above parameters with the range of values provided in Chen, *e.g.*: casting of a wet film with a solid content between 5 and 50% and a viscosity between 500 and 15000 cps (both at Chen, p. 15), a thickness between 1 and 20 mil (Chen, p. 13), dried under aeration at a temperature between 40 and 100°C (Chen, p. 15); and the hydrocolloid includes a polymer selected from the group consisting of a natural, semi-natural and synthetic biopolymer being exemplified by a polysaccharide and a polypeptide (Chen, p. 4).

Given the above, the solid content even if taken in 5% increments gives rise to 9 variations, the thickness even if taken in 1 mil increments give rise to 20 variations, the viscosity even if taken in 500 cps increments gives rise to 29 variations, the temperature even if taken in 5°C increments gives rise to 12 variations, and the polymer even if only one from each of the three groups gives rise to 3 variations. With so many variations and potential combinations, the number of experiments potentially necessary to "minimize active content variation by optimizing the available parameters in Chen's process" is enormous, and by their sheer numbers demonstrate that such optimization would require undue experimentation. It is clear that even if, *arguendo*, Chen or the other prior art recognized the problems and attempted to solve them (which they did

not), it would require a herculean effort, without Patentee's disclosure, to design and perform the experiments. Thus, the claimed '080 Patent is not obvious.

Thus, these rejections are improper and should be withdrawn.

2. Rejections under 35 U.S.C. §103(a) as being obvious over Chen and Staab (RAN, pp. 45-48) are improper.

Claims 2, 3, 32, 55, 72-81, 111, 134, 151-160, 193, 216 and 233-242 stand rejected under 35 U.S.C. §103(a) as being unpatentable over the combined teaching of Chen and Staab. These rejections are improper and should be withdrawn. Appellant incorporates all its comments to Chen, above and Stabb, below. All the above claims are allowable for all the reasons provided in the sections dealing with Chen, above, and Staab, below and even combined Chen and Staab do not render obvious the pending claims of this rejection.

Thus, these rejections are improper and should be withdrawn

3. Rejections under 35 U.S.C. §103(a) as being obvious over Chen and Arter (RAN, pp. 48-50).

Claims 317 and 318 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over the combined teachings of Chen and Arter. These rejections are improper and should be withdrawn. The Examiner relies on Chen for the reasons set forth in the rejections directly addressed above. For the same reasons given by Appellant regarding Chen above, Chen and Arter do not render obvious the pending claims of this rejection.

The Examiner has ignored key aspects of the step (c) in applying Chen to claims 317 and 318, namely, "to form a visco-elastic film, having said active substantially uniformly distributed

throughout, **within about the first 4 minutes by rapidly increasing the viscosity** of said flowable polymer matrix **upon initiation of drying to maintain** said substantially uniform distribution of said active **by locking-in or substantially preventing migration of said active** within said visco-elastic film, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units . . . **varies by no more than 10%** . . . ". Emphasis supplied.

As previously noted, the Examiner has provided no evidence that Chen locks-in the uniformity within the about the first 4 minutes by increasing the visocosity upon initiation of drying in order to achieve the 10% uniformity of content as measured by analytical chemical testing (assaying) the substantially equal sized dosage units. He merely concludes this because he assumes that Chen has achieved the 10% uniformity. Chen provides no information as to what happens to his wet mixture at any point during the 9 minutes he is drying. *See* Chen, Examples 1-3. From the Chen disclosure there is no way of determining whether locking-in of the uniformity of content can or has been attained within the first 4 minutes of drying such that when unit doses are assayed (analytical chemical testing) they do not vary by more than +/- 10% in active content.

The claim elements missing in Chen are not provided by Arter. Arter is cited for its disclosure of foraminous shields which form a "quiescent region" between the shields and the coated surface. Arter is a customized process and apparatus useful for making photographic coatings. Such a process and apparatus is not at all transferrable to drying methods for

pharmaceutical films, and particularly pharmaceutical films which are aqueous-based and self-supporting.

There are several important distinctions between the Arter process and the present claims. **First, Arter states that his objective is to prevent "mottle" or non-uniform density of surface features ("blotches")**. Arter, col. 2, l. 22. Mottle is thus, an entirely different problem and characteristic from uniformity of active content expressed in the claims. Moreover, Arter states that "coating mottle" is distinct from "drying mottle", the former apparently being the appearance in the wet stage and the later being the appearance formed in drying the coating. Arter, col. 4, l. 44 - col. 5, l. 1.

Second, a coating by definition requires a substrate to which it is attached. The films of the present invention are not coatings but films from which pharmaceutical active-containing unit dosages are made, and such unit dosages must be self-supporting.

Again, analytical chemical testing is required for demonstrating the level of content uniformity of pharmaceutical active in unit dosage films by measuring the actual amount of active present. Thus, absent any determinations in Arter based on analytical chemical testing, as required, *e.g.*, by Ex. 7 and Ex 8, see discussion above, Arter does not and cannot inherently disclose or make obvious Patentee's resulting film having the claimed levels of uniformity of content.

All the above claims are allowable for all the reasons provided herein and in connection with the Chen discussions above. Chen and Arter do not render obvious the pending claims of this rejection.

Thus, these rejections are improper and should be withdrawn

4. Rejections under 35 U.S.C. §103(a) as being obvious over Chen and Strobush (RAN, pp. 50-52) are improper.

Claims 317 and 318 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over the combined teachings of Chen and Strobush. These rejections are improper and should be withdrawn.

The Examiner relies on Chen for the reasons set forth in the rejections above. For the same reasons given by Appellant regarding Chen above, Chen and Strobush do not render obvious the pending claims of this rejection. The coatings of Strobush are photographic coatings, and not the films of the '080 Patent and thus the disclosure is inapplicable.

The Examiner cites Strobush to "strengthen the teachings", but actually discloses another deficiency of Chen, that is, its failure to disclose let alone teach "using air currents which have forces below a yield value of the polymer matrix during drying". RAN, p. 50. Strobush does not meet this deficiency and more importantly does not, either separately or when taken together with Chen disclose or make obvious same. At best, Strobush teaches that evaporation of the solvent must be performed very slowly (low $h\Delta T$), in multiple stages, so that the silver atoms lined up on the coating's surface are not disturbed so as to not cause a mottled appearance to the photographic coating. Strobush states "increasing the initial rate of heat transfer ($h\Delta T$), increases the severity of mottle." Strobush, col. 20, ll. 39-40. It is the $h\Delta T$ rate (heat transfer rate) which determines whether mottle will occur. Strobush, col. 20, ll. 34-37. Strobush suggests nothing about controlling the force of the air so as not to exceed a yield value of the polymer matrix during drying.

In fact, Strobush's teachings are completely contrary to Patentee's claims. The independent claims of the '080 Patent all require high heat transfer rates (contrary to Strobush), as reflected in the language " rapidly increasing the viscosity . . . upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in . . . said active within said visco-elastic film".

Again, analytical chemical testing is required for demonstrating the level of content uniformity of pharmaceutical active in unit dosage films by measuring the actual amount of active present. Thus absent any determinations in Strobush based on analytical chemical testing, as required, *e.g.*, by Ex. 7 and Ex 8, see discussion above, Strobush does not and cannot inherently disclose or make obvious Patentee's resulting film having the claimed levels of uniformity of content. Strobush does not and cannot inherently form or make obvious a viscoelastic film within about the first 4 minutes, which locks-in the uniformity of content of active within the recited levels of uniformity of content. Finally, coatings such as Strobush's with the disclosed wet thicknesses, are not self-supporting, while Appellant's dosage unit films must be self-supporting. Strobush adds nothing to cure the deficiencies in the teachings of Chen which would render the '080 claims obvious.

All the above claims are allowable for all the reasons provided herein and in connection with the Chen discussions above.

Thus, these rejections are improper and should be withdrawn.

5. Rejections under 35 U.S.C. §102(b) as anticipated by or, in the alternative, under 35 U.S.C. §103(a) as being obvious over Staab (RAN, pp. 52-62) are improper, especially where Staab's films demonstrate a 100% variance in amount of active from the expected amount.

Claims 1-5, 10, 13-15, 21, 24, 25, 32, 44-46, 54, 55, 59, 63-70, 72-75, 78-84, 89, 92-94,100,103,104,111,123-125,133,134,138, 142-149, 151-154, 157-166,171, 174-176, 182, 185, 186, 193, 205-207, 215, 216, 220, 224-231, 233-236, 239-242, 249-252, 258-260, 267-270, 276-278, 285-288 and 294-318 stand rejected under 35 U.S.C. § 102(b) as anticipated by or, in the alternative under 35 U.S.C. § 103(a) as being obvious over Staab. These rejections are improper and should be withdrawn. Those arguments from above are incorporated herein.

The Examiner asserts that Staab teaches the preparation of a film for local administration of an active agent in an internal body area that includes a polymer, active and solvent. With respect to steps (d) and (e) in Claim 1 and with respect to steps (c) and (d) in Claims 81, 161 and 315-318, the Examiner asserts that Staab exemplifies drying the film in a temperature regulated oven for approximately 20 minutes at 160° or for 20-40 minutes when using a continuously moving belt that enters a dryer. The Examiner presumes that "since Staab's film in the example at cols. 11-12 is inherently viscoelastic before drying, then within about the first 4 minutes of drying, a viscoelastic film having less water than before drying is formed." RAN, p. 56.

Once again, the Examiner has failed to consider the '080 Patent claim element that the viscoelastic film, having the active substantially uniformly distributed throughout, is locked-in or substantially prevented from migrating within the viscoelastic film by rapidly increasing viscosity of the flowable polymer matrix upon initiation of drying within the first 4 minutes. Staab contains no disclosure whatsoever that such locking-in or prevention of migration of the

active ingredient is occurring within the viscoelastic film within the first 4 minutes. Thus, there is no evidence or suggestion at all in Staab or in Chen of this claim requirement.

The Examiner alternatively asserts that to the extent that Staab's blended mixture before drying is not viscoelastic, then within about the first 4 minutes of the drying, a viscoelastic film is inherently formed. It is not understood on what basis the Examiner reaches this conclusion, because Staab is not only silent on this issue, it fails to suggest it. But even if, *arguendo*, Staab had disclosed or suggested it, this argument also fails to consider the "locking-in" of the active in order to maintain the substantially uniformly distribution of the active required by the '080 Patent. In addition, similar to Chen, there is no indication that the parameters set forth in columns 11 and 12 of Staab would necessarily lock-in or substantially prevent migration of the active within the viscoelastic film within the first 4 minutes by rapidly increasing the viscosity of the flowable polymer matrix upon initiation of drying to ensure the required uniformity. To the contrary, the disclosure in Staab of an extended drying time of 20 minutes suggests that the viscosity of the matrix is not rapidly increased such that the uniform distribution of the active is locked-in and prevented from migrating within the film, as set forth in the pending claims.

a. Staab's examples show a 100% difference from the desired amount

The Examiner falls into the same trap as the prior art, presuming that if one forms a uniform mixture of active with other film-forming ingredients, further processing this mixture necessarily preserves such uniformity of active content in the resultant film product. Read properly, Staab not only dispels this erroneous presumption, but solidifies Appellant's contention

that no prior art, alone or in combination, teaches or suggest the related claims. Staab states in an apparently prophetic example (Staab, col. 11, l. 22 to col. 12, l. 3) that when he incorporated 10% of a 50% by weight benzalkonium chloride aqueous solution into a film-forming mixture, he obtained, after drying, a film product having 19 mg benzalkonium chloride ("active") in a 190 mg film. According to the Examiner, as all the samples had 19 mg of active, this demonstrated a 0% variation in uniformity of content in the active, and the Examiner relied on this 0% in his rejections. **0% is wrong! The Examiner erred drastically in his calculations.**

Staab's resulting film demonstrates **a variation in the uniformity of active content of 100% from the desired amount**. Staab was careful in providing the percent by weight of active in the base materials in his example, and expected the same percent by weight in his resulting films. Staab added 10% by weight of benzalkonium chloride (50% aqueous) as a component of the base materials. Thus, the 10% by weight of the original benzalkonium chloride (50% aqueous) contributed 5% by weight of water to the base materials and 5% by weight of benzalkonium chloride to the base materials. Thus, Staab expected (*i.e.,* desired) that his resulting films contain 5% by weight of active for any film sample taken.

However, when he weighed out 190 mg samples of his films, instead of the expected 9.5 mg (5% of 190 mg) of active, he found that there was twice as much active as desired, *i.e.*, 19 mg of active. Staab's samples fail to even remotely approach the degree of uniformity required by the '080 Patent claims. See Chart I below for calculations.

Chart I - Staab's 100% Variation in Uniformity of Distribution of Active

Staab's Film Components	% Weight	Staab's Film Samples (5% by weight is desired amount)
10% benzalkonium chloride (50% aqueous) ("BC active")	5% BC active 5% water	190 mg film contains 19 mg BC active
HPMC & Glycerine	90%	(This is twice the desired amount- 5% of 190 mg = 9.5 mg)
1.	Staab starts with a film mixture having 10% by weight of benzalkonium chloride (50% aqueous solution).	
2.	Staab's starting film mixture therefore has 5% by weight of benzalkonium chloride active.[5]	
3.	Staab expected the dry resulting film would maintain the 5% by weight of benzalkonium chloride active.	
4.	Staab cut out 190 mg samples from his resulting film.	
5.	Staab expected each 190 mg sample to contain 5% by weight of benzalkonium chloride active.	
6.	Staab's expected or desired amount of active in theses samples was 190 mg x 5% = 9.5 mg of benzalkonium chloride active (**9.5 mg is the desired amount of active**) .	
7.	Instead Staab's samples each contained 19 mg of benzalkonium chloride active **(19 mg is the actual amount of active**).	

[5] This analysis is supported by the Examiner. "The ingredients blended to prepare the film are 52.5% HPMC, 37.5% glycerin and 10.0% of a 50% aqueous solution of the benzalkonium chloride (see [Staab] col. 11, lines 30-34). Since the water content before drying is 5% (i.e., half of the 10% of the 50% aqueous solution of benzalkonium chloride)...". RAN, p. 55. This requires that the benzalkonium chloride content before drying is also 5% (i.e., half of the 10% of the 50% aqueous solution of benzalkonium chloride).

8. **The variation in uniformity of distribution of benzalkonium chloride active in Staab's resulting films was 100%.**

$$\frac{\text{19.0 mg (actual amount of active) - 9.5 mg (desired amount of active)}}{\text{9.5 mg (desired amount of active)}}$$

$$= (9.5)/(9.5)$$

$$= \mathbf{100\%}$$

Staab, instead of having a variation from the desired amount of active of 0%, had a variation from the desired amount of active of 100%. [((19.0 (desire amount) - 9.5 (amount of active))/(9.5 desired amount) = (9.5)/(9.5) = 100%]. Staab expected his 190 mg samples to contain 9.5 mg of active, instead the dry film samples contained twice as much active, *i.e.*, 19 mg than desired. Certainly, dosage forms containing twice (2x) as much pharmaceutical active than desired, would neither meet the FDA requirements nor the claim limitations of the '080 Patent with respect to uniformity of content of active per unit dose.

b. Staab cannot be "optimized" so as to make the '080 Patent obvious

The Examiner bases his Staab obviousness rejections on the expectation that one ordinarily skilled in the art would have "optimized" Staab.

> A skilled artisan would minimize active content variation by optimizing the available parameters in Staab's process, which are the same as or similar to those in the '080 patent. These include the polymer material[1], drying temperature[2], hot air application[2], drying time[3], viscosity[4], etc.[5] . . . .
>
> RAN, pp. 59, 96.

> A skilled artisan would obtain the variation of no [more] than 10% from the desired amount by optimizing said available parameters in Staab's process.
>
> RAN, p. 60.

Again, as was the case with Chen, *inter alia*, with so many variations and potential combinations, the number of experiments potentially necessary to "minimize active content variation by optimizing the available parameters in Staab's process" is enormous, and by their sheer numbers demonstrate that such optimization would require undue experimentation. See *Leo*, 726 F.3d at 1356.

Finally, absent statements based on analytical chemical testing, as required by the claims to determine the actual uniformity of content in the amount of active present in the film, Staab does not and cannot inherently disclose or make obvious Patentee's resulting film having the claimed levels of uniformity of content, with respect to the amount of the active present in substantially equally sized individual dosage units sampled from different locations of the resulting film and/or of different resulting films. Again, Staab does not and cannot inherently form or make obvious a viscoelastic film within about the first 4 minutes, which locks-in the uniformity of content within the recited levels of uniformity of content. All the above claims are allowable for all the reasons provided herein. Stabb neither anticipates nor renders obvious the pending claims of this rejection.

Thus, these rejections are improper and should be withdrawn

6. Rejections under 35 U.S.C. §103(a) as being obvious over Staab (RAN, pp. 62-63) are improper.

Claims 8, 9, 76, 77, 87, 88, 155, 156, 169, 170, 237 and 238 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Staab. These rejections are improper and should be withdrawn.

The Examiner relies on Staab for the reasons set forth in the discussion above. For the same reasons given by Appellant, Staab does not render obvious the pending claims of this rejection. All the above claims are allowable for all the reasons provided herein. Stabb does not render obvious the pending claims of this rejection.

Thus, these rejections are improper and should be withdrawn.

7. Rejections under 35 U.S.C. §103(a) as being obvious over Le Person (RAN, pp. 63-71) are improper.

Claims 82, 89, 90, 92, 161, 171, 172, 174, 274, 292, 304-311 and 313-318 under 35 U.S.C. § 103(a) as being unpatentable over Le Person. These rejections are improper and should be withdrawn.

a. Le Person cannot be "optimized" so as to make the '080 Patent obvious

The Examiner bases his Le Person obviousness rejections on the concept that one ordinarily skilled in the art would have "optimized" Le Person.

> A skilled artisan would minimize active content variation by optimizing the available parameters in Le Person's process, which are the same as or similar to those in the '080 patent. These include drying temperature[1], drying time[2], air velocity[3], humidity[4] etc [5] (see pp. 258-259 of Le Person). RAN, p. 69.

> A skilled artisan would obtain the variation of no [more] than 10% from the desired amount by optimizing said available parameters in Le Person's process. RAN, p. 70.

Hence, with so many variations and potential combinations, the number of experiments potentially necessary to "minimize active content variation by optimizing the available parameters in Le Person's process" is enormous, and by their sheer numbers demonstrate that such optimization would require undue experimentation. *See Leo*, 726 F.3d at 1356, and discussion above.

In fact Le Person comments on the importance of drying to form the final thin film product and the necessity and **difficulties** involved in mastering the process variables and microscopic aspects of quality control, without disclosing how to solve them.

> In the pharmaceutical industry some films are used in patches for transdermal drug delivery. Drying is the essential unit operation necessary to form the final product. In all cases, mastering of process variable and microscopic aspects of the product quality entails chemical and process engineering and transport phenomena as basic sciences.
>
> Le Person, page 257, first column.

Le Person went on to say:

> **In the end, one must be sure that the selected process and its conditions is able to ensure** the right product quality; a limited remanence of the process solvent (generally a mixture of volatile solvents) and a given quality product, i.e. physical and chemical homogeneity and **an appropriate distribution of active substance.**
>
> The tools to design the correct process are pilot plant experiments, bench scale experiments and modelisation of transfers. In this paper, small scale experiments were opted for and an experimental approach of internal transfers. Evidently, the diffusional approach of complex systems containing two immiscible solvents, a shrinking polymeric macromolecule network and an active substance, **cannot be tracked from the basic**

> **text-book equations**. What is modelisable is already intuitively and/or experimentally known. **It would take a lot of basic investigation on simpler systems to make a substantial progress on the only problem of cross diffusivities**.
>
> Le Person, page 257, first column-second columns (emphasis supplied).

There is no **teaching in Le Person,** as to **how to make films** with the required degree of uniformity of content in the amount of active. Finally, Le Person went on to support Patentee's position that the only way to actually determine uniformity of content in the amount of active is through assaying (analytical chemical testing). **"Adding an integral chemical analysis of the film, one is then able to quantify the absolute distribution for films produced under variable conditions."** Le Person, p. 257, second column.

Thus, these rejections are improper and should be withdrawn

IX. CONCLUSION

For the reasons set forth herein, all rejections should be withdrawn and a reexamination certificate issued.

If a reexamination certificate is not issued, Appellant requests that prosecution in this reexamination should be reopened and/or remanded, with directions that its reply to the ACP, including remarks and amendment should be entered therein, for consideration and the Examiner to respond with a non-final office action.

Appellant authorizes the Commissioner to charge all fees associated therewith, including, without limitation, the $2,000.00 fee for filing this brief in support of an appeal in an *inter partes* reexamination proceeding, pursuant to 37 C.F.R. § 41.20(b)(2)(i), to Deposit Account No. 08-2461.

Dated: March 10, 2014

Respectfully submitted,

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CLAIMS APPENDIX - ALL INDEPENDENT CLAIMS

1. (Twice Amended) A process for manufacturing a resulting film suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said [making a]film having a substantially uniform distribution of components comprising a substantially uniform distribution of said active in individual dosage units of said resulting film, comprising the steps of:

(a) forming a masterbatch pre-mix comprising a solvent and a polymer selected from the group consisting of water-soluble polymers, water-swellable polymers and combinations thereof;

(b) adding [an]said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, to a pre-determined amount of said masterbatch pre-mix to form a flowable polymer matrix, said matrix having a substantially uniform distribution of said active;

(c) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(d) controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus and evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first [10]4 minutes [or fewer]by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, wherein during said drying said flowable polymer matrix temperature is 100 °C or less; [and]

(e) forming [a]said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained; and

(f) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units sampled from different locations of said resulting film, said tests indicating that uniformity of content in the amount of the active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration.

82. (Twice Amended) A process for manufacturing resulting films suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said [making a]films having a substantially uniform distribution of components comprising a substantially uniform distribution of a desired amount of said active in individual dosage units of said resulting films, comprising the steps of:

(a) forming a flowable polymer matrix comprising a polymer selected from the group consisting of a water-soluble polymer, a water swellable polymer and combinations thereof, a solvent and [an]said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives[, drugs, medicaments] and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus and evaporating at least a portion of said solvent from said flowable

polymer matrix to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first [10]4 minutes [or fewer]by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, wherein during said drying said flowable polymer matrix temperature is 100 °C or less, and wherein uniformity of content of said active in substantially equal sized individual dosage units of said visco-elastic film is such that the amount of the active varies by no more than 10%; [and]

(d) forming [a]said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained;

(e) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units sampled from different locations of said resulting film, said tests indicating that uniformity of content in the amount of said active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration; and

(f) repeating steps (a) through (e) to form additional resulting films, such that uniformity of content in the amount of said active in said resulting film and said additional resulting films varies no more than 10% from the desired amount of the active as indicated by said analytical chemical tests.

161. (Twice Amended) A process for manufacturing a resulting film suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said[making a] film capable of being

administered to a body surface and having a substantially uniform distribution of components comprising a substantially uniform distribution of said active in individual dosage units of said resulting film, comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and [an]said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus and evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first [10]4 minutes [or fewer]by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, wherein during said drying said flowable polymer matrix temperature is 100 °C or less, and wherein uniformity of content of said active in substantially equal sized individual dosage units of said visco-elastic film is such that the amount of the active varies by no more than 10%;

(d) forming [a]said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained; [and]

(e) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units sampled from different locations of said resulting film, said

tests indicating that uniformity of content in the amount of said active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration, and

[(e)](f) administering said resulting film to a body surface.

315. (New) A process for manufacturing resulting films suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said films having a substantially uniform distribution of components comprising a substantially uniform distribution of a desired amount of said active in individual dosage units of said resulting films, comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said polymer matrix through a drying apparatus and evaporating at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, wherein during said drying said flowable polymer matrix temperature is 100 °C or less;

(d) forming said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of said active by said locking-in or substantially preventing migration of said active is maintained, such that uniformity of content in the amount of the active in substantially equal sized individual dosage units, sampled from different locations of said resulting film, varies by no more than 10%;

(e) performing analytical chemical tests for uniformity of content of said active in said substantially equal sized individual dosage units of said sampled resulting film, said tests indicating that uniformity of content in the amount of the active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration; and

(f) repeating steps (a) through (e) to form additional resulting films, such that uniformity of content in the amount of said active in said resulting film and said additional resulting films varies no more than 10% from the desired amount of said active as indicated by said analytical chemical tests.

316. (New) A process for manufacturing a resulting film suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said film having a substantially uniform distribution of components comprising a substantially uniform distribution of said active in individual dosage units of said resulting film, comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said polymer matrix through a drying apparatus and evaporating at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, wherein during said drying said flowable polymer matrix temperature is 100 °C or less;

(d) forming said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said resulting film, varies by no more than 10%; and

(e) performing analytical chemical tests for uniformity of content of said active in said substantially equal sized individual dosage units of said sampled resulting film, said tests indicating that uniformity of content in the amount of said active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration.

317. (New) A process for manufacturing a resulting film suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said film having a substantially uniform distribution of components

comprising a substantially uniform distribution of said active in individual dosage units of said resulting film, comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus using air currents, which have forces below a yield value of said flowable polymer matrix during drying, to evaporate at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said visco-elastic film, varies by no more than 10%, and wherein during said drying said flowable polymer matrix temperature is 100 °C or less;

(d) forming said resulting film from said visco-elastic film by further controlling drying by continuing evaporation to a water content of said resulting film of 10% or less and wherein said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said resulting film, varies by no more than 10%; and

(e) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units of said sampled resulting film, said tests indicating that uniformity of content in the amount of said active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration.

318. (New) A process for manufacturing a resulting film suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said film having a substantially uniform distribution of components comprising a substantially uniform distribution of said active in individual dosage units of said resulting film, comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus at a temperature of about 60 °C and using air currents, which have forces below a yield value of the polymer matrix during drying, to evaporate at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said visco-elastic film, varies

by less than 5%, and wherein during said drying said flowable polymer matrix temperature is 100 °C or less;

(d) forming said resulting film from said visco-elastic film by further controlling by continuing evaporation to a water content of said resulting film of 10% or less and wherein said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said resulting film, varies by less than 5%; and

(e) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units of said sampled resulting film, said tests indicating that uniformity of content in the amount of said active varies by less than 5% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration.

CLAIMS APPENDIX - ALL CLAIMS

1. (Twice Amended) A process for manufacturing a resulting film suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said [making a]film having a substantially uniform distribution of components comprising a substantially uniform distribution of said active in individual dosage units of said resulting film, comprising the steps of:

(a) forming a masterbatch pre-mix comprising a solvent and a polymer selected from the group consisting of water-soluble polymers, water-swellable polymers and combinations thereof;

(b) adding [an]said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, to a pre-determined amount of said masterbatch pre-mix to form a flowable polymer matrix, said matrix having a substantially uniform distribution of said active;

(c) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(d) controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus and evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first [10]4 minutes [or fewer]by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, wherein during said drying said flowable polymer matrix temperature is 100 °C or less; [and]

(e) forming [a]said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained; and

(f) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units sampled from different locations of said resulting film, said tests indicating that uniformity of content in the amount of the active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration.

2. (Original) The process of claim 1, wherein said pre-determined amount of master batch pre-mix is controllably fed via a first metering pump and a control valve to a first mixer and a second mixer.

3. (Original) The process of claim 2, wherein said first mixer and said second mixer are arranged in parallel, series or a combination thereof.

4. (Original) The process of claim 1, wherein said water-soluble polymer comprises polyethylene oxide.

5. (Original) The process of claim 1, wherein said polymer comprises a polymer selected from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.

6. (Original) The process of claim 5, wherein said polymer further comprises a water insoluble polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone and combinations thereof.

7. (Original) The process of claim 5, wherein said polymer further comprises a polymer selected from the group consisting of methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(ά-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof.

8. (Original) The process of claim 5, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

9. (Original) The process of claim 5, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(d-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch,

gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

10. (Original) The process of claim 1, wherein said solvent is selected from the group consisting of water, polar organic solvent, and combinations thereof.

11. (Original) The process of claim 10, wherein said solvent is selected from the group consisting of ethanol, isopropanol, acetone, and combinations thereof.

12. (Canceled)

13. (Amended) The process of claim 1, wherein said active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators,

psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, [anti-tumor drugs,]anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, [anti-convulsants,]neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, [anti-asthmatics,]cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

14. (Amended) The process of claim 1, wherein said active is selected from the group consisting of [cosmetic actives,]antigens, allergens, spores, microorganisms, seeds, [mouthwash components, flavors, fragrances,]enzymes, [preservatives, sweetening agents, colorants, spices,]vitamins and combinations thereof.

15. (Original) The process of claim 1, wherein said active is a bioactive active.

16. (Canceled)

17. (Original) The process of claim 1, wherein said active is an opiate or opiate-derivative.

18. (Original) The process of claim 1, wherein said active is an anti-emetic.

19. (Original) The process of claim 1, wherein said active is an amino acid preparation.

20. (Original) The process of claim 1, wherein said active is selected from the group consisting of sildenafils, tadalafils, vardenafils, apomorphines, yohimbine hydrochlorides, alprostadils and combinations thereof.

21. (Original) The process of claim 1, wherein said active is a protein.

22. (Original) The process of claim 1, wherein said active is insulin.

23. (Original) The process of claim 1, wherein said active is an anti-diabetic.

24. (Original) The process of claim 1, wherein said active is an antihistamine.

25. (Original) The process of claim 1, wherein said active is an anti-tussive.

26. (Original) The process of claim 1, wherein said active is a non-steroidal anti-inflammatory.

27. (Original) The process of claim 1, wherein said active is an anti-asthmatics.

28. (Amended) The process of claim 1, wherein said active is an anti-diarrhea preparation.

29. (Original) The process of claim 1, wherein said active is an alkaloid.

30. (Original) The process of claim 1, wherein said active is an anti-psychotic.

31. (Original) The process of claim 1, wherein said active is an anti-spasmodic.

32. (Original) The process of claim 1, wherein said active is a biological response modifier.

33. (Original) The process of claim 1, wherein said active is an anti-obesity drug.

34. (Original) The process of claim 1, wherein said active is an H_2-antagonist.

35. (Original) The process of claim 34, wherein said H_2-antagonist is selected from the group consisting of cimetidine, ranitidine hydrochloride, famotidine, nizatidine, ebrotidine, mifentidine, roxatidine, pisatidine, aceroxatidine and combinations thereof.

36. (Original) The process of claim 1, wherein said active is a smoking cessation aid.

37. (Original) The process of claim 1, wherein said active is an anti-parkinsonian agent.

38. (Original) The process of claim 1, wherein said active is an anti-depressant.

39. (Original) The process of claim 1, wherein said active is an anti-migraine.

40. (Original) The process of claim 1, wherein said active is an anti-Alzheimer's agents.

41. (Original) The process of claim 1, wherein said active is a dopamine receptor agonist.

42. (Original) The process of claim 1, wherein said active is a cerebral dilator.

43. (Original) The process of claim 1, wherein said active is a psychotherapeutic agent.

44. (Original) The process of claim 1, wherein said active is an antibiotic.

45. (Original) The process of claim 1, wherein said active is an anesthetic.

46. (Original) The process of claim 1, wherein said active is a contraceptive.

47. (Original) The process of claim 1, wherein said active is an anti-thrombotic drug.

48. (Original) The process of claim 1, wherein said active is diphenhydramine.

49. (Original) The process of claim 1, wherein said active is nabilone.

50. (Original) The process of claim 1, wherein said active is albuterol sulfate.

51. (Original) The process of claim 1, wherein said active is an anti-tumor drug.

52. (Original) The process of claim 1, wherein said active is a glycoprotein.

53. (Original) The process of claim 1, wherein said active is an analgesic.

54. (Original) The process of claim 1, wherein said active is a hormone.

55. (Original) The process of claim 1, wherein said active is a decongestant.

56. (Original) The process of claim 1, wherein said active is a loratadine.

57. (Original) The process of claim 1, wherein said active is dextromethorphan.

58. (Original) The process of claim 1, wherein said active is chlorpheniramine maleate.

59. (Original) The process of claim 1, wherein said active is selected from the group consisting of an analgesic, an anti-inflammatory, an antihistamine, a decongestant, a cough suppressant and combinations thereof.

60. (Original) The process of claim 1, wherein said active is an appetite stimulant.

61. (Original) The process of claim 1, wherein said active is a gastrointestinal agent.

62. (Original) The process of claim 1, wherein said active is a hypnotic.

63. (Original) The process of claim 1, wherein said active is taste-masked.

64. (Original) The process of claim 1, wherein said active is taste-masked using a flavor.

65. (Original) The process of claim 1, wherein said active is coated with a controlled release composition.

66. (Original) The process of claim 65, wherein said controlled release composition provides an immediate release.

67. (Original) The process of claim 65, wherein said controlled release composition provides a delayed release.

68. (Original) The process of claim 65, wherein said controlled release composition provides a sustained release.

69. (Original) The process of claim 65, wherein said controlled release composition provides a sequential release.

70. (Original) The process of claim 1, wherein said active is a particulate.

71. (Original) The process of claim 1, further comprising adding a degassing agent to said masterbatch premix.

72. (Original) The process of claim 1, further comprising a step of providing a second film layer.

73. (Original) The process of claim 72, wherein said second film layer is coated onto said resulting film.

74. (Original) The process of claim 72, wherein said second film layer is spread onto said resulting film.

75. (Original) The process of claim 72, wherein said second film layer is cast onto said resulting film.

76. (Original) The process of claim 72, wherein said second film layer is extruded onto said resulting film. .

77. (Original) The process of claim 72, wherein said second film layer is sprayed onto said resulting film.

78. (Original) The process of claim 72, wherein said second film is laminated onto said resulting film.

79. (Original) The process of claim 72, further comprising laminating said resulting film to another film.

80. (Original) The process of claim 72, wherein said second film layer comprises an active.

81. (Amended) The process of claim [72]80, wherein said active in said second film is different than said active in said resulting film.

82. (Twice Amended) A process for manufacturing resulting films suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said [making a]films having a substantially uniform distribution of components comprising a substantially uniform distribution of a desired amount of said active in individual dosage units of said resulting films, comprising the steps of:

(a) forming a flowable polymer matrix comprising a polymer selected from the group consisting of a water-soluble polymer, a water swellable polymer and combinations thereof, a solvent and [an]said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives[, drugs, medicaments] and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus and evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first [10]4 minutes [or fewer]by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, wherein during said drying said flowable polymer matrix temperature is 100 °C or less, and wherein uniformity of content of said active in substantially equal sized individual dosage units of said visco-elastic film is such that the amount of the active varies by no more than 10%; [and]

(d) forming [a]said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained;

(e) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units sampled from different locations of said resulting film, said tests indicating that uniformity of content in the amount of said active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration; and

(f) repeating steps (a) through (e) to form additional resulting films, such that uniformity of content in the amount of said active in said resulting film and said additional resulting films varies no more than 10% from the desired amount of the active as indicated by said analytical chemical tests.

83. (Original) The process of claim 82, wherein said water-soluble polymer comprises polyethylene oxide.

84. (Original) The process of claim 82, wherein said polymer comprises a polymer selected from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.

85. (Original) The process of claim 84, wherein said polymer further comprises a water insoluble polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone and combinations thereof.

86. (Original) The process of claim 84, wherein said polymer further comprises a polymer selected from the group consisting of methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(ά-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof.

87. (Original) The process of claim 84, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

88. (Original) The process of claim 84, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(ά-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

89. (Original) The process of claim 82, wherein said solvent is selected from the group consisting of water, polar organic solvent, and combinations thereof.

90. (Original) The process of claim 89, wherein said solvent is selected from the group consisting of ethanol, isopropanol, acetone, and combinations thereof.

91. (Canceled)

92. (Amended) The process of claim 82, wherein the active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents,

anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, [anti-tumor drugs,]anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, [anti-convulsants,]neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, [anti-asthmatics,]cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

93. (Amended) The process of claim 82, wherein said active is selected from the group consisting of [cosmetic actives,]antigens, allergens, spores, microorganisms, seeds, [mouthwash components, flavors, fragrances,]enzymes, [preservatives, sweetening agents, colorants, spices,]vitamins and combinations thereof.

94. (Original) The process of claim 82, wherein said active is a bioactive active.

95. (Canceled)

96. (Original) The process of claim 82, wherein said active is an opiate or opiate-derivative.

97. (Original) The process of claim 82, wherein said active is an anti-emetic.

98. (Original) The process of claim 82, wherein said active is an amino acid preparation.

99. (Original) The process of claim 82, wherein said active is selected from the group consisting of sildenafils, tadalafils, vardenafils, apomorphines, yohimbine hydrochlorides, alprostadils and combinations thereof.

100. (Original) The process of claim 82, wherein said active is a protein.

101. (Original) The process of claim 82, wherein said active is insulin.

102. (Original) The process of claim 82, wherein said active is an anti-diabetic.

103. (Original) The process of claim 82, wherein said active is an antihistamine.

104. (Original) The process of claim 82, wherein said active is an anti-tussive.

105. (Original) The process of claim 82, wherein said active is a non-steroidal anti-inflammatory.

106. (Original) The process of claim 82, wherein said active is an anti-asthmatics.

107. (Amended) The process of claim 82, wherein said active is an anti-diarrhea preparation.

108. (Original) The process of claim 82, wherein said active is an alkaloid.

109. (Original) The process of claim 82, wherein said active is an anti-psychotic.

110. (Original) The process of claim 82, wherein said active is an anti-spasmodic.

111. (Original) The process of claim 82, wherein said active is a biological response modifier.

112. (Original) The process of claim 82, wherein said active is an anti-obesity drug.

113. (Original) The process of claim 82, wherein said active is an H_2-antagonist.

114. (Amended) The process of claim [82]113, wherein said H_2-antagonist is selected from the group consisting of cimetidine, ranitidine hydrochloride, famotidine, nizatidine, ebrotidine, mifentidine, roxatidine, pisatidine, aceroxatidine and combinations thereof.

115. (Original) The process of claim 82, wherein said active is a smoking cessation aid.

116. (Original) The process of claim 82, wherein said active is an anti-parkinsonian agent.

117. (Original) The process of claim 82, wherein said active is an anti-depressant.

118. (Original) The process of claim 82, wherein said active is an anti-migraine.

119. (Original) The process of claim 82, wherein said active is an anti-Alzheimer's agents.

120. (Original) The process of claim 82, wherein said active is a dopamine receptor agonist.

121. (Original) The process of claim 82, wherein said active is a cerebral dilator.

122. (Original) The process of claim 82, wherein said active is a psychotherapeutic agent.

123. (Original) The process of claim 82, wherein said active is an antibiotic.

124. (Original) The process of claim 82, wherein said active is an anesthetic.

125. (Original) The process of claim 82, wherein said active is a contraceptive.

126. (Original) The process of claim 82, wherein said active is an anti-thrombotic drug.

127. (Original) The process of claim 82, wherein said active is diphenhydramine.

128. (Original) The process of claim 82, wherein said active is nabilone.

129. (Original) The process of claim 82, wherein said active is albuterol sulfate.

130. (Original) The process of claim 82, wherein said active is an anti-tumor drug.

131. (Original) The process of claim 82, wherein said active is a glycoprotein.

132. (Original) The process of claim 82, wherein said active is an analgesic.

133. (Original) The process of claim 82, wherein said active is a hormone.

134. (Original) The process of claim 82, wherein said active is a decongestant.

135. (Original) The process of claim 82, wherein said active is a loratadine.

136. (Original) The process of claim 82, wherein said active is dextromethorphan.

137. (Original) The process of claim 82, wherein said active is chlorpheniramine maleate.

138. (Original) The process of claim 82, wherein said active is selected from the group consisting of an analgesic, an anti-inflammatory, an antihistamine, a decongestant, a cough suppressant and combinations thereof.

139. (Original) The process of claim 82, wherein said active is an appetite stimulant.

140. (Original) The process of claim 82, wherein said active is a gastrointestinal agent.

141. (Original) The process of claim 82, wherein said active is a hypnotic.

142. (Original) The process of claim 82, wherein said active is taste-masked.

143. (Original) The process of claim 82, wherein said active is taste-masked using a flavor.

144. (Original) The process of claim 82, wherein said active is coated with a controlled release composition.

145. (Original) The process of claim 144, wherein said controlled release composition provides an immediate release.

146. (Original) The process of claim 144, wherein said controlled release composition provides a delayed release.

147. (Original) The process of claim 144, wherein said controlled release composition

provides a sustained release.

148. (Original) The process of claim 144, wherein said controlled release composition provides a sequential release.

149. (Original) The process of claim 82, wherein said active is a particulate.

150. (Original) The process of claim 82, further comprising adding a degassing agent to said flowable polymer matrix.

151. (Original) The process of claim 82, further comprising a step of providing a second film layer.

152. (Original) The process of claim 151, wherein said second film layer is coated onto said resulting film.

153. (Original) The process of claim 151, wherein said second film layer is spread onto said resulting film.

154. (Original) The process of claim 151, wherein said second film layer is cast onto said resulting film.

155. (Original) The process of claim 151, wherein said second film layer is extruded onto said resulting film.

156. (Original) The process of claim 151, wherein said second film layer is sprayed onto said resulting film.

157. (Original) The process of claim 151, wherein said second film layer is laminated onto

said resulting film.

158. (Original) The process of claim 151, further comprising laminating said resulting film to another film.

159. (Original) The process of claim 151, wherein said second film comprises an active.

160. (Amended) The process of claim [151]159, wherein said active in said second film is different than said active in said resulting film.

161. (Twice Amended) A process for manufacturing a resulting film suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said[making a] film capable of being administered to a body surface and having a substantially uniform distribution of components comprising a substantially uniform distribution of said active in individual dosage units of said resulting film, comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and [an]said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus and evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film, having said active substantially uniformly distributed

throughout, within about the first [10]4 minutes [or fewer]by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, wherein during said drying said flowable polymer matrix temperature is 100 °C or less, and wherein uniformity of content of said active in substantially equal sized individual dosage units of said visco-elastic film is such that the amount of the active varies by no more than 10%;

(d) forming [a]said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained; [and]

(e) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units sampled from different locations of said resulting film, said tests indicating that uniformity of content in the amount of said active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration, and

[(e)](f) administering said resulting film to a body surface.

162. (Original) The process of claim 161, wherein said body surface is a mucous membrane.

163. (Original) The process of claim 162, wherein said mucous membrane is oral, anal, vaginal or ophthalmological.

164. (Original) The process of claim 161, wherein said body surface is the surface of a wound.

165. (Original) The process of claim 161, wherein said water-soluble polymer comprises polyethylene oxide.

166. (Original) The process of claim 161, wherein said polymer comprises a polymer selected from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.

167. (Original) The process of claim 166, wherein said polymer further comprises a water insoluble polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone and combinations thereof.

168. (Original) The process of claim 166, wherein said polymer further comprises a polymer selected from the group consisting of methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(ά-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof.

169. (Original) The process of claim 166, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

170. (Original) The process of claim 166, wherein said polymer further comprises a polymer

selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(ά-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

171. (Original) The process of claim 161, wherein said solvent is selected from the group consisting of water, polar organic solvent, and combinations thereof.

172. (Original) The process of claim 161, wherein said solvent is selected from the group consisting of ethanol, isopropanol, acetone, and combinations thereof.

173. (Canceled)

174. (Amended) The process of claim 161, wherein said active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary

supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, [anti-tumor drugs,]anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, [anti-convulsants,]neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, [anti-asthmatics,]cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

175. (Amended) The process of claim 161, wherein said active is selected from the group consisting of [cosmetic actives,]antigens, allergens, spores, microorganisms, seeds, [mouthwash components, flavors, fragrances,]enzymes, [preservatives, sweetening agents, colorants, spices,]vitamins and combinations thereof.

176. (Original) The process of claim 161, wherein said active is a bioactive active.

177. (Canceled)

178. (Original) The process of claim 161, wherein said active is an opiate or opiate-derivative.

179. (Original) The process of claim 161, wherein said active is an anti-emetic.

180. (Original) The process of claim 161 wherein said active is an amino acid preparation.

181. (Original) The process of claim 161, wherein said active is selected from the group consisting of sildenafils, tadalafils, vardenafils, apomorphines, yohimbine hydrochlorides, alprostadils and combinations thereof.

182. (Original) The process of claim 161, wherein said active is a protein.

183. (Original) The process of claim 161, wherein said active is insulin.

184. (Original) The process of claim 161, wherein said active is an anti-diabetic.

185. (Original) The process of claim 161, wherein said active is an antihistamine.

186. (Original) The process of claim 161, wherein said active is an anti-tussive.

187. (Original) The process of claim 161, wherein said active is a non-steroidal anti-inflammatory.

188. (Original) The process of claim 161, wherein said active is an anti-asthmatics.

189. (Amended) The process of claim 161, wherein said active is an anti-diarrhea preparation.

190. (Original) The process of claim 161, wherein said active is an alkaloid.

191. (Original) The process of claim 161, wherein said active is an anti-psychotic.

192. (Original) The process of claim 161, wherein said active is an anti-spasmodic.

193. (Original) The process of claim 161, wherein said active is a biological response modifier.

194. (Original) The process of claim 161, wherein said active is an anti-obesity drug.

195. (Original) The process of claim 161, wherein said active is an H_2-antagonist.

196. (Original) The process of claim 195, wherein said H_2-antagonist is selected from the group consisting of cimetidine, ranitidine hydrochloride, famotidine, nizatidine, ebrotidine, mifentidine, roxatidine, pisatidine, aceroxatidine and combinations thereof.

197. (Original) The process of claim 161, wherein said active is a smoking cessation aid.

198. (Original) The process of claim 161, wherein said active is an anti-parkinsonian agent.

199. (Original) The process of claim 161, wherein said active is an anti-depressant.

200. (Original) The process of claim 161, wherein said active is an anti-migraine.

201. (Original) The process of claim 161, wherein said active is an anti-Alzheimer's agents.

202. (Original) The process of claim 161, wherein said active is a dopamine receptor agonist.

203. (Original) The process of claim 161, wherein said active is a cerebral dilator.

204. (Original) The process of claim 161, wherein said active is a psychotherapeutic agent.

205. (Original) The process of claim 161, wherein said active is an antibiotic.

206. (Original) The process of claim 161, wherein said active is an anesthetic.

207. (Original) The process of claim 161, wherein said active is a contraceptive.

208. (Original) The process of claim 161, wherein said active is an anti-thrombotic drug.

209. (Original) The process of claim 161, wherein said active is diphenhydramine.

210. (Original) The process of claim 161, wherein said active is nabilone.

211. (Original) The process of claim 161, wherein said active is albuterol sulfate.

212. (Original) The process of claim 161, wherein said active is an anti-tumor drug.

213. (Original) The process of claim 161, wherein said active is a glycoprotein.

214. (Original) The process of claim 161, wherein said active is an analgesic.

215. (Original) The process of claim 161, wherein said active is a hormone.

216. (Original) The process of claim 161, wherein said active is a decongestant.

217. (Original) The process of claim 161, wherein said active is a loratadine.

218. (Original) The process of claim 161, wherein said active is dextromethorphan.

219. (Original) The process of claim 161, wherein said active is chlorpheniramine maleate.

220. (Original) The process of claim 161, wherein said active is selected from the group

consisting of an analgesic, an anti-inflammatory, an antihistamine, a decongestant, a cough suppressant and combinations thereof.

221. (Original) The process of claim 161, wherein said active is an appetite stimulant.

222. (Original) The process of claim 161, wherein said active is a gastrointestinal agent.

223. (Original) The process of claim 161, wherein said active is a hypnotic.

224. (Original) The process of claim 161, wherein said active is taste-masked.

225. (Original) The process of claim 161, wherein said active is taste-masked using a flavor.

226. (Original) The process of claim 161, wherein said active is coated with a controlled release composition.

227. (Original) The process of claim 226, wherein said controlled release composition provides an immediate release.

228. (Original) The process of 226, wherein said controlled release composition provides a delayed release.

229. (Original) The process of claim 226, wherein said controlled release composition provides a sustained release.

230. (Original) The process of claim 226, wherein said controlled release composition provides a sequential release.

231. (Original) The process of claim 161, wherein said active is a particulate.

232. (Original) The process of claim 161, further comprising adding a degassing agent to said flowable polymer matrix.

233. (Original) The process of claim 161, further comprising a step of providing a second film layer.

234. (Original) The process of claim 233, wherein said second film layer is coated onto said resulting film.

235. (Original) The process of claim 233, wherein said second film layer is spread onto said resulting film.

236. (Original) The process of claim 233, wherein said second film layer is cast onto said resulting film.

237. (Original) The process of claim 233, wherein said second film layer is extruded onto said resulting film.

238. (Original) The process of claim 233, wherein said second film layer is sprayed onto said resulting film.

239. (Original) The process of claim 233, wherein said second film layer is laminated onto said resulting film.

240. (Original) The process of claim 233, further comprising laminating said resulting film to another film.

241. (Original) The process of claim 233, wherein said second film comprises an active.

242. (Amended) The process of claim [233]241, wherein said active in said second film is different than said active in said resulting film.

243. (Original) The process of claim 1, said active is an anti-nauseant.

244. (Amended) The process of claim 1, said active is an erectile dysfunction drug.

245. (Original) The process of claim 1, said active is a vasoconstrictor.

246. (Original) The process of claim 1, said active is a stimulant.

247. (Original) The process of claim 1, said active is a migraine treatment.

248. (Original) The process of claim 1, said active is granisetron hydrochloride.

249. (Original) The process of claim 1, wherein said resulting film provides administration of said active to an individual through the buccal cavity of said individual.

250. (Original) The process of claim 1, wherein said resulting film provides administration of said active through gingival application of said individual.

251. (Original) The process of claim 1, wherein said resulting film provides administration of said active through sublingual application of said individual.

252. (Original) The process of claim 1, wherein said resulting film provides administration of said active to an individual through a mucosal membrane of said individual.

253. (Original) The process of claim 1, wherein said resulting film provides administration of

said active to an individual by administration within the body of the individual during surgery.

254. (Canceled)

255. (Canceled)

256. (Original) The method of claim 1, wherein said resulting film contains less than about 6% by weight solvent.

257. (Canceled)

258. (Original) The method of claim 1, wherein said resulting film is orally administrable.

259. (Original) The method of claim 1, wherein said active is in the form of a particle.

260. (Original) The method of claim 1, wherein said matrix comprises a dispersion.

261. (Original) The process of claim 82, said active is an anti-nauseant.

262. (Amended) The process of claim 82, said active is an erectile dysfunction drug.

263. (Original) The process of claim 82, said active is a vasoconstrictor.

264. (Original) The process of claim 82, said active is a stimulant.

265. (Original) The process of claim 82, said active is a migraine treatment.

266. (Original) The process of claim 82, said active is granisetron hydrochloride.

267. (Original) The process of claim 82, wherein said resulting film provides administration of said active to an individual through the buccal cavity of said individual.

268. (Original) The process of claim 82, wherein said resulting film provides administration of said active through gingival application of said individual.

269. (Original) The process of claim 82, wherein said resulting film provides administration of said active through sublingual application of said individual.

270. (Original) The process of claim 82, wherein said resulting film provides administration of said active to an individual through a mucosal membrane of said individual.

271. (Original) The process of claim 82, wherein said resulting film provides administration of said active to an individual by administration within the body of the individual during surgery.

272. (Canceled)

273. (Canceled)

274. (Original) The method of claim 82, wherein said resulting film contains less than about 6% by weight solvent.

275. (Canceled)

276. (Original) The method of claim 82, wherein said resulting film is orally administrable.

277. (Original) The method of claim 82, wherein said active is in the form of a particle.

278. (Original) The method of claim 82, wherein said matrix comprises a dispersion.

279. (Original) The process of claim 161, said active is an anti-nauseant.

280. (Amended) The process of claim 161, said active is an erectile dysfunction drug.

281. (Original) The process of claim 161, said active is a vasoconstrictor.

282. (Original) The process of claim 161, said active is a stimulant.

283. (Original) The process of claim 161, said active is a migraine treatment.

284. (Original) The process of claim 161, said active is granisetron hydrochloride.

285. (Original) The process of claim 161, wherein said resulting film provides administration of said active to an individual through the buccal cavity of said individual.

286. (Original) The process of claim 161, wherein said resulting film provides administration of said active through gingival application of said individual.

287. (Original) The process of claim 161, wherein said resulting film provides administration of said active through sublingual application of said individual.

288. (Original) The process of claim 161, wherein said resulting film provides administration of said active to an individual through a mucosal membrane of said individual.

289. (Original) The process of claim 161, wherein said resulting film provides administration of said active to an individual by administration within the body of the individual during surgery.

290. (Canceled)

291. (Canceled)

292. (Original) The method of claim 161, wherein said resulting film contains less than about 6% by weight solvent.

293. (Canceled)

294. (Original) The method of claim 161, wherein said resulting film is orally administrable.

295. (Original) The method of claim 161, wherein said active is in the form of a particle.

296. (Original) The method of claim 161, wherein said matrix comprises a dispersion.

297. (Original) The method of claim 1, wherein said matrix comprises an emulsion, a colloid or a suspension.

298. (Original) The method of claim 82, wherein said matrix comprises an emulsion, a colloid or a suspension.

299. (Original) The method of claim 161, wherein said matrix comprises an emulsion, a colloid or a suspension.

300. (New) The process of claim 1, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 5%.

301. (New) The process of claim 1, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 2%.

302. (New) The process of claim 1, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 1%.

303. (New) The process of claim 1, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 0.5%.

304. (New) The process of claim 82, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 5%.

305. (New) The process of claim 82, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 2%.

306. (New) The process of claim 82, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 1%.

307. (New) The process of claim 82, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 0.5%.

308. (New) The process of claim 161, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 5%.

309. (New) The process of claim 161, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 2%.

310. (New) The process of claim 161, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 1%.

311. (New) The process of claim 161, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 0.5%.

312. (New) The process of claim 1, wherein said evaporating is conducted by applying radiant energy selected from the group consisting of hot air currents, heat, infrared radiation, radio frequency radiation and combinations thereof.

313. (New) The process of claim 82, wherein said evaporating is conducted by applying radiant energy selected from the group consisting of hot air currents, heat, infrared radiation, radio frequency radiation and combinations thereof.

314. (New) The process of claim 161, wherein said evaporating is conducted by applying radiant energy selected from the group consisting of hot air currents, heat, infrared radiation, radio frequency radiation and combinations thereof.

315. (New) A process for manufacturing resulting films suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said films having a substantially uniform distribution of components comprising a substantially uniform distribution of a desired amount of said active in individual dosage units of said resulting films, comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said polymer matrix through a drying apparatus and evaporating at least a portion of said solvent to form a visco-elastic film,

having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, wherein during said drying said flowable polymer matrix temperature is 100 °C or less;

(d) forming said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of said active by said locking-in or substantially preventing migration of said active is maintained, such that uniformity of content in the amount of the active in substantially equal sized individual dosage units, sampled from different locations of said resulting film, varies by no more than 10%;

(e) performing analytical chemical tests for uniformity of content of said active in said substantially equal sized individual dosage units of said sampled resulting film, said tests indicating that uniformity of content in the amount of the active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration; and

(f) repeating steps (a) through (e) to form additional resulting films, such that uniformity of content in the amount of said active in said resulting film and said additional resulting films varies no more than 10% from the desired amount of said active as indicated by said analytical chemical tests.

316. (New) A process for manufacturing a resulting film suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said film having a substantially uniform distribution of components comprising a substantially uniform distribution of said active in individual dosage units of said resulting film, comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said polymer matrix through a drying apparatus and evaporating at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, wherein during said drying said flowable polymer matrix temperature is 100 °C or less;

(d) forming said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said resulting film, varies by no more than 10%; and

(e) performing analytical chemical tests for uniformity of content of said active in said substantially equal sized individual dosage units of said sampled resulting film, said tests indicating that uniformity of content in the amount of said active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration.

317. (New) A process for manufacturing a resulting film suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said film having a substantially uniform distribution of components comprising a substantially uniform distribution of said active in individual dosage units of said resulting film, comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus using air currents, which have forces below a yield value of said flowable polymer matrix during drying, to evaporate at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said visco-elastic film, varies by no more than 10%, and wherein during said drying said flowable polymer matrix temperature is 100 °C or less;

(d) forming said resulting film from said visco-elastic film by further controlling drying by continuing evaporation to a water content of said resulting film of 10% or less and wherein said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained, such that uniformity of content in the amount of said

active in substantially equal sized individual dosage units, sampled from different locations of said resulting film, varies by no more than 10%; and

(e) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units of said sampled resulting film, said tests indicating that uniformity of content in the amount of said active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration.

318. (New) A process for manufacturing a resulting film suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said film having a substantially uniform distribution of components comprising a substantially uniform distribution of said active in individual dosage units of said resulting film, comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus at a temperature of about 60 °C and using air currents, which have forces below a yield value of the polymer matrix during drying, to evaporate at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of

said active by locking-in or substantially preventing migration of said active within said visco-elastic film, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said visco-elastic film, varies by less than 5%, and wherein during said drying said flowable polymer matrix temperature is 100 °C or less;

(d) forming said resulting film from said visco-elastic film by further controlling by continuing evaporation to a water content of said resulting film of 10% or less and wherein said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said resulting film, varies by less than 5%; and

(e) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units of said sampled resulting film, said tests indicating that uniformity of content in the amount of said active varies by less than 5% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration.

CLAIM AMENDMENTS AFTER ACP - NOT ENTERED[6]

1. (Twice Amended) A process for manufacturing a resulting film which is **self-supporting and** suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said [making a]film having a substantially uniform distribution of components comprising a substantially uniform distribution of said active in individual dosage units of said resulting film, comprising the steps of:

(a) forming a masterbatch pre-mix comprising a solvent and a polymer selected from the group consisting of water-soluble polymers, water-swellable polymers and combinations thereof;

(b) adding [an]said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, to a pre-determined amount of said masterbatch pre-mix to form a flowable polymer matrix, said matrix having a substantially uniform distribution of said active;

(c) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(d) controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus and evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first [10]4 minutes [or fewer]by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active

[6] Matter added after ACP is in bold. Matter deleted after ACP is shown in bold and bracketed.

within said visco-elastic film, wherein during said drying said flowable polymer matrix temperature is 100 °C or less; [and]

(e) forming [a]said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained; and

(f) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units sampled from different locations of said resulting film, said tests indicating that uniformity of content in the amount of the active varies by no more than 10% and said resulting film is **self-supporting and** suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration.

82. (Twice Amended) A process for manufacturing resulting films which are **self-supporting and** suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said [making a]films having a substantially uniform distribution of components comprising a substantially uniform distribution of a desired amount of said active in individual dosage units of said resulting films, comprising the steps of:

(a) forming a flowable polymer matrix comprising a polymer selected from the group consisting of a water-soluble polymer, a water swellable polymer and combinations thereof, a solvent and [an]said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives[, drugs, medicaments] and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus and evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first [10]4 minutes [or fewer]by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, wherein during said drying said flowable polymer matrix temperature is 100 °C or less, and wherein uniformity of content of said active in substantially equal sized individual dosage units of said visco-elastic film is such that the amount of the active varies by no more than 10%; [and]

(d) forming [a]said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained;

(e) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units sampled from different locations of said resulting film, said tests indicating that uniformity of content in the amount of said active varies by no more than 10% and said resulting film is **self-supporting and** suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration; and

(f) repeating steps (a) through (e) to form additional resulting films, such that uniformity of content in the amount of said active in said resulting film and said additional resulting films

varies no more than 10% from the desired amount of the active as indicated by said analytical chemical tests.

161. (Twice Amended) A process for manufacturing a resulting film which is **self-supporting and** suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said[making a] film capable of being administered to a body surface and having a substantially uniform distribution of components comprising a substantially uniform distribution of said active in individual dosage units of said resulting film, comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and [an]said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus and evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first [10]4 minutes [or fewer]by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, wherein during said drying said flowable polymer matrix temperature is 100 °C or less, and wherein uniformity of content of said active in substantially

equal sized individual dosage units of said visco-elastic film is such that the amount of the active varies by no more than 10%;

(d) forming [a]said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained; [and]

(e) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units sampled from different locations of said resulting film, said tests indicating that uniformity of content in the amount of said active varies by no more than 10% and said resulting film is **self-supporting and** suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration, and

[(e)](f) administering said resulting film to a body surface.

315. (New) A process for manufacturing resulting films which are **self-supporting and** suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said films having a substantially uniform distribution of components comprising a substantially uniform distribution of a desired amount of said active in individual dosage units of said resulting films, comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said polymer matrix through a drying apparatus and evaporating at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, wherein during said drying said flowable polymer matrix temperature is 100 °C or less;

(d) forming said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of said active by said locking-in or substantially preventing migration of said active is maintained, such that uniformity of content in the amount of the active in substantially equal sized individual dosage units, sampled from different locations of said resulting film, varies by no more than 10%;

(e) performing analytical chemical tests for uniformity of content of said active in said substantially equal sized individual dosage units of said sampled resulting film, said tests indicating that uniformity of content in the amount of the active varies by no more than 10% and said resulting film is **self-supporting and** suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration; and

(f) repeating steps (a) through (e) to form additional resulting films, such that uniformity of content in the amount of said active in said resulting film and said additional resulting films varies no more than 10% from the desired amount of said active as indicated by said analytical chemical tests.

316. (New) A process for manufacturing a resulting film which is **self-supporting and** suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said film having a substantially uniform distribution of components comprising a substantially uniform distribution of said active in individual dosage units of said resulting film, comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said polymer matrix through a drying apparatus and evaporating at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, wherein during said drying said flowable polymer matrix temperature is 100 °C or less;

(d) forming said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said resulting film, varies by no more than 10%; and

(e) performing analytical chemical tests for uniformity of content of said active in said substantially equal sized individual dosage units of said sampled resulting film, said tests indicating that uniformity of content in the amount of said active varies by no more than 10% and said resulting film is **self-supporting and** suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration.

317. (New) A process for manufacturing a resulting film which is **self-supporting and** suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said film having a substantially uniform distribution of components comprising a substantially uniform distribution of said active in individual dosage units of said resulting film, comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus using air currents, which have forces below a yield value of said flowable polymer matrix during drying, to evaporate at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, such that

uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said visco-elastic film, varies by no more than 10%, and wherein during said drying said flowable polymer matrix temperature is 100 °C or less;

(d) forming said resulting film from said visco-elastic film by further controlling drying by continuing evaporation to a water content of said resulting film of 10% or less and wherein said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said resulting film, varies by no more than 10%; and

(e) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units of said sampled resulting film, said tests indicating that uniformity of content in the amount of said active varies by no more than 10% and said resulting film is **self-supporting and** suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration.

318. (New) A process for manufacturing a resulting film which is **self-supporting** suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said film having a substantially uniform distribution of components comprising a substantially uniform distribution of said active in individual dosage units of said resulting film, comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus **[at a temperature of about 60** °C **and]** using air currents, which have forces below a yield value of the polymer matrix during drying, to evaporate at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said visco-elastic film, varies by less than 5%, and wherein during said drying said flowable polymer matrix temperature is 100 °C or less;

(d) forming said resulting film from said visco-elastic film by further controlling by continuing evaporation to a water content of said resulting film of 10% or less and wherein said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said resulting film, varies by less than 5%; and

(e) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units of said sampled resulting film, said tests indicating that uniformity of content in the amount of said active varies by less than 5% and said resulting film is **self-supporting and** suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration.

EVIDENCE APPENDIX

1 Declaration of B. Arlie Bogue, Ph.D. Under 37 C.F.R. § 1.132, dated March 13, 2013, earlier submitted by Patentee with March 13, 2013 Response to Office Action ("Bogue Declaration I")

2 Declaration of B. Arlie Bogue, Ph.D. Under 37 C.F.R. § 1.132, executed August 29, 2013 ("Bogue Declaration II")

The above declarations included below were submitted by MonoSol/Appellant, they were admitted in the record, and referred to in the Examiner's Right of Appeal Notice, mailed Decmber 6, 2013, *see*, *inter alia*, pp. 2, 68-69, 71-72, 83-84, 87-88. Pursuant to 37 C.F.R. § 41.71, Appellant is using these declarations which ***were*** admitted.

Declaration of B. Arlie Bogue, Ph.D. Under 37 C.F.R. § 1.132, dated March 13, 2013 ("Bogue Declaration I")

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patentee:	Yang et al.	Examiner:	Diamond, Alan D.
Patent No.:	U.S. 7,897,080	Group Art Unit:	3991
Reexamination Control No.:	95/002,170	Confirmation No.	6418
Filed:	September 10, 2012	H&B Docket:	1199-26 RCE/CON/REX
Dated:	March 13, 2013	M&E Docket:	117744-00023

Mail Stop Inter Partes Reexam
Central Reexamination Unit
Commissioner for Patents
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

Certificate of EFS-Web Transmission
I hereby certify that this correspondence is being transmitted via the U.S. Patent and Trademark Office electronic filing system (EFS-Web) to the USPTO on
March 13, 2013.
Signed: Michael I. Chakansky /Michael I Chakansky/

DECLARATION OF B. ARLIE BOGUE, PH.D. UNDER 37 C.F.R. § 1.132

Madame:

I, B. Arlie Bogue, Ph.D., do hereby make the following declaration:

I. Technical Background

1. I have worked in the field of pharmaceutical development, and particularly oral dosage form development, for 22 years. I am employed by MonoSol Rx, LLC. ("Patentee" and/or "MonoSol"), the assignee of issued patent U.S. 7,897,080 ("the '080 Patent"), as Senior Director for Manufacturing Strategy and Innovation.

2. I have a BS in Physical Chemistry from Colorado State University and a Ph.D. in Chemical and BioEngineering from Arizona State University. I have participated in postdoctoral studies in Biochemical Engineering at the University of Virginia. During my career, I have been named as an inventor on over 23 U.S. patents and numerous foreign patents directed to the formulation,

processing and/or packaging of pharmaceutical oral disintegrating unit doses (tablets and film strips). I have direct experience with the commercial scale processing of pharmaceutical film systems as well as an understanding of the uniformity of content of active and methods for testing the same.

3. I have read the '080 Patent and the Office Action issued on November 29, 2012 in the reexamination of the '080 Patent ("Office Action") and the references cited therein, and I have also reviewed the amendment as to the independent claims set forth in Patentee's Reply to the Office Action concurrently filed herewith.

II. Producing resulting films in accordance with the '080 Patent

4. Each of the 73 lots of resulting films (Lots 1-73) containing approximately 2,000,000 individual dosage units per lot discussed herein were manufactured: (i) for commercial use and regulatory approval; (ii) in compliance with U.S Food and Drug Administration ("FDA") standards and regulations, including those relating to analytical chemical testing for variation in active in individual dosage units; and (iii) in accordance with the invention disclosed in the '080 Patent, and as claimed by the '080 Patent both as issued and as amended in the Patentee's Reply to the Office Action; by:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and a pharmaceutical active, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said polymer matrix through a drying apparatus and evaporating at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film wherein the polymer matrix temperature is 100 °C or less;

(d) forming the resulting pharmaceutical film from said visco-elastic film, wherein said resulting pharmaceutical film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained, such that uniformity of content in the amount of the active in substantially equal sized individual dosage units, sampled from different locations of said resulting pharmaceutical film, varies by no more than 10%; and

(e) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units of said sampled resulting pharmaceutical film, said tests indicating that uniformity of content in the amount of the active varies by no more than 10%, [see Appendix A] said resulting pharmaceutical film suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration.

5. Additionally, the uniformity of content in the amount of active as sampled from the 73 lots of resulting film varies no more than 10% from the desired amount of the active as indicated by said analytical chemical tests from 4(e) above. [See Appendix B]

III. Analytical Chemical Testing for Uniformity of Content of Patentee's Resulting Films

6. To demonstrate the uniformity of individual dosage unit films, I compiled individual dosage unit assay data for individual Lots 1- 73, all of which were disclosed in MonoSol's 2012 Annual Product Review to the FDA.

7. Ten (10) individual dosage units all having the same dimensions were cut out from different locations of each of the 73 lots of resulting films using a commercial packaging machine, thus providing 730 randomly sampled individual dosage units, ten each from the 73 separate lots. All samples were analyzed by a validated method, in compliance with FDA guidelines and regulations regarding same, using analytical chemical testing, in which the pharmaceutical active

was extracted and analyzed by High Performance Liquid Chromatography (HPLC) against an external standard to quantify the amount of active present in each individual dosage unit.

8. According to the inventive process set forth and claimed in the '080 Patent, and in accordance with FDA nomenclature, I have prepared tables shown as Appendices A, B and C, reflecting the uniformity of content of active of individual dosage units within particular lots and across different lots.

9. First, the uniformity of content of active in a lot is determined through establishing the amount of active ($A_{N(i)}$) actually present in each sampled individual dosage unit from the same lot (N) as determined by taking the difference between the amount of active in the sample with the most active ($Max_{LOT(N)}$) minus the amount of active in the sample with the least amount of active ($Min_{LOT(N)}$) and dividing the difference by the average amount of active in the lot samples ($Lot_{(N)}$ Sample Average). That is: $(Max_{LOT(N} - Min_{LOT(N)}) / ((A_{N(1)} + A_{N(2)} + + + A_{N(10)})/10)$. The results are shown in Appendix A.

10. Second, the uniformity of content across different lots is determined through establishing the amount of active actually present in each sampled individual dosage unit from all 73 lots and comparing that amount of active with a "target" or "desired" amount of active contained therein. The target amount of active, when it is a pharmaceutical, is referred to as the "Label Claim", thus identifying the amount of pharmaceutical active in the film to a user. The desired amount is 100% of the target amount. Each individual dosage unit film cut from any individual lot must have the desired content of pharmaceutical active, varying no more that 10% from the target or desired amount. See Appendix B.

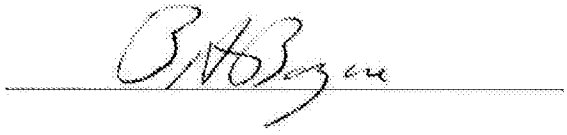
IV. '080 Patent Process Produces Films With Required Uniformity of Content of Active

11. The results shown in the appendices establish that the resulting films produced by the inventive method of the '080 Patent as disclosed and claimed have the required uniformity of content based on analytical chemical testing. First, the amount of active varies by no more than 10% between individual dosage units sampled from a particular lot of resulting film. See Appendix A.

Second, the amount of active across different lots of resulting film varies no more than 10% from the desired amount of the active. See Appendix B. Finally, the uniformity of content of the 73 lots of resulting film meets even more stringent standards, for example, the data shows: (i) 46 lots of resulting film wherein the uniformity of content of active is shown with the amount of active varying by less than 5%; (ii) 15 lots of resulting film wherein the uniformity of content of active is shown with the amount of active varying by less than 4%; 4 lots of resulting film wherein the uniformity of content of active is shown with the amount of active varying by less than 3%; and 1 lot of resulting film wherein the uniformity of content of active is shown with the amount of active varying by only 2%. See Appendix C.

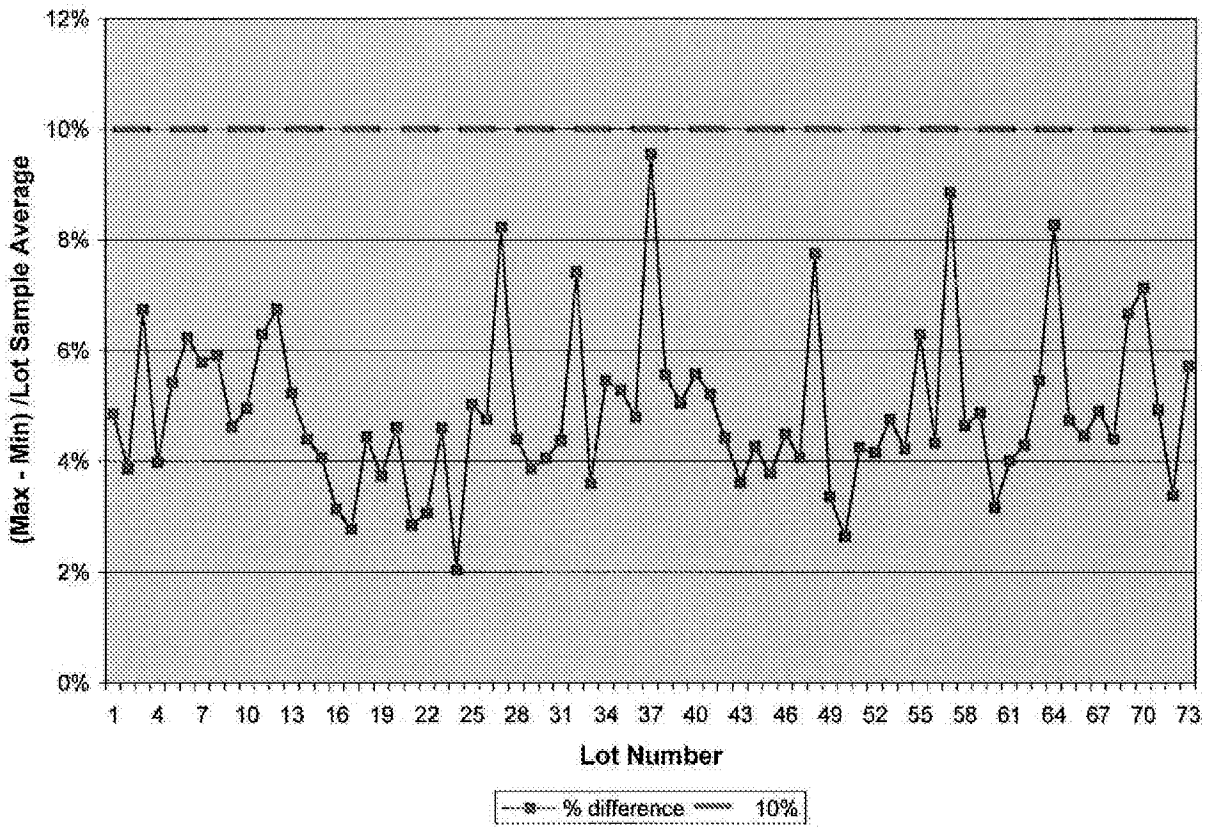
I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and. that such statements may jeopardize the validity of the application or any patents issued thereon.

Dated this 13th day of March, 2013

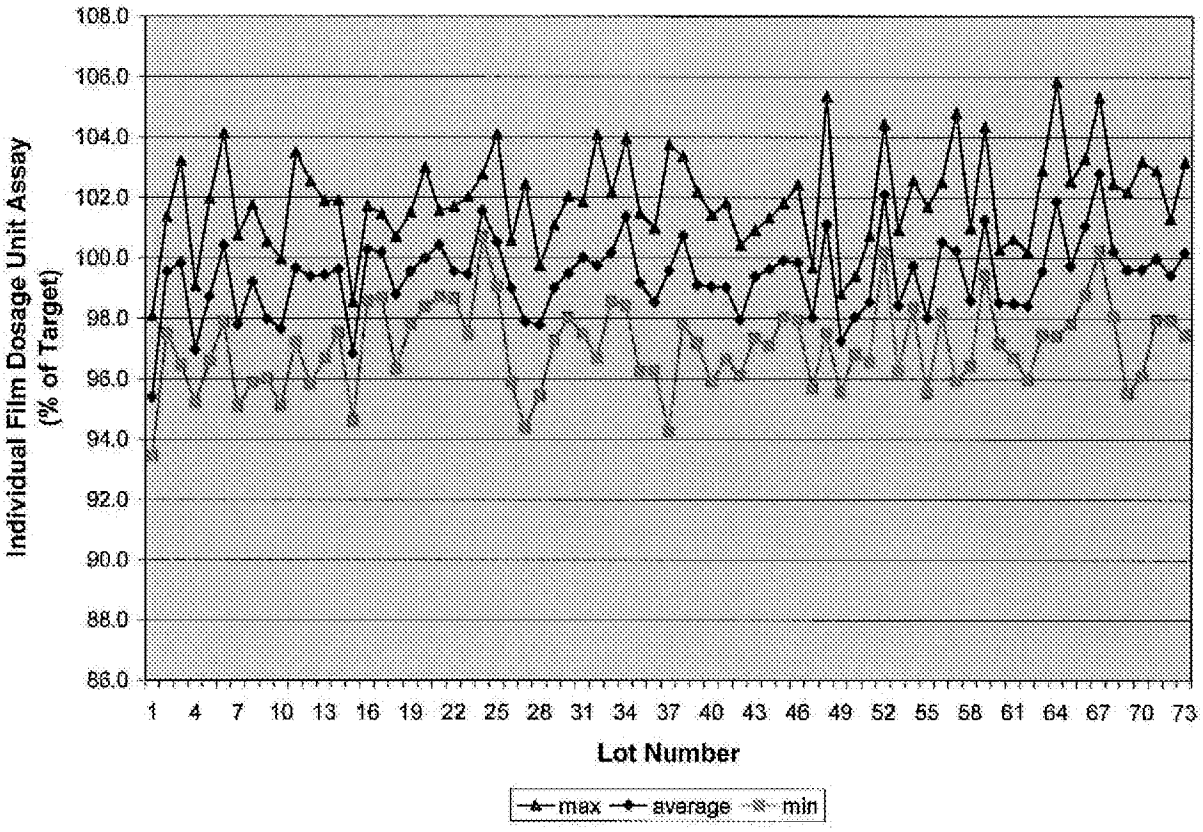


B. Arlie Bogue

APPENDIX A


12%
10%
8%
6%
4%
2%
0%
(Max - Min) /Lot Sample Average
1 4 7 10 13 16 19 22 25 28 31 34 37 40 43 46 49 52 55 58 61 64 67 70 73
Lot Number
% difference
10%

APPENDIX B


Individual Film Dosage Unit Assay
(% of Target)
108.0
106.0
104.0
102.0
100.0
98.0
96.0
94.0
92.0
90.0
88.0
86.0
1 4 7 10 13 16 19 22 25 28 31 34 37 40 43 46 49 52 55 58 61 64 67 70 73
Lot Number
max
average
min

APPENDIX C

Lots less than 5%			lots 5% to 10%	
Lot #	% Difference		Lot #	% Difference
24	2.0%		10	5.0%
45	2.6%		25	5.0%
17	2.8%		39	5.0%
21	2.8%		41	5.2%
22	3.1%		13	5.2%
16	3.1%		35	5.3%
60	3.2%		5	5.4%
50	3.4%		63	5.5%
72	3.4%		34	5.5%
33	3.6%		38	5.6%
43	3.6%		40	5.6%
19	3.7%		73	5.7%
46	3.8%		7	5.8%
29	3.9%		8	5.9%
2	3.9%		6	6.2%
4	4.0%		11	6.3%
61	4.0%		55	6.3%
30	4.0%		69	6.7%
48	4.1%		3	6.7%
15	4.1%		12	6.7%
52	4.2%		70	7.1%
54	4.2%		32	7.4%
51	4.2%		49	7.8%
44	4.3%		27	8.2%
62	4.3%		64	8.3%
56	4.3%		57	8.9%
31	4.4%		37	9.5%
28	4.4%			
14	4.4%			
68	4.4%			
42	4.4%			
18	4.4%			
66	4.5%			
47	4.5%			
23	4.6%			
20	4.6%			
9	4.6%			
58	4.6%			
65	4.7%			
26	4.8%			
53	4.8%			
36	4.8%			
1	4.9%			
59	4.9%			
67	4.9%			
71	4.9%			
total	46		total	27

Declaration of B. Arlie Bogue, Ph.D. Under 37 C.F.R. § 1.132, executed August 29, 2013 ("Bogue Declaration II")

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patentee:	Yang et al.	Examiner:	Diamond, Alan D.
Patent No.:	U.S. 7,897,080	Group Art Unit:	3991
Reexamination Control No.:	95/002,170	Confirmation No.	6418
Filed:	September 10, 2012	H&B Docket:	1199-26 RCE/CON/REX
Dated:	September 3, 2013	M&E Docket:	117744-00023

Mail Stop Inter Partes Reexam
Central Reexamination Unit
Commissioner for Patents
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

Certificate of EFS-Web Transmission
I hereby certify that this correspondence is being transmitted via the U.S. Patent and Trademark Office electronic filing system (EFS-Web) to the USPTO on September 3, 2013.
Signed: Michael I. Chakansky /Michael I Chakansky/

DECLARATION OF B. ARLIE BOGUE, PH.D. UNDER 37 C.F.R. § 1.132

Madame:

I, B. Arlie Bogue, Ph.D., do hereby make the following declaration:

I. Technical Background

1. I have worked in the field of pharmaceutical development, and particularly oral dosage form development, for 22 years. I am employed by MonoSol Rx, LLC. ("Patentee" and/or "MonoSol"), the assignee of issued patent U.S. 7,897,080 ("the '080 Patent"), as Senior Director for Manufacturing Strategy and Innovation.

2. I have a BS in Physical Chemistry from Colorado State University and a Ph.D. in Chemical and BioEngineering from Arizona State University. I have participated in postdoctoral studies in Biochemical Engineering at the University of Virginia. During my career, I have been named as an inventor on over 23 U.S. patents and numerous foreign patents directed to the formulation, processing and/or packaging of pharmaceutical oral disintegrating unit doses (tablets and film

strips). I have direct experience with the commercial scale processing of pharmaceutical film systems as well as an understanding of the uniformity of content of active and methods for testing the same.

3. My declaration dated March 13, 2013 was submitted in support of Patentee's response to the Office Action issued on November 29, 2012 in the reexamination of the '080 Patent ("Bogue Declaration I").

4. In Bogue Declaration I, I disclosed Patentee's method of producing resulting films in accordance with the '080 Patent and analytical chemical testing for uniformity of content thereof.

5. I hereby identify the resulting films in Bogue Declaration I as Suboxone® sublingual unit dose film products, and further declare that the Suboxone® sublingual unit dose film products were manufactured for Reckitt Benckiser Pharmaceuticals Inc. by Patentee, MonoSol.

6. Patentee is the exclusive source of Suboxone® sublingual unit dose film products for Reckitt Benckiser.

7. Suboxone® sublingual unit dose film products are FDA approved drug products.

8. In Patentee's production of unit dose film products, described in the '080 Patent, including its production of Suboxone® sublingual unit dose film products, the wet film thicknesses, from which the dry resulting products such as Suboxone® sublingual unit dose film products are produced, are always significantly greater in thickness than the dry resulting unit dose film products.

9. The Suboxone® sublingual unit dose film products made by MonoSol, and described in Bogue Declaration I, have dry thicknesses ranging from approximately 110 to approximately 175 microns, depending on the particular Suboxone® sublingual unit dose film product. Hence, the wet films from which these products are made have wet film thicknesses significantly greater than approximately 110 to approximately 175 microns.

10. I have reviewed the documents attached as Exhibits 7 and 8 to the Response by Patentee to the Action Closing Prosecution and referred to as Chapter <905> Uniformity of Dosage Units (2011) (Ex. 7) and Chapter <905> Uniformity of Dosage Units (2007) (Ex. 8).

11. Chapter <905> Uniformity of Dosage Units (2007), Ex. 8, specifies at p.1 that: "Content Uniformity is the default test and may be applied in all cases. The test for Weight Variation is applicable for dosage forms specified as W1, W2, W3, and W4.

12. Patentee's unit dose film products manufactured in accordance with the '080 Patent, including its Suboxone® sublingual unit dose film products are **not** dosage forms W1, W2, W3 or W4 as disclosed in the box on page 1, first column, in Chapter <905> Uniformity of Dosage Units (2011), Ex. 7.

13. **Patentee's unit dose film products manufactured in accordance with the '080 Patent, including its Suboxone® sublingual unit dose film products are considered an "Others" dosage form for which CU or Content Uniformity with assaying is required.** See, Table 1, second column, Chapter <905> Uniformity of Dosage Units (2011), Ex. 7.

14. Patentee's unit dose film products manufactured in accordance with the '080 Patent, including its Suboxone® sublingual unit dose film products, are **not** the "Tablets-Coated-with-a-Film" dosage forms in Table 1, Chapter <905> Uniformity of Dosage Units (2011), Ex. 7, second column.

15. **Weight Variation always requires that the relevant party "[c]arry out an assay for the drug substance(s) on a representative sample of the batch using an appropriate analytical method."** *See* Chapter <905> Uniformity of Dosage Units (2011), Ex. 7, p. 3, first column.

Dated this 29th day of August, 2013

B. Arlie Bogue

RELATED PROCEEDINGS APPENDIX

NONE.

CERTIFICATE OF SERVICE

It is certified that a copy of this Appellant'S APPEAL BRIEF has been served, by first class mail, postage prepaid, on March 10, 2014, in its entirety on the third party requester as provided in 37 CFR § 1.903 and 37 CFR § 1.248 at the address below.

DANIELLE L. HERRITT
McCARTER & ENGLISH LLP
265 FRANKLIN STREET
BOSTON, MASSACHUSETTS 02110

/Michael I. Chakansky/
Michael I. Chakansky
Registration No.: 31,600
Attorney for the Patentee/Appellant

Electronic Patent Application Fee Transmittal

Application Number:	95002170
Filing Date:	10-Sep-2012
Title of Invention:	POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM
First Named Inventor/Applicant Name:	7897080
Filer:	Michael I. Chakansky
Attorney Docket Number:	117744-00023

Filed as Large Entity

inter partes reexam Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Filing Appeal Brief Inter Partes Reexam	1404	1	2000	2000
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**2000**

Electronic Acknowledgement Receipt

EFS ID:	18426707
Application Number:	95002170
International Application Number:	
Confirmation Number:	6418
Title of Invention:	POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM
First Named Inventor/Applicant Name:	7897080
Customer Number:	23869
Filer:	Michael I. Chakansky
Filer Authorized By:	
Attorney Docket Number:	117744-00023
Receipt Date:	10-MAR-2014
Filing Date:	10-SEP-2012
Time Stamp:	22:47:50
Application Type:	inter partes reexam

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$2000
RAM confirmation Number	8637
Deposit Account	
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if app.)

1	Appeal Brief Filed	APPEALBRIEF.pdf	1651231 9d348a24d46525d18d5075c948a7b167e9513330	no	142
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30166 a706269ece67b5f649a39e228a1577db6943e67d	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	1681397	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re *Inter Partes* Reexamination of:	)	
	)	
US Patent No. 7,897,080	)	
Issued: March 1, 2011	)	Confirmation No.: 6418
	)	
Named Inventor: Robert K. Yang *et al.*	)	Group Art Unit: 3991
	)	
Control No.: 95/002,170	)	Examiner: Alan D. Diamond
	)	
Request Filed: September 10, 2012	)	M&E Docket: 117744-00023
	)	
Title: POLYETHYLENE OXIDE-BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM	)	H&B Docket: 1199-26 RCE/CON/REX
	)	
Mailing Date: October 3, 2013	)	

Mail Stop *Inter Partes* Reexam
Attn: Central Reexamination Unit
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

NOTICE OF CROSS-APPEAL

Pursuant to the provisions of 37 CFR §41.61(b)(2) and responsive to the Notice of Appeal filed in this matter by the Patent Owner, the Third Party Requester in the above-identified matter hereby serves notice of it's Cross-Appeal of the decision of the examiner to not adopt the proposed rejections of all claims under 35 USC §112 set forth in the section entitled "Proposed 35 USC 112 rejections not adopted" on pages 12-28 of the Right of Appeal Notice mailed December 6, 2013.

This Notice of Cross-Appeal is being served this day on the representative of the Patent Owner. The fee specified in 37 CFR. §41.20(b)(1) is submitted herewith.

Dated: January 9, 2014

Respectfully submitted,

McCarter & English LLP

By: /Danielle L. Herritt/

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Deborah M. Vernon (Reg. 55,699)
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Attorneys for Requester, BioDelivery Sciences International, Inc.

CERTIFICATE OF FIRST CLASS SERVICE

It is certified that a copy of the foregoing Notice of Cross-Appeal, including this Certificate of First Class Service have been served, by first class mail, on January 9, 2014, in their entirety on the Patent Owner in accordance with 37 C.F.R. §§ 1.903 and 1.248. The name and address of the party served is:

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(Attn: Daniel A. Scola, Jr.)
6900 JERICHO TURNPIKE
SYOSSET, NY 11791

By: /Danielle L. Herritt/

Danielle L. Herritt
Reg. 43,670

Attorney for Requester,
BioDelivery Sciences International, Inc.

McCarter & English, LLP
265 Franklin Street
Boston, MA 02110

Direct Dial: 617-449-6513
Email: dherritt@mccarter.com

Electronic Patent Application Fee Transmittal

Application Number:	95002170
Filing Date:	10-Sep-2012
Title of Invention:	POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM
First Named Inventor/Applicant Name:	7897080
Filer:	Danielle L. Herritt/Maureen Tierney
Attorney Docket Number:	117744-00023

Filed as Large Entity

inter partes reexam Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Notice of Appeal	1401	1	800	800
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**800**

Electronic Acknowledgement Receipt

EFS ID:	17873096
Application Number:	95002170
International Application Number:	
Confirmation Number:	6418
Title of Invention:	POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM
First Named Inventor/Applicant Name:	7897080
Customer Number:	23869
Filer:	Danielle L. Herritt/Maureen Tierney
Filer Authorized By:	Danielle L. Herritt
Attorney Docket Number:	117744-00023
Receipt Date:	09-JAN-2014
Filing Date:	10-SEP-2012
Time Stamp:	19:03:50
Application Type:	inter partes reexam

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$800
RAM confirmation Number	5882
Deposit Account	504876
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if app.)

1		117744_00023_080_Notice_of_CrossAppeal2014JAN9.pdf	11094 081c8c09defca7b7eb32db40c889ecd9b4f394d6	yes	3

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Notice of Cross Appeal - Third Party Requester	1	2
Reexam Certificate of Service	3	3

Warnings:

Information:

2	Fee Worksheet (SB06)	fee-info.pdf	30020 e3bd1ca306ae7a6234dd2dc20e40f78c254caa69	no	2

Warnings:

Information:

Total Files Size (in bytes):	41114

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patentee:	Yang et al.	Examiner:	Diamond, Alan D.
Patent No.:	U.S. 7,897,080	Group Art Unit:	3991
Reexamination Control No.:	95/002,170	Confirmation No.	6418
Filed:	September 10, 2012	H&B Docket:	1199-26 RCE/CON/REX
Dated:	December 26, 2013	M&E Docket:	117744-00023

Mail Stop Inter Partes Reexam
Central Reexamination Unit
Commissioner for Patents
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

Certificate of EFS-Web Transmission
I hereby certify that this correspondence is being transmitted via the U.S. Patent and Trademark Office electronic filing system (EFS-Web) to the USPTO on December 26, 2013
Signed: /Michael I Chakansky/
Michael I. Chakansky

NOTICE OF APPEAL

Dear Madame:

Pursuant to 37 C.F.R. § 41.61(a)(1), the patent owner MonoSol Rx, LLC ("Patentee") appeals to the Board of Patent Appeals and Interferences all of the Examiner's rejections of all claims delineated as rejected in the Right of Appeal Notice mailed December 6, 2013 ("RAN"), in the above-identified *inter partes* reexamination.

The filing of this Notice of Appeal does not constitute a concession or admission that the RAN was properly issued.

A fee in the amount of $800.00 is due, pursuant to 37 C.F.R. § 41.20(b)(1), for filing this Notice of Appeal. The Commissioner is authorized to charge this fee and all fees due in connection with this submission to Deposit Account No. 08-2461, and to credit any overpayments to Deposit Account No. 08-2461.

.

Respectfully submitted,

/Michael I. Chakansky/
Michael I. Chakansky
Registration No. 31,600
Attorney for the Patentee

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6900 Jericho Turnpike
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CERTIFICATE OF FIRST CLASS SERVICE

It is certified that a copy of this **NOTICE OF APPEAL** has been served, by first class mail, on Decmber 26, 2013, in its entirety on the third party requester as provided in 37 CFR § 1.903 and 37 CFR § 1.248 at the addess below.

DANIELLE L. HERRITT
McCARTER & ENGLISH LLP
265 FRANKLIN STREET
BOSTON, MASSACHUSETTS 02110

//Michael I. Chakansky/
Michael I. Chakansky
Registration No. 31,600
Attorney for the Patentee

Electronic Patent Application Fee Transmittal

Application Number:	95002170
Filing Date:	10-Sep-2012
Title of Invention:	POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM
First Named Inventor/Applicant Name:	7897080
Filer:	Michael I. Chakansky
Attorney Docket Number:	117744-00023

Filed as Large Entity

inter partes reexam Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Notice of Appeal	1401	1	800	800
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**800**

Electronic Acknowledgement Receipt

EFS ID:	17756926
Application Number:	95002170
International Application Number:	
Confirmation Number:	6418
Title of Invention:	POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM
First Named Inventor/Applicant Name:	7897080
Customer Number:	23869
Filer:	Michael I. Chakansky
Filer Authorized By:	
Attorney Docket Number:	117744-00023
Receipt Date:	26-DEC-2013
Filing Date:	10-SEP-2012
Time Stamp:	11:02:14
Application Type:	inter partes reexam

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$800
RAM confirmation Number	4134
Deposit Account	
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if app.)

1	Notice of Appeal Filed	Notice_of_Appeal_080.pdf	493656 f4fa611239bff0e0545f553c7e51298407281b41	no	3
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30097 e597780643b09818565a5688508db9edc46dbb10	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	523753	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
95/002,170	09/10/2012	7897080	117744-00023	6418

23869 7590 12/06/2013

Hoffmann & Baron LLP
6900 Jericho Turnpike
Syosset, NY 11791

EXAMINER	
DIAMOND, ALAN D	
ART UNIT	PAPER NUMBER
3991	
MAIL DATE	DELIVERY MODE
12/06/2013	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Right of Appeal Notice (37 CFR 1.953)	Control No. 95/002,170	Patent Under Reexamination 7897080
	Examiner Alan Diamond	Art Unit 3991

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address. --

Responsive to the communication(s) filed by:
Patent Owner on 03 September, 2013
Third Party(ies) on 03 October, 2013

Patent owner and/or third party requester(s) may file a notice of appeal with respect to any adverse decision with payment of the fee set forth in 37 CFR 41.20(b)(1) within **one-month or thirty-days (whichever is longer)**. See MPEP 2671. In addition, a party may file a notice of **cross** appeal and pay the 37 CFR 41.20(b)(1) fee **within fourteen days of service** of an opposing party's timely filed notice of appeal. See MPEP 2672.

All correspondence relating to this inter partes reexamination proceeding should be directed to the **Central Reexamination Unit** at the mail, FAX, or hand-carry addresses given at the end of this Office action.

If no party timely files a notice of appeal, prosecution on the merits of this reexamination proceeding will be concluded, and the Director of the USPTO will proceed to issue and publish a certificate under 37 CFR 1.997 in accordance with this Office action.

The proposed amendment filed 03 September, 2013 ☐ will be entered ☒ will not be entered*

*Reasons for non-entry are given in the body of this notice.

1a. ☒ Claims See Continuation Sheet are subject to reexamination.
1b. ☐ Claims _____ are not subject to reexamination.
2. ☒ Claims See Continuation Sheet have been cancelled.
3. ☐ Claims _____ are confirmed. [Unamended patent claims].
4. ☐ Claims _____ are patentable. [Amended or new claims].
5. ☒ Claims See Continuation Sheet are rejected.
6. ☐ Claims _____ are objected to.
7. ☐ The drawings filed on _____ ☐ are acceptable. ☐ are not acceptable.
8. ☐ The drawing correction request filed on _____ is ☐ approved. ☐ disapproved.
9. ☐ Acknowledgment is made of the claim for priority under 35 U.S.C. 119 (a)-(d) or (f). The certified copy has:
   ☐ been received. ☐ not been received. ☐ been filed in Application/Control No. _____.
10. ☐ Other _____

Attachments

1. ☐ Notice of References Cited by Examiner, PTO-892
2. ☐ Information Disclosure Citation, PTO/SB/08
3. ☐ _____

Continuation of 1a. Claims subject to reexamination are: 1-11,13-15,17-90,92-94,96-172,174-176,178-253,256,258-271,274,276-289,292 and 294-318.

Continuation of 2. Claims have been canceled are: 12,16,91,95,173,177,254,255,257,272,273,275,290,291 and 293.

Continuation of 5. Claims rejected are: 1-11,13-15,17-90,92-94,96-172,174-176,178-253,256,258-271,274,276-289,292 and 294-318.

Summary of Proceedings

A Request pursuant to 37 CFR 1.913 for inter partes reexamination of claims 1-299 of U.S. Patent 7,897,080 (hereinafter "the '080 patent") was filed September 10, 2012 by Third Party Requester. Accompanying the request was a Rule 1.132 declaration of Edward D. Cohen ("Cohen Declaration"). An Order granting inter partes reexamination and a non-final Office action rejecting claims 1-299 of the '080 patent were mailed October 22, 2012. The Office action was re-mailed November 29, 2012.

On March 13, 2013, Patent Owner filed a response including an amendment which amends claims 1, 13, 14, 28, 81, 82, 92, 93, 107, 114, 160, 161, 174, 175, 189, 242, 244, 262 and 280; cancels claims 12, 16, 91, 95, 173, 177, 254, 255, 257, 272, 273, 275, 290, 291 and 293; and adds new claims 300-318. The response further includes a Rule 1.132 declaration by Arlie Bogue (hereafter "Bogue Declaration I") and a Rule 1.132 declaration by David T. Lin (hereafter "Lin Declaration").

On April 12, 2013, Third Party Requester filed comments including Rule 1.132 declarations by Jason O. Clevenger (hereafter "Clevenger Declaration") and Maureen Reitman (hereafter "Reitman Declaration").

An Action Closing Prosecution (ACP) rejecting claims 1-11, 13-15, 17-90, 92-94, 96-172, 174-176, 178-253, 256, 258-271, 274, 276-289, 292 and 294-318 was mailed July 31, 2013.

On September 3, 2013, Patent Owner filed a response, including a proposed claim amendment and another Rule 1.132 declaration by Arlie Bogue (hereafter "Bogue Declaration II").

On October 3, 2013, Third Party Requester filed comments.

Art Cited in Rejections in this Right of Appeal Notice (RAN)

Chen et al, WO 00/42992, hereafter “Chen”.

Staab, U.S. Patent 5,393,528.

Le Person et al, “Near infrared drying of pharmaceutical thin films: experimental analysis of internal mass transport,” Chemical Engineering and Processing, Vol. 37, pp. 257-263, (1998), hereafter "Le Person".

Horstmann et al, U.S. Patent 5,629,003, hereafter “Horstmann”.

U.S. Patent 4,365,423 to Arter et al, hereafter “Arter”. Arter was made of record in the instant reexamination proceeding by Patent Owner in an IDS filed 01/29/13.

U.S. Patent 5,881,476 to Strobush et al, hereafter “Strobush”. Strobush is of record in grandparent U.S. Patent 7,357,891, as well as being made of record in the instant reexamination proceeding by Patent Owner in an IDS filed 01/29/13.

Claim Amendment Not Entered

The proposed amendment filed September 3, 2013 will not be entered for the following reasons. The amendment of each independent claim to recite that the resulting film is "self-supporting” would not advance prosecution and would not place the proceeding in better form for appeal by materially reducing or simplifying the issues for appeal. The Chen reference alone and in combination with Staab have been relied upon to reject all claims in the non-final Office action mailed 11/29/12 and in the ACP. Patent Owner acknowledged in the earlier Remarks filed 03/13/13 (pp. 75-56) that Chen at p. 15, lines 30-31 specifically describes its films are stand-alone and self-supporting. The proposed amendment would not ameliorate any prior art rejection of record.

Scope of Claims

In reexamination, patent claims are construed broadly. *In re Yamamoto*, 740 F.2d 1569, 1571, 222 USPQ 934, 936 (Fed. Cir. 1984) (claims given "their broadest reasonable interpretation consistent with the specification"). This reexamination proceeding contains claims 1-11, 13-15, 17-90, 92-94, 96-172, 174-176, 178-253, 256, 258-271, 274, 276-289, 292 and 294-318 directed to a process for manufacturing a resulting film(s) suitable for commercialization and regulatory approval. The claim amendment containing these claims is dated 07/26/13 and is a corrected version of the informal amendment filed 03/13/13. Claim 1 is representative:

1. (Twice Amended) A process for manufacturing a resulting film suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said [making a]film having a substantially uniform distribution of components comprising a substantially uniform distribution of said active in individual dosage units of said resulting film, comprising the steps of:

(a) forming a masterbatch pre-mix comprising a solvent and a polymer selected from the group consisting of water-soluble polymers, water-swellable polymers and combinations thereof;

(b) adding [an]said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, to a pre-determined amount of said masterbatch pre-mix to form a flowable polymer matrix, said matrix having a substantially uniform distribution of said active;

(c) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(d) controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus and evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first [10]4 minutes [or fewer]by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, wherein during said drying said flowable polymer matrix temperature is 100 ℃ or less; [and]

(e) forming [a]said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained; and

(f) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units sampled from different locations of said resulting film, said tests indicating that uniformity of content in the amount of the active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration.

Claims 1, 82, 161 and 315-318 recite a step of forming a flowable polymer matrix comprising a recited polymer, a solvent and a recited active, said matrix having a

substantially uniform distribution of said active. With respect to the “matrix”, the ‘080 patent, for example, states the following:

> When the active is combined with the polymer in the solvent, the type of matrix that is formed depends on the solubilities of the active and the polymer. If the active and/or polymer are soluble in the selected solvent, this may form a solution. However, if the components are not soluble, the matrix may be classified as an emulsion, a colloid, or a suspension (see col. 22, lines 22-28).
>
> After the desired components are combined to form a multi-component matrix, including the polymer, water, and an active or other components as desired … (see col. 25, lines 55-57).

Accordingly, the "matrix” is taken to be the material that results from mixing the polymer, solvent and active.

With respect to viscoelasticity in steps (d) and (e) of claim 1 and in steps (c) and (d) of claims 82, 161 and 315-318, it is noted that the matrix prior to evaporating the solvent (water) may be viscoelastic, and the viscoelasticity is present due, for example, to the fact that a hydrocolloid has been added. In particular, the '080 patent teaches the following (bold emphasis added):

> The viscosity of the liquid phase is critical and is desirably modified by customizing the liquid composition to a **viscoelastic** non-Newtonian fluid with low yield stress values .... Formation of a **viscoelastic** or a highly structured fluid phase provides additional resistive forces to particle sedimentation. (Col. 8, lines 32-38).
>
> The addition of hydrocolloids to the aqueous phase of the suspension increases viscosity, may produce **viscoelasticity**, and can impart stability depending on the type of **hydrocolloid**, its concentration and the particle composition, geometry, size and volume fraction. (Col. 8, lines 42-46).
>
> For **viscoelastic** fluid systems, a rheology that yields stable suspensions for extended time period, such as 24 hours, must be balanced with the requirements of high-speed film casting operations. (Col. 8, line 66 through Col. 9, line 2).

> The rheology requirements for the inventive compositions and films are quite severe. This is due to the need to produce a stable suspension of particles, for example 30-60 wt. %, in a **viscoelastic** fluid matrix with acceptable viscosity values throughout a broad shear rate range...
>
> In film casting or coating, rheology is also a defining factor with respect to the ability to form films with the desired uniformity. Shear viscosity, extensional viscosity, **viscoelasticity**, structural recovery will influence the quality of the film. (Col. 9, lines 9-20).
>
> Desirably, the films or film-forming compositions of the present invention have a very rapid structural recovery, i.e. as the film is formed during processing, it doesn't fall apart or become discontinuous in its structure and compositional uniformity. Such very rapid structural recovery retards particle settling and sedimentation. Moreover, the films or film-forming compositions of the present invention are desirably shear-thinning pseudoplastic fluids. Such fluids with consideration of properties, such as **viscosity and elasticity**, promote thin film formation and uniformity. (Col. 9, lines 31-40).
>
> Compositions P-R show the effects of **visco-elastic** properties on the ability to coat the film composition mixture onto the substrate for film formation .... This product coated the substrate but would not stay level due to the change in the **visco-elastic** properties of the wet foam. (Col. 35, lines 55-57, and 61-63).

While the ‘080 does not state what is an example of a hydrocolloid, a well-known hydrocolloid in the art is the water-soluble polymer hydroxypropyl methylcellulose (HPMC), which is used in most of the examples of the ‘080 patent. The Chen reference teaches that HPMC is a hydrocolloid (see p. 14, lines 22-27).

Each of the independent claims recites the added term “analytical chemical tests”. This term is not stated or defined in the '080 patent specification. However, the '080 patent teaches that "[i]t may be desirable to test films of the present invention for chemical and physical uniformity during the manufacturing process"; and that “[a]ny conventional means for examining and testing the film pieces may be employed, such as, for example, visual inspection, use of analytical equipment, and any other suitable

means known to those skilled in the art (see col. 28, line 66 through col. 29, line 1; and col. 29, lines 35-39). The '080 patent teaches checking film thickness, overall appearance, examination by the naked eye or under slight magnification, cutting the films into dosage forms and weighing the doses, or dissolving individual doses and testing for the amount of active therein (see col. 29, lines 3-47; and col. 31, line 37 through col. 32, line 39). It is clear that when the '080 patent refers to “physical” uniformity it is referring to, for example, uniformity based on the appearance of the film or the weight of individual doses cut from the film. Likewise, it is clear that when the '080 patent refers to “chemical” uniformity, it is referring to uniformity with respect to the actual amount of active, i.e., chemical, present in the sample. Accordingly, the term “analytical chemical tests” when read in light of the ‘080 patent specification means analytical tests for determining the amount of active content in the recited sample. Pages 56-57 of the Remarks filed 03/13/13 state that physical tests do not determine the actual amount of active in the sample, and that with "chemical uniformity type tests involving analytical equipment … [there is] actual testing of the uniformity of content of the amount of active."

It is noted the ‘080 patent teaches at col. 31, lines 37-44, that a “uniform distribution of components” can be determined by examination by either the naked eye or under slight magnification, and that "by viewing the films it was apparent that they were substantially free of aggregation, i.e. the carrier and the actives remained substantially in place and did not move substantially from one portion of the film to another … [t]herefore, there was substantially no disparity among the amount of active

in any portion of the film." An alternative means for evaluating uniformity is to cut the film into individual doses and measure the weight of the doses (col. 31, line 46 through col. 32, line 45). The '080 patent notes that "films of substantially similar size cut from different locations of the same film contain substantially the same amount of active." (col. 32, lines 37-39).

Proposed Claim Rejection - 35 U.S.C. § 314(a)

On pages 9-11 of the Comments filed 04/12/13, Third Party Requester proposes that all the claims be rejected under 35 USC 314(a) as enlarging the scope of the patent claims. This proposed rejection **is not adopted** for the reasons that follow.

Third Party Requester argues the following on pp. 9-10 of the Comments filed 04/12/13:

> Applicant amends every independent claim to broaden the term "flowable" to encompass viscosities that are not flowable. Step (c) of issued claim 1 and step (b) of issued claims 82 and 161 have been amended as follows:
>
> > casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;
>
> Each and every new independent claim also includes this recitation. Exhibit E provides the viscosity of common materials. As Exhibit E indicates, a viscosity of 100,000 cps corresponds to mincemeat. Materials having the viscosity of mincemeat are not flowable. The new recitation expands the polymer matrix cast in this step beyond that claimed in issued claims 1, 82, and 161--i.e., to include a polymer matrix that is not flowable--and thereby impermissibly broadens the scope of the claims beyond those issued in the '080 Patent.

This is unpersuasive. Exhibit E of the Comments filed 04/12/13 shows the viscosities of "common liquids", and mincemeat as well as toothpaste are in the list and

can have a viscosity as high as 100,000 cps. Viscosity is equal to shear stress/shear rate, and is a measure of resistance to flow. The higher the viscosity, the more resistance to flow. While mincemeat and toothpaste have more resistance to flow compared to other liquids in Table E, such as milk (viscosity of 1 or 2 cps) and mayonnaise (viscosity of 20,000 cps), mincemeat and toothpaste are flowable. Accordingly, contrary to Third Party Requester's argument, a flowable polymer matrix as here claimed can have a viscosity of about 400 to about 100,000 cps (paragraph bridging cols. 16-17 of the '080 patent) and the instant claims are not broadened.

Third Party Requester argues the following on pp. 10-11 of the Comments filed 04/12/13:

> The issued claims referred to forming a visco-elastic film in less than 10 minutes. The only discussion in the specification, including the examples, for drying for 10 minutes is referring to total drying time:
>
> > For instance, the films of the present invention desirably are dried for 10 minutes or less. Drying the films at 80 °C for 10 minutes produces a temperature differential of about 5 °C. This means that after 10 minutes of drying, the temperature of the inside of the film is 5 °C less than the outside exposure temperature.
> >
> > '080 Patent 13:23-28.
>
> The '080 Patent teaches in this passage that keeping the total drying time short, allows the films to be dried at higher temperatures without heat degradation.
>
> Applicants amends every independent claim to broaden the drying step to require only that viscosity be increased in the first 4 minutes. Step (d) of issued claim 1 and step (c) of issued claims 82 and 161 have been amended as follows:
>
> > ...evaporating at least a portion of said solvent.., to form a visco-elastic film...within about the <u>first</u> [10] 4 minutes [or fewer] <u>by rapidly increasing</u>

> the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution...of said film ....

Each and every new independent claim also includes this recitation.

This amendment attempts to "redefine" the evaporating step by shifting from what would be construed as a total drying requirement to what is now merely an initial drying requirement. This amendment thus broadens the step. As newly recited, this step now is accomplished "by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying." This new claim does not require 10 minutes drying time, but only requires an increase in viscosity in the first 4 minutes.

This is unpersuasive. In issued independent claims 1, 82 and 161, the evaporating of at least a portion of the solvent was done "to form a visco-elastic film within about 10 minutes or fewer to maintain said substantially uniform distribution...of said film ....". This is not a total drying requirement. In fact, the '080 patent expressly teaches the following at col. 13, lines 53-59 (bold emphasis added):

> The resulting dried film is a visco-elastic solid. The components desirably are locked into a uniform distribution throughout the film. Although minor amounts of liquid carrier, i.e., water, may remain subsequent to formation of the visco-elastic, the film may be **dried further** without movement of particles, if desired.

Accordingly, the "within about the first 4 minutes" does not broaden the "within about 10 minutes or fewer" time period in the issued independent claims.

Proposed Claim Rejections - 35 USC § 112

The following is a quotation of 35 U.S.C. 112 (pre-AIA), first paragraph:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Proposed 35 USC 112 rejections not adopted:

On pages 11-23 of the Comments filed 04/12/13, Third Party Requester proposes several rejections under 35 USC 112, first and second paragraphs. For the following reasons, Third Party Requester's proposed 35 USC 112 rejections **are not adopted**. The lettering used below is consistent with the lettering used by Third Party Requester on pp. 11-23.

A. Third Party Requester proposes that all pending claims be rejected as lacking enablement, clarity and written description due to the recitation "suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units" (see the Comments of 04/12/13, pp. 11-14; and the first paragraph in each of the independent claims).

With respect to enablement, Third Party Requester argues that Patent Owner has taken the position that Chen lacks an enabling disclosure because it "lacks sufficient information contained within to allow regulatory FDA approval" of its films; and that if FDA approvability is the standard for enablement, then the '080 patent specification is similarly lacking (Comments of 04/12/13, pp. 11-13). Third Party Requester cites ¶ 8 of the Clevenger Declaration and argues that "[e]ven the Bogue Declaration [I] fails to provide evidence that its "lots" meet the recited standards." (Comments of 04/12/13, p. 13). ¶ 6 of the Clevenger Declaration states the following:

> 6. The analysis in the Bogue Declaration [l] is not consistent with the currently adopted definition of content uniformity as described in USP <905> Uniformity of Dosage Units. The calculation in paragraphs 9 and 10 of the Bogue Declaration [l] are not included within the definition of content uniformity as described in USP <905> Uniformity of Dosage Units.

With respect to lack of clarity, Third Party Requester argues the recitation is ambiguous and unclear because there is no set chemical tests or standards required; and that USP General Chapter <905> which is cited in ¶ 16 of the Lin Declaration "sets forth a number of standards, each of which is entirely different from anything claimed, argued or described in the '080 Patent." (Comments of 04/12/13, pp.13-14)

With respect to written description, Third Party Requester argues the following on p. 14 of the Comments filed 04/12/13:

> Finally, because the new "suitable..." recitation in the pending claims extends beyond what was disclosed or referenced in the specification, the claims lack written description. That is, even if the FDA did have one standard that would apply to all of the films manufactured by the methods claimed in the '080 Patent--which it does not--the standards have changed over time. For example, in order to harmonize with international standards, the USP General Chapter <905> cited by Applicant in the Lin Declaration, was updated at least twice (i.e., on April 20, 2007, and again on December 1, 2011). See Exhibit J and Exhibit K, and Clevenger Decl. ¶ 4. Accordingly, this new recitation appears to reference something that did not exist when the application was filed, and therefore the claims lack written description.

This proposed rejection **is not adopted** for the following reasons. Said recitation is enabled and definite in view of the recitation in each of the independent claims of a process step of performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units sampled from different locations of said resulting film, said tests indicating that uniformity of content in the amount of the active varies by no more than 10% in independent claims 1, 82, 161, and

315-317, or less that 5% in claim 318. The claims do not require commercialization and regulatory approval, they set forth suitability for commercialization and regulatory approval. The bright line test for such suitability is based on performing analytical chemical tests for uniformity of content of active, said tests showing a particular variation of active, for example, not more than 10%.

The fact that no specific tests are mentioned in the claims is of no consequence since one of ordinary skill in the art knows what tests can be used. The '080 patent teaches testing the films for physical and chemical uniformity (col. 28, lines 6-67) and that "[a]ny conventional means for examining and testing the film pieces may be employed, such as, for example … the use of analytical equipment, and any other suitable means known to those skilled in the art." (col. 29, lines 35-38). In fact, ¶ 7 of Third Party Requester's Reitman Declaration uses a well-known technique, i.e., HPLC.

The Clevenger Declaration argues that the calculations in paragraphs 9 and 10 of Bogue Declaration I are not included within the definition of content uniformity as described in USP <905> Uniformity of Dosage Units. However, the instant claims do not state that any calculation has to meet the definition of content uniformity as described in USP <905> Uniformity of Dosage Units. The claims require a resulting film "suitable" for commercialization and regulatory approval which meets FDA standards. The bright line test in the claims for such suitability, as seen, for example, in step (f) of claim 1, is an active content that varies by no more than a particular percentage. In claim 1, the active content varies by no more than 10%.

Said recitation has written description in the '080 patent. The desire to prepare films that are suitable for commercialization and regulatory approval is noted in the Background of the Related Technology section of the '080 patent at col. 3, lines 58-60. Likewise, the Background of the Related Technology section teaches the following at col. 2, lines 36-46:

> Failure to achieve a high degree of accuracy with respect to the amount of active ingredient in the cut film can be harmful to the patient. For this reason, dosage forms formed by processes such as Fuchs, would not likely meet the stringent standards of governmental or regulatory agencies, such as the U.S. Federal Drug Administration ("FDA"), relating to the variation of active in dosage forms. Currently, as required by various world regulatory authorities, dosage forms may not vary more than 10% in the amount of active present. When applied to dosage units based on films, this virtually mandates that uniformity in the film be present."

Even further, col. 15, lines 37-42 of the '080 patent teach "the uniformity of the present invention is determined by the presence of no more than a 10% by weight of pharmaceutical and/or cosmetic variance throughout the matrix. Desirably, the variance is less than 5% by weight, less than 2% by weight, less than 1% by weight, or less than 0.5% by weight."

B. Third Party Requester proposes that all pending claims be rejected as lacking clarity and written description due to the recitation "chemical analytical tests" (Comments of 04/12/13, pp. 14-15). In particular, Third Party Requester argues the following on pp. 14-15 of the Comments filed 04/12/13:

> 1. *Lack of Clarity*
>
> Independent claims 1, 82, 161 and 315-318 newly recite the term "analytical chemical tests." The term "analytical chemical tests" is vague and unclear. What is an "analytical chemical test" and how does it differ from a non-

chemical test or a non-analytical test? Applicant does not disclose any analytical chemical tests or testing of active in the specification, but rather the desirability of testing for chemical and physical uniformity. Testing for chemical uniformity would include weight variation testing according to the FDA, but Applicant insists this is not an analytical chemical test. Compare Exhibit J at p. 1 to Reply at p. 58-59.

Is a chemical transformation required? If so, HPLC testing would not be an analytical chemical test. And HPLC testing is commonly used to assess active content. The confusion is compounded by Applicant's statements that weighing cannot be relied upon to assess uniformity of content data. However, the FDA clearly provides that weight variation testing is a content uniformity test. Exhibit J at p. 1. In short, based upon the plain language in the '080 Patent and compounded by Applicant's arguments, it is not clear what is, and what is not, an analytical chemical test.

2. *Lack of Written Description*

Nowhere in the '080 Patent does the Applicant describe the type, much less the amount, of analytical chemical testing required for regulatory approval. And even if it did, as discussed above, requirements for regulatory approval vary greatly, and change over time. Nowhere in the specification is the term "analytical chemical tests" written or described.

This proposed rejection **is not adopted** for the following reasons. As noted above in the Scope of Claims section, which cites to the '080 patent specification for support, the term “analytical chemical tests” means analytical tests for determining the amount of active content in the recited sample. The distinguishing point between analytical chemical tests as here claimed and physical testing (analytical or non-analytical) is whether there is direct testing for the amount of active. Accordingly, the term “analytical chemical tests” is clear and has written description.

C. Third Party requester proposes that all pending claims be rejected as lacking clarity and enablement since the claims now recite that the individual dosage units vary by no more than 10%, 5%, 2%, 1% or 0.5% (Comments of 04/12/13, pp. 15-17).

In particular, with respect to lack of clarity, Third Party requester argues the following on p. 16 of the Comments filed 04/12/13:

> The data presented in the Bogue Declaration [I] reflect "the uniformity of content of active of individual dosage units within particular lots and across different lots." Bogue Decl. [I,] ¶ 8 (emphasis added) and Appendices A, B and C. But "lots" are not equated to "resulting films." And there is also no reference to a "lot," "lots," or "lots of resulting films" in any of the claims. While Applicant may act as its own lexicographer in drafting the specification, it may not do so after the application has been filed. The fact is, Applicant's "uniformity" data--presented in the Bogue Declaration [I]--fails to demonstrate individual dosage units where the active varies by no more than 10%, 5%, 2%, 1% or 0.5% as claimed.
>
> Moreover, Bogue' s Appendix A, which conceals lot variation by dividing it by the lot average, does not negate Bogue's Appendix B, which clearly shows that even the lot data does not satisfy the 10% variance limitation. It only introduces confusion with respect to the meaning of the claims.

With respect to lack of enablement, Third Party Requester argues the following on p. 16-17 of the Comments filed 04/12/13:

> Applicant's arguments also create an enablement problem as to the claimed uniformity. Applicant argues that the prior art does not demonstrate its claimed uniformity because "physically observable properties of the resulting film product, for example, its appearance and weight...do not indicate that the amount of active in individual dosage units varies by no more than 10%..." Reply pp. 54-55. "Even if the film appears uniform, analytical chemical tests must then be conducted to verify uniformity of content at the prescribed level." Reply p. 59. In short, Applicant argues that uniformity may only be determined by analytical chemical testing of film, not merely by physically observable properties of film. There is no indication or evidence in the '080 Patent that the disclosed methods result in a film with the claimed uniformity as determined by analytical chemical testing. In over 100 examples, the '080 Patent never demonstrates that any disclosed method results in a film that satisfies the recited active variation

> limitation as determined by analytical chemical testing. Applicant erroneously states that "analytical chemical testing is used in the '080 Patent to establish the actual amount of active in samples," citing Example M. Reply p. 59, last full ¶. The '080 Patent discloses no analytical chemical test for active with respect to Example M. '080 Patent 33:10-34:34. In fact, Example M contains no active. A red dye does not fall into the broadest reasonable interpretation of a bioactive or a pharmaceutical active.
>
> Applicant now improperly attempts to remediate its enablement problem by providing the data in the Bogue Declaration [I]. First, a declaration cannot be used to provide enablement after the fact. This is particularly true when the declaration methods are not well-described, and what is described does not match even a single claim. Second, and most importantly, the data does not even meets [sic] its own recited requirement. Appendix B of the Bogue Declaration [I] shows that the active in the individual dosage units does vary by more than 10%. Indeed, Applicant admits in the Bogue Declaration [I] that only 46 of the 73 lots (i.e., only 63% of the lots) have active varying less than 5%, and only 1 lot (i.e., only 1% of the lots) has active varying less than 2%. Finally, absolutely no lots have active varying less than 1% or 0.5%.
>
> In short, none of these variation requirements are enabled in the '080 Patent specification. And the Bogue Declaration [I] only serves to prove that its own commercial method--even if it were to fall within the claims--fails to produce films that meet the claimed variation requirements. By Applicant's own admission, without a demonstration of chemical tests, there is no indication that the disclosed methods met these requirements. Reply p. 67, lines 10-15. And physical tests are not enough, according to Applicant. *Id.*

This proposed rejection **is not adopted** for the following reasons. It is noted that issued claim 255, 273 and 291 (now cancelled), respectively, depended from issued independent claims 1, 82 and 161 and required a step of forming a plurality of individual dosage units of substantially the same size, wherein the active content of individual dosage units varies no more than 10%. Also, as discussed above, col. 15, lines 37-42 of the ‘080 patent teach “the uniformity of the present invention is determined by the presence of no more than a 10% by weight of pharmaceutical and/or cosmetic variance throughout the matrix. Desirably, the variance is less than 5% by weight, less than 2%

by weight, less than 1% by weight, or less than 0.5% by weight." There is no requirement that a specification present working examples of a claimed invention. In any event, Example E of the 080 patent, a film is prepared containing loratadine as an active ingredient and is cut into dosage forms of substantially identical size (see col. 31-32). It was found that each dosage consistently weighed 0.04 grams, "which show the distribution of the components within the film was consistent and uniform. This is based on the simple principle that each component has a unique density. Therefore, when the components of different densities are combined in a uniform manner in a film, as in the present invention, individual dosages [sic] forms from the same film of substantially equal dimensions, will contain the same mass." (See col. 32, lines 26-33). Likewise, the cut pieces in the example at col. 37, lines 52-67 weighed 70 mg $\pm$ 0.7 mg "demonstrating the uniformity of the composition of the film."

Patent Owner's Bogue Declaration I is not part of the '080 patent specification, but supports non-adoption of the proposed lack of enablement and clarity rejections. ¶ 4 of Bogue Declaration I states that each of 73 lots containing 2,000,000 individual dosage units per lot were manufactured according to the steps set forth in ¶ 4, which include forming a resulting pharmaceutical film and performing chemical analytical tests for uniformity of content of the active in substantially equally sized dosage units of the sampled resulting pharmaceutical film. As seen in Appendices A and C of Bogue Declaration I, a variation as low as 2% was obtained. The variation was calculated by taking the maximum active content of a lot minus the minimum active content of that lot, divided by the average active content of that lot (see ¶ 9). While the red dye of the '080

Patent's Example M is not a pharmaceutical active or bioactive active, a similar calculation is made in Example M at col. 34, lines 18-20 based on absorbance measurements, which are directly related to concentration of the red dye (see also col. 33, lines 49-51). Further, ¶¶ 10-11 of Bogue Declaration I, citing Appendix B, allege that "the amount of active across different lots of resulting film varies no more than 10% from the desired amount of the active."

D. Third Party Requester proposes that claims 82-90, 92-94, 96-160, 261-271, 274, 276-278, 298, 304-307, 313 and 315 be rejected as lacking clarity, written description and enablement due to the term "varies by no more than 10% from desired amount of active" (Comments of 04/12/13, pp. 17-19). In particular, Third Party Requester argues the following on pp. 18-19 of the Comments filed 04/12/13:

> In contrast to the maximum active variance limit recited in each of the independent claims and discussed directly above--step (f) of claims 82 and 315 includes the new recitation that "the amount of said active in said resulting film and said additional resulting films varies no more than 10% from the desired amount of the active."
>
> 1. *Lack of clarity*
>
> Whereas the previously discussed new recitation allows a larger maximum variation of active content, this new recitation allows a maximum variation of 20% (±10% around a target) in active content. Again, Applicant introduces clarity issues by attempting to amend its claims to match its new data. This new recitation in step (f) of claims 82 and 315 is particularly confusing because it appears to be broader than the uniformity recitation already present in step (e) of claims 82 and 315. The new language only appears to indicate that repeating the claimed method need not produce consistent films.
>
> 2. *Lack of written description*
>
> The new language introduced into claims 82 and 315 allows a maximum variation of 20% (±10% around a desired amount or target) in the active content. Nowhere in the '080 Patent is this language found. Nor is this new definition of

> uniformity described or exemplified. Also there is absolutely no support for the idea that some uniformity is required within a resulting film and another is required between films. This language has been entirely fabricated in an attempt to retroactively support their claims with new data, but data in the specification does not support newly recited maximum variation of 20% in active content. As set forth in the MPEP: "If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from...the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application." MPEP 2163.02. The claims lack written description because nowhere in the specification are these new limitation [sic] described.
>
> 3. *Lack of enablement*
>
> Applicant's arguments also create the same enablement problem as to the maximum variation of active as discussed above. That is, there is no evidence in the '080 Patent that the disclosed methods result in a film with the claimed uniformity--as determined by analytical chemical testing. And a declaration cannot be used to provide enablement after the fact.

This proposed rejection **is not adopted** for the following reasons. There is no lack of clarity because "the amount of said active in said resulting film and said additional resulting films varies no more than 10% from the desired amount of the active" means that the amount of active is in said resulting film and said additional resulting films is $\pm$ 10% around the desired amount. In fact, the '080 patent teaches that "as required by various world regulatory authorities, dosage forms may not vary more than 10% in the amount of active present." (See col. 2, lines 42-45). It is well-known and conventional in the art that active content of a dosage is allowed to be $\pm$ 10% from the desired amount, e.g., the amount of active the dosage is supposed to have.

Further, there is no requirement that a specification present working examples of a claimed invention. In any event, as discussed above, in Example E at col. 30, line 64 through col. 32, line 44, a film is prepared containing loratadine as an active ingredient, then cut into substantially identical size dosage forms that are weighed and shown to

have a consistent weight of 0.04 gm. This is evidence that the distribution of components within the film is consistent and uniform. The '080 patent teaches an alternative method of determining uniformity of the active is to cut the film into individual doses, and then dissolve and test the doses for amount of active (see col. 32, lines 34-39). This alternative type of testing is the analytical chemical testing here claimed.

E. Third Party Requester proposes that all pending claims be rejected as lacking clarity due to the term "rapidly increasing the viscosity of said flowable polymer matrix" (Comments of 04/12/13, p. 19). In particular, Third Party Requester argues that "rapidly" is a relative term with no benchmark; it only refers to the timing at which a desired result is obtained; and there is no indication of the degree to which the viscosity must be increased (Comments of 04/12/13, p. 19).

This proposed rejection **is not adopted** for the following reasons. The rapid increase in viscosity takes place during the step of evaporating the solvent from the flowable polymer matrix, and each of the independent claims sets forth the time period during evaporation in which the rapid increase takes place, i.e., within the first 4 minutes. Thus, the rapid increase occurs within this time frame. The claims also set forth the reason for such an evaporation time, i.e., "to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film." Accordingly, it is unnecessary to set forth a degree of viscosity increase for "rapidly increasing the viscosity".

F. Third Party Requester proposes that all claims be rejected as lacking clarity due to the recitation "during said drying said flowable polymer matrix temperature is 100 °C or less" (Comments of 04/12/13, pp. 19-20). In particular, Third Party Requester argues the limitation describes the temperature of the flowable polymer matrix (i.e., the matrix before it has been dried to a film), not the visco-elastic film; and that it is unclear whether the limitation may be satisfied if the flowable polymer matrix began the drying at a temperature of 100°C or less, or if it requires the temperature to be less than 100°C throughout the drying step (Comments of 04/12/13, p. 19).

This proposed rejection **is not adopted** for the following reasons. The recitation states "during drying" the flowable polymer matrix temperature is 100°C or less. The claims specify that the flowable polymer matrix has a viscosity of about 400 to about 100,000 cps. As long as the polymer matrix has this viscosity during drying, it is a flowable polymer matrix and its temperature must be 100°C or less.

Third Party Requester argues that "[s]ince every single recited solvent has a boiling point of 100 °C or less, it is not clear how the matrix would reach a temperature above the boiling point of the solvent contained therein"; and it is not clear what the recitation excludes "[s]ince the oven temperatures utilized in the Examples of the '080 patent are less than 100 °C." (Comments of 04/12/13, p. 20).

This argument is unpersuasive because the instant claims do not specify an oven temperature or specific solvent, and the '080 patent is not limited to its examples. The '080 patent specification teaches drying temperatures of "about 100°C or less" (col. 27, lines 53-55), which includes temperatures slightly above 100°C.

H. Third Party Requester proposes that all pending claims be rejected as lacking clarity, written description and enablement for the following reasons which are set forth on pp. 21-23 of the Comments filed 04/12/13 and reproduced below:

> 1. *Lack of clarity*
>
> Applicant adds so many new and different recitations regarding variation limitations to its independent claims, with multiple distinct variation levels, even within the same claim, that the claims are mired in ambiguity and uncertainty.
>
> Taking independent claim 82 as a representative claim, the problem with Applicant' s approach is readily apparent. The preamble recites that the film must be suitable for regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the FDA relating to variation of an active in individual dosage units. Later in step (e), claim 82 requires that the film is suitable for FDA approval without connecting the suitability to analytical chemical tests or the standards of the FDA relating to variation of active content recited in the preamble. Are analytical chemical tests required to show the FDA standards are met? Must the film meet the FDA standards relating to variation of an active? Those limitations are not recited in the body of the claim. Then, to add more confusion, analytical chemical tests are required in a different part of step (e) to "indicate" that the active varies by no more than 10% in individual dosage units. First, this is not the FDA standard for approval. As discussed above, the standard is defined in USP General Chapter <905>. See Exhibit J. Second, what does it mean to "indicate" that the active varies by no more than 10%? Yet, there is one more layer of confusion. New step (f) requires that the amount of active varies no more than 10% from the desired amount of active. What is the desired active content? New step (f) also recites "said resulting film and said additional resulting films." How does a "resulting film" differ from "additional resulting films"? Where is that described in the specification? Or demonstrated for that matter? There is simply no discussion of $\pm$10% from a target anywhere in the specification. And certainly not with respect to comparison of "resulting films." And why is the amount of variation so large? This new claim amendment, and the data presented in the Bogue Declaration [I], only serve to demonstrate that repeating the claimed method does not produce consistent films. The Applicant has neither described nor enabled the method it now seeks to claim.
>
> Every single independent claim is similarly confusing, each with their own combination of the many shades of "uniformity" that individually and collectively create a hopeless morass of confusion.

> 2. *Lack of written description*.
>
> As discussed above, there is absolutely no support for the recitation of "varying by no more an [sic] 10% from a desired target." And certainly none for this variation between "resulting films" and "additional resulting films." In addition, if Chen's disclosure is not enabling with respect to the various regulatory authority recitations, neither is its own. See Section above regarding the Lin Declaration.
>
> 3. *Lack of enablement*
>
> Nowhere in any of the over 100 examples in the '080 Patent is any film demonstrated to meet any of the newly recited "uniformity" limitations. No analytical chemical tests are performed with respect to an active. No results of analytical chemical tests of active are provided. No demonstration is made that the active varies by no more than 10% in individual dosage units. No demonstration is made that "resulting films" and "additional resulting films" vary by no more than 10% from a desired target. It almost seems like Applicant is not familiar with the '080 Patent because every recitation added to distinguish claims from the cited art lacks written description and/or enablement in the '080 Patent specification.

This proposed rejection **is not adopted** for the following reasons. As noted above, the instant claims do not require a step of getting regulatory approval. Rather, they set forth suitability for regulatory approval based on performing analytical chemical tests for uniformity of content of active, said tests showing a particular variation of active. For example, in step (f) of claim 1 and step (e) of claim 82, the active content varies by no more than 10%. A skilled artisan, using known analytical chemical tests, knows how to measure active content and determine uniformity of active content in substantially equally sized dosage units sampled from different locations of the film. The “indicating” in step (f) of claim 1 and step (e) of claim 82 means that the analytical chemical test results show that uniformity of content in the amount of the active varies

by no more than 10%. Accordingly, the film is suitable for commercialization and the recited regulatory approval.

The issue of ±10% from a target or desired value is discussed above. The '080 patent teaches that "as required by various world regulatory authorities, dosage forms may not vary more than 10% in the amount of active present." (See col. 2, lines 42-45). It is well-known and conventional in the art that the active content of a dosage is allowed to be ± 10% from the desired amount, e.g., the amount of active the dosage is supposed to have. The '080 patent further teaches in the Abstract that "the films also contain a pharmaceutical and/or cosmetic active agent with no more than a 10% variance of the active agent pharmaceutical and/or cosmetic active agent per unit area of the film"; and teaches at col. 15, lines 32-40 that "[c]onsideration of the above discussed parameters, such as but not limited to rheology properties, viscosity, mixing method, casting method and drying method, also impact material selection for the different components of the present invention. Furthermore, such consideration with proper material selection provides the compositions of the present invention, including a pharmaceutical and/or cosmetic dosage form or film product having no more than a 10% variance of a pharmaceutical and/or cosmetic active per unit area. In other words, the uniformity of the present invention is determined by the presence of no more than a 10% by weight of pharmaceutical and/or cosmetic variance throughout the matrix."

As also noted above, there is no requirement of a working example. In any event, as also discussed above, in Example E at col. 30, line 64 through col. 32, line 44, a film was prepared, then cut into substantially identical size dosage forms that were

weighed and shown to have a consistent weight of 0.04 gm. The '080 patent teaches this is evidence that the distribution of components within the film is consistent and uniform "based on the simple principle that each component has a unique density." (col. 32, lines 26-39).

Proposed 35 USC 112 rejections that are adopted:

Claim 318 is rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor or a joint inventor, or for pre-AIA the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection was proposed by Third Party Requester on pp. 20-21 of the Comments filed 04/12/13 and **is adopted** for the reasons that follow.

Claim 318 requires that the controlled drying is through a drying apparatus at a temperature of "about 60 °C", and also requires uniformity of active varies by less than 5%. This combination of elements is found in unconnected passages of the specification and lacks adequate written description. In particular, as noted by Third Party Requester on p. 21 of the Comments filed 04/12/13:

> There are only two instances in the '080 Patent where a temperature of "about 60 °C" appears. The first instance, Example CF, makes no reference whatsoever to: (i) the yield value of the film; (ii) control of air velocities; or (iii) visco-elasticity of film at 4 minutes. See '080 Patent 41:49-50. The second instance, Examples P1-P3 use a "second heater section" at 60 °C with no top air flow, but does not exemplify a method suitable for film formation. See '080 Patent 35:57-59

("Composition P displayed a stringy elastic property. The wet film would not stay level, the coating was uneven, and the film did not dry.").

Moreover, the desired property relating to variation in active content--"[d]esirably, the variance is less than 5% by weight, less than 2% by weight, less than 1% by weight, or less than 0.5% by weight" (see '080 Patent 15:40-43)--cannot be attributed to any one of the 60 °C temperature, the air currents, or the formation of a visco-elastic film within 4 minutes. Indeed, there are no examples showing a variation of less than 5% in active content.

Claim 318 is rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention. This rejection was proposed by Third Party Requester on pp. 19-20 of the Comments filed 04/12/13 and **is adopted** for the reasons that follow.

Claim 318 recites "during said drying said flowable polymer matrix temperature is 100°C or less". This is at odds with another requirement of claim 318 that the controlled drying is through a drying apparatus at a temperature of about 60°C. It is not clear how the matrix would ever reach a temperature that is 40° hotter than the drying apparatus.

Proposed Claim Rejections - 35 USC § 102 and § 103

The following is a quotation of the appropriate paragraphs of pre-AIA 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. Claims 1-11, 13-15, 17-71, 82-90, 92-94, 96-150, 161-172, 174-176, 178-232, 243-253, 256, 258-271, 274, 276-289, 292 and 294-318 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen.

On pages 28-36 of the Comments filed 04/12/13, Third Party Requester proposes that claims 1, 4, 5, 8-11, 13-15, 17, 18, 20-32, 34, 36-40, 44-47, 51, 53, 54, 59, 62-71, 82-84, 87-90, 92-94, 96, 97, 99-111, 113, 115-119, 123-126, 130, 132, 133, 138, 141-150, 161-166, 169-172, 174-176, 178, 179, 181-193, 195, 197-201, 205-208, 212, 214, 215, 220, 223-232, 243, 244, 246, 247, 249-253, 256, 258-262, 264, 265, 267-271, 274, 276-280, 282, 283, 285-289, 292 and 294-318 be rejected under 35 USC 102(b) as anticipated by, or alternatively, under 35 USC 103(a) as being unpatentable over Chen. Further, on p. 36 of the Comments filed 04/12/13, Third Party Requester proposes that claims 2, 3, 6, 7, 19, 33, 35, 41-43, 48-50, 52, 55-58, 60, 61, 85, 86, 98, 112, 114, 120-122, 127-129, 131, 134-137, 139, 140, 167, 168, 180, 194, 196, 202-204, 209-211, 213, 216-219, 221, 222, 245, 248, 263, 266, 281 and 284 be rejected under 35 USC 103(a) as being unpatentable over Chen. For the reasons that follow, the proposed anticipatory rejection under 35 USC 102(b) of claims 1, 4, 5, 8-11, 13-15, 17, 18, 20-32, 34, 36-40, 44-47, 51, 53, 54, 59, 62-71, 82-84, 87-90, 92-94, 96, 97, 99-111, 113, 115-119, 123-126, 130, 132, 133, 138, 141-150, 161-166, 169-172, 174-176, 178,

179, 181-193, 195, 197-201, 205-208, 212, 214, 215, 220, 223-232, 243, 244, 246, 247, 249-253, 256, 258-262, 264, 265, 267-271, 274, 276-280, 282, 283, 285-289, 292 and 294-318 **is not adopted**. For the reasons that follow, the proposed obviousness rejection of claims 1-11, 13-15, 17-71, 82-90, 92-94, 96-150, 161-172, 174-176, 178-232, 243-253, 256, 258-271, 274, 276-289, 292 and 294-318 **is adopted**.

The proposed anticipatory rejection of claims 1, 4, 5, 8-11, 13-15, 17, 18, 20-32, 34, 36-40, 44-47, 51, 53, 54, 59, 62-71, 82-84, 87-90, 92-94, 96, 97, 99-111, 113, 115-119, 123-126, 130, 132, 133, 138, 141-150, 161-166, 169-172, 174-176, 178, 179, 181-193, 195, 197-201, 205-208, 212, 214, 215, 220, 223-232, 243, 244, 246, 247, 249-253, 256, 258-262, 264, 265, 267-271, 274, 276-280, 282, 283, 285-289, 292 and 294-318 is not adopted because independent claims 1, 82 and 161 have been amended to require, and newly added independent claims 315-318 require, performing analytical chemical tests for uniformity content. As noted above, such tests are analytical tests for determining the amount of active content in the recited sample. Chen exemplifies testing for uniformity as evidenced by Table 4 on p. 20 where the g/dosage of films is reported. However, Chen does not teach measuring the amount of active in the dosage films.

With respect to the obviousness rejection, Chen teaches a dosage unit including a water-soluble hydrocolloid, mucosal surface-coat-forming film, such film including an effective dose of a pharmaceutical or bioactive active agent (see p. 3, lines 30-32; and p. 10, line 22 through p. 11, line 12). In Examples 5-8, Chen prepares hydroxypropyl methylcellulose (HPMC, i.e., “Methocel E5”) based quick dissolving intraoral films

containing active agents (see p. 20, lines 17-20 and Tables 5 and 7). In particular, the films in Examples 5-8 contain an active agent, e.g., nicotine, hydromorphone, oxybutynin or estradiol; HPMC; and a solvent, i.e., water (see Tables 5 and 7). Further, the film in Tables 7 and 8 of Chen uses sildenafil citrate as an active ingredient and is prepared using HPMC, i.e. “Methocel E15”, and water as the solvent. The film in Chen’s Example 1 contains HPMC; peppermint, citric acid and aspartame as actives; and water as the solvent (see Tables 1 to 4). The film in Chen’s Example 2 contains "Pullalan (P-20) [sic, Pullulan (P-20)]” as the polymer; peppermint, citric acid and aspartame as actives; and water and ethanol as solvents (see Tables 1 and 2). Peppermint, citric acid and aspartame are also actives in Chen’s Examples 5-8, and peppermint and aspartame are actives in the film in Chen's Tables 7 and 8. Under the general category of "Actives", the '080 patent teaches flavors such as mint oil, flavor enhancers such as citric acid, and sweeteners such as aspartame (see col. 21, lines 35-63 and col. 22, lines 9-13). Peppermint has a high menthol content, is a breath freshener; and the ‘080 patent teaches that breath fresheners are drugs (col. 20, lines 35-38). Other taste modifying agents, i.e., taste masking agents, are disclosed at p. 10, lines 7-14 of Chen.

The specific water-soluble polymer, solvent and actives exemplified in Chen are identical to those exemplified in the ‘080 patent. HPMC is employed in almost every example of the ‘080 patent. HPMC and pullulan are taught by the ‘080 patent as being water soluble (col. 15, lines 45-57). The same solvent, i.e., water is employed in almost every example in the '080 patent. Sildenafil is exemplified in Examples CI and FB of the

'080 patent (see Tables 16 and 30). Likewise, peppermint oil and/or sweetener are used in numerous examples in the '080 patent, such as Examples A, B, C, D, F, G, H, BA, BB, BC, etc (see Tables 1 and 9).

The following is a list of hydrocolloid polymers, including said HPMC and pullulan, disclosed by Chen for forming the film (see p. 14, line 12 through page 15, line 3):

> In embodiments of the invention, the hydrocolloid may be a water soluble non-gelling (at room temperature) natural polysaccharide or derivatives including pectin and derivatives, guar gum arabic, tragacanth gum, xanthan gum, gellan sodium salt, propyleneglycol alginate, starches (amylose, amylopectin), modified starches, hydroxyethyl starch, pullulan, carboxymethyl starch, gum ghatti, okra gum, karaya gum, dextrans, dextrins and maltodextrins, konjac, acemannan from aloe, locust bean gum, tara gum, quince seed gum, fenugreek seed gum, scleroglucan, gum arabic, psyllium seed gum, tamarind gum, oat gum, quince seed gum, carrageenans, scleraglucan, succinoglucan, larch arabinogalactan, flaxseed gum, chondroitin sulfates, hyaluronic acid, curdlan, chitosan, deacetylated konjac, and rhizobium gum.
>
> In embodiments of the invention, the hydrocolloid may be a water soluble non-gelling polypeptide or protein exemplified by gelatins, albumins, milk proteins, soy protein, and whey proteins. The hydrocolloid may further be selected from a group of synthetic hydrocolloids exemplified by any of the following: polyethylene-imine, hydroxyethyl cellulose, sodium carboxymethyl cellulose, carboxymethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, methyl cellulose, ethyl cellulose, polyacrylic acids, low molecular weight polyacrylamides and their sodium salts (carbomers), polyvinylpyrollidone, polyethylene glycols, polyethylene oxides, polyvinyl alcohols, pluronics, tetronics, and other block co-polymers, carboxyvinyl polymers, and colloidal silicon dioxide. A preferred embodiment of the invention utilizes a hydroxypropyl methyl cellulose having a methoxy content of about 19-30% and hydroxypropyl content of 7-12% and a molecular weight of approximately 50,000-250,000 daltons (Table 9).

In addition to the specific active materials noted above, i.e., nicotine, hydromorphone, oxybutynin, estradiol, sildenafil citrate, peppermint, citric acid and

aspartame, the following is a list of active agents disclosed by Chen (see p. 10, line 22 through page 11, line 12):

> Active agents (for human and veterinary applications) include therapeutic agents, nutritional supplements and hygiene aids. The therapeutic agents are exemplified by analgesics, a-adrenergic receptor blockers, anti-Alzheimer's disease medication, antianginal, antianxiety, antiarrythmics, antiarthritics, antibiotics, anticoagulants/thrombolytics, anticonvulsants/anti-Parkinson medication, anti-depressants, anti-diabetics, anti-diarrheal, anti-epileptics, anti-fungal, anti-gout, anti-heartworm medication for dogs, anti-histamines, anti-hypertensives, anti-inflammatories, anti-infectives, antimigraines, anti-nasuants/anti-emetics, anti-neoplastics/anti-tumor active agents, anti-pruitics, anti-psychotics, anti-pyretics, anti-spasmodics, anti-virals, bronchial dilators/anti-asthmatics, calcium antagonists, cardiac agents, cardiotonics, central nervous system actives, contraceptives, coronary vasodilators, cough/cold remedies, dietary supplements, including vitamins and minerals, diuretics, fertility active agents, flea control agents for animals (Ivermectin), H_2 receptor antagonists, herbal actives, hormones, hypoglycemics, hypolipidemics, muscle relaxants, ovulation stimulators, peptide active agents, polypeptide active agents, proteins such as insulin, calcitonin, LHRH and the like. Sedatives and hypnotics, sexual dysfunction active agents, sleep aids, smoking cessation aids, steroids and steroidals, tranquilizers, laxatives, ophthalmic preparations, nutritional supplements, breath fresheners, breath deodorants, saliva substitutes, antigingivitis agents, anti-cavity agents, anti-plaque agents, diagnostic indicators, and local anesthetics. Also included are active agents for treatment of osteoporosis, hormone replacement, treatment of periodontal disease, antiseptics, corticosteroids, non steroidal anti-inflammatory agents, antiviral agents and vaccines.

In the method of preparation of the films, the HPMC or pullulan, which Chen teaches is a hydrocolloid, is dissolved in water under agitated mixing to form a uniform and viscous solution which reads on the instant masterbatch pre-mix, and the additional ingredients are added under agitated mixing until they are uniformly dispersed (i.e., suspended) or dissolved in the hydrocolloid (see p. 14, line 22 through p. 15, line 3; and p. 17, lines 6-19). The resultant mixture, i.e. the instant flowable polymer matrix, which Chen teaches has a viscosity of 500 to 15,000 cps, is degassed in a vacuum chamber

until trapped air bubbles are removed, and then coated, i.e., casted as per step (b) of claims 82, 161 and 315-318, and as per step (c) of claim 1, on the non-siliconized side of a polyester film (see p. 15, lines 24-29; and p. 17, lines 13-15).

With respect to steps (c) and (d) of claims 82, 161 and 315-318, and with respect to steps (d) and (e) of claim 1, Chen controls drying and evaporates water from the cast matrix in 9 minutes of drying in a hot air circulating oven at 50°C (see p. 17, lines 13-15 and Fig. 2). In particular, as seen schematically in the drying apparatus of Chen's Fig. 2, the air flow is less direct at the film surface at the beginning of the drying and becomes more direct as the film proceeds through the drying oven, which has an aeration controller (see also p. 5, line 31 through p. 6, line 3). Chen's Example 1 starts with 74.42% water content and is dried to 1.7% water content (see Tables 1 and 4). Chen's Examples 5 to 8 start with 73.03%, 71.51%, 70.72% and 72.94% water content and are dried to 2.93%, 2.42%, 2.32% and 2.31% water content, respectively. Chen's Example 2 starts with 10.6% ethanol and 67.025% water and, after drying for 9 minutes at 50°C, the water content is 8.5% (see Tables 1 and 2). Since the drying is at 50°C, the temperature of the flowable polymer matrix is "100°C or less" as here claimed. In fact, Chen's general drying temperature range of 40-100°C is entirely with the range of about 100°C or less taught at col. 27, lines 53-55 of the '080 patent.

Further with respect to steps (c) and (d) of claims 82, 161 and 315-318, and steps (d) and (e) of claim 1, and with respect to viscoelasticity, it is the Specialist's position that Chen's mixture before drying is viscoelastic. In particular, as noted above, the '080 patent teaches that "[t]he addition of hydrocolloids to the aqueous phase of the

suspension increases viscosity, may produce viscoelasticity, and can impart stability depending on the type of hydrocolloid, its concentration and the particle composition, geometry, size and volume fraction" (see col. 8, lines 42-46). Chen adds the same hydrocolloid as in the '080 patent, i.e. said HPMC, to water, and Chen's wet matrix before drying has a viscosity of 500-15,000 cps (p. 15, line 26), which is within the instantly claimed range of about 400-100,000 cps and overlaps the '080 patent specification's most preferred range of about 1,000-40,000 cps (see the paragraph bridging cols. 16 and 17 of the '080 patent). Accordingly, Chen's films in Examples 1, 2 and 5-8 and the Example in Tables 7 and 8 are inherently viscoelastic before drying. Within 4 minutes of the 9 minutes of drying in Chen's Examples 1, 2 and 5-8 and the Example in Tables 7 and 8, a more dry viscoelastic film is obtained.

Alternatively, to the extent that Chen's wet film in Examples 1, 2 and 5-8 and the example in Tables 7 and 8 before drying are not viscoelastic, then within about 4 minutes in the hot air circulating oven at 50°C, a viscoelastic film is inherently formed. In particular, in order to arrive at a dried film product as in Chen, which is made using the same materials as disclosed in the '080 patent and the same basic process steps here claimed, wherein the dried film is glossy and substantially transparent and has the gram per dosage, thickness, density and water content set forth in Chen's Table 4 for Example 1, then a viscoelastic film is inherently formed within about 4 minutes. The remaining time after the viscoelastic film is formed further dries the viscoelastic film.

As an even further alternative, if Chen's viscoelastic film is formed after about the first 4 minutes but within Chen's 9 minute drying time, then a skilled artisan would

recognize that with a higher drying temperature, a shorter drying time than 9 minutes can be used. In other words, a higher drying temperature than the 50°C exemplified by Chen would result in formation of Chen's viscoelastic film product sooner. In fact, Chen teaches that its drying temperature can be in the range of 40-100°C (see p. 15, line 28). It would have been obvious to one of ordinary skill in the art at the time the invention was made to have used a higher drying temperature than the 50°C exemplified by Chen because Chen teaches that the drying temperature can be as high as 100°C, and the resulting expectation of a shorter drying time using a higher temperature.

With respect to the claimed percent variation of active, and thus also the claimed substantial uniform distribution and locking-in or substantially preventing migration, Chen's ingredients are mixed until they are uniformly dispersed or dissolved in the hydrocolloid (p. 17, lines 8-11), and Chen uses the same criteria exemplified in the '080 patent specification for evaluation of uniformity, i.e., weight of dosages and visual inspection (see col. 31, line 37 through col. 32, line 34, and col. 37, lines 61-63 of the '080 patent). In particular, Chen's dried film product of Example 1 is cut into equal sized dosage units ready for packing (p. 17, lines 31-32; Table 4) and has a weight of 0.028 $\pm$ 0.001 g/dosage film, a density of 1.0485 $\pm$ 0.009 g/cm^2, a water content of 1.7 $\pm$ 0.24%, a thickness of 2.1 $\pm$ 0.12 mil (see Table 4); and the dried films are glossy and substantially transparent (p. 17, line 15), i.e., they are visually free of aggregation. The 0.028 $\pm$ 0.001 g/dosage film has variation of (0.001/0.028) x 100 = 3.6%. When film weight is rounded to two decimal places as in Table 2 at col. 31 of the '080 patent, then the weight is 0.03 gram/dosage film with a variation of 0%. Accordingly, the claimed

percent variation of active of no more than 10%, less than 5%, less than 2%, less than 1% and less than 0.5% is inherent in Chen's films and thus, the films are suitable for regulatory approval by the U.S. Food and Drug Administration (FDA) and commercialization, as here claimed.

Furthermore, as noted in the Cohen Declaration submitted with the request, when working with a homogeneous or completely dissolved coating mixture as in Chen, it would be difficult for a person of ordinary skill in the film art not to obtain a film that has a uniform content of active, and the drying method disclosed in Chen would not be expected to create any agglomeration, aggregation or otherwise non-uniform content of active (see ¶¶ 8-10).

Alternatively, to the extent the claimed percent variation of active is not inherent from Chen's process, then such would have been obvious. Chen also differs from the instant claims in that while Chen cuts its film into equal sized dosage units and checks for uniformity by weighing the units and comparing the weights which, as noted above, have 0% variation, Chen does not perform "analytical chemical tests" on the equal sized dosage units to determine the amount of active in the dosage units.

However, Chen's films are cut into dosage units intended for human use so as to deliver an effective dose of an active agent (p. 1, lines 8-22; p. 3, lines 30-33; p. 16, lines 2-8; p. 17, lines 31-32). It is well-known in the art that world regulatory authorities do not permit dosage forms to vary by more than 10% in the amount of active present. It is also well-known in the art that to verify such uniformity, the actual content of active in individual dosages is measured, i.e., conventional analytical testing is used.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to minimize the active content variation among Chen's dosages as close to zero as possible, including the instantly claimed no more than 10%, less than 5%, less than 2%, less than 1%, and less than 0.5%, in view of the well-known goal of a skilled artisan to prepare dosages that do not vary by more than 10% in the amount of active present, in view of the 0.03 gram/dosage film with a variation of 0% for the dosages in Chen's Table 4, and a desire to obtain FDA approval and commercialize the product. A skilled artisan would minimize active content variation by optimizing the available parameters in Chen's process, which are the same as or similar to those in the '080 patent specification. These include, mixing/degassing, casting of the wet film, viscosity of the wet film, drying temperature, drying time, control of air flow in Chen's Fig. 2, selection of appropriate colloid material, etc.

Further, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have performed known analytical chemical tests on Chen's dosages so as to determine the actual amount of active in the dosages and thus, assure active content uniformity.

With respect to claim 82 and 315, Chen does not specifically teach repeating its process and said analytical chemical tests. Further, Chen does not specifically teach that the active content of the first film obtained from the process and additional films prepared by repeating the process varies no more than 10% from a desired amount as indicated by analytical chemical tests.

However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have repeated Chen's process and the analytical chemical tests for each film prepared by the process so as to prepare more films and dosages, seek regulatory approval and commercialize the product. It further would have been obvious to a skilled artisan at the time the invention was made to have prepared the multiple films such that the active content in each film does not vary by more than 10% from the amount of active the dosages are supposed to contain as required by various world regulatory authorities, in order to minimize dosage variation and commercialize the product. A skilled artisan would obtain the variation of no than 10% from the desired amount by optimizing said available parameters in Chen's process.

With respect to claims 32, 111 and 193, which require that the active is a biological response modifier, it is noted that all of the actives listed by Chen at p. 10, line 22 through page 11, line 12 are biological response modifiers. Alternatively, biological response modifiers are well-known actives in the art. It would have been obvious to one of ordinary skill in the art to have used any well-known active, such as a biological response modifier, as the active in Chen's film with the resulting expectation of preparing a film for delivery of the agent and so as to take advantage of the agent's known function.

With respect to claims 25, 104 and 186, which require that the active is an anti-tussive, Chen, as noted above, teaches that its active can be a cough/cold remedy (see p. 10, line 32 through page 11, line 1). A cough/cold remedy encompasses and thus, renders obvious an anti-tussive, i.e., cough relieving/depressing, agent.

With respect to claims 65-69, 144-148 and 226-230, which require that the active is coated with a controlled release composition, Chen discloses that its films may release the active agent over a period of time that is determined by a number of different factors (see page 6, line 30 through page 7, line 21). More specifically, Chen discloses: "Depending on the optimal program for a specific application of the invention, the disintegration time and the dissolution time can be controlled within a prescribed range by adjustment of the formulation and the thickness of the film. In some cases, it is desirable for release of the active agent to occur after dissolution of the film. For these applications, the active agent may be encapsulated in a material with dissolution properties that are different from those of the hydrocolloid. Encapsulation of the active agent may also be utilized to achieve masking of taste for active agents that are bitter. In some cases, two or more different active agents may be included in the film." (See page 9, lines 9-16). Slow release films are also discussed, e.g., at page 7, lines 16-21. Accordingly, immediate, delayed, sustained or sequential release of active as here claimed, if not disclosed by Chen, would have been obvious so as to obtain a desired release of the active(s).

With respect to claims 70, 149, 231, 259, 260, 277, 278 and 295-297, Chen teaches that the active material can be in the form of a particle, e.g., a colloid particle or microencapsulated (see p. 7, lines 17-21). As noted above, Chen's polymers such as HPMC are hydrocolloids (p. 14, line 24-31), and Chen's matrix has the ingredients uniformly dispersed, i.e., suspended, in the hydrocolloid (p. 17, lines 6-11).

With respect to claims 71, 150 and 232, which require the addition of a degassing agent, as noted above Chen teaches peppermint (see p. 10, line 9; Examples 1-8 and the example in Tables 7 and 8). During prosecution U.S. patent application Serial No. 11/858,214, Patent Owner admits that peppermint is a foam reducing flavoring agent which “act[s] to both flavor the film and prevent and/or remove air from the film-forming compositions.” (See the last paragraph on p. 5 of the response filed 12/20/10 and claim 5 of the 11/858,214 application).

With respect to claims 162, 163, 249-252, 258, 267-270, 276, 285-288 and 294, Chen teaches that the films are suitable for administration of the active material through buccal, gingival, sublingual and mucosal surfaces (see p. 8, lines 4 and 9-10, and Fig. 1). With respect to claim 164, Chen teaches that the mucosal surface can be a wound (see p. 7, lines 31-32).

With respect to claim 253, 271 and 289, which require that the film provides administration of the active within the body of the individual during surgery, as noted above, Chen teaches that its films can be applied to a mucosal surface, which refers to any moist surface in the body, including a wound (see p. 7, lines 31-32 and p. 8, line 4). Accordingly, Chen's films can be administered at any time, including surgery. Chen discloses several active agents that are highly suitable for use "during surgery", including sedatives, local anesthetics, antiseptics, anti-inflammatory agents, anti-viral agents, muscle relaxants, and steroids (see p. 10, line 29 through p. 11, line 12). Further, Chen teaches that "[e]mbodiments of the invention include .... for a quick dissolving film for local and systemic delivery of pharmaceutical agents to a mucosal

surface in a subject .... The dosage unit of the invention may be applied to any mucosal surface as deemed appropriate for the systemic or local delivery of an active agent including vaginal, rectal and ocular surfaces ... [e]mbodiments [may be administered easily by] physicians, parents, patients ..." (*see* p. 8, lines 2-4, 6-10, and 19-20). Chen also teaches the application of films to a wound surface "where lymph fluid bathes the tissue surface" at p. 7, lines 32 through p. 8, line 1. Thus, Chen discloses or renders obvious that its film “provides administration of said active to an individual by administration within the body of the individual during surgery” as here claimed.

With respect to claims 2 and 3, Chen does not specifically teach that its premix of polymer and solvent, i.e., instant masterbatch premix, is controllably fed via a first metering pump and a control valve to a first mixer and a second mixer, and that the first and second mixers are arranged in parallel, series or a combination thereof.

However, metering pumps, mixing vessels and control valves are standard equipment in the art, and so is their arrangement in parallel, series or a combination thereof. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have used metering pumps, mixing vessels and control valves when preparing Chen's wet film because such equipment is standard in the art, and so as to mix Chen’s masterbatch premix and active.

With respect to claims 6, 7, 85, 86, 167 and 168, Chen does not specifically teach using combinations of its hydrocolloids, such as a mixture of the exemplified HPMC with any of the other hydrocolloids taught by Chen such as ethylcellulose, polyacrylic acid polymer, etc.

However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have used combinations of Chen's hydrocolloids in place of a single hydrocolloid with the expectation that a film for mucosal delivery of active agent would be obtained. The rationale to use a combination of Chen's hydrocolloids flows logically from their each having been individually taught as useful as the hydrocolloid component of Chen's film.

Claims 19, 33, 35, 41-43, 48-50, 52, 55-58, 60, 61, 98, 112, 114, 120-122, 127-129, 131, 134-137, 139, 140, 180, 194, 196, 202-204, 209-211, 213, 216-219, 221, 222, 245, 248, 263, 266, 281 and 284 are directed to particular active materials. These active agents are either well-known in the art or are species of the generic active agents taught by Chen at p. 10, line 22 through p. 11, line 12. See also the discussion of these claims in the claim chart of the request on pp. 77-82 and 84-89, which are hereby incorporated by reference.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have used the actives here claimed so as to prepare Chen's film because such actives are well-known in the art or are species of the generic active agents taught by Chen; the reasonable expectation of success in preparing a film for mucosal delivery of the active; and so as to take advantage of the active's known function.

Claim 318 further requires that the drying is at a temperature of "about 60°C". As noted above, Chen exemplifies a drying temperature of 50°C (p. 17, line 15), and more generally teaches that drying can be done at a temperature between 40-100°C (p. 15,

line 28). It would have been obvious to one of ordinary skill in the art at the time the invention was made to have used a higher temperature than 50°C within the temperature range of between 40-100°C taught by Chen so as to dry the film. It is expected that a higher drying temperature would permit a shorter drying time.

New claims 317 and 318 also require that the drying uses “air currents, which have forces below a yield value of the polymer matrix". The '080 Patent states that "air velocities are desirably below the yield values of the film, i.e., below any force level that can move the liquids in the film-forming compositions." (See col. 11, lines 21-23). Moving liquids in the matrix during drying could produce defects in the film. However, as noted above, Chen's Fig. 2 shows air flow is less direct at the film surface at the beginning of the drying and becomes more direct as the film proceeds through the drying oven, which has an aeration controller (see also p. 5, line 31 through p. 6, line 3). As also noted above, Chen produces a film that is glossy, substantially transparent, has a weight of 0.028 $\pm$ 0.001 g/dosage film, a density of 1.0485 $\pm$ 0.009 g/cm^2, a water content of 1.7 $\pm$ 0.24%, a thickness of 2.1 $\pm$ 0.12 mil (seep. 17, lines 15-16; and Table 4). The 0.028 $\pm$ 0.001 g/dosage film, when rounded to two decimal places as in Table 2 at col. 31 of the ‘080 patent, is 0.03 gram/dosage film with a variation of 0%. Accordingly, the air flow of Chen either inherently or obviously has forces below a yield value of the polymer matrix in order to arrive at the, glossy, substantially transparent, essentially uniform films exemplified therein.

2. Claims 2, 3, 32, 55, 72-81, 111, 134, 151-160, 193, 216 and 233-242 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teaching of Chen and Staab.

This rejection was proposed by Third Party Requester on p. 37 of the Comments filed 04/12/13 and **is adopted** for the reasons that follow.

With respect to claims 2 and 3, to the extent that Chen does not render obvious controllably feeding its master batch pre-mix via a metering pump and a control valve to a first mixer and a second mixer such that the first and second mixer are arranged in parallel, series or a combination thereof, then such is rendered obvious in combination with the teachings of Staab.

Staab teaches films made of dissolvable polymer material and/or complex carbohydrate material which are food grade materials, wherein the films also contain an agent such as a drug or medication (see abstract). Staab teaches that "[t]he agent material is evenly distributed throughout the film, so as the film slowly dissolves, it releases the agent material in the proper dosage ...." (see col. 5, line 68 through col. 6, line 3). Staab also discloses that “[t]he device of the invention thus is composed of a biologically compatible material that has been blended homogeneously" with the drug (see col. 6, lines 6-10). Staab teaches forming a pre-mix including a water soluble polymer and water in proper concentrations at a first temperature in a first vessel and then transferring to another vessel of a cooler temperature (in series with the first vessel), and then stirring in heat sensitive ingredients (see col. 7, lines 37-48). Staab’s Fig. 5 depicts three mixing vessels that can readily be employed for practicing the

claimed method, the top two vessels being in parallel with each other, the lower vessel being in series with the top two vessels. Any transfer from one vessel to another would inherently or obviously involve a metering pump and control valve. Arrangement of the vessels in parallel would accommodate a choice of heat sensitive ingredients, such as those disclosed in Staab (see col. 7, lines 37-51).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have prepared Chen's matrix by forming a pre-mix including a water soluble polymer and water in proper concentrations at a first temperature, then to have transferred the contents of the vessel to another vessel of a cooler temperature, and then to have stirred in heat sensitive ingredients, e.g., drug(s) as in Staab, so as to protect the drug(s), which is usually the most expensive component.

With respect to claims 32, 111 and 193, to the extent that Chen does not teach or render obvious that its active can be a biological response modifier, then such is rendered obvious in combination with the teachings of Staab. Likewise, with respect to claims 55, 134 and 216, to the extent that Chen does not teach or render obvious that its active can be a decongestant, then such is rendered obvious in combination with the teachings of Staab.

Staab teaches that its active agent can be monoclonal antibodies, i.e., biological response modifiers, such as those useful against cell surface components or against pathogenic organisms such as HIV (see col. 6, lines 49-53). Likewise, Staab teaches that its active agent can be a decongestant (see col. 7, line 1).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have used a monoclonal antibody or decongestant for Chen's active because such actives are conventional in the art, as shown by Staab; so as to take advantage of the active material's known function; and the reasonable expectation of success.

With respect to claims 72-81, 151-160 and 233-242, Chen does not specifically teach, for example, providing a second film layer having an active. Staab teaches that its film may be a laminate of two or more layers (see col. 5, lines 30-31; col. 9, lines 28-43; and Fig. 2). Staab teaches that the laminates can be formed in the conventional manner, for example the mixture in liquid form is poured or cast onto a plate or into a mold and allowed to begin to set, at which time another liquid mixture with different composition is poured on the first mixture, and both mixtures are allowed to set up completely producing a laminate or layers of different materials (see col. 5, lines 51-58). The extruding and spraying of the second film in claims 76, 77, 155, 156, 237 and 238 are conventional methods that are obvious variants of the pouring and casting exemplified by Staab.

Staab teaches that the first and second layers can comprise an active. In particular, referring to Fig. 2, Staab teaches the following at col. 9, lines 28-43:

> A first film layer 13 is made of, for example, a faster dissolving polymer material for release of a drug material 14a. A second film layer 15 is made of slower dissolving polymer material for release of more drug or another drug material 14b in combination, for example, a spermicide and an anti-infective or anti-inflammatory medication. A third (and additional) layer(s) 16 with additional drug can also be employed for sustained release of the drug.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have laminated a second film to Chen's drug-containing film as per the teachings of Staab so as to control the release rate of the drug, provide for release of more drug, or provide for release of another drug in addition to the drug in Chen's film.

3. Claims 317 and 318 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Chen and Arter.

The rejection of claim 318 was proposed by Third Party Requester on pp. 37-38 of the Comments filed 04/12/13 and **is adopted** for the reasons that follow. The rejection of claim 317 is Specialist-initiated.

Chen is relied upon for the reasons stated above in rejection No. 1. As discussed above, Chen renders obvious all the limitations of new claims 317 and 318. Nevertheless, with respect to the newly presented limitation in claims 317 and 318 of using air currents which have forces below a yield value of the polymer matrix during drying, the teachings of Arter strengthen the teachings of Chen.

Arter is directed, in general, to the drying of liquid coating compositions that have been coated in the form of a layer, or in the form of two more superposed layers, on a sheet material (see col. 1, lines 6-9). Arter teaches that "[o]ne of the most common and difficult problems that is encountered in the drying of coating compositions is the formation of mottle." (See col. 2, lines 18-20). In particular, Arter teaches "[i]t is a problem that is encountered under a wide variety of circumstances. For example,

mottle, or non-uniform density, is frequently encountered when compositions consisting of solutions of a polymeric resin in an organic solvent are coated in layer form onto sheet materials, such as webs of synthetic organic plastic material. Mottle is an especially severe problem when the coating solvent is a volatile organic solvent but can occur to a significant extent even with aqueous coating compositions or with coating compositions utilizing an organic solvent of low volatility. The mottle is an undesirable defect in some instances because it detracts from the appearance of the finished product … ." (See col. 2, lines 20-53).

Arter teaches drying wet films in a two zone dryer, as shown in Figs. 1-3. In the first zone, the film is dried while being protected by a shield that creates a quiescent zone above the top surface of the film in which there are no turbulent flow conditions and uniform drying is promoted (see col. 3, line 57 through col. 4, line 18). Accordingly, Arter teaches "using air currents, which have forces below a yield value of the polymer matrix during drying, to evaporate at least a portion of said solvent," as required by step (c) of claims 317 and 318. Following the first zone, the film is further dried in a second zone to remove residual liquid medium from the film (see col. 13, lines 24-29).

Arter exemplifies films that are dried in about 3 seconds at 60 °C (Example 1 and Table 1). In particular, in Test No. 1 in Example 1, the film velocity is 355 cm/sec (Table 1), the dryer length is 4 x 0.3 m = 1.2 m, and the drying time is (1200 cm)/(355 cm/sec) = 3 sec. In Example 2, the residence time for the web in each of the first and second sections of the drier is 5.2 seconds (see col. 17, lines 4-6).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have applied the drying method taught by Arter, which uses a quiescent zone above the top surface of the film in which there are no turbulent flow conditions and uniform drying is promoted, to the film formation method disclosed by Chen in order to avoid the formation of mottle.

4. Claims 317 and 318 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Chen and Strobush.

The rejection of claim 318 was proposed by Third Party Requester on pp. 38-39 of the Comments filed 04/12/13 and **is adopted** for the reasons that follow. The rejection of claim 317 is Specialist-initiated.

Chen is relied upon for the reasons stated above in rejection No. 1. As discussed above, Chen renders obvious all the limitations of new claims 317 and 318. Nevertheless, with respect to the newly presented limitation in claims 317 and 318 of using air currents which have forces below a yield value of the polymer matrix during drying, the teachings of Strobush strengthen the teachings of Chen.

Strobush discloses an apparatus and method for evaporating a coating solvent from a coating on a first substrate surface of a substrate while minimizing formation of mottle during evaporation (Abstract; col. 1, lines 9-18 and 27-29). Strobush teaches that the process of applying a coating to and drying that coating on a substrate can inherently create defects such as mottle, where "mottle" is defined as "an irregular pattern or non-uniform density defect that appears blotchy when viewed," and the usual

cause of mottle is air movement over the coating before it enters the dryer, as it enters the dryer, or in the dryer (col. 1, line 43 through col. 2, line 5). Strobush teaches that mottle is a problem when the coating solution contains a volatile organic solvent "but can also occur to a significant extent even with aqueous coating compositions" (col. 2, lines 10-15). Strobush teaches that the prior art substrates which have been coated are often dried using a drying oven which contains a drying gas such as air (col. 2, lines 20-22). Strobush discloses the drying of coated substrates without introducing significant mottle while running at higher web speeds by supplying drying gas (heated air) toward the bottom surface of the coated substrate such that the substrate rides on a cushion of drying gas, while the top side receives little or no drying gas, and where the coating comprises any film-forming material dispersed in any evaporable liquid vehicle (col. 6, lines 20-27; col. 9, lines 1-11 and 47-50; col. 11, lines 1-6 and 16-27; col. 12, lines 14-21, 27- 31, and 48-55; and col. 19, lines 43-46). In other words, Strobush teaches "using air currents, which have forces below a yield value of the polymer matrix during drying, to evaporate at least a portion of said solvent," as required by step (c) of claims 317 and 318. In fact, Strobush teaches that “if desired, topside air bars (34) can be used such that no gas is supplied by the air bars when topside gas is not needed or desired." (See col. 11, lines 15-17 and 24-27).

Strobush teaches that its apparatus and method are suitable for a "wide variety of coatings" (col. 9, line 9), with materials particularly suited for drying by this apparatus including "[a]ny mottle-susceptible material" such as graphic arts materials, magnetic media, and photothermographic imaging constructions (col. 16, lines 60-66). In fact, the

coating composition can comprise a film forming material or other solid material dissolved, dispersed or emulsified in an evaporable liquid (see col. 9, lines 1-4).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have applied the drying method taught by Strobush, which uses little of no drying gas on the top side of the coated substrate, to the film formation method disclosed by Chen in order to avoid the formation of mottle.

5. Claims 1-5, 10, 13-15, 21, 24, 25, 32, 44-46, 54, 55, 59, 63-70, 72-75, 78-84, 89, 92-94, 100, 103, 104, 111, 123-125, 133, 134, 138, 142-149, 151-154, 157-166, 171, 174-176, 182, 185, 186, 193, 205-207, 215, 216, 220, 224-231, 233-236, 239-242, 249-252, 258-260, 267-270, 276-278, 285-288 and 294-318 are rejected under 35 USC 102(b) as anticipated by or, in the alternative under 35 U.S.C. 103(a) as being obvious over Staab.

This rejection was proposed by Third Party Requester on pages 39-41 of the Comments filed 04/12/13 and **is adopted** for the reasons that follow.

Staab teaches the preparation of a film for local administration of an active agent in an internal body area (see col. 2, lines 34-62). Staab teaches films made of dissolvable polymer material, e.g., PEO and/or HPMC, both of which are identified as water soluble polymers in the '080 patent at col. 15, lines 50-51, and Staab's film also contains a drug or medication as the active agent (see Abstract; and col. 2, lines 34-46). Staab teaches that "[t]he agent material is evenly distributed throughout the film, so as the film slowly dissolves, it releases the agent material in the proper dosage..." (See col.

5, line 68 through col. 6, line 3). Staab teaches that "the polymer solids, water, or other solvent, contraceptive [i.e., an active]…, are admixed in the proper concentrations and the mixture heated to the appropriate temperature for dissolution and formation of a uniform blend to take place." (See col. 7, lines 37-41). In the Example at cols. 11-12, the ingredients are mixed together in a blender until just blended (see col. 11, lines 22-27). As such, Staab teaches formation of a flowable polymer matrix. A masterbatch pre-mix as in instant claim 1 can be formed containing polymer and solvent, and the pre-mix is then transferred to a cooler vessel for addition of heat-sensitive pharmaceuticals or other agents (see col. 7, lines 37-51). Other polymers that can be used along with PEO and/or HPMC include polyvinyl alcohol (see col. 2, line 41; and col. 4, lines 22-61).

The active agents that can be used in Staab's film include spermicides for contraceptive use and/or drugs or medications (see col. 5, lines 66-68). The following is a list of active agents taught by Staab at col. 6, line 35 through col. 7, line 3:

(1) anti-infectives such as antibiotics, sulfonamides, antivirals, antifungals, antiprotozoan and antibacterials;

(2) anti-inflammatories, such as hydrocortisone, dexamethasone, triamcinolone, and various prednisolone compounds;

(3) estrogenic steroids, such as estrone;

(4) progestational agents, such as progesterone;

(5) prostaglandins;

(6) coronary vasodilators;

(7) antitussives;

(8) antihistamines;

(9) anesthetics and

(10) decongestants.

> Monoclonal antibodies [which are biological response modifiers] such as those useful against cell surface components or against pathogenic organisms such as the human-immuno-deficiency (HIV) family of viruses may be incorporated into the device of the present invention … . Other drugs include clotrimazole, miconazole, ticonazole, benzalkonium chloride, nystatin, dermally active steroids, hormones, benzocaine, sulfas, biologically prepared actives, decongestants, cough/cold remedies, psychotropics, nitroglycerine, etc.

Staab also teaches the use of flavors, fragrances and coloring agents (see col. 7, lines 28-29). Thus, Staab's active material can be taste-masked.

Staab also discloses that "[t]he device of the invention thus is composed of a biologically compatible material that has been blended homogeneously" with the drug (see col. 6, lines 5-10). In the Example at cols. 11-12, Staab prepares a four-foot wide film which is then cut into two inch by two inch films each weighing 190 mg and containing 19 mg of benzalkonium chloride as the active agent (see col. 11, line 52 through col. 12, line 3).

With respect to step (c) in claim 1 and with respect to step (b) in claims 82, 161 and 315-318, Staab further discloses that "the mixture in liquid form will be poured or cast on to a plate or into a mold..." (See col. 5, lines 51-58 and the casting lines depicted in Fig. 5). In the Example at cols. 11-12, the blended mixture is poured onto a glass plate and spread to an even 3 mil thick film covering the surface of the glass (see col. 11, lines 41-44). Since Staab teaches a pourable polymer matrix containing the same components here claimed, it necessarily or obviously has a viscosity of within

about 400 to about 100,000 cps, which is a viscosity ranging from thin castor oil to mincemeat. In fact, Staab teaches that "[t]he dissolution of the film can be readily adjusted by using different viscosities of the hydroxypropyl methyl cellulose ranging from less than 80 to more than 4,000 centipoises." (See col. 5, lines 10-14).

With respect to steps (d) and (e) in claim 1 and with respect to steps (c) and (d) in claims 82, 161 and 315-318, Staab exemplifies drying the film in a temperature regulated oven for approximately 20 minutes at 160°F, i.e., 71°C, or for 20 to 40 minutes when using a continuously moving belt that enters a drier (see col. 11, lines 45 and 65). Generally, Staab teaches drying at a controlled temperature of 130°F to 140°F (col. 11, lines 1-6), i.e. 54°C to 60°C, which either anticipates the "about 60°C" in claim 318 or encompasses and thus, renders obvious the "about 60°C". Since the temperature is regulated, and heat is applied by underbelt steam and overbelt hot air which are each adjustable (col. 10, lines 28-34), the drying is controlled as here claimed. Likewise, since the oven temperature is 71°C, or 54°C to 60°C, the polymer matrix temperature during drying is 100°C or less as here claimed. The ingredients blended to prepare the film are 52.5% HPMC, 37.5% glycerin and 10.0% of a 50% aqueous solution of the benzalkonium chloride (see col. 11, lines 30-34). Since the water content before drying is 5% (i.e., half of the 10% of the 50% aqueous solution of benzalkonium chloride), the dried film must have a water content of 10% or less as here claimed.

Further, either Staab's mixture in the Example at cols. 11-12 before drying is viscoelastic and thus, a more dry film that is also viscoelastic is obtained within about

the first 4 minutes of drying. Alternatively, if the blended mixture before drying is not viscoelastic, then it becomes viscoelastic as the drying proceeds, and the film becomes viscoelastic within about the first 4 minutes of drying.

In particular, as noted above, the '080 patent teaches that "[t]he addition of hydrocolloids to the aqueous phase of the suspension increases viscosity, may produce viscoelasticity, and can impart stability depending on the type of hydrocolloid, its concentration and the particle composition, geometry, size and volume fraction (see col. 8, lines 42-46). Staab uses the same hydrocolloid as in the '080 patent, i.e. said HPMC. As noted above, Staab teaches that "[t]he dissolution of the film can be readily adjusted by using different viscosities of the hydroxypropyl methyl cellulose ranging from less than 80 to more than 4,000 centipoises." (See col. 5, lines 10-14). Accordingly, since Staab's film in the Example at cols. 11-12 is inherently viscoelastic before drying, then within about the first 4 minutes of drying, a viscoelastic film having less water than before drying is formed.

Alternatively, to the extent that Staab's blended mixture before drying is not viscoelastic, then within about the first 4 minutes of the drying, a viscoelastic film is inherently formed. In particular, in order to arrive at a dried film product as in Staab, which is made using the same materials as disclosed in the '080 patent and the same basic process steps here claimed and each dosage film weighing 190 mg and containing 19 mg of benzalkonium chloride as the active agent (col. 11, line 35 through col. 12, line 3), i.e., a variation in active content of 0%, then a viscoelastic film is inherently formed within about the first 4 minutes of drying.

The claimed percent variation of active of no more than 10%, less than 5%, less than 2%, less than 1% and less than 0.5%, and thus also the claimed substantially uniform distribution and locking-in or substantially preventing migration are inherent in Staab's films in view of the fact that, as noted above, each dosage film contains 19 mg of benzalkonium chloride, i.e., a variation of 0%. Accordingly, Staab's films are suitable for regulatory approval by the FDA and commercialization, as here claimed.

Performing analytical chemical tests as here claimed is inherent in Staab's process because Staab reports the amount of active, e.g., 19 mg of benzalkonium chloride, in the 190 mg samples (see col. 11, line 35 through col. 12, line 3).

With respect to claims 82 and 315, Staab teaches repeating the process for producing larger quantities of film (see col. 11, lines 52-53). Thus, repeating said analytical chemical tests for each additional film that is prepared is inherent. Further, performing analytical chemical tests to show that all films prepared have a uniformity of active content that varies no more than 10% from a desired amount is inherent in view of the fact that Staab reports the amount of active, e.g., 19 mg of benzalkonium chloride, in the 190 mg samples, and in view of the fact that it is well-known and conventional in the art that active content of a dosage is allowed to be $\pm$ 10% from the desired amount, e.g., the amount of active the dosage is supposed to have.

While Staab does not discuss viscosity, viscoelasticity, the percent variation of active in the film, or performing analytical chemical tests, Staab, as cited above, discloses a process which reasonably appears to be either the same as or an obvious variation of the instantly claimed process. Accordingly, claims 1-5, 10, 13-15, 21, 24,

25, 32, 44-46, 54, 55, 59, 63-70, 72-75, 78-84, 89, 92-94, 100, 103, 104, 111, 123-125, 133, 134, 138, 142-149, 151-154, 157-166, 171, 174-176, 182, 185, 186, 193, 205-207, 215, 216, 220, 224-231, 233-236, 239-242, 249-252, 258-260, 267-270, 276-278, 285-288 and 294-318, if not anticipated under 35 USC 102(b), would be obvious under 35 USC 103(a).

In particular, to the extent the claimed flowable matrix viscosity of about 400 to about 100,000 cps is not inherent in Staab's matrix, then such would have been obvious. It would have been obvious to one of ordinary skill in the art at the time the invention was made to have optimized the viscosity of Staab's matrix, i.e., Staab's blended mixture, in order to be able pour the mixture onto a glass plate and obtain a film, after drying, that can be, for example, cut into dosages weighing 190 mg containing 19 mg of active (see col. 11, line 35 through col. 12, line 3 of Staab). In fact, as noted above, Staab teaches that "[t]he dissolution of the film can be readily adjusted by using different viscosities of the hydroxypropyl methyl cellulose ranging from less than 80 to more than 4,000 centipoises." (See col. 5, lines 10-14). Staab's viscosity range overlaps with and thus, renders obvious, the claimed viscosity range.

To the extent the claimed percent variation of active and performing analytical chemical tests are not inherent in Staab's process, then such would have been obvious.

Staab's films are intended for human use so as to deliver an effective dose of an active agent (col. 1, lines 10-64; col. 2, lines 34-46; and col. 11, line 52 through col. 12, line 50). As noted above, it is well-known in the art that world regulatory authorities do not permit dosage forms to vary by more than 10% in the amount of active present. It is

also well-known in the art that to verify such uniformity, the actual content of active in individual dosages is measured, i.e., conventional analytical testing is used.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to minimize the active content variation among Staab's dosages as close to zero as possible, including the instantly claimed no more than 10%, less than 5%, less than 2%, less than 1%, and less than 0.5%, in view of the well-known goal of a skilled artisan to prepare dosages that do not vary by more than 10% in the amount of active present, in view of Staab's 19 mg of benzalkonium chloride per dosage film, and a desire to obtain FDA approval and commercialize the product. A skilled artisan would minimize active content variation by optimizing the available parameters in Staab's process, which are the same as or similar to those in the '080 patent. These include the polymer material, drying temperature, hot air application, drying time, viscosity, etc.

Further, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have performed known analytical chemical tests on Staab's dosages so as to determine the actual amount of active in the dosages and thus, assure the active content uniformity.

With respect to claims 82 and 315, it would have been obvious to one of ordinary skill in the art at the time the invention was made to repeat said analytical chemical tests with each additional film that is prepared by repeating Staab's process in order to seek regulatory approval and commercialize the product. It further would have been obvious to a skilled artisan at the time the invention was made to have prepared the multiple films such that the active content in each film does not vary by more than 10%, as

determined by analytical chemical tests, from the amount of active the dosages are supposed to contain as required by various world regulatory authorities, in order to minimize dosage variation and so as to commercialize the product. A skilled artisan would obtain the variation of no than 10% from the desired amount by optimizing said available parameters in Staab's process.

Further, with respect to claims 2 and 3, as noted above, Staab teaches a masterbatch pre-mix can be formed containing polymer and solvent, and the pre-mix is then transferred to a cooler vessel, i.e., a second vessel in series, for addition of heat-sensitive pharmaceuticals or other agents (see col. 7, lines 37-51). Staab's Fig. 5 depicts three mixing vessels, the top two vessels being in parallel with each other, the lower vessel being in series with the top two vessels. Any transfer from one vessel to another would inherently or obviously involve a metering pump and control valve.

With respect to claims 65-69, 144-148 and 226-230 which require that the active is coated with a controlled release composition, and with respect to claims 72-75, 78-81, 151-154, 157-160, 233-236 and 239-242 which require providing a second film layer, Staab teaches that its film may be a laminate of two or more layers (see col. 5, lines 30-31; col. 9, lines 28-43; and Fig. 2). Staab teaches that the laminates can be formed in the conventional manner, for example the mixture in liquid form is poured or cast onto a plate or into a mold and allowed to begin to set, at which time another liquid mixture with different composition is poured on the first mixture, and both mixtures are allowed to set up completely producing a laminate or layers of different materials (see

col. 5, lines 51-58). Staab teaches that the first and second film can comprise an active. In particular, referring to Fig. 2, Staab teaches the following at col. 9, lines 28-43:

> A first film layer 13 is made of, for example, a faster dissolving polymer material for release of a drug material 14a. A second film layer 15 is made of slower dissolving polymer material for release of more drug or another drug material 14b in combination, for example, a spermicide and an anti-infective or anti-inflammatory medication. A third (and additional) layer(s) 16 with additional drug can also be employed for sustained release of the drug.

Thus, the layers provide for controlled release of the drug material, i.e., a fast and slow release, and thus a sequential release, and also a sustained release. Staab also teaches immediate release since Staab teaches that "in case of medications to be administered via the oral cavity, it is advantageous that dissolution take place fairly rapidly." (See col. 4, lines 59-61). Immediate release and sustained release are also exemplified at col. 13, lines 13-41.

With respect to claims 70, 149, 231, 259, 260, 277, 278 and 295-297, Staab teaches many actives that are particulate, such as monoclonal antibodies (see col. 5, lines 49-53). The particulate monoclonal antibodies would be dispersed, i.e., suspended, in the matrix during the uniform blending (see col. 6, lines 5-10; col. 7, line 41; and col. 11, lines 26-35). Also, it is noted that polymers such as said PEO and HPMC are hydrocolloids.

With respect to claims 162, 163, 249-252, 258, 267-270, 276, 285-288 and 294, Staab teaches that if the drug can be applied on or in a moist area of the body, such as the mouth, vagina, rectum or eye, then the film can be used to deliver the drug effectively (see col. 7, lines 3-8). Application on or in the mouth either anticipates or

renders obvious gingival, sublingual and buccal application. With respect to claim 164, Staab teaches the treatment of burn wounds with its films (see col. 7, lines 7-9).

With respect to claims 317 and 318, air currents which have forces below the yield value of the polymer matrix are inherent in Staab's process because, as noted above, Staab's cut films each contain 19 mg of active and thus, the variation of active in the dosage units is 0% and Staab obtains a consistent product. Alternatively, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have adjusted Staab's overbelt hot air (col. 10, lines 28-34) so that the film is not excessively blown and thus, a consistent product can be obtained.

6. Claims 8, 9, 76, 77, 87, 88, 155, 156, 169, 170, 237 and 238 are rejected under 35 U.S.C. 103(a) as being unpatentable over Staab.

This rejection was proposed by Third Party Requester on pages 41-42 of the Comments filed 04/12/13 and **is adopted** for the reasons that follow.

Staab is relied upon for the reasons stated above in rejection No. 5.

With respect to claims 8, 9, 87, 88, 169, and 170, Staab teaches that its polymer can be a dissolvable complex carbohydrate (col. 4, line 6 through col. 5, line 29), but does not specifically teach the complex carbohydrates here claimed, such as sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum and starch. However, these are conventional dissolvable polymers in the art. Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have used sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum,

arabic gum and/or starch for the dissolvable complex carbohydrate to prepare Staab's film because these are conventional, dissolvable complex carbohydrates in the art and the reasonable expectation of success in preparing Staab's film.

With respect to claims 76, 77, 155, 156, 237 and 238, Staab does not specifically teach that its second film layer is extruded or sprayed onto its first film layer. As noted above, Staab teaches that the laminates can be formed in the conventional manner, for example the mixture in liquid form is poured or cast onto a plate or into a mold and allowed to begin to set, at which time another liquid mixture with different composition is poured on the first mixture, and both mixtures are allowed to set up completely producing a laminate or layers of different materials (see col. 5, lines 51-58). The instantly claimed extrusion and spraying are well known alternative techniques to coating and casting for forming a layer.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have used extrusion or spraying in place of coating and casting to form Staab's second film layer because extrusion and spraying are well known alternative techniques to coating and casting, and the resulting reasonable expectation of success in preparing Staab's second film layer.

7. Claims 82, 89, 90, 92, 161, 171, 172, 174, 274, 292, 304-311 and 313-318 are rejected under 35 U.S.C. 103(a) as being unpatentable over Le Person.

On pages 42-44 of the Comments filed 04/12/13, Third Party Requester proposes that claims 82, 89, 90, 161, 171, 172, 274, 292 and 300-318 be rejected under

35 USC 102(b) as anticipated by, or alternatively, under 35 USC 103(a) as being unpatentable over Le Person. Further, on p. 44 of the Comments filed 04/12/13, Third Party Requester proposes that claims 92 and 174 be rejected under 35 USC 103(a) as being unpatentable over Le Person. For the reasons that follow, the proposed anticipatory rejection under 35 USC 102(b) of claims 82, 89, 90, 161, 171, 172, 274, 292 and 300-318 and the proposed obviousness rejection of claims 300-303 and 312 **are not adopted**. For the reasons that follow, the proposed obviousness rejection of claims 82, 89, 90, 92, 161, 171, 172, 174, 274, 292, 304-311 and 313-318 **is adopted**.

The proposed anticipatory rejection of claims 82, 89, 90, 161, 171, 172, 274, 292 and 300-318 is not adopted because independent claims 82 and 161 have been amended to require, and newly added independent claims 315-318 require, performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units sampled from different locations of the resulting film. Le Person does not teach such testing of the resulting film.

Further, the proposed anticipatory and obviousness rejections of claims 300-303 and 312 are not adopted because these claims depend from claim 1. Neither in the request for reexamination nor in the Comments filed 04/12/13 has Third Party Requester shown how Le Person alone teaches or renders obvious all the limitations in claim 1.

With respect to the obviousness rejection, Le Person provides and compares several processes for the drying of pharmaceutical wet films including drying by convection, conduction, and infrared drying (see p. 258, first sentences of § 2.2). The

films of Le Person contain an acrylic adhesive polymer, its solvents, which include water, and an active substance which is a pharmaceutical or drug (see p. 258, line 5 and the first sentence of § 2.1; and Table 1). Le Person teaches that the constituents of the active phase, including the pharmaceutical or drug, in the matrix are homogeneously distributed (see p. 262, col. 2, lines 4-6). Le Person teaches that "[a]fter preparation, the coating mixture is spread on a web and submitted to drying in a tunnel or an oven. Frequently, impinging jets and Infra-red Radiation accomplish the work in a short drying time (100 s as an order of magnitude)." (See p. 257, col. 1, lines 10-14). Using a short infrared drying process, Le Person teaches that in 10 minutes, 99% of the initial water from a 100 µm thick coating is evaporated (see p. 260, col. 2, lines 12-14 and Fig. 5). As seen in Le Person's Fig. 3, the average temperature of the film during drying stays well below 100°C. As seen in Table 2, Le Person teaches a heated slab temperature, T_c, of 60°C and a wind tunnel air temperature, $T_{\infty db}$ of 65°C (see also p. 258), which render obvious the drying apparatus temperature of about 60°C in claim 318. The drying is controlled since, for example, Le Person teaches "a conventional drying rig where temperature ($T_{\infty db}$), velocity (U_∞) and humidity (Y_∞) of air are controlled." (See p. 258, col. 2 and Fig. 1).

As noted above, Le Person teaches that the active substance is homogeneously distributed throughout the initially wet film (see p. 262, col. 2, lines 4-6). Le Person then studies the migration of the active material vertically, i.e. throughout the thickness, of the film throughout the drying process (see p. 262, col. 1, lines 11 to col. 2, line 3). Le Person discloses that after 5 min of the drying, "the polymeric network is not turgescent

and the meshes are densely packed. The polymer skeleton acts as a filter for the active substance [i.e., pharmaceutical or drug] when the system reequilibrates." (See p. 262, col. 2, third full paragraph.) Le Person also teaches that "[b]etween the 5^{th} and 10^{th} min of drying the heavy solvent migrates… active substance, slowed down in its migration, stays in the bottom of the layer." (See the last four lines at page 262, col. 2). It is noted that the heavy solvent only accounts for 2% of the wet composition of the coating (see page 258, Table 1). The active material homogenizes and a quasi-equilibrium is obtained for the components of the active phase, taking into account evaporation of the heavy solvent (p. 263, col. 1, lines 8-13). Le Person also teaches that the films are used in patches for transdermal drug delivery (see Abstract and p. 257, col. 1). Thus, plural dosage units of the same size, e.g., plural transdermal patches of the same size, are rendered obvious by Le Person.

As noted above, after 10 minutes of drying, 99% of the water has been evaporated (see p. 260, col. 2, lines 12-14 and Fig. 5). In fact, the water is intensely removed from the film in the first 3 minutes with the short infrared drying process (see p. 261, col. 2, lines 21-24 and 27-30). Also, as can be seen from Fig. 2 on p. 259, similar intense drying is seen using conduction, convention, etc. As seen in Fig. 5, after 4 minutes of drying, about 98% of the water, i.e., the major solvent as seen in Table 1, has been evaporated. Further, Le Person's Fig. 2 shows that at 4 minutes, or approximately 15 $s^{0.5}$, solvent content is less than 20% by weight in the films dried by MIR and SIR and less than 35 % by weight in all dried films.

Within about 4 minutes of drying, Le Person's film is inherently viscoelastic. In particular, a compact polymer skeleton, wherein the polymer network is not turgescent and the meshes are densely packed, has been formed. Le Person uses the same type of polymer as disclosed in the '080 patent, i.e., an acrylic polymer (see p. 258 of Le Person; and col. 15, lines 55-56 of the '080 patent). As the drying proceeds, the active substance homogenizes, and after 15 minutes of drying, a quasi-equilibrium is obtained for the components of the active phase, taking into account evaporation of the heavy solvent (see pp. 262-263).

Le Person teaches the limitations of the instant claims, other than the differences discussed below.

Le Person does not teach the viscosity of its wet mixture of ingredients, whereas the instant claims require a viscosity from about 400 to about 100,000 cps. It would have been obvious to one of ordinary skill in the art at the time the invention was made to have prepared Le Person's coating mixture of acrylic polymer, solvents and active with an appropriate viscosity so that it can be spread on a substrate and dried to form a film useful for transdermal delivery of the active (see p. 257). The claimed viscosity from about 400 to about 100,000 cps corresponds to a viscosity ranging from thin castor oil to mincemeat. It would been obvious to one of ordinary skill in the art at the time the invention was made to prepare Le Person's mixture such that the viscosity is not too low, and thus, the mixture doesn't run like water, but not too high so the mixture is spreadable on a substrate; and so as to ultimately form a transdermal delivery film which is a quality product with physical and chemical homogeneity and an appropriate

distribution of active substance (see the paragraph bridging the left and right columns on p. 257 of Le Person).

The claimed percent variation of active of no more than 10%, less than 5%, less than 2%, less than 1% and less than 0.5%, and thus also the claimed substantially uniform distribution and locking-in or substantially preventing migration are inherent in Le Person's films in view of the fact that, as noted above, Le Person's active material homogenizes and a quasi-equilibrium is obtained for the components of the active phase, taking into account evaporation of the heavy solvent. Accordingly, Le Person's films are suitable for regulatory approval by the FDA and commercialization, as here claimed.

Alternatively, to the extent the claimed percent variation of active is not inherent from Le Person's process, then such would have been obvious. Le Person also differs from the instant claims in that while Le Person teaches the active material homogenizes and a quasi-equilibrium is obtained for the components of the active phase, taking into account evaporation of the heavy solvent, Le Person does not perform "analytical chemical tests" on the equal sized dosage units.

However, Le Person's films are intended for human use for delivery of pharmaceuticals, such as transdermal drug delivery (see p. 257). It is well-known in the art that world regulatory authorities do not permit dosage forms to vary by more than 10% in the amount of active present. It is also well-known in the art that to verify such uniformity, the actual content of active in individual dosages is measured, i.e., conventional analytical testing is used.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to minimize the active content variation among Le Person's dosages, as measured by analytical chemical tests, as close to zero as possible, including the instantly claimed no more than 10%, less than 5%, less than 2%, less than 1%, and less than 0.5%, in view of the well-known goal of a skilled artisan to prepare dosages that do not vary by more than 10% in active, in view of the fact that Le Person's active material homogenizes and a quasi-equilibrium is obtained for the components of the active phase, taking into account evaporation of the heavy solvent, and a desire to obtain FDA approval and commercialize the product. A skilled artisan would minimize active content variation by optimizing the available parameters in Le Person's process, which are the same as or similar to those in the '080 patent. These include drying temperature, drying time, air velocity, humidity, etc (see pp. 258-259 of Le Person).

Further, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have performed known analytical chemical tests on Le Person's dosages so as to determine the actual amount of active in the dosages and thus, assure active content uniformity.

With respect to claim 82 and 315, Le Person does not specifically teach repeating its process and said analytical chemical tests. Further, Le Person does not specifically teach that the active content of the first film obtained from the process and additional films prepared by repeating the process varies no more than 10% from a desired amount as indicated by analytical chemical tests.

However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have repeated Le Person's process and the analytical chemical tests for each film prepared by the process so as to prepare more films and dosages, seek regulatory approval and commercialize the product. It further would have been obvious to a skilled artisan at the time the invention was made to have prepared the multiple films such that the active content in each film does not vary by more than 10% from the amount of active the dosages are supposed to contain as required by various world regulatory authorities, in order to minimize dosage variation and commercialize the product. A skilled artisan would obtain the variation of no than 10% from the desired amount by optimizing said available parameters in Le Person's process.

With respect to claims 90 and 172, Le Person teaches that its coating mixture contains three light solvents (Sl_i) (see p. 258, section 2.1). Table 1 indicates that solvent Sl_2 has a molecular weight of 46, which is the molecular weight of ethanol. While dimethyl ether also has a molecular weight of 46, it cannot be used as a solvent due to its low boiling point of -24°C. Accordingly, the Le Person's light solvent of molecular weight 46 is either the same as or renders obvious ethanol as here claimed.

With respect to claims 274 and 292, which require that the resulting film contains less than about 6% by weight solvent, the solvent content in Le Person's dried films is far under about 6% as evidenced by Figs. 2 and 5. Le Person teaches that using a short-infrared drying process, in 10 minutes 99% of the initial water content from a 100 µm thick coating is evaporated (see § 3.1 at pp. 260-261, in particular Fig. 5 and the

second paragraph of right col. at page 260). In view of the water and heavy solvent content in Fig. 5, the total solvent content is well under about 6%.

Le Person does not teach the pharmaceutical or drug active materials listed in claims 92 and 174. However, these materials are conventional pharmaceuticals and drugs.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have used the conventional pharmaceutical or drug materials here claimed as the pharmaceutical or drug material in Le Person's film so as to take advantage of the intended function of the pharmaceutical or drug, and because of a reasonable expectation of success.

With respect to claims 317 and 318, while Le Person does not specifically teach using air currents which have forces below the yield value of the polymer matrix, such is either inherent or obvious. It's inherent because Le Person teaches air velocities of 2 m/s and 4 m/s (Table 2), which correspond to 4.5 miles/hr and 8.9 miles/hr, respectively. These are light winds that even with water (viscosity 1 cp) would produce only small wavelets.

Alternatively, since Le Person's resulting, dried films are homogeneous with respect to active material, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have adjusted Le Person's air velocity so that the film is not excessively blown and thus, a consistent product can be obtained.

8. On pages 45-46 of the Comments filed 04/12/13, Third Party Requester proposes that claims 1, 5, 7-10, 13, 14, 23, 63, 64, 82, 84, 86-89, 92, 93, 102, 142, 143, 161, 166, 168-171, 174, 175, 184, 224, 225, 249, 267, 285 and 300-317 be rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Horstmann.

9. On page 46 of the Comments filed 04/12/13, Third Party Requester proposes that claim 318 be rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Horstmann and Arter.

10. On pages 46-47 of the Comments filed 04/12/13, Third Party Requester proposes that claim 318 be rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Horstmann and Strobush.

These proposed rejection Nos. 8 to 10 **are not adopted** for the reasons that follow.

Independent claims 1, 82 and 161 have been amended to require, and new independent claims 315-318 require, performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units sampled from different locations of said resulting film, said tests indicating that uniformity of content in the amount of the active varies by no more than 10%. This requirement is similar to the imitation set forth in patented dependent claims 255, 273 and 291 (now canceled), which depended from claims 1, 82 and 161, respectively, and required the step of forming a plurality of individual dosage units of substantially the same size, wherein the active content of individual dosage units varies no more than 10%. Neither

in the request for reexamination nor in the Comments filed 04/12/13 has Third Party Requester shown how Horstmann teaches or renders obvious said requirement. Further, Horstmann is discussed in the Background of the Related Technology section of the '080 patent, where difficulty in achieving a uniform film after drying is discussed (col. 1, line 52 through col. 4, line 23). Neither Arter nor Strobush solves Horstmann's deficiency.

Response to Arguments

Patent Owner's arguments filed September 3, 2013, including Bogue Declarations I and II and the Lin Declaration, have been fully considered but they are not persuasive. Patent Owner's arguments have been considered to the extent they apply to the 07/26/13 claims.

Bogue Declarations I and II and Patent Owner's citation of *Leo Pharmaceuticals* are unpersuasive:

Patent Owner cites Bogue Declaration I for demonstration of uniformity of content and forming a viscoelastic film that locks-in a substantially uniform distribution of active(s) within about the first 4 minutes of drying (Remarks of 09/03/13, pp. 51-55).

Bogue Declaration I has been fully considered but is unpersuasive for several reasons. It does not make a comparison with the prior art of record, and thus, does not show anything unexpected with respect to the prior art of record. Other than the general process steps in the claims, which, as noted above, are performed by the prior

art either explicitly, inherently or obviously, Bogue Declaration I lacks specific details about the film production. For example, it is not clear in Bogue Declaration I which materials, e.g., the specific polymers and solvent, are used; it is not clear if other materials are present when preparing the films; it is not clear exactly what is done to form the flowable polymer matrix or how and on what it is casted, or, in particular, exactly how the controlled drying is performed and for what exact amount of time the drying is done, etc. Accordingly, a definitive conclusion cannot be reached from Bogue Declaration I.

As noted above in the rejections, the prior art either explicitly, inherently and/or obviously performs the claimed generic manufacturing steps using the claimed generic ingredients. In fact, as also noted above, Chen analyzes its resulting film using the same criteria exemplified in the '080 patent specification for evaluation of substantial uniform distribution, i.e., weight of dosages and visual inspection (see col. 31, line 37 through col. 32, line 34, and col. 37, lines 61-63 of the '080 patent). In particular, Chen's dried film product of Example 1 is cut into equal sized dosage units ready for packing (p. 17, lines 31-32; Table 4) and has a weight of 0.028 $\pm$ 0.001 g/dosage film, a density of 1.0485 $\pm$ 0.009 g/cm^2, a water content of 1.7 $\pm$ 0.24%, a thickness of 2.1 $\pm$ 0.12 mil (see Table 4); and the dried films are glossy and substantially transparent (p. 17, line 15), i.e., they are visually free of aggregation. The 0.028 $\pm$ 0.001 g/dosage film has variation of (0.001/0.028) x 100 = 3.6%. When film weight is rounded to two decimal places as in Table 2 at col. 31 of the '080 patent, then the weight is 0.03

gram/dosage film with a variation of 0%. Such small variation when following Chen's process was confirmed in the Reitman Declaration submitted by Third Party Requester.

Likewise, in the Example at cols. 11-12, Staab prepares a four-foot wide film which is then cut into two inch by two inch films each weighing 190 mg and containing 19 mg of benzalkonium chloride as the active agent (see col. 11, line 52 through col. 12, line 3). Le Person teaches the active material homogenizes and a quasi-equilibrium is obtained for the components of the active phase, taking into account evaporation of the heavy solvent (p. 263, col. 1, lines 8-13),

Patent Owner cites *Leo Pharmaceutical Products, Ltd., v. Teresa Staneck Rea, Acting Director, USPTO*, 2012-1520 (Fed. Cir. August 12, 2013) and argues that "the '080 Patent teaches that the prior art did not obtain the required level of uniformity content because of many problems in processing"; argues that "[p]rior to the '080 Patent there was no disclosure that anyone recognized there were problems with obtaining the higher degrees of uniformity of content of active in films claimed in the '080 Patent and that 'locking-in' by controlled drying, among other things claimed in the '080 Patent, could successfully address the problems"; argues that "since except for Le Person (and Le Person merely identified a problem, its complexity, the strict requirement for including assaying, but did not solve it (Le Person, see e.g., p. 257)), none of the other prior art references Chen, Staab, Strobush, Horstmann and/or Arter recognized the problem with obtaining the higher levels of uniformity of content, the record shows no reason for one of ordinary skill in the art to attempt to improve upon each other by

combining their disclosures"; and argues that "without recognition of the problem, there could be no optimization, because they would not have known to even try to solve it." (Remarks of 09/03/13, pp. 56-59). Patent Owner cites Exhibit 4 of the Remarks filed 09/03/13, i.e., a 2001 article co-authored by Li-Lan Chen who is a co-inventor of the Chen reference (WO 00/42992), and argues that it was patentee who recognized the problems associated with achieving uniformity of content of active (Remarks of 09/03/13, pp. 60-62).

These arguments are unpersuasive. While the '080 patent states at col. 3, lines 33-37 that "[c]onventional drying methods generally include the use of forced hot air using a drying oven, drying tunnel, and the like" and that "[t]he difficulty in achieving a uniform film is directly related to the rheological properties and the process of water evaporation in the film-forming process", it is noted that none of the processes of Chen, Staab or Le Person, which are essentially the same as here claimed, with the exception of running conventional "analytical chemical tests", is addressed in the '080 patent.

Patent Owner's alleged uniformity issue was addressed by the prior art. Using Chen as an example and as noted above in the rejection, Chen's ingredients are mixed until they are uniformly dispersed or dissolved in the hydrocolloid (p. 17, lines 8-11). Chen's mixture of ingredients, i.e., the instant flowable polymer matrix, which Chen teaches has a viscosity of 500 to 15,000 cps, is degassed in a vacuum chamber until trapped air bubbles are removed, and then coated on the non-siliconized side of a polyester film (see p. 15, lines 24-29; and p. 17, lines 13-15). Chen controls drying and evaporates water from the cast matrix in 9 minutes of drying in a hot air circulating oven

at 50°C (see p. 17, lines 13-15 and Fig. 2). In particular, as seen schematically in the drying apparatus of Chen's Fig. 2, the air flow is less direct at the film surface at the beginning of the drying and becomes more direct as the film proceeds through the drying oven, which has an aeration controller (see also p. 5, line 31 through p. 6, line 3).

Analyzing the resulting film for uniformity, Chen uses the same criteria exemplified in the '080 patent specification for such evaluation, i.e., weight of dosages and visual inspection (see col. 31, line 37 through col. 32, line 34, and col. 37, lines 61-63 of the '080 patent). In particular, Chen's dried film product of Example 1 is cut into equal sized dosage units ready for packing (p. 17, lines 31-32; Table 4) and has a weight of 0.028 $\pm$ 0.001 g/dosage film, a density of 1.0485 $\pm$ 0.009 g/cm^2, a water content of 1.7 $\pm$ 0.24%, a thickness of 2.1 $\pm$ 0.12 mil (see Table 4); and the dried films are glossy and substantially transparent (p. 17, line 15), i.e., they are visually free of aggregation. The 0.028 $\pm$ 0.001 g/dosage film has variation of (0.001/0.028) x 100 = 3.6%. When film weight is rounded to two decimal places as in Table 2 at col. 31 of the '080 patent, then the weight is 0.03 gram/dosage film with a variation of 0%. In fact the Reitman Declaration, which reproduced Chen's Example 7, obtained films each weighing 0.034 grams/dosage unit and having a variation of active content, i.e., oxybutynin content, of less than 10% as here claimed.

Furthermore, with respect to Patent Owner's Exhibit 4, i.e., the article co-authored by Chen, Third Party Requester notes the following on p. 21 of the Comments filed 10/03/13:

> In addition--even if the problem was not already solved by Chen, which it was as described in Chen and confirmed by the Reitman Declaration--it is

> unclear how Exhibit 3 [sic, Exhibit 4] (the newly submitted 2001 article authored by Liang &Chen) is relevant to patentability. Exhibit 3 [sic, 4] says nothing about any alleged uniformity problem. Nor does it rebut any finding that Chen teaches forming a visco-elastic film within about 4 minutes. The portion quoted and bolded by MonoSol [i.e., Patent Owner] (Reply at 65 [sic, 61-62]) only discusses further work related to, e.g., high stability, transportability, and good patient acceptability to achieve an "ideal fast-dissolving system." No connection is made by MonoSol as to how this relates to the alleged problem or solution. And none is discernible to Requester.

Patent Owner cites Bogue Declaration II for the proposition of commercial success (Remarks of 09/03/13, pp. 56 and 59-63).

Patent Owner's argument of commercial success and Bogue Declaration II are unpersuasive for the reasons set forth by Third Party Requester on pages 8-10 of the Comments filed 10/03/13, reproduced below:

> MonoSol fails to establish (or even argue) any nexus between the claims and the sales it relies on. The evidence demonstrates that Suboxone® sales are derived from market exclusivity, not the merits of the claimed methods. Finally, the evidence directed to Suboxone® films is not commensurate in scope with the claims and thus is not relevant to patentability.
>
> 1. *MonoSol has failed to establish a nexus between commercial success and the claimed methods*
>
> MonoSol bears the burden of proof with respect to establishing a nexus between its evidence and its claims. *Lingamfelter v. Kappos*, No. 2011-1449, 2012 WL 3218529 (Fed. Cir. 2012) (holding that secondary considerations of obviousness did not rebut *prima facie* case of obviousness in *inter partes* proceedings for reexamination where patent owner failed to sufficiently establish nexus between economic success and the claimed features).
>
> The declarations do not state how the Suboxone® films were made, or if they were made in accordance with any of the 313 claims in this proceeding. Dr. Bogue only states that they were made in accordance with general steps set forth in paragraph 4 of Bogue I that do not correspond to any claim. Bogue I; see all Bogue II at ¶ 4. Dr. Bogue has not disclosed or linked this generic process

with one or more of the 313 claims. See MPEP 716 ("7.66.03 Reason Why Affidavit or Declaration Under 37 CFR 1.132 Is Insufficient: Refers Only to Invention, Not to Claims."). Moreover, Dr. Bogue has not disclosed any links between the added analytical chemical testing step and the rest of the recited method for forming Suboxone® films. Accordingly, MonoSol failed to show with any particularity how the Suboxone® films were made and how that process may correspond to one or more of the rejected claims. See MPEP 716.03(a) (nexus is not established by generic statements regarding construction of products or process from declarants.); see also *Ex parte Standish*, 1988 WL 252397, 10 USPQ.2d 1454, 1458 (BPAI 1988). Instead, as discussed directly below, the evidence actually proves a nexus between the Suboxone® film sales and the conversion of existing sales from an existing product, by the voluntary and deliberate withdrawal of the existing product.

2. *The new evidence demonstrates that that* [sic] *the alleged commercial success is derived from product conversion, not the merits of the claimed methods*

MonoSol has failed to demonstrate how Suboxone® film sales are attributable to the processes now claimed. Evidence of commercial success must be directly derived from the invention claimed and not from a business event extraneous to the merits of the claimed invention. See MPEP 716.03(b)(I). In the instant case, MonoSol's new evidence demonstrates that there were extraneous business events which are causally tied to the sales of Suboxone® films. Specifically, the tablet form of Suboxone® was recently discontinued. As a result, existing users of the tablet form who were treating their opiate dependence and wanted to continue with the same branded drug are left with no option but to convert to the Suboxone® film. Exhibit 4 [sic, Exhibit 5] states:

> Suboxone [tablet] lost the exclusivity afforded by its orphan drug status on 8 October 2009.
>
> On 31 August 2010, the Group announced that it had received approval from the US Food and Drug Administration for its New Drug Application to manufacture and market Suboxone sublingual film ....
>
> As with all prescription drugs, the protection of the business has a finite term unless replaced with new treatments or forms.
>
> RB Pharmaceuticals recently announced its voluntary discontinuation of Suboxone tablets in the US due to increasing concerns with paediatric exposure .... The approval of generic tablets has been anticipated since the loss of orphan drug status in 2009.

> 2012 net revenue increased +10% .... Conversion from tablets to film in the US continued to increase with market volume share at the end of 2012 of 64%, up from 48% at the end of 2011, creating significantly more sustainable business.

In short, MonoSol's own evidence demonstrates that the sales of Suboxone® film are not directly attributable to any claimed feature - but rather a branded distributor's conversion between the discontinued tablet formulation to a film formulation that enjoys regulatory exclusivity for sales.

3. *Suboxone® films are not commensurate in scope with MonoSol's claims*

MonoSol's newly submitted evidence relates to Suboxone® films. But, the claims are not limited to this particular active. For example, MonoSol provides new evidence of Suboxone® film sales (Exhibits 5 and 6, Exhibit 2, Bogue II statements 6 and 7), new evidence of Suboxone® film thicknesses (Exhibit 2, statements 8 and 9), and new evidence of dosage forms of Suboxone® films (Exhibits 2, statements 12 and 14). None of this evidence is commensurate in scope with the claims. For example, tablets or films branded as Suboxone® may derive their sales from the attributes of the particular active, which was in the past exclusively sold by Reckitt Benckiser. As a result, evidence of sales of Suboxone® films is not commensurate in scope with claims that are not limited to Suboxone®. In order to be commensurate in scope with the claims, commercial success must be due to claimed features--not due to unclaimed features. MPEP 716.03(a) (I); see also *Joy Technologies, Inc. v. Manbeck*, 751 F. Supp. 225, 229, 17 USPQ.2d 1257 (D. DC. 1990).

In addition, evidence of the dry film thickness of Suboxone® films is not commensurate in scope to the claims because the claims are not limited to Suboxone®, and recite no thickness limitation. Thus, it is unclear how evidence of the dry thickness of Suboxone® films pertains to patentability of the claims.

Patent Owner's further arguments on pp. 63-75 of the Remarks filed 09/03/13:

Patent Owner argues the following on pp. 63-64 of the Remarks filed 09/03/13:

In the ACP, p. 76, the Specialist states that "[n]owhere does the '080 patent provide a special definition for the term 'visco-elastic film'." Respectfully, Patentee strongly disagrees. The visco-elastic film of the present invention is rapidly formed upon controlled drying of the flowable polymer matrix so as to lock-in the uniformity of content throughout the visco-elastic film.

> As mentioned above, the controlled drying process of the present invention allows for uniform drying to occur, whereby evaporative cooling and thermal mixing contribute to the rapid formation of viscoelastic film and the "locking- in" of uniformity of content throughout the film. '080 Patent, col. 44, ll.9-14.
>
> Thus, the '080 Patent's visco-elastic film is novel, for example, in that it is rapidly formed from the polymer matrix in accordance with the teachings of the '080 patent so as to lock-in the desired degree of uniformity of content. Moreover, while a film may be in a visco-elastic state, and a fluid may be in a visco-elastic state, a visco-elastic fluid is NOT a visco-elastic film as disclosed and claimed in the '080 Patent. Further, while a film may be a visco-elastic film, nothing can be said about whether any actives or other components have been locked-in during the first about 4 minutes of its formation, so as to provide a specified degree of uniformity of pharmaceutical active content. Hence, the uniformity of active content present in the locking-in step(s) of the claims of the '080 Patent are directed to visco-elastic films. A visco-elastic material, let alone a visco-elastic film formed by any process which does not lock-in the content uniformity of the active cannot be compared to the '080 Patent's visco-elastic films, for purposes of inherency, novelty or obviousness.

These arguments are unpersuasive. Nowhere does the ‘080 patent provide a special definition for the term “visco-elastic film”. As noted above in the Scope of Claims section, the matrix prior to evaporating the solvent (water) may be viscoelastic, and the viscoelasticity is present due, for example, to the fact that a hydrocolloid has been added. While the ‘080 does not state what is an example of a hydrocolloid, a well-known hydrocolloid in the art is the water-soluble polymer hydroxypropyl methylcellulose (HPMC), which is used in most of the examples of the ‘080 patent, as well as in most of Chen’s examples, including Chen’s Examples 1 and 5-8 cited above. The Chen reference teaches that HPMC is a hydrocolloid (see p. 14, lines 22-27).

The instant claims recite “controlled drying … to form a visco-elastic film having said active substantially uniformly distributed throughout …”. However, as noted in the

rejections, Chen, Staab and Le Person use controlled drying and obtain the claimed substantial uniformity of active in a viscoelastic film.

Further, as noted by Third Party Requester on pages 12-14 of the Comments filed 10/03/13:

> MonoSol quotes the specification at column 44, lines 9-14, as providing a special definition of "visco-elastic film." The relevant portion of the specification states: "the controlled drying process allows for uniform drying to occur whereby evaporative cooling and thermal mixing contribute to the rapid formation of visco-elastic film and the 'locking-in' of uniformity." Reply at 63:18-23. But the quoted passage does not provide a special definition of "visco-elastic" or "visco-elastic film." If anything, the quoted passage is only a very general description of drying polymer-solvent mixtures with heat.
>
> Instead of reciting steps that would distinguish the prior art, MonoSol relies on the alleged "special definition" to challenge the propriety of the prior art, which does not recite the alleged special definition. Reply at ¶ bridging pp. 63-64 ("A visco-elastic material, let alone a visco-elastic film formed by any process which does not lock-in the content uniformity of the active cannot be compared to the '080 patent's visco-elastic films, for purposes of inherency, novelty, or obviousness.") And, most telling, MonoSol has never explained why the cited prior art when using the claimed polymer (e.g., hydrocolloids), and removing the same solvent employing the claimed drying steps, would *not* increase viscosity, and in turn, produce the "locking-in" that it argues is so special. Indeed, it is unclear to Dr. Cohen, who has more than 45 years of experience in the field of coating and drying, how this would *not* happen. Cohen Dec. ¶ 8-10. ("When working with a homogenous ... coating mixture [as disclosed in Chen], for example, it would be difficult for a person of ordinary skill in the film art not to obtain a film that has uniform content of active."). ACP at 83:17-84:19.
>
> MonoSol has never rebutted this opinion. MonoSol claims a method of making a film. Significantly, MonoSol has not disputed the Specialist's conclusion that the prior art teaches "the same materials and the same process steps as claimed." ACP at 35:12-16; 35-39 (Chen); 95:5-8 (Staab). Despite multiple opportunities during these proceedings, *MonoSol has not explained what step or condition is claimed but not taught by the cited art*. MonoSol has not explained why performing all of the claimed process steps with the claimed materials, as the prior art does, would not necessarily produce a film that has "locked-in" uniformity.
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> *********

> MonoSol effectively seeks a reach-through claim to capture any process that results in a uniform film. That is, it seeks to cover any process that produces a desired result by reciting a very generic process and the desired result. To prevent this very possibility, the Supreme Court in Markman made clear that scientific theories and desired results of claimed process steps, such as "locking in," do not have patentable weight. Markman, at 363. A process claim must recite the process that it seeks to protect, not a wish-list of desired properties and/or results of unrecited process steps. The prior art is replete with examples of the drying of polymer mixtures producing increased viscosity and increase [sic] visco-elasticity. Accordingly, the prior art's teaching of every claimed process limitation, which MonoSol does not dispute, suffices for invalidity.
>
> In short, the "locking-in" language, so heavily relied upon throughout MonoSol's Reply, is no more than a scientific theory, a natural consequence of evaporating solvent, or perhaps a desired result. It is not a process step and, it alone, does not distinguish the prior art. If there is a unique step to MonoSol's process, or if "locking-in" is meant to indicate a physical step or process condition, such step or condition has not yet been identified or claimed. Accordingly, the Specialist correctly stated: "[n]owhere does the '080 patent provide a special definition for the term 'visco-elastic film'." ACP at 76.

Patent Owner argues that Exhibits 7 and 8 of the Remarks filed 09/03/13 “stand for the requirement that **assays (analytical chemical testing) must always be made of film drug products**”; and argues “prior art that does not disclose that they assayed to establish the uniformity of any active, cannot be relied upon to establish any level of degree of uniformity, let alone the ‘080 Patents [sic] claimed degree of uniformity of content.” (Remarks of 09/03/13, pp. 64-66). Patent Owner cites said Exhibit 7, i.e., Chapter <905> Uniformity of Dosage Units (2011), and Bogue Declarations I and II and argues that their Suboxone® sublingual dose units are considered "Others" dosage forms thus requiring content uniformity with assaying, i.e., that the Suboxone® film product does not fit into the category of dosage forms where weight testing is acceptable (Remarks of 09/03/13, pp. 64-66).

These arguments are unpersuasive. As noted above, the '080 patent teaches analytical chemical testing can be done (see col. 28, line 66 through col. 29, line 1; col. 29, lines 35-39; and col. 32, lines 34-39). It is well-known in the art that world regulatory authorities do not permit dosage forms to vary by more than 10% in the amount of active present. It is also well-known in the art that to verify such uniformity, the actual content of active in individual dosages can be directly measured, e.g., conventional analytical testing can be used. However, none of the '080 patent examples uses chemical analytical testing for determining degree of uniformity content of a bioactive active or pharmaceutical active. The only analytical chemical testing exemplified in the '080 patent is in Example M at col. 33-34, and this testing is done for content of McCormick red dye, which is not a pharmaceutical active or bioactive active.

As noted by Third Party Requester on p. 14 of the Comments filed 10/03/13 and citing to col. 31, lines 38-45, col. 32, lines 26-34 and col. 33, lines 4-8 of the '080 patent, "[w]ithout ambiguity the '080 patent discloses that weight, visual inspection, and dissolution testing are acceptable and alternative ways to measure uniformity of active content". At cols. 31-32, the '080 patent teaches that uniform distribution of components within the film was apparent by examination by either the naked eye or under slight magnification. Also, the individual dosages in Table 2 consistently weighed 0.04 grams, "which shows that the distribution of components within the film was consistent and uniform … based on the simple principle that each component has a unique density. Therefore, when the components of different densities are combined in a uniform manner in a film, as in the present invention, individual dosages [sic] forms

from the same film of substantially equal dimensions, will contain the same mass." (See col. 32, lines 26-33). Similarly, at col. 37, lines 52-67 of the '080 patent, the dried film was cut into 1 in. x 0.75 in. pieces weighing 70 mg ± 0.7 mg.

As noted above, Chen's dried film product of Example 1 is cut into dosage units (p. 17, lines 31-32), which have a weight of 0.028 ± 0.001 g/dosage film, i.e., 28 mg ± 0.1 mg/dosage film or 0.03 gram/dosage film with a variation of 0%, just as Table 2 of the '080 patent has 0.04 g/dosage film and just as said col. 37, lines 52-67 of the '080 patent has 70 mg ± 0.7 mg. Chen's films are glossy and substantially transparent (p. 17, line 15), i.e., they are visually free of aggregation.

Just as the example at cols. 31-32 in the '080 patent prepares dosage units weighing 0.04 grams, i.e., 40 mg, Staab's dosage units weigh 190 mg (col. 11, lines 49-51). Staab goes further and provides the pharmaceutical active material (benzalkonium chloride) weight in the dosage films, i.e., 19 mg of benzalkonium chloride in each two inch by two inch cut film of 190 mg weight (col. 11, line 49 through col. 12, line 3).

As also noted above, Le Person teaches that as drying proceeds, the active substance homogenizes, and after 15 minutes of drying, a quasi-equilibrium is obtained for the components of the active phase, taking into account evaporation of the heavy solvent (see pp. 262-263).

Further, as noted by Third Party Requester on pp. 14-15 of the Comments filed 10/03/13:

> MonoSol attempts to distinguish prior art based on the fact that the Suboxone® film product does not fit into the category of dosage forms where weight testing is acceptable. Reply at 64. But MonoSol does not claim only Suboxone® film. The above '080 patent admission remains: weight, visual

inspection, and dissolution are each acceptable and alternative ways to measure uniformity of active. See also '080 patent at Examples A-L.

Based on one statement in the regulation (Chapter 905> Uniformity of Dosage Units), MonoSol also argues that analytical chemical testing is "required at some point even with weight variation." Reply at 65 (quoting the regulations "Carry out an assay for the drug substance(s) on a representative sample of the batch using an appropriate analytical method.") Even if the quote references an analytical chemical test--which is not clear from the quote or the larger regulation--it does not state or imply that weight variation is not an acceptable, alternative way to measure uniformity of active.

In response to the argument that McCormick red dye in the only example in the '080 patent, i.e., Example M, where analytical chemical testing is used is not a pharmaceutical active or bioactive active per the instant claims, Patent Owner cites col. 19, lines 40-48 of the '080 patent and argues that "[a]s set forth in the '080 Patent, in the section entitled Actives, no distinction is made between pharmaceutical actives and colorants actives, such as red dye"; and that "it is improper to rely on the fact that red dye is not a pharmaceutical active to support an argument that in accordance with the '080 Patent analytical chemical testing is not required to establish the exact amount of active present." (Remarks of 09/03/13, p. 66).

This argument is unpersuasive for the reasons set forth by Third Party Requester on pp. 15-16 of the Comments filed 10/03/13, reproduced below:

C. Example M is not relevant to the claims and does not support MonoSol's argument

The Specialist correctly noted on page 79 of the ACP that Example M is not an example of an analytical chemical test of a claimed pharmaceutical active or bioactive. MonoSol's response is that it agrees. Reply at 66.

This thread of argument was started by MonoSol's repeated and emphatic arguments that the recitation of "analytical chemical tests" distinguishes the claims from the cited prior art because analytical chemical tests were so critically

different from weight variation and visual inspection tests. See, e.g., Reply dated March 13, 2013 at 53-59 and Reply dated September 3, 2013 at 64-66. The Specialist wondered why, if analytical chemical tests are so critical to the claimed invention, the '080 patent teaches that weight variation and visual inspection tests are acceptable alternatives. See block quotes in section immediately above. The Specialist also wondered why--if they were so critical--MonoSol never employed them in over a hundred examples in the '080 patent. Those questions remain unanswered.

MonoSol argues that it doesn't matter that Example M is not an example of the claimed subject matter, because the specification makes no distinction between actives and pharmaceutical actives. Id. But even if MonoSol's argument were true--which it is not--Example M remains a single example outweighed by more than a dozen other examples that use weight variation and/or visual inspection (Examples A-L) to demonstrate uniformity. Moreover, the criticality or "distinctiveness" of analytical chemical tests is not demonstrated by Example M. And the '080 patent still unambiguously teaches that weight variation and visual inspection tests are acceptable alternatives to analytical chemical tests.

Finally, MonoSol admits the step of "performing analytical chemical tests for uniformity of content of said active..." was known. '080 patent 2:40-47 ("Currently, as required by various regulatory authorities, dosage forms may not vary more than 10% in the amount of active present."). Indeed, analytical chemical tests were among many known ways to measure the amount of active in each dosage form. Reply at 64-66; '080 patent, cols. 31-32. Thus, the ACP does not and need not rely on Example M for the rejection of claims including the step of performing analytical chemical testing. Even in the interpretation most favorable to MonoSol--which may or may not be correct--Example M only confirms what is already admittedly known regarding this post-manufacturing step. That is, measuring active content in samples from pharmaceutical commercial runs is obvious. ACP at 37-38.

Patent Owner argues the following on p. 67 of the Remarks filed 09/03/13:

The Specialist claims that Chen inherently discloses an active content of less than 10%, see, e.g., ACP, pp. 36-37, 87-90. However, no proof has been provided that Chen's process examples when accurately followed by one of ordinary skill in the art and not an expert will inherently disclose or make obvious the '080 Patent as claimed. Importantly, Third Party Requester's Reitman Declaration suffers from many infirmities. The Reitman Declaration discloses that in its attempt to replicate a Chen example, they could not faithfully follow the

> Chen disclosure, but needed to rely on substitution of components (e.g., substituing [sic] "Oxybutynin chloride" for "Oxybutynin", and "Kolliphor EL" for "Cremophor EL40") and drying conditions (e.g., "backing was not looped", samples not "die cut in line"). Reitman Declaration, pp. 3-4.
>
> In all likelihood, these substitutions were made because Reitman is declared to be an expert and not one ordinarily skilled in the art. Perhaps, other parameters of the process were also adjusted based on Reitman's inherent skill as an expert, perhaps even without any overt intention. Pointedly, Reitman does not conclude that the process she used to make the film was suitable for the commercial manufacture of pharmaceutical unit dosage films which are regulatory approvable by the FDA, and which exhibit the levels of uniformity of content in actual amount of active claimed by Patentee's processes. Moreover, as noted below in detail, Chen Figure 5 supports the opposite conclusion.

These arguments are unpersuasive. As noted above, Chen's dried film product of Example 1 is cut into equal sized dosage units ready for packing (p. 17, lines 31-32; Table 4) and has a weight of 0.028 $\pm$ 0.001 g/dosage film, a density of 1.0485 $\pm$ 0.009 g/cm^2, a water content of 1.7 $\pm$ 0.24%, a thickness of 2.1 $\pm$ 0.12 mil (see Table 4); and the dried films are glossy and substantially transparent (p. 17, line 15), i.e., they are visually free of aggregation. The 0.028 $\pm$ 0.001 g/dosage film has variation of (0.001/0.028) x 100 = 3.6%. When film weight is rounded to two decimal places as in Table 2 at col. 31 of the '080 patent, then the weight is 0.03 gram/dosage film with a variation of 0%. Accordingly, the claimed percent variation of active of no more than 10%, less than 5%, less than 2%, less than 1% and less than 0.5% is inherent in Chen's films and thus, the films are suitable for regulatory approval by the U.S. Food and Drug Administration (FDA) and commercialization, as here claimed. Alternatively, the claimed percent variation would have been obvious for the reasons set forth in the rejection.

As noted on page 75 of the ACP, Patent Owner has shown nothing unexpected with respect to the prior art of record. Third Party Requester, by way of the Reitman Declaration, replicated Example 7 of Chen, which uses the same process in Example 1 of Chen as well as here claimed, and obtained the content uniformity by dose weight set forth in Chen, and obtained a variation of active of less than 10% as here claimed. As noted by Third Party Requester on pp. 16-17 of the Comments filed 10/03/13:

> Contrary to MonoSol's unsupported assertions about burdens (Reply at 69: 8-70:16), it is MonoSol's burden to prove that Chen does not teach or suggest films with the claimed uniformity. Initially, the Office has the burden of "providing reasonable proof that a claim limitation is an inherent characteristic of the prior art." *In re Best*, 562 F.2d 1252, 1254-55 (CCPA 1977). The Office meets this burden by "adequately explaining the shortcomings it perceives so that the applicant is properly notified and able to respond." *In re Jung*, 637 F.3d 1356, 1362 (Fed.Cir. 2011) (quoting *Hyatt v. Dudas*, 492 F.3d 1365, 1370 (Fed. Cir. 2007). The burden of proof then shifts to the applicant "to prove that the subject matter shown to be in the prior art does not possess the characteristic relied on." *Best*, 562 F.2d at 1254-55.
>
> The Office has met its burden of "providing reasonable proof that a claim limitation is an inherent characteristic of the prior art" in multiple, independently valid ways. As stated in the ACP, Chen teaches using both weight variance of sample units and visual inspection to establish uniformity of content of active per dosage unit. ACP at 36:6-19. Using either of these methods conforms to the teaching of, and at least a dozen examples in, the '080 patent: namely, the demonstration of uniformity by visual inspection, weight measurement, and/or analytical testing. See *Id.*; '080 patent at cols. 31-33, and 37 (Examples A-L). Indeed, Dr. Reitman has confirmed that weight, visual inspection and analytical chemical (HPLC) testing of films made in accordance with Chen meet the uniformity requirements of the pending claims. See Reitman ¶¶ 5-7. Most telling, MonoSol is effectively silent in the face of the Office's repeated point that the prior art teaches "the same materials and the same basic process steps" as those claimed in the '080 patent. ACP at 35:12-16. "[W]here the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established." MPEP 2112.01(I). This is reasonable proof that the less than 10% variation limitation is an inherent characteristic of Chen.

Furthermore, Patent Owner's argument that the substitutions the Reitman Declaration made somehow amount to expert skill rather than ordinary skill in the art is unsupported. Footnote 1 on page 3 of the Reitman Declaration notes the following with respect to substitution of Kolliphor EL for the Cremophor EL40 used in Example 7 of Chen:

> [1] The Cremophor line of products now owned by BASF and renamed Kolliphor. Based on the naming convention of the Cremophor/Kolliphor products, EL40 is Polyoxyl 40 Castor Oil and EL is Polyoxyl 35 Castor oil (i.e., they are based on 1:40 and 1:35 ratio, respectively, of castor oil:ethylene oxide). They are different materials. However, one of skill in the art would recognize Kolliphor EL as an appropriate substitute, as Cremophor EL40 is no longer available.

Additionally, footnote 2 on p. 4 of the Reitman Declaration states "[o]ur backing was not looped and we did not die cut in line, but the solvent and casting and drying under aeration is matched." In Chen's Fig. 2, the polyester backing belt (10) loops around to get more formulation after dried intraoral film (12) is removed from the belt (10). The dried film (12) taken off of belt (10) is sent to die cutting (13) to be cut into unit doses (14). Nothing unusual has been shown about using a looping belt versus a non-looping belt or cutting in-line versus not in-line. The bottom line here is that either way, the matrix is cast on a polyester belt which then moves through the controlled dryer in Chen's Fig. 2, and the resulting dried film is then cut (see pp. 3-4 of the Reitman Declaration). Further, as noted by Third Party Requester on pp. 19-20 of the Comments filed 10/03/13:

> According to MonoSol, the Reitman Declaration is defective because "oxybutynin chloride" was substituted for "oxybutynin" and "Kolliphor EL" for "Cremophor EL40." Reply at 67:8-10. MonoSol has not explained why these standard ingredient substitutions would only be done by an expert or would

> provide superior results. MonoSol speculates that these and other parameters unspecified by Chen were deliberate and "expert" rather than "ordinary skill" substitutions, and thus Reitman's production of uniform films would be beyond one of ordinary skill. Reply at 67:11-14. But as demonstrated in paragraph 4, Dr. Reitman and her team followed every available guidance or instruction disclosed in Chen, as is easily seen in the point- to-point correspondence of the Chen disclosure to the methods employed by Reitman. MonoSol has failed to point to a single instance of something that Dr. Reitman's team did (some step or condition) that is unusual.[3] [footnote 3: "Notably, both the '080 specification and the '080 patent claims are more devoid of detail than Chen. Moreover, the process descrived [sic] in the Bogue Declarations is so devoid of detail that it would be impossible not only to reproduce the experiments but also to confirm which claims are exemplified or supported by the experiments. Having chosen this breadth and vagueness in its specification, its claims, and its declarations, MonoSol cannot complain that the methods cannot be practiced without undue experimentation."]

Patent Owner cites Chen's Fig. 5 and argues that "the films of Chen do not achieve the uniformity of pharmaceutical active of +/- 10% of the deired [sic]/label amount claimed in the '080 patent." (Remarks of 09/03/13, pp. 67-70). In particular, ¶ 22 of the Lin Declaration argues the following:

> 22. Finally, Chen's patent discloses the release profiles of four active agents from films. See Chen, Figure 5. The release profile data presented in Figure 5 show a high degree of variability at each data point. For example, the release profile for nicotine containing film product show that the amount of nicotine released at the 5 minute and 8 minute time point can be as high as approximately 115-120%. This level of active agent is greater them the 110% level (from an expected amount of 100%) that is considered acceptable to FDA for regulatory approval of a product that purports to be manufactured consistently with acceptable content uniformity. These data indicate that the test method used in the analysis is not reproducible and/or there is a lack of active agent content uniformity between individual dosage units. These deficiencies demonstrate the lack of manufacturing consistency and lack of active agent content uniformity in the film.

This argument is unpersuasive. Nowhere does the '080 patent or USP general chapter <905> cited in ¶ 16 of the Lin Declaration (see also Exhibits J and K of the

Comments filed 04/12/13 and Exhibits 7 and 8 of the Remarks filed 09/03/13) rely solely on a release profile to evaluate uniformity of content in the amount of active, as here claimed. Further, as noted by Third Party Requester on p. 7 of the Comments filed 04/12/13:

> Lin concludes his Declaration with a logical fallacy. Based on a possible relationship between data and a film problem, and despite evidence that indicates an alternative possibility is more likely, Lin illogically finds that the data necessarily shows a film problem. Lin states that Chen's interim release data indicates a problem with the test method "and/or" a variation in dosage unit active content. See Lin Decl. ¶ 20 [sic, ¶ 22] (emphasis added). Reduced to its logical components, Lin' s premise is that X (Chen' s interim release data) indicates A (test problem) and/or B (film problem). As an initial matter, the fact that Chen' s maximum release error bars decrease over time indicates that the error noted by Lin is an artifact of the test method--not a characteristic of the film. Nonetheless, without further support or explanation, Lin concludes that Chen's data demonstrates unacceptable variation in dosage unit active content (film problem). Reduced to its logical components, Lin's conclusion (X demonstrates B) does not follow from Lin's own premise (X indicates A and/or B). In other words, Lin's conclusion is logically invalid based on Lin' s own stated premise. Because it lacks viable support or explanation, Lin's conclusory allegation based on Chen's interim release data cannot overcome any rejections based on Chen. See MPEP 716.01 (C).III (requiring consideration of the absence of factual support for an expert opinion in assessing its probative value).

Even further, as noted by Third Party Requester on pp. 17-19 of the Comments filed 10/03/13:

> In view of the Office's showing, the burden of proof has been shifted to MonoSol. The question remaining is: Has MonoSol met its burden "to prove that the subject matter shown to be in Chen does not possess the desired result"? The answer is no. MonoSol merely repeats arguments concerning Fig. 5 that the ACP deemed unpersuasive and attacks the Reitman Declaration. ACP at 87:7-90:18; Reply at 67-70.
>
> 1. *Figure 5* [of Chen] *fails to disprove the uniformity of the films of Chen*

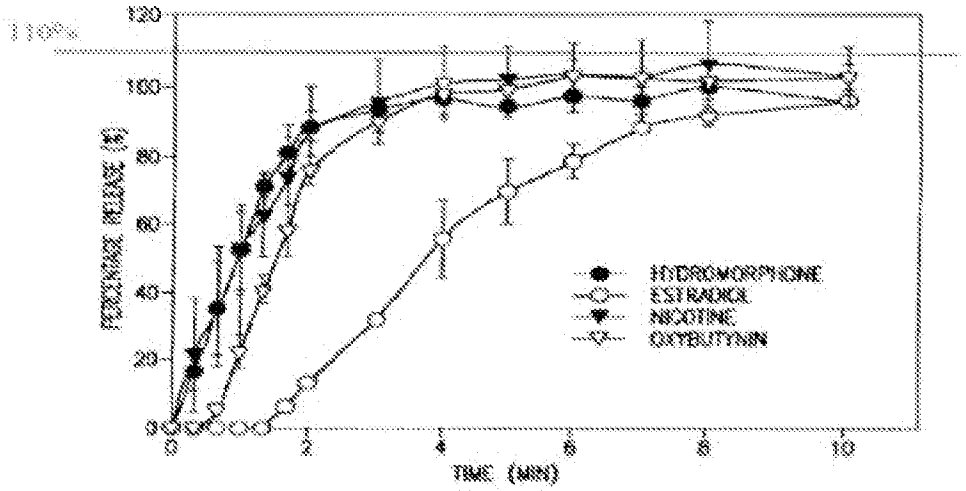

FIG.5

Chan, Figure 5 (110% line added by Patentee for clarity).

MonoSol relies on its hand-drawn line to show instances where percentage release in Figure 5 is allegedly greater than 110% and concludes that there is a lack of uniformity. But MonoSol's own expert, Dr. Lin, stated "these data [in Figure 5] indicate that the test method used in the analysis is not reproducible ***and/or*** there is a lack of active agent uniformity between individual dosage units." Lin Declaration at ¶ 22; ACP at 88:11-14 (emphasis added). That is, MonoSol's expert admits that the release date in Figure 5 could indicate a test problem.

Indeed, Figure 5 itself proves that there is a test problem. For example, the solid circles (hydromorphone) fluctuate down between 8 and 10 minutes. Similarly, the open triangles (oxybutynin) go down between 6 and 8 minutes. But the total amount of active that has been released cannot decrease over time--no matter how irregular the film samples might be. The decrease in total release can only indicate a problem with the test itself, which may include human error in performing the test.

Furthermore, MonoSol claims uniformity per dosage unit, not active released over time. Thus, the most relevant measurement, if any, is the last or latest release measurement as the closest representation to the total amount. Here, at 10 minutes, there is only one error bar over MonoSol's hand-drawn line (allegedly 110%). The gap between that error bar and MonoSol's line is less than or equal to the variation from the test or human error, as shown for hydromorphone (between 4 and 5 minutes) and oxybutynin (between 6 and 8 minutes). Thus, the clear problems with Figure 5 kill MonoSol's argument.

2. *Reitman confirms the prima facie case*

Requester has provided conclusive evidence that the methods of Chen anticipate the claims. Specifically, the data provided in the Reitman Declaration demonstrates active uniformity per dosage unit within a 10% variance in films prepared according to Chen. Reitman Decl. at ¶¶ 5-7. Dr. Reitman confirmed active uniformity employing each of the three alternative, acceptable methods disclosed in the '080 patent: visual inspection, weight variance, and dissolution. Thus, the Reitman Declaration independently proves that Chen's films satisfy the claimed desired result (uniformity of content in the amount of active varies by no more than 10%).

Patent Owner argues the following on pp. 70-71 of the Remarks filed 09/03/13:

The Specialist holds skilled artisans to a level of knowledge and experience to that of an expert, because only an expert could possibly "minimize active content variation" and "obtain the variation of no [more] than 10% from the desired amount," by somehow optimizing the parameters available in the prior art references, without undue experimentation. See, e.g., ACP, pp. 38, 59, 69, 70, 96, 100. Importantly, none of these references discuss or even mention "locking-in uniformity of content within 4 minutes of initiation of drying". Moreover, as discussed further below, in the case of inherency, even if the various parameters disclosed in the references cited could be manipulated to achieve such a result, their disclosure is not sufficient. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ 2d 1955, 1957 (Fed. Cir. 1993).

In particular, citing the parameters in Chen that are noted above as being the same as or similar to those in the '080 patent, i.e., mixing/degassing, casting of the wet film, viscosity of the wet film, drying temperature, drying time, control of air flow in Chen's Fig. 2, selection of appropriate colloid material, Patent Owner cites the *Leo Pharmaceuticals* case and argues there is undue experimentation in view of an enormous number of parameters (Remarks of 09/03/13, pp. 71-72).

These arguments are unpersuasive because, as noted above, Chen uses the same process steps as here claimed, has the same or similar process parameters as in the '080 patent specification, and achieves the same level of content uniformity disclosed in the '080 patent and here claimed. In particular, Patent Owner's argument of undue experimentation is unpersuasive and unsupported by factual evidence because Chen obtains dosage films having 0.03 gram/dosage film with a variation of 0% using the same process steps here claimed well before Patent Owner's alleged invention.

Patent Owner similarly argues that Staab and Le Person would require undue experimentation in view of "so many variations and potential combinations" (Remarks of 09/03/13, pp. 73-75).

These arguments are unpersuasive because, as noted above, Staab's and Le Person's process steps are essentially the same as here claimed. In fact, Staab prepares a four-foot wide film which is then cut into two inch by two inch films each weighing 190 mg and containing 19 mg of benzalkonium chloride as the active agent (see col. 11, line 52 through col. 12, line 3) i.e., a variation in active content of 0%. Le Person teaches the active material homogenizes and a quasi-equilibrium is obtained for the components of the active phase, taking into account evaporation of the heavy solvent (p. 263, col. 1, lines 8-13).

Arguments with respect to the 35 USC 103(a) rejection of claims 1-11, 13-15, 17-71, 82-90, 92-94, 96-150, 161-172, 174-176, 178-232, 243-253, 256, 258-271, 274, 276-289, 292 and 294-318 over Chen:

Patent Owner argues that step (d) not only requires creation of a viscoelastic film within about the first 4 minutes of drying, but also rapidly increasing the viscosity upon initiation of the drying process such that active is locked-in or substantially prevented from migrating within the film; and argues that Chen's Fig. 2 and Examples 1, 2, 5-8 and the Example in Tables 7 and 8 do not disclose the locking-in or substantially preventing migration (Remarks of 09/03/13, pp. 77-78 and 80-81). In particular, Patent Owner argues the following on p. 80 of the Remarks of 09/03/13:

> In view of the multitude of variations and potential combinations of processing parameters along with the excessive amounts of pharmaceutical active shown to be released and thus contained in the drug dosage units tested for content and shown in Figure 5 of Chen, it is abundantly clear that Examples 1, 2 and 5-6 and the Example in Tables 7 and 8 would not necessarily produce a viscoelastic film having the active substantially uniformly distributed throughout, within the first 4 minutes of drying by rapidly increasing the viscosity upon initiation of drying to maintain said substantially uniformed distribution of said pharmaceutical active by locking-in or substantially preventing migration of said active within said viscoelastic film, as claimed by the '080 Patent. Even if the various parameters disclosed in Chen et al. could be manipulated to achieve such a result, the disclosure is not sufficient. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ 2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily presented in the prior art).

These arguments are unpersuasive. For the reasons discussed above, forming a viscoelastic film within about the first 4 minutes of drying, and increasing the viscosity upon initiation of the drying process such that active is locked-in or substantially prevented from migrating within the film, inherently or obviously occur in Chen's

process. This is based on the fact that, as noted above, Chen prepares a wet polymer mixture using the same film forming polymers, i.e., HPMC or pullulan, and solvent disclosed and exemplified in the '080 patent; the mixture has the same viscosity here claimed; the casted mixture is dried with controlled drying as per Chen's Fig. 2 within the same total amount of time, i.e., 9 minutes and at the same temperature, i.e., 50°C as disclosed in the '080 patent to obtain a glossy, substantially transparent, stand-alone, self-supporting, non-tacky and flexible film; and the film is subsequently cut into dosage units having the same level of uniformity as disclosed in the '080 patent as determined using the same criteria disclosed in the '080 patent, i.e., weight of doses and visual inspection.

In particular, as noted above, Chen's dried film product of Example 1 is cut into dosage units (p. 17, lines 31-32), which have a weight of 0.028 $\pm$ 0.001 g/dosage film, i.e., 28 mg $\pm$ 0.1 mg/dosage film or 0.03 gram/dosage film with a variation of 0%, just as Table 2 of the '080 patent has 0.04 g/dosage film and just as said col. 37, lines 52-67 of the '080 patent has 70 mg $\pm$ 0.7 mg. Such small variation when following Chen's process was confirmed in the Reitman Declaration submitted by Third Party Requester. In fact, the data provided in the Reitman Declaration demonstrates active uniformity per dosage unit within a 10% variance in films prepared according to Chen's Example 7 (see Reitman Decl. at ¶¶ 5-7). Further, the Reitman Declaration, upon repeating Chen's Example 7, specifically states in ¶ 8 that "[w]ithin about 4 minutes after initiation of drying, the film was self-supporting, non-tacky, flexible and viscoelastic, as verified by my team."

Patent Owner again cites Chen's Fig. 5 and argues a non-uniform distribution of active in Chen's films (Remarks of 09/03/13, pp. 79-80).

This arguments is unpersuasive for the reason discussed above.

Patent Owner's further arguments with respect to Chen are rebutted by Third Party Requester on pp. 23-24 of the Comments filed 10/03/13, reproduced below:

> *5. Misquote of ACP*
>
> MonoSol distorts the rejection by taking a quote out of context. According to MonoSol, "the Specialist appears to be saying that Chen does not disclose or suggest that its viscoelastic film is formed within 4 minutes. Thus, Chen cannot inherently disclose or suggest or make obvious [MonoSol's] claim limitation that its invention locks-in or substantially locks-in the active...within the first four minutes of drying." Reply at 80:21-24.
>
> In that very context, however, the ACP points out that Chen uses the same solvent, same polymer (which '080 describes as producing viscoelasticity), and a viscosity that overlaps with the claimed viscosity range and even the preferred viscosity range. ACP at 34-35. Then the ACP states on page 35, lines 6-9 and 17-21:
>
> > "Accordingly, Chen's films ... are inherently viscoelastic before drying. Within 4 minutes of the 9 minute drying in Chen's Examples... a more dry viscoelastic film is obtained. As an even further alternative, if Chen's viscoelastic film is formed after about the first 4 minutes but with Chen's 9 minute drying time, then a skilled artisan would recognize that with a higher drying temperature, a shorter time than 9 minutes can be used. In other words, a higher drying temperature than the 50°C exemplified by Chen would result in a formation of Chen's visco-elastic film product sooner."
>
> Thus, the Specialist was clearly providing an alternative argument.
>
> *6. A higher drying temperature will allow a shorter drying time*

> According to MonoSol, "one skilled in the art would not necessarily recognize that a higher drying temperature and shorter drying time than 9 minutes could be used or would be desirable." Reply at 81:5-8. But the combination is a common sense prediction of a physical relationship. Anyone who uses a clothes dryer with two settings would understand that a higher drying temperature allows for a shorter drying time. As an illustrative example in the film prior art, Strobush clearly teaches several ways to dry films by raising the temperature without exceeding the threshold of heat transfer rate such that film defects are formed.
>
> In view of the above, the outstanding rejection was proper and has not been overcome by MonoSol.

Patent Owner's Lin Declaration argues that Chen's disclosure is insufficient to provide the manufacture of drug-containing films with the uniformity content in amount of drug (active) in individual dosage units to make FDA approvable film products (see ¶¶ 17-21).

The Lin Declaration is unpersuasive. As noted by Third Party Requester on pp. 5-6 of the Comments filed 04/12/13, the issue here is not whether Chen provides the thousands of pages of documentation required for the FDA to approve a drug product for administration to humans. The issue here is one of meeting the well-known requirement of a variation in active content of no more than 10%. As noted in the Background of the Related Technology section of the '080 patent, it is well-known from various world regulatory authorities that dosage forms may not vary more than 10% in the amount of active present (col. 2, lines 38-45). Independent claims 1, 82, 161, and 315-317 require a level of uniformity in the amount of active which varies by no more than 10%, independent claim 318 requires variation by no more than 5%, and claims 82 and 315 further require no more than 10% from a desired amount across additional

films prepared by repeating the process. As discussed above, while the '080 patent teaches analytical chemical tests can be used as an alternative to visual inspection and weight of dosages films for determining uniformity (col. 31, line 37 through col. 32, line 39), the only analytical chemical tests exemplified in the '080 patent are in Example M at cols. 33-34, and these tests are done for content of McCormick red dye, which is not a pharmaceutical active or bioactive active.

As also discussed in detail above, the criteria used by Chen to evaluate uniformity is the same as used in the examples of '080 patent, i.e., visual inspection and weight of dosage films. Chen's dried film product of Example 1 is cut into dosage units ready for packing (p. 17, lines 31-32) and has a weight of 0.028 $\pm$ 0.001 g/dosage film, a density of 1.0485 $\pm$ 0.009 g/cm^2, a water content of 1.7 $\pm$ 0.24%, and a thickness of 2.1 $\pm$ 0.12 mil (see Table 4); and the dried films are glossy and substantially transparent (p. 17, line 15), i.e., they are visually free of aggregation and the weight is 0.028 $\pm$ 0.001 g/dosage, i.e., 0.03 gram/dosage with a variation of 0% when rounded to two decimal places as in Table 2 at col. 31 of the '080 patent. In fact, the Reitman Declaration confirms that Chen's dosage units have an active (oxybutynin) content variation of less than 10% as here claimed (see ¶ 7).

Further, as noted in the rejection, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have performed known analytical tests on Chen's dosages so as to determine the actual amount of active in the dosages and assure active content uniformity.

Further, as noted above, it would have been obvious to one of ordinary skill in the art at the time the invention was made to minimize the active content variation among Chen's dosages as close to zero as possible, including the instantly claimed no more than 10%, less than 5%, less than 2%, less than 1%, and less than 0.5%, in view of the well-known goal of a skilled artisan to prepare dosages that do not vary by more than 10% in the amount of active present, in view of the 0.03 gram/dosage film with a variation of 0% for the dosages in Chen's Table 4, and a desire to obtain FDA approval and commercialize the product. A skilled artisan would minimize active content variation by optimizing the available parameters in Chen's process, which are the same as or similar to those in the '080 patent specification. These include, mixing/degassing, casting of the wet film, viscosity of the wet film, drying temperature, drying time, control of air flow in Chen's Fig. 2, selection of appropriate colloid material, etc.

Arguments with respect to the 35 USC 103(a) rejection of claims 2, 3, 32, 55, 72-81, 111, 134, 151-160, 193, 216 and 233-242 over the combined teachings of Chen and Staab:

Patent Owner relies upon the arguments above with respect to Chen and the arguments set forth "below" with respect to Staab (Remarks of 09/03/13, p. 81).

Patent Owner's arguments "below" with respect to Staab are with respect to limitations, such as locking-in or substantially preventing migration within about the first 4 minutes of drying, etc, which are present in the independent claims from which claims 2, 3, 32, 55, 72-81, 111, 134, 151-160, 193, 216 and 233-242 depend. However, for the

reasons set forth in detail above, Chen alone renders obvious the independent claims from which claims 2, 3, 32, 55, 72-81, 111, 134, 151-160, 193, 216 and 233-242 depend. In any event, Patent Owner's arguments with respect to Staab, which are addressed later in the RAN, are unpersuasive.

With respect to claims 2 and 3, the Examiner maintains that it would have been obvious to one of ordinary skill in the art at the time the invention was made to have prepared Chen's matrix by forming a pre-mix including a water soluble polymer and water in proper concentrations at a first temperature, then to have transferred the contents of the vessel to another vessel of a cooler temperature, and then to have stirred in heat sensitive ingredients, e.g., drug(s) as in Staab, so as to protect the drug(s), which is usually the most expensive component.

With respect to claims 32, 55, 111, 134, 193 and 216, the Examiner maintains that it would have been obvious to one of ordinary skill in the art at the time the invention was made to have used a monoclonal antibody or decongestant for Chen's active because such actives are conventional in the art, as shown by Staab; so as to take advantage of the active material's known function; and the reasonable expectation of success.

With respect to claims 72-81, 151-160 and 233-242, the Examiner maintains that it would have been obvious to one of ordinary skill in the art at the time the invention was made to have laminated a second film to Chen's drug-containing film as per the teachings of Staab so as to control the release rate of the drug, provide for release of more drug, or provide for release of another drug in addition to the drug in Chen's film.

Arguments with respect to the 35 USC 103(a) rejection of claims 317 and 318 over the combined teachings of Chen and Arter:

For the same reasons set forth above with respect to the rejection over Chen alone, Patent Owner argues that Chen is deficient (Remarks of 09/03/13, pp. 81-82). Patent Owner further argues that missing elements in Chen are not provided by Arter (Remarks of 09/03/13, p. 83). Patent Owner argues that Arter "does not and cannot inherently form or make obvious a viscoelastic film within about the first 4 minutes, which locks-in the uniformity of content of active within the recited levels of uniformity of content." (Remarks of 09/03/13, p. 85)

These arguments are unpersuasive and unsupported by factual evidence. For the reasons set forth in detail above, Chen is not deficient and either inherently or obviously forms a viscoelastic film within about the first 4 minutes, which locks-in the uniformity of content of active within the recited levels of uniformity of content.

Furthermore, as noted above, Chen alone already renders obvious claims 317 and 318. Claims 317 and 318 require that the drying uses "air currents, which have forces below a yield value of the polymer matrix". The '080 Patent states that "air velocities are desirably below the yield values of the film, i.e., below any force level that can move the liquids in the film-forming compositions." (See col. 11, lines 21-23). Moving liquids in the matrix during drying could produce defects in the film. However, as noted above, Chen's Fig. 2 shows air flow is less direct at the film surface at the beginning of the drying and becomes more direct as the film proceeds through the

drying oven, which has an aeration controller (see also p. 5, line 31 through p. 6, line 3). As also noted above, Chen produces a film that is glossy, substantially transparent, has a weight of 0.028 $\pm$ 0.001 g/dosage film, a density of 1.0485 $\pm$ 0.009 g/cm^2, a water content of 1.7 $\pm$ 0.24%, a thickness of 2.1 $\pm$ 0.12 mil (seep. 17, lines 15-16; and Table 4). The 0.028 $\pm$ 0.001 g/dosage film, when rounded to two decimal places as in Table 2 at col. 31 of the '080 patent, is 0.03 gram/dosage film with a variation of 0%. Accordingly, the air flow of Chen either inherently or obviously has forces below a yield value of the polymer matrix in order to arrive at the, glossy, substantially transparent, essentially uniform films exemplified therein.

Further, as also discussed above, with respect to the limitation in claims 317 and 318 of using air currents which have forces below a yield value of the polymer matrix during drying, the teachings of Arter strengthen the teachings of Chen. In particular, in order to prevent mottle, i.e., non-uniform density, Arter teaches drying wet films in a two zone dryer, as shown in Figs. 1-3. In the first zone, the film is dried while being protected by a shield that creates a quiescent zone above the top surface of the film in which there are no turbulent flow conditions and uniform drying is promoted (see col. 3, line 57 through col. 4, line 18). Accordingly, Arter teaches "using air currents, which have forces below a yield value of the polymer matrix during drying, to evaporate at least a portion of said solvent," as required by step (c) of claims 317 and 318. Following the first zone, the film is further dried in a second zone to remove residual liquid medium from the film (see col. 13, lines 24-29).

Patent Owner argues that mottle is non-uniform density of surface features (blotches) and is a different problem from uniformity of active content (Remarks of 09/03/13, p. 83).

This argument is unpersuasive. Chen already solved Patent Owner's alleged uniformity of content problem, as discussed in detail above and evidenced by the results in Chen's Table 4 and the Reitman Declaration. Arter's process is applicable to the manufacture of any product in which a gaseous drying medium is utilized in the drying of a coated layer formed from a mottle-prone coating composition; and Arter teaches that mottle occurs to a significant extent with aqueous coating compositions (see col. 2, lines 26-31 and col. 5, lines 32-44) as in Chen. In fact, Arter teaches evaporation "from aqueous solutions of hydrophilic colloids." (See col. 9, line 8). As noted by Third Party on p. 26 of the Comments filed 10/03/13, "[l]ike Arter, Chen teaches the use of 'hydrocolloids' in preparation of films. Chen, e.g., at 4:1, 3, 11, and 25."

Accordingly, the Specialist maintains it would have been obvious to one of ordinary skill in the art at the time the invention was made to have applied the drying method taught by Arter, which uses a quiescent zone above the top surface of the film in which there are no turbulent flow conditions and uniform drying is promoted, to the film formation method disclosed by Chen in order to avoid the formation of mottle. Another benefit of Arter's drying process is increased coating speed without resulting increase in mottle.

Patent Owner argues the films of the present invention are not coatings (Remarks of 09/03/13, p. 83).

This argument is unpersuasive. The casting step of the instant claims encompasses casting of the polymer matrix onto a substrate; and in the controlled drying step the matrix is dried on the substrate (see Fig. 7; col. 14, lines 20-46; col. 25, line 53 through col. 27, line 11; and almost all the examples in the '080 patent). Likewise, Chen's polymer matrix is coated on a substrate and dried (see Fig. 2 and p. 17, lines 6-19), and Arter dries a coated substrate (see, for example, col. 3, lines 16-38).

Patent Owner argues that Arter's films in Examples 1 and 2 have wet thicknesses of 27 microns and 75 microns respectively, and that "even dry, Patentee's films can be 5 to 7 times thicker that Arter's wet coatings (Remarks of 09/03/13, p. 84). Patent Owner also cites Bogue Declarations I and II and argues that the Suboxone® dose film has a dry thickness ranging from approximately 110 to approximately 175 microns (Remarks of 09/03/13, p. 84).

Patent Owner's arguments are misguided since the claims are silent with respect to thickness. In any event, as noted above, Chen exemplifies dried film thicknesses of 2.1 $\pm$ 0.12 mil and 3.2 $\pm$ 0.1 mil (see p. 17, line 14; Table 4; and Table 8), which are within the '080 patent specification's range of about 2 mils to about 10 mils or the more desired range of about 3 mils to about 6 mils (see col. 28, lines 61-63). Arter is not limited to any thickness, and teaches coated film thickness as a process variable (see

col. 9, lines 61-68; and each of Arter's claims, which do not require any particular thickness).

Arguments with respect to the 35 USC 103(a) rejection of claims 317 and 318 over the combined teachings of Chen and Strobush:

Patent Owner relies on the same reasons set forth above with respect to the rejection over Chen alone (Remarks of 09/03/13, pp. 85). Patent Owner argues that Strobush "does not and cannot inherently disclose or make obvious Patentee's resulting film having the claimed levels of uniformity of content" and "does not and cannot inherently form or make obvious a viscoelastic film within about the first 4 minutes, which locks-in the uniformity of content of active within the recited levels of uniformity of content." (Remarks of 09/03/13, p. 87). Patent Owner argues that Strobush "actually discloses another deficiency of Chen, that is, its failure to disclose let alone teach 'using air currents which have forces below a yield value of the polymer matrix during drying.'" (Remarks of 09/03/13, p. 86).

These arguments are unpersuasive. For the reasons set forth in detail above, Chen either inherently or obviously forms a viscoelastic film within about the first 4 minutes, which locks-in the uniformity of content of active within the recited levels of uniformity of content. Furthermore, as noted above, Chen alone already renders obvious claims 317 and 318 and in particular, the requirement of using air currents which have forces below a yield value of the polymer matrix during drying. In any event, as also discussed above, with respect to the limitation in claims 317 and 318 of using air

currents which have forces below a yield value of the polymer matrix during drying, the teachings of Strobush strengthen the teachings of Chen.

Strobush teaches that the process of applying a coating to and drying that coating on a substrate can inherently create defects such as mottle, where "mottle" is defined as "an irregular pattern or non-uniform density defect that appears blotchy when viewed," and the usual cause of mottle is air movement over the coating before it enters the dryer, as it enters the dryer, or in the dryer (col. 1, line 43 through col. 2, line 5). Strobush teaches that mottle is a problem when the coating solution contains a volatile organic solvent "but can also occur to a significant extent even with aqueous coating compositions" (col. 2, lines 10-15) as in Chen. Strobush teaches that the prior art substrates which have been coated are often dried using a drying oven which contains a drying gas such as air (col. 2, lines 20-22) as in Chen. Strobush discloses the drying of coated substrates without introducing significant mottle while running at higher web speeds by supplying drying gas (heated air) toward the bottom surface of the coated substrate such that the substrate rides on a cushion of drying gas, while the top side receives little or no drying gas, and where the coating comprises any film-forming material dispersed in any evaporable liquid vehicle (col. 6, lines 20-27; col. 9, lines 1-11 and 47-50; col. 11, lines 1-6 and 16-27; col. 12, lines 14-21, 27- 31, and 48-55; and col. 19, lines 43-46). In other words, Strobush teaches "using air currents, which have forces below a yield value of the polymer matrix during drying, to evaporate at least a portion of said solvent," as required by step (c) of claims 317 and 318. In fact, Strobush teaches that “if desired, topside air bars (34) can be used such that no gas is

supplied by the air bars when topside gas is not needed or desired." (See col. 11, lines 15-17 and 24-27).

Patent Owner argues that Strobush "is directed to drying coatings on a substrate, wherein, e.g., an existing polyester substrate is coated with a photographic emulsion and top-coat solution, passed through a coating die and dried." (Remarks of 09/03/13, p. 86). Patent Owner argues the following on p. 86 of the Remarks filed 09/03/13:

> At best, Strobush teaches that evaporation of the solvent must be performed very slowly (low hΔT), in multiple stages, so that the silver atoms lined up on the coating's surface are not disturbed so as to not cause a mottled appearance to the photographic coating. Strobush states "increasing the initial rate of heat transfer (hΔT), increases the severity of mottle." Strobush, col. 20, 11.39-40. It is the hΔT rate (heat transfer rate) which determines whether mottle will occur. Strobush, col. 20, 11.34-37. Strobush suggests nothing about controlling the force of the air so as not to exceed a yield value of the polymer matrix during drying.

These arguments are unpersuasive. Strobush is directed to methods for drying coatings on a substrate and is not limited to any particular coating or substrate (see col. 1, lines 9-11). In fact, the mottle problem that Strobush addresses occurs to a significant extent with aqueous coating compositions (col. 2, lines 10-15) as in Chen. The casting step of the instant claims encompasses casting of the polymer matrix onto a substrate; and in the controlled drying step the matrix is dried on the substrate (see Fig. 7; col. 14, lines 20-46; col. 25, line 53 through col. 27, line 11; and almost all the examples in the '080 patent). Likewise, Chen's polymer matrix is coated on a substrate and dried (see Fig. 2 and p. 17, lines 6-19), and Strobush dries a coated substrate (see, for example, col. 6, lines 21-27).

Further, as noted by Third Party Requester on pp. 27-28 of the Comments filed 10/03/13:

> In an appeal of a related application, rejecting MonoSol's similar arguments, the Board found that "Strobush may … reasonably be considered to be within the field of Appellants endeavor (as stated under the 'Field of the Invention' on page 1 of the Specification)." Board Decision regarding U.S. Application No. 10/074,272 which resulted in U.S. Patent No. 7,425,292 [over which the '080 patent is terminally disclaimed], Feb. 21, 2008, at 13:21-24. The fields of invention of the '080 patent and of the related '292 patents are remarkably similar. Compare Fields of Invention in the '080 patent, at 1:37-47, and of the '292 patent, at 1:11-17 (each stating: "The even or uniform distribution [of active ingredient throughout the film] is achieved by controlling one or more parameters, ... and the use of a drying process that reduces aggregation or conglomeration of the components in the film as it forms into a solid structure."). Consistent with the Board decision, Strobush may reasonably be considered to be within the '080 patent's field of endeavor. Thus, one of skill in the art would have been motivated to consider Strobush's drying methods and apparatus with respect to Chen.
>
> "Strobush relates to drying aqueous systems to achieve more uniform distribution (uniform density) of the active component (the flavor ingredient), while distinguishing over the conventional drying oven systems of the prior art which produce surface and density defects such as mottle." Board Decision regarding U.S. Application No. 10/074,272 which resulted in U.S. Patent No. 7,425,292, Feb. 21, 2008, at 13:14-18. Although its arguments about Strobush have failed to convince the Board, MonoSol again mischaracterizes Strobush in an effort to create deficiencies where none actually exist and thereby exclude pertinent prior art. Reply at 86.
>
> For example, Strobush teaches that top air velocity can contribute to film defects. See Strobush at 1:67-2:2; 6:24-27; and 12:65-67. Strobush teaches that film defects can be minimized by reducing top air velocity to approximately match the velocity of the coated substrate so that there is no differential top airflow. See Strobush at 16:14-26. Without differential top airflow, there can be no shearing force acting on the top of the polymer matrix, and the inherent viscosity or yield value of the wet matrix cannnot [sic] be overcome. See Strobush at 16:20-22. Thus, contrary to MonoSol's argument (Reply at 86:12-14), Strobush teaches controlling the force of the air so as not to exceed a yield value of the polymer matrix.
>
> Indeed, the Board already found: "Strobush teaches that the use of conventional drying ovens for drying aqueous coated film systems results in non-

> uniform density defects, and the solution to this problem is to apply hot air currents to only the bottom side of the coated film." Board Decision regarding U.S. Application No. 10/074,272 which resulted in U.S. Patent No. 7,425,292, Feb. 21, 2008, at 15:15-19.
>
> Contrary to MonoSol's argument, Strobush teaches how to maximize the heat transfer rate hΔT, and dry films rapidly. See, e.g., Strobush at 14:30-36 ("FIGS. 21-22 show that by increasing the heat transfer rate to correspond to the increasing maximum allowable heat transfer rate, the rate of drying can be increased even more rapidly than the simplified case in FIGS 19-20 in which the maximum allowable heat transfer rate is assumed constant (emphasis added); 13:63-14:12 ("At all times, the heat transfer rate is at or below the maximum allowable heat transfer rate").

Citing Bogue Declaration II, Patent Owner argues that the resulting dried films of the '080 patent can be significantly thicker than Strobush's wet coatings (Remarks of 09/03/13, p. 87).

Patent Owner's argument is misguided since the claims are silent with respect to thickness. In any event, as noted above, Chen exemplifies dried film thicknesses of 2.1 ± 0.12 mil and 3.2 ± 0.1 mil (see p. 17, line 14; Table 4; and Table 8), which are within the '080 patent specification's range of about 2 mils to about 10 mils or the more desired range of about 3 mils to about 6 mils (see col. 28, lines 61-63). Strobush is not limited to any thickness, and teaches coated film thickness as a process variable (see col. 13, lines 13-26; and each of Strobush's claims, which do not require any particular thickness).

Arguments with respect to the 35 USC 102(b)/103(a) rejection of claims 1-5, 10, 13-15, 21, 24, 25, 32, 44-46, 54, 55, 59, 63-70, 72-75, 78-84, 89, 92-94, 100, 103, 104, 111, 123-125, 133, 134, 138, 142-149, 151-154, 157-166, 171, 174-176, 182, 185, 186, 193,

205-207, 215, 216, 220, 224-231, 233-236, 239-242, 249-252, 258-260, 267-270, 276-278, 285-288 and 294-318 over Staab:

Patent Owner's arguments on pp. 88-89 of the Remarks filed 09/03/13 are addressed by Third Party Requester on pp. 30-31 of the Comment filed 10/03/13, reproduced below:

> MonoSol wishes to claim a process for making any pharmaceutical film. Yet, MonoSol failed to identify a single claimed manipulative step (e.g., mixing, casting, or evaporating) or claimed process condition (e.g., temperature, time, speed, or pH) that is not taught by Staab. MonoSol has misunderstood the ACP and/or Staab, in two ways.
>
> 1. *Locking-in/preventing migration*
>
> According to MonoSol, Staab does not teach that "locking in or prevention of migration of the active ingredient is occurring within the viscoelastic film within the first 4 minutes." Reply at ¶ bridging pp. 88-89. This argument is addressed in the discussion of the Supreme Court case Markman in the introduction to Section IV and in Section IV(A). Staab uses "the same materials as disclosed in the '080 patent, and the same basic process steps here claimed, and each dosage film has the same weight with the same amount of active agent." ACP at 95:7- 11; Staab at 11:35-12:3. Again, there is nothing patentable about reciting what necessarily happens (solvent removal increases viscosity) when one takes the same materials and follow the same process steps taught in Staab. MonoSol has not pointed out which process claim limitation or condition has not been taught by Staab. The rejection should be affirmed because there is no basis for expecting a different result.
>
> 2. *Analytical tests*
>
> Relying on Staab's alleged failure to disclose uniformity confirmation based on "assaying," MonoSol argues that Staab "does not and cannot inherently disclose or make obvious Patentee's resulting film having the claimed levels of uniformity of content .... " Reply at 89:18-21. But none of the claims recite "assaying," and the Office found that Staab discloses an analytical chemical test. ACP at 57:1-3. MonoSol did not refute that finding. In any event, the state of uniformity in a film is an objective fact, i.e., a result, that is not influenced by any post-manufacturing test step. Indeed, the ACP acknowledges that the films of Staab have a variation 0% in active content. ACP at 56:17-21 (referencing Staab 11:35-12:3).

> Once again, there is nothing patentable about reciting a property that results from taking the same materials and following the same process steps taught in Staab. MonoSol has not pointed out which process claim limitation or condition has not been taught by Staab. The rejection should be affirmed because there is no basis for expecting a different result.
>
> MonoSol has not presented any arguments based on fact or law that would overcome the rejection, which should be affirmed.

Further, as noted in the ACP (pp. 94-97), the '080 patent teaches "[t]he addition of hydrocolloids to the aqueous phase of the suspension increases viscosity, may produce viscoelasticity, and can impart stability depending on the type of hydrocolloid, its concentration and the particle composition, geometry, size and volume fraction (see col. 8, lines 42-46). Staab uses the same hydrocolloid as in the '080 patent, i.e. HPMC. As noted above, Staab teaches that "[t]he dissolution of the film can be readily adjusted by using different viscosities of the hydroxypropyl methyl cellulose ranging from less than 80 to more than 4,000 centipoises." (See col. 5, lines 10-14). Staab's film in the Example at cols. 11-12 is inherently viscoelastic before drying. Accordingly, within about the first 4 minutes of drying, a viscoelastic film having less water that before drying is formed.

Alternatively, to the extent that Staab's blended mixture before drying is not viscoelastic, then within about the first 4 minutes of the drying, a viscoelastic film is inherently formed. In particular, in order to arrive at a dried film product as in Staab, which is made using the same materials as disclosed in the '080 patent and the same basic process steps here claimed and each dosage film weighing 190 mg and containing 19 mg of benzalkonium chloride as the active agent (col. 11, line 35 through

col. 12, line 3), i.e., a variation in active content of 0%, then a viscoelastic film is inherently formed within about the first 4 minutes of drying.

With respect to uniformity, the claimed percent variations as measured by analytical chemical tests, as well as the claimed "substantially uniform distribution of components" and "locking-in or substantially preventing migration" are inherent in Staab's films in view of the fact that each dosage film contains 19 mg of benzalkonium chloride, i.e., a variation of 0%. Alternatively, such would have been obvious to one of ordinary skill in the art at the time the invention was made in view of the well-known goal of a skilled artisan to prepare dosages that do not vary by more than 10% in the amount of active present, in view of Staab's 19 mg of benzalkonium chloride per dosage film, and to commercialize the product. A skilled artisan would minimize active content variation by optimizing the available parameters in Staab's process, which are the same as or similar to those in the '080 patent. These include the polymer material, drying temperature, hot air application, drying time, viscosity, etc.

There are no examples in the '080 patent specification where analytical chemical testing is used to measure an amount of pharmaceutical active or bioactive active. With respect to how each and every sample turned out to be 19 mg, Staab uses essentially the same process steps as here claimed. In fact, none of the examples in the '080 patent measures or reports a weight or weight percent of pharmaceutical active or bioactive in a cut dosage film. Just as the example at cols. 31-32 in the '080 patent prepares dosage units weighing 0.04 grams, i.e., 40 mg, Staab's dosage units weigh

190 mg. Staab goes further and provides the active material weight in the dosage films, i.e., 19 mg.

Arguments with respect to the 35 USC 103(a) rejection of claims 8, 9, 76, 77, 87, 88, 155, 156, 169, 170, 237 and 238 over Staab:

Patent Owner relies on the same arguments above with respect to the 102(b)/103(a) rejection over Staab (Remarks of 09/03/13, p. 90).

These arguments are unpersuasive for the reasons stated above.

Arguments with respect to the 35 USC 103(a) rejection of claims 82, 89, 90, 92, 161, 171, 172, 174, 274, 292, 304-311 and 313-318 over Le Person:

Patent Owner's arguments on pp. 90-93 of the Remarks filed 09/03/13 are addressed by Third Party Requester on pp. 31-33 of the Comment filed 10/03/13, reproduced below:

1. *Locking-in/preventing migration*

> According to MonoSol, "Le Person does not inherently disclose locking-in or substantially preventing migration of the active within the visco-elastic film within the first 4 minutes." Reply at 91:21-22. First, MonoSol has not challenged the Specialist's factual reading of Le Person, Fig. 5. In Figure 5, at about 4 minutes of drying, 98% of the water has been removed, and thus the viscosity of the films must necessarily have been increased. ACP at 66:11-13. In addition, after 5 minutes, "the system tends to re-equilibrate the mechanical stresses...the meshes are densely packed." In any event, MonoSol's repetition of the argument does not change the fact that it has already been found unpersuasive. ACP at 66. "Locking-in" is addressed in the discussion of the Supreme Court case Markman in introduction to Section IV and in Section (IV)(A). MonoSol has not pointed out which process claim limitation or condition has not been taught by Le Person. The rejection should be affirmed because there is no basis for expecting a different result.

2. *Locking in / Uniformity*

According to MonoSol, the displacement of active along the z-axis is evidence that Le Person's films do not lock-in active and thus the active is not uniform. Reply at 92-93. But MonoSol claims uniformity of active per dosage unit, not uniformity along the z-axis. As pointed out by the Specialist, Le Person's temporary displacement of active along the vertical z-axis is not relevant to the question of whether Le Person's films are uniform (or locked-in or migration-resistant) per dosage unit, that is, in the x-y plane. See ACP at 64-69, especially 65:12-66-7; Reply at 92:3-12. Nowhere in the '080 patent or anywhere else in the record is there support for the theory that "locking in" and "substantially uniform" mean total immobilization along all three spatial axes. And even if there were, MonoSol's preferred method for measuring uniformity, by dissolution, could not distinguish films with z-axis migration from films without z-axis migration.

3. *Stresses*

According to MonoSol, Le Person teaches that the "stresses imposed by the early drying process and different reaction by the active to such stresses can cause the active to become unevenly distributed." Reply at 92:12-22. Again, temporary displacement along the z-axis does not affect the total amount of active per dosage unit (x-y plane).

4. *The importance of 4 minutes*

Strangely, MonoSol admits in its Reply that the resulting films of Le Person are homogeneous after 15 minutes, but that uniform distribution of active (along the z-axis) does not occur until well after 4 minutes. Reply at 93:1-7. Thus, their argument concedes that 4 minutes is not critical to obtaining a film with uniform content of active.

Finally, Requester notes that MonoSol did not challenge many of findings in the ACP and, therefore, has conceded them. In view of the above, the rejection over Le Person has not been overcome, and is proper.

Further, as noted on pp. 100-102 of the ACP, all of the claimed percent variation as measured by analytical chemical tests, as well as the claimed "substantially uniform distribution of components" and "locking-in or substantially preventing migration" are

inherent in Le Person's films in view of the fact that, as noted above, Le Person's active material homogenizes and a quasi-equilibrium is obtained for the components of the active phase, taking into account evaporation of the heavy solvent.

Alternatively, such would have been obvious in view of the well-known goal of a skilled artisan to prepare dosages that do not vary by more than 10% in active, in view of the fact that Le Person's active material homogenizes and a quasi-equilibrium is obtained for the components of the active phase, taking into account evaporation of the heavy solvent, and to commercialize the product. A skilled artisan would minimize active content variation by optimizing the available parameters in Le Person's process, which are the same as or similar to those in the '080 patent. These include drying temperature, drying time, air velocity, humidity etc (see pp. 258-259 of Le Person).

In fact, Le Person teaches air velocities of 2 m/s and 4 m/s (Table 2), which correspond to 4.5 miles/hr and 8.9 miles/hr, respectively. These are light winds that even with water (viscosity 1 cp) would produce only small wavelets. For example, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have adjusted Le Person's air velocity so that the film is not excessively blown and thus, a consistent product can be obtained.

Conclusion

The patent owner is reminded of the continuing responsibility under 37 CFR 1.985 to apprise the Office of any litigation activity, or other prior or concurrent proceeding, involving Patent No. 7,897,080 throughout the course of this reexamination

proceeding. The third party requester is also reminded of the ability to similarly apprise the Office of any such activity or proceeding throughout the course of this reexamination proceeding. MPEP 2686.

This is a RIGHT OF APPEAL NOTICE (RAN); see MPEP § 2673.02 and § 2674. The decision in this Office action as to the patentability or unpatentability of any original patent claim, any proposed amended claim and any new claim in this proceeding is a FINAL DECISION.

No amendment can be made in response to the Right of Appeal Notice in an *inter partes* reexamination. 37 CFR 1.953(c). Further, no affidavit or other evidence can be submitted in an *inter partes* reexamination proceeding after the right of appeal notice, except as provided in 37 CFR 1.981 or as permitted by 37 CFR 41.77(b)(1). 37 CFR 1.116(f).

Each party has a **thirty-day or one-month time period, whichever is longer**, to file a notice of appeal. The patent owner may appeal to the Board of Patent Appeals and Interferences with respect to any decision adverse to the patentability of any original or proposed amended or new claim of the patent by filing a notice of appeal and paying the fee set forth in 37 CFR 41.20(b)(1). The third party requester may appeal to the Board of Patent Appeals and Interferences with respect to any decision favorable to the patentability of any original or proposed amended or new claim of the patent by filing a notice of appeal and paying the fee set forth in 37 CFR 41.20(b)(1).

In addition, a patent owner who has not filed a notice of appeal may file a notice of cross appeal within **fourteen days of service** of a third party requester's timely filed notice of appeal and pay the fee set forth in 37 CFR 41.20(b)(1). A third party requester who has not filed a notice of appeal may file **a notice of cross appeal within fourteen days of service** of a patent owner's timely filed notice of appeal and pay the fee set forth in 37 CFR 41.20(b)(1).

Any appeal in this proceeding must identify the claim(s) appealed, and must be signed by the patent owner (for a patent owner appeal) or the third party requester (for a third party requester appeal), or their duly authorized attorney or agent.

Any party that does not file a timely notice of appeal or a timely notice of cross appeal will lose the right to appeal from any decision adverse to that party, but will not lose the right to file a respondent brief and fee where it is appropriate for that party to do so. If no party files a timely appeal, the reexamination prosecution will be terminated, and the Director will proceed to issue and publish a certificate under 37 CFR 1.997 in accordance with this Office action.

All correspondence relating to this *inter partes* reexamination proceeding should be directed:

By EFS: Registered users may submit via the electronic filing system EFS-Web at https://efs.uspto.gov/efile/myportal/efs-registered

By Mail to: Attn: Mail Stop "Inter Partes Reexam"
Central Reexamination Unit
Commissioner for Patents
P. O. Box 1450
Alexandria VA 22313-1450

Please FAX any communications to:
(571) 273-9900
Central Reexamination Unit

Please hand-deliver any communications to:
Customer Service Window
Attn: Central Reexamination Unit
Randolph Building, Lobby Level
401 Dulany Street
Alexandria, VA 22314

Signed:

/Alan Diamond/
Patent Reexamination Specialist
Central Reexamination Unit 3991

/Jerry D. Johnson/
Patent Reexamination Specialist
Central Reexamination Unit 3991

/Deborah D Jones/
Supervisory Patent Examiner, Art Unit 3991

Transmittal of Communication to Third Party Requester *Inter Partes* Reexamination	Control No.	Patent Under Reexamination	
	95/002,170	7897080	
	Examiner	Art Unit	
	Alan Diamond	3991	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address. --

(THIRD PARTY REQUESTER'S CORRESPONDENCE ADDRESS)

Danielle L. Herrit
McCarter & English LLP
265 Franklin Street
Boston, MA 02110

Enclosed is a copy of the latest communication from the United States Patent and Trademark Office in the above-identified reexamination proceeding. 37 CFR 1.903.

Prior to the filing of a Notice of Appeal, each time the patent owner responds to this communication, the third party requester of the *inter partes* reexamination may once file written comments within a period of 30 days from the date of service of the patent owner's response. This 30-day time period is statutory (35 U.S.C. 314(b)(2)), and, as such, it cannot be extended. See also 37 CFR 1.947.

If an *ex parte* reexamination has been merged with the *inter partes* reexamination, no responsive submission by any *ex parte* third party requester is permitted.

All correspondence relating to this inter partes reexamination proceeding should be directed to the **Central Reexamination Unit** at the mail, FAX, or hand-carry addresses given at the end of the communication enclosed with this transmittal.

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	95002170	7897080
	Examiner	Art Unit
	ALAN DIAMOND	3991

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	10/08/2012	07/11/2013	11/25/2013						
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	35	✓	✓	✓						
	36	✓	✓	✓						

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
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☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	10/08/2012	07/11/2013	11/25/2013						
	37	✓	✓	✓						
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CLAIM		DATE								
Final	Original	10/08/2012	07/11/2013	11/25/2013						
	73	✓	✓	✓						
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	108	✓	✓	✓						

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☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	10/08/2012	07/11/2013	11/25/2013						
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Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
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CLAIM		DATE								
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CLAIM		DATE								
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CLAIM		DATE								
Final	Original	10/08/2012	07/11/2013	11/25/2013						
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Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	95002170	7897080
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=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
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	287	✓	✓	✓						
	288	✓	✓	✓						

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	95002170	7897080
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☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	10/08/2012	07/11/2013	11/25/2013						
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	315		✓	✓						
	316		✓	✓						
	317		✓	✓						
	318		✓	✓						

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re *Inter Partes* Reexamination of:	)	
	)	
US Patent No. 7,897,080	)	
Issued: March 1, 2011	)	Confirmation No.: 6418
	)	
Named Inventor: Robert K. Yang *et al.*	)	Group Art Unit: 3991
	)	
Control No.: 95/002,170	)	Examiner: Alan D. Diamond
	)	
Request Filed: September 10, 2012	)	M&E Docket: 117744-00023
	)	
Title: POLYETHYLENE OXIDE-BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM	)	H&B Docket: 1199-26 RCE/CON/REX
	)	
Mailing Date: October 3, 2013	)	

Mail Stop *Inter Partes* Reexam
Attn: Central Reexamination Unit
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

***INTER PARTES* REEXAMINATION COMMENTS UNDER 37 CFR § 1.947**

Pursuant to 37 CFR § 1.947, the Third Party Requester hereby submits the following comments to the Action Closing Prosecution mailed on July 31, 2013 (the "ACP") and the Applicant's Response to Action Closing Prosecution thereto dated September 3, 2013 (the "Reply"). These Comments are filed on October 3, 2013, which date is 30 days from the service of the Reply.

TABLE OF CONTENTS

I. INTRODUCTION

If MonoSol has discovered a new and nonobvious method, it has yet to claim it. And its Reply to the ACP does not address in a meaningful way the many outstanding rejections of the Office. Instead, MonoSol presents proposed amendments and new evidence without the required reasons for entry after the close of prosecution. Its proposed amendments and new evidence go beyond mere form, could have been presented earlier, raise new issues, and place an undue burden on the examiner to yet again examine the claims. Further, the proposed amendments and new evidence do not address a core issue presented in the ACP – that the process claimed is dislcosed in the cited prior art.

II. RULE 116 PROHIBITS ENTRY OF THE PROPOSED AMENDMENTS: NO SHOWING HAS BEEN MADE; THE AMENDMENTS RESOLVE NOTHING; AND THE AMENDMENTS RAISE NEW 112 REJECTIONS

Upon issuance of the ACP, MonoSol lost its right to freely amend the claims. Unless a proposed amendment merely cancels claims, adopts Specialist's suggestions to remove issues for appeal, or otherwise requires only a cursory review—a showing must be made under Rule 116 of *"good and sufficient reasons why the amendment is necessary and was not earlier presented."* Rule 116, MPEP 2673(III) (emphasis added).

Each and every proposed amendment must comply with the strict standards of Rule 116. MPEP 2672(III). Other than underlining a comma that was added in the first amendment (p. 45), MonoSol's proposed amendments do not comply with Rule 116. There is simply no reason why the proposed amendments could not have been presented earlier. They do not present the claims in better form for appeal. They do not address any requirement of form expressly set forth in the ACP. And the proposed amendments raise new rejections under 35 USC 112.

A. No showing has been made: Adding "*self-supporting*" to ALL claims is not necessitated by the new rejection of only TWO claims

MonoSol proposes to amend every claim to recite "*self-supporting*" in multiple places. Reply at 44-45. MonoSol makes no showing of good and sufficient reasons why the proposed amendment is necessary and was not earlier presented under Rule 116. It only states that the

claims are amended to address new rejections over *Arter* and *Strobush*. Reply at 44. But the new rejections employing *Arter* and *Strobush* are made against only two new claims (claims 317 and 318), and those claims only. The remaining 300+ claims are not rejected over *Arter* or *Strobush*. Thus, an amendment to the other claims cannot be necessitated to overcome a rejection that has not been made. In addition, as set forth in the new proposed rejections below, entry of the proposed amendment raises issues under 35 USC 112 for lack of clarity, lack of written description, and lack of enablement.

B. The recitation "*self-supporting*" resolves nothing

MonoSol proposes to amend all claims to require that the resulting films be "self-supporting," and argues that *Arter* and *Strobush* are not properly combinable with *Chen* because they are allegedly not self-supporting. Reply at 44:19-20. But *Strobush* and *Arter* are both relied upon for drying methods, *i.e.*, not for a disclosure of "self-supporting" films. And the primary reference, *Chen*, already discloses self-supporting films. *Chen* at 17:15, 15:31. Thus, the combination still teaches the claimed methods.

Moreover, regarding MonoSol's statements that the films of *Strobush* and *Arter* are not self-supporting because they are too thin (Reply at 83:5-8; 87:9-14; 87:23-24; etc.), the '080 patent discloses no link between thickness and self-supporting films, or any criticality regarding the thickness of its films and its drying methods. (Reply at 84:17-85:2). Thus, there is no credible reason why the teachings of *Strobush* and *Arter* cannot be combined with *Chen.*

Finally, MonoSol argued during the prosecution of very similar subject matter in the grandparent (US 7,425,292) of the '080 patent that *Strobush* (which discusses *Arter* extensively) was not applicable based on very similar arguments. But the Board disagreed and found that *Strobush* is within the field of MonoSol's endeavor:

> "Accordingly, we determine that *Strobush* is not only pertinent to the problem facing Appellant (improving drying of coated films over conventional drying ovens to produce films with reduced surface defects and more uniform distribution of components), but *Strobush* may also reasonably be considered to be within the field

> of Appellants endeavor (as stated under the "Field of the Invention" on page 1 of the Specification). Therefore, we determine that *Strobush* is analogous prior art."
>
> Board Decision decided February 21, 2008, p. 13, lines 18-24, in USSN 12/102,071, later issued as US 7,425,292.

Accordingly, one of skill in the art would naturally consider *Strobush*.

In short, adding "self-supporting" accomplishes nothing. The combination was proper in the ACP, and remains proper. The claims are not limited by film thicknesses, and even if they were, no criticality has been demonstrated. The only thing the proposed amendment accomplishes is the introduction of new 112 issues that necessitate new 112 rejections.

C. Proposed rejections of all claims under 35 USC 112 (if proposed amendments are entered)

The proposed amendment, if entered, would render the claims indefinite and lacking in written description and enablement, necessitating rejections under 35 USC 112, first and second paragraphs. MonoSol has added the phrase "self-supporting" to each independent claim within the "performing analytical chemical tests" step (*e.g.*, step (f) in claim 1, step (e) in claim 82, *etc.*). The "performing analytical chemical tests" step now recites "said tests indicating that uniformity of content in the amount of said active varies by no more than 10% and said resulting film is self-supporting and suitable for commercial and regulatory approval," (underlining showing added phrase). Under the proposed amendment, the claims require that the analytical chemical tests indicate that the resulting film is self-supporting. It is unclear how an analytical chemical test might indicate that a resulting film is self-supporting. Thus, these claims, if amended, are unclear. Nowhere in the '080 patent is such analytical chemical testing (*i.e.*, which indicates that a resulting film is "self-supporting") described or enabled. And the sections cited by MonoSol as support for "self-supporting" fail to describe analytical chemical testing or any tie thereto. *See* Reply at 46. In short, if the claims are amended as proposed, new rejections are required for lack of clarity, lack of written description, and lack of enablement.

D. Removing the limitation *"at a temperature of about 60 ºC"* resolves nothing

MonoSol proposes to amend Claim 318 by removing the recitation *"at a temperature of about 60 ºC."* Reply at 45. But MonoSol makes no showing of good and sufficient reasons why the proposed amendment is necessary and was not earlier presented under Rule 116. It merely states that the recitation was deleted "to address certain concerns…as expressed by the Specialist at pages 26-28 of the ACP." But there are two different rejections under 112 at pages 26-28. And while the proposed amendment may address the second rejection based on clarity (due to an inconsistency in the claim), it fails to address the larger lack of written description and possession rejection. And, if entered, the proposed amendment would necessitate a new written description rejection.

The outstanding lack of written description rejection in the ACP is based on the fact that the subject matter of claim 318 was not described in the specification in such a way as to reasonably convey that the inventor, at the time the application was filed, possessed the claimed invention. ACP at 27 (adopting rejection in Comments at p. 20). That is, prior to this proposed amendment, claim 318 was determined to be merely the result of cobbling together disparate concepts that are unconnected in the original specification. Id. The proposed amendment does nothing to change this. There is still no disclosure of a method that achieves the desired result of film having a variance of less than 5%. Such a variance only appears in a boilerplate passage. '080 patent at 15:24-48. Deleting the 60ºC temperature recitation does not cure the lack of possession as there is still no connection between the other cobbled together claim recitations, *e.g.*, the recitations regarding air currents and regarding formation of a visco-elastic film within 4 minutes.

E. Proposed rejection of claim 318 under 35 USC 112, first paragraph (if amendments are entered)

MonoSol proposes to delete the phrase "at a temperature of about 60°C" to address the outstanding 112 clarity rejection. Reply at 45:9-12 and 75:4-22. However, even if amended as proposed, claim 318 still recites a combination of elements that are found, if at all, in unconnected passages. For the same reasons as stated in the ACP at 26-28, the proposed

amended claim lacks written description. For example, "there are no examples showing a variation of less than 5% in active content" and such a result cannot be attributed to any specific methods or combination of steps in the claims. ACP at 27:3-21. Moreover, there is no disclosure of a connection between this desired result and any of the other recitations of the claim, *e.g.*, the viscosity range, the air current recitations, yield value recitations, and the formation of visco-elastic film within 4 minutes. Accordingly, if claim 318 is amended as proposed by MonoSol's Reply to the ACP (September 3, 2013), claim 318 would still lack a written description.

In sum, MonoSol has failed to provide the showing under Rule 116 required for each and every proposed amendment. In addition, the proposed amendments—if entered—accomplish nothing but necessitate new rejections under 35 USC 112. Finally, the proposed amendments fail to advance prosecution in any way as all rejections, with or without amendment, are proper and should be maintained for the reasons discussed in Section V.

III. RULE 116 PROHIBITS ENTRY OF THE NEW EVIDENCE; AND THE EVIDENCE FAILS TO SUPPORT MONOSOL'S POSITIONS

A. There has been no showing of good or sufficient reasons as to why the evidence is necessary or was not earlier presented

After the issuance of an ACP, an affidavit or other submitted evidence "*may be admitted upon a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented.*" Rule 116(e) (emphasis added).

MonoSol submits a new Declaration of Dr. Bogue ("Bogue II") presenting new opinions on sales of Suboxone® films, providing various dry film thicknesses of Suboxone® films, and arguing that Suboxone® films are not particular types of dosage forms or coated tablets. In addition, MonoSol submits three new exhibits (Ex. 4-6), each representing new evidence that was available and could have been presented in its March 2013 Reply.

MonoSol fails to provide the showing required for entry of any of this new evidence or opinion. With respect to the new opinions (Bogue II), MonoSol argues it is warranted by the *Leo*

decision[1] and by "new references, exhibits and arguments made in Third Party Requester's Comments and the ACP (*see*, *e.g.*, pp. 3, 48-51, 79), and also to advance the prosecution of the reexamination." Reply at 48.

First, with respect to the *Leo* decision, it appears that MonoSol's rationale for failing to earlier present evidence of secondary considerations (*e.g.*, commercial success) is that only in the wake of the August 2013 *Leo* decision would the Office properly consider and weigh this evidence. Reply at 48. This is not true. *Leo* provides no new law or insights into the requirement to consider evidence of commercial success. *Leo* merely reiterates established law already set forth in the MPEP, *i.e.*, that evidence of commercial success must be considered when such evidence is timely presented. MPEP 716.01(a) ("Affidavits or declarations, when timely presented, containing evidence of … commercial success… must be considered by the examiner in determining the issue of obviousness of the claims for patentability.") (emphasis added).

Importantly, *Leo* does not disturb the requirement that the evidence must be timely presented in order for it to be considered without a showing under Rule 116. In fact, the portions of *Leo* cited by MonoSol in connection with commercial success (Reply at 59-60) each include citation to other cases, but do not depart or distinguish from them. Accordingly, there is no justification for entry of the untimely new opinions (or for that matter any new evidence) based on the *Leo* decision.

MonoSol argues the second reason to enter the new opinion evidence is to address new references, exhibits and arguments on pages 3, 48-51 and 79 of the ACP "and to advance prosecution." Reply at 48. This too is a deficient showing. MonoSol's articulated excuse for presenting untimely evidence fails to link the new opinions of Dr. Bogue to how they address one or more of the new references, exhibits, and arguments of the ACP at 3, 48-51, and 79. Examination of MonoSol's untimely new opinion evidence reveals that MonoSol cannot make a showing that they are "necessary" as required by Rule 116.

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[1] *Leo Pharmaceutical Products, Ltd. v. Rea, Acting Director, USPTO*, 2012-1520 (Fed. Cir., 2013).

Bogue II contains at least 11 new statements by Dr. Bogue. *See e.g.*, Bogue II statements 5-15. Eight of the new statements are directed to Suboxone® films, purportedly a single embodiment of the '080 claims[2]. None of the claims in this proceeding are directed or limited to Suboxone® films so it is unclear how entry of any of these untimely new opinions would advance prosecution in this reexamination. Additionally, it is unclear why new opinions limited to Suboxone® films are necessary or why they could not have been earlier presented. Suboxone® films are also not responsive to *Arter* and *Strobush* or any of the new arguments or exhibits.

Finally, MonoSol fails to make any showing under Rule 116 for new Exhibits 4-6. In particular, MonoSol is silent as to reasons why it could not have presented any of Exhibits 4-6 when it filed its first response in March 2013. And the facts show that the new evidence relied upon by MonoSol was available prior to the ACP. Its new Exhibit 3 was published in 2001. The information contained in new Exhibits 5 and 6, directed to sales of Suboxone®, was taken from an annual report published in 2012, and sales data that would have been available by March 2013. Thus, it appears that MonoSol failed to provide the requisite showing under Rule 116 for Exhibits 4-6 because it could not. There is no justification for entry of any of new Exhibits 4-6.

To summarize, MonoSol has failed to meet its burden under Rule 116. Its failure to earlier present available evidence is not excused by the *Leo* decision, or any other articulated reason. In addition, MonoSol has failed to provide any reason why evidence limited to one alleged embodiment, Suboxone®, is necessary or even particularly relevant to the claimed subject matter. Accordingly, MonoSol has failed to provide the required "*showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented.*" Rule 116(e) (emphasis added).

[2] The other three new statements lay the groundwork for these eight new statements.

B. MonoSol's new evidence does not even support patentability

MonoSol seeks to enter new evidence to bolster its new positions with respect to commercial success and to "address references, exhibits and arguments"presented on page 3, 48-51, and 79 of the ACP. But, MonoSol's conclusions are not even supported by its own evidence. MonoSol fails to establish (or even argue) any nexus between the claims and the sales it relies on. The evidence demonstrates that Suboxone® sales are derived from market exclusivity, not the merits of the claimed methods. Finally, the evidence directed to Suboxone® films is not commensurate in scope with the claims and thus is not relevant to patentability.

1. *MonoSol has failed to establish a nexus between commercial success and the claimed methods*

MonoSol bears the burden of proof with respect to establishing a nexus between its evidence and its claims. *Lingamfelter v. Kappos*, No. 2011-1449, 2012 WL 3218529 (Fed. Cir. 2012) (holding that secondary considerations of obviousness did not rebut *prima facie* case of obviousness in *inter partes* proceedings for reexamination where patent owner failed to sufficiently establish nexus between economic success and the claimed features).

The declarations do not state how the Suboxone® films were made, or if they were made in accordance with any of the 313 claims in this proceeding. Dr. Bogue only states that they were made in accordance with general steps set forth in paragraph 4 of Bogue I that do not correspond to any claim. Bogue I; *see* all Bogue II at ¶ 4. Dr. Bogue has not disclosed or linked this generic process with one or more of the 313 claims. *See* MPEP 716 ("7.66.03 Reason Why Affidavit or Declaration Under 37 CFR 1.132 Is Insufficient: Refers Only to Invention, Not to Claims."). Moreover, Dr. Bogue has not disclosed any links between the added analytical chemical testing step and the rest of the recited method for forming Suboxone® films. Accordingly, MonoSol failed to show with any particularity how the Suboxone® films were made and how that process may correspond to one or more of the rejected claims. *See* MPEP 716.03(a) (nexus is not established by generic statements regarding construction of products or process from declarants.); *see* also *Ex parte Standish,* 1988 WL 252397, 10 USPQ.2d 1454, 1458

(BPAI 1988). Instead, as discussed directly below, the evidence actually proves a nexus between the Suboxone® film sales and the conversion of existing sales from an existing product, by the voluntary and deliberate withdrawal of the existing product.

2. *The new evidence demonstrates that that the alleged commercial success is derived from product conversion, not the merits of the claimed methods*

MonoSol has failed to demonstrate how Suboxone® film sales are attributable to the processes now claimed. Evidence of commercial success must be directly derived from the invention claimed and not from a business event extraneous to the merits of the claimed invention. *See* MPEP 716.03(b)(I). In the instant case, MonoSol's new evidence demonstrates that there were extraneous business events which are causally tied to the sales of Suboxone® films. Specifically, the tablet form of Suboxone® was recently discontinued. As a result, existing users of the tablet form who were treating their opiate dependence and wanted to continue with the same branded drug are left with no option but to convert to the Suboxone® film. Exhibit 4 states:

> Suboxone [tablet] lost the exclusivity afforded by its orphan drug status on 8 October 2009.
>
> On 31 August 2010, the Group announced that it had received approval from the US Food and Drug Administration for its New Drug Application to manufacture and market Suboxone sublingual film. …
>
> As with all prescription drugs, the protection of the business has a finite term unless replaced with new treatments or forms.
>
> RB Pharmaceuticals recently announced its voluntary discontinuation of Suboxone tablets in the US due to increasing concerns with paediatric exposure. … The approval of generic tablets has been anticipated since the loss of orphan drug status in 2009.
>
> 2012 net revenue increased +10% …. Conversion from tablets to film in the US continued to increase with market volume share at the end of 2012 of 64%, up from 48% at the end of 2011, creating significantly more sustainable business.

In short, MonoSol's own evidence demonstrates that the sales of Suboxone® film are not directly attributable to any claimed feature – but rather a branded distributor's conversion between the discontinued tablet formulation to a film formulation that enjoys regulatory exclusivity for sales.

3. *Suboxone® films are not commensurate in scope with MonoSol's claims*

MonoSol's newly submitted evidence relates to Suboxone® films. But, the claims are not limited to this particular active. For example, MonoSol provides new evidence of Suboxone® film sales (Exhibits 5 and 6, Exhibit 2, Bogue II statements 6 and 7), new evidence of Suboxone® film thicknesses (Exhibit 2, statements 8 and 9), and new evidence of dosage forms of Suboxone® films (Exhibits 2, statements 12 and 14). None of this evidence is commensurate in scope with the claims.

For example, tablets or films branded as Suboxone® may derive their sales from the attributes of the particular active, which was in the past exclusively sold by Reckitt Benckiser. As a result, evidence of sales of Suboxone® films is not commensurate in scope with claims that are not limited to Suboxone®. In order to be commensurate in scope with the claims, commercial success must be due to claimed features—not due to unclaimed features. MPEP 716.03(a) (I); *see* also *Joy Technologies, Inc. v. Manbeck*, 751 F. Supp. 225, 229, 17 USPQ.2d 1257 (D. DC. 1990).

In addition, evidence of the dry film thickness of Suboxone® films is not commensurate in scope to the claims because the claims are not limited to Suboxone®, and recite no thickness limitation. Thus, it is unclear how evidence of the dry thickness of Suboxone® films pertains to patentability of the claims.

Finally, evidence regarding which categories of dosage forms Suboxone® films fit into, or do not fit into, (Exhibit 2, Bogue II statements 12 and 14) is also not commensurate in scope with the claims. Again, the claims are not limited to Suboxone® films. And there is no

evidence that the methods recited in the rejected claims exclude or are unable to produce, for example, dosage forms W1, W2, W3 or W4 referenced in Exhibit 2.

In sum, MonoSol's new evidence related to Suboxone® film is not relevant because it is not commensurate in scope with the claims. Accordingly, this new evidence cannot advance prosecution.

IV. REBUTTAL OF MONOSOL'S ARGUMENTS: A PROPER *PRIMA FACIE* REJECTION OF ALL CLAIMS HAS BEEN MADE BY THE OFFICE AND MONOSOL HAS FAILED TO REBUT IT

MPEP 2112.01(I) provides that "[w]here the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established." The claim charts submitted by Requester, the Office Action, and the Action Closing Prosecution (ACP) have each set forth the position that *Chen* "teaches the same materials and the same process steps." ACP at 34-39, especially 35:12-16. *See* the same position for *Staab* (ACP at 95:5-8). In its Reply, MonoSol fails to point out any claimed process step or process condition that is not taught by the cited art. MonoSol also fails to point out the additional step or condition in the prior art that would prevent the production of films with the claimed desired results.

Instead, MonoSol argues about limitations that are not recited in the claims. MonoSol also argues about claim language that does not carry patentable weight, such as scientific theories (e.g, "locking-in" or "preventing migration") or desired results of the claimed process steps (*e.g.*, "substantially uniform distribution of active" or "self-supporting"). But, it is well-settled law that a recitation of an intended result of the claimed process steps is a limitation inherent to the claimed process. *Texas Instruments v. U.S. Int'l Trade Comm'n*, 988 F.2d 1165, 1172 (Fed. Cir. 1993) (whereby clause concerning a process expressed the necessary result of what was recited in the claims). Even the Supreme Court has explained that desired or resulting properties and scientific explanations are not entitled to patentable weight. "A claim covers and secures a process, machine, manufacture, a composition of matter, or a design, but never the

function or result of either, nor the scientific explanation of their operation." *Markman v. Westview Instruments, Inc.*, 517 US 370, 373 (1996) (emphasis added). In short, no patentable distinction is provided, because desired results do not inform the public or the Office how (and if) the claimed process is different from prior art processes.

In response to the outstanding rejections of the ACP, MonoSol makes five arguments. We address these points in the same order presented by MonoSol for easy reference.

A. Prior art is not distinguished by "visco-elastic" or "locking-in" recitations

1. *Visco-Elastic: the '080 patent does not provide a special definition for the term that applies only to film and the term cannot be used to distinguish prior art*

Without clearly identifying its proposed construction, MonoSol argues that there is a special meaning of the term "visco-elastic" that applies to film that has experienced some drying. *See* Reply at 63-64. As noted in the ACP, however, "the matrix prior to evaporating the solvent (water) may be viscoeleastic, and the viscoelasticity is due, for example, to the fact that a hydrocolloid has been added." ACP at 76. MonoSol's very unusual proposal fails to create a characteristic that distinguishes the cast matrix before and after it has experienced some drying, and cannot be used to distinguish the cited art.

MonoSol quotes the specification at column 44, lines 9-14, as providing a special definition of "visco-elastic film." The relevant portion of the specification states: "the controlled drying process allows for uniform drying to occur whereby evaporative cooling and thermal mixing contribute to the rapid formation of visco-elastic film and the 'locking-in' of uniformity." Reply at 63:18-23. But the quoted passage does not provide a special definition of "visco-elastic" or "visco-elastic film." If anything, the quoted passage is only a very general description of drying polymer-solvent mixtures with heat.

Instead of reciting steps that would distinguish the prior art, MonoSol relies on the alleged "special definition" to challenge the propriety of the prior art, which does not recite the alleged special definition. Reply at ¶ bridging pp. 63-64 ("A visco-elastic material, let alone a

visco-elastic film formed by any process which does not lock-in the content uniformity of the active cannot be compared to the '080 patent's visco-elastic films, for purposes of inherency, novelty, or obviousness.") And, most telling, MonoSol has never explained why the cited prior art when using the claimed polymer (*e.g.*, hydrocolloids), and removing the same solvent employing the claimed drying steps, would *not* increase viscosity, and in turn, produce the "locking-in" that it argues is so special. Indeed, it is unclear to Dr. Cohen, who has more than 45 years of experience in the field of coating and drying, how this would *not* happen. Cohen Dec. ¶ 8-10. ("When working with a homogenous … coating mixture [as disclosed in *Chen*], for example, it would be difficult for a person of ordinary skill in the film art not to obtain a film that has uniform content of active."). ACP at 83:17-84:19. MonoSol has never rebutted this opinion.

MonoSol claims a method of making a film. Significantly, MonoSol has not disputed the Specialist's conclusion that the prior art teaches "the same materials and the same process steps as claimed." ACP at 35:12-16; 35-39 (*Chen*); 95:5-8 (*Staab*). Despite multiple opportunities during these proceedings, *MonoSol has not explained what step or condition is claimed but not taught by the cited art*. MonoSol has not explained why performing all of the claimed process steps with the claimed materials, as the prior art does, would not necessarily produce a film that has "locked-in" uniformity.

2. *Locking-in and preventing migration cannot distinguish the prior art*

MonoSol effectively seeks a reach-through claim to capture *any* process that results in a uniform film. That is, it seeks to cover any process that produces a desired result by reciting a very generic process and the desired result. To prevent this very possibility, the Supreme Court in Markman made clear that scientific theories and desired results of claimed process steps, such as "locking in," do not have patentable weight. Markman, at 363. A process claim must recite the process that it seeks to protect, not a wish-list of desired properties and/or results of unrecited process steps. The prior art is replete with examples of the drying of polymer mixtures producing increased viscosity and increase visco-elasticity. Accordingly, the prior art's teaching of every claimed process limitation, which MonoSol does not dispute, suffices for invalidity.

In short, the "locking-in" language, so heavily relied upon throughout MonoSol's Reply, is no more than a scientific theory, a natural consequence of evaporating solvent, or perhaps a desired result. It is not a process step and, it alone, does not distinguish the prior art. If there is a unique step to MonoSol's process, or if "locking-in" is meant to indicate a physical step or process condition, such step or condition has not yet been identified or claimed. Accordingly, the Specialist correctly stated: "[n]owhere does the '080 patent provide a special definition for the term 'visco-elastic film'." ACP at 76.

B. The '080 patent teaches that weight variation is an acceptable alternative to assaying; and so does the evidence of record

Without ambiguity, the '080 patent discloses that weight, visual inspection, and dissolution testing are acceptable and alternative ways to measure uniformity of active content:

> The uniform distribution of the components within the film was apparent by examination by either the naked eye or under slight magnification. By viewing the films it was apparent that they were substantially free of aggregation, *i.e.* the carrier and the actives remained substantially in place and did not move substantially from one portion of the film to another. Therefore, there was substantially no disparity among the amount of active found in any portion of the film. (31:38-45)
>
> The individual dosages were consistently 0.04 gm, which shows that the distribution of the components within the film was consistent and uniform. This is based on the simple principal that each component has a unique density. Therefore, when the components of different densities are combined in a uniform manner in a film, as in the present invention, individual dosages forms from the same film of substantially equal dimensions, will contain the same mass. (32:26-34)
>
> The uniformity of the films prepared from inventive compositions J-L may also be tested by either visual means measuring the weights of individual dosage films, or by dissolving the films and testing for the amount of active as described above. (33:4-8).

MonoSol attempts to distinguish prior art based on the fact that the Suboxone® film product does not fit into the category of dosage forms where weight testing is acceptable. Reply

at 64. But MonoSol does not claim only Suboxone® film. The above '080 patent admission remains: weight, visual inspection, and dissolution are each acceptable and alternative ways to measure uniformity of active. *See* also '080 patent at Examples A-L.

Based on one statement in the regulation (Chapter <905> Uniformity of Dosage Units), MonoSol also argues that analytical chemical testing is "required at some point even with weight variation." Reply at 65 (quoting the regulations "Carry out an assay for the drug substance(s) on a representative sample of the batch using an appropriate analytical method.") Even if the quote references an analytical chemical test—which is not clear from the quote or the larger regulation—it does not state or imply that weight variation is not an acceptable, alternative way to measure uniformity of active.

C. Example M is not relevant to the claims and does not support MonoSol's argument

The Specialist correctly noted on page 79 of the ACP that Example M is not an example of an analytical chemical test of a claimed pharmaceutical active or bioactive. MonoSol's response is that it agrees. Reply at 66.

This thread of argument was started by MonoSol's repeated and emphatic arguments that the recitation of "analytical chemical tests" distinguishes the claims from the cited prior art because analytical chemical tests were so critically different from weight variation and visual inspection tests. *See, e.g.*, Reply dated March 13, 2013 at 53-59 and Reply dated September 3, 2013 at 64-66. The Specialist wondered why, if analytical chemical tests are so critical to the claimed invention, the '080 patent teaches that weight variation and visual inspection tests are acceptable alternatives. *See* block quotes in section immediately above. The Specialist also wondered why—if they were so critical—MonoSol never employed them in over a hundred examples in the '080 patent. Those questions remain unanswered.

MonoSol argues that it doesn't matter that Example M is not an example of the claimed subject matter, because the specification makes no distinction between actives and pharmaceutical actives. Id. But even if MonoSol's argument were true—which it is not—

Example M remains a single example outweighed by more than a dozen other examples that use weight variation and/or visual inspection (Examples A-L) to demonstrate uniformity. Moreover, the criticality or "distinctiveness" of analytical chemical tests is not demonstrated by Example M. And the '080 patent still unambiguously teaches that weight variation and visual inspection tests are acceptable alternatives to analytical chemical tests.

Finally, MonoSol admits the step of "performing analytical chemical tests for uniformity of content of said active…" was known. '080 patent 2:40-47 ("Currently, as required by various regulatory authorities, dosage forms may not vary more than 10% in the amount of active present."). Indeed, analytical chemical tests were among many known ways to measure the amount of active in each dosage form. Reply at 64-66; '080 patent, cols. 31-32. Thus, the ACP does not and need not rely on Example M for the rejection of claims including the step of performing analytical chemical testing. Even in the interpretation most favorable to MonoSol—which may or may not be correct— Example M only confirms what is already admittedly known regarding this post-manufacturing step. That is, measuring active content in samples from pharmaceutical commercial runs is obvious. ACP at 37-38.

D. MonoSol has failed to rebut the *prima facie* case; Figure 5 fails to disprove what Reitman confirms

MonoSol argues that a burden on the office has not been met. But it is MonoSol's burden that has not been met.

Contrary to MonoSol's unsupported assertions about burdens (Reply at 69:8-70:16), it is MonoSol's burden to prove that *Chen* does not teach or suggest films with the claimed uniformity. Initially, the Office has the burden of "providing reasonable proof that a claim limitation is an inherent characteristic of the prior art." *In re Best*, 562 F.2d 1252, 1254-55 (CCPA 1977). The Office meets this burden by "adequately explaining the shortcomings it perceives so that the applicant is properly notified and able to respond." *In re Jung*, 637 F.3d 1356, 1362 (Fed.Cir. 2011) (quoting *Hyatt v. Dudas*, 492 F.3d 1365, 1370 (Fed. Cir. 2007). The

burden of proof then shifts to the applicant "to prove that the subject matter shown to be in the prior art does not possess the characteristic relied on." *Best*, 562 F.2d at 1254-55.

The Office has met its burden of "providing reasonable proof that a claim limitation is an inherent characteristic of the prior art" in multiple, independently valid ways. As stated in the ACP, *Chen* teaches using both weight variance of sample units and visual inspection to establish uniformity of content of active per dosage unit. ACP at 36:6-19. Using either of these methods conforms to the teaching of, and at least a dozen examples in, the '080 patent: namely, the demonstration of uniformity by visual inspection, weight measurement, and/or analytical testing. *See Id.*; '080 patent at cols. 31-33, and 37 (Examples A-L). Indeed, Dr. Reitman has confirmed that weight, visual inspection and analytical chemical (HPLC) testing of films made in accordance with *Chen* meet the uniformity requirements of the pending claims. *See* Reitman ¶ ¶ 5-7. Most telling, MonoSol is effectively silent in the face of the Office's repeated point that the prior art teaches "the same materials and the same basic process steps" as those claimed in the '080 patent. ACP at 35:12-16. "[W]here the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established." MPEP 2112.01(I). This is reasonable proof that the less than 10% variation limitation is an inherent characteristic of *Chen*.

In view of the Office's showing, the burden of proof has been shifted to MonoSol. The question remaining is: Has MonoSol met its burden "to prove that the subject matter shown to be in *Chen* does not possess the desired result"? The answer is no. MonoSol merely repeats arguments concerning Fig. 5 that the ACP deemed unpersuasive and attacks the Reitman Declaration. ACP at 87:7-90:18; Reply at 67-70.

1. *Figure 5 fails to disprove the uniformity of the films of Chen*

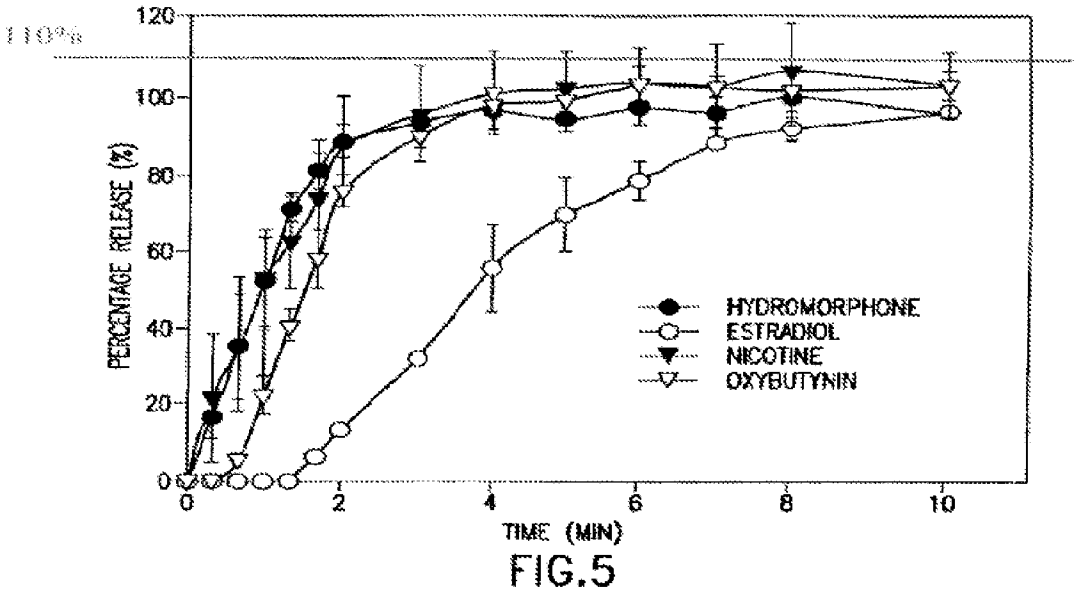

FIG.5

Chen, Figure 5 (110% line added by Patentee for clarity).

MonoSol relies on its hand-drawn line to show instances where percentage release in Figure 5 is allegedly greater than 110% and concludes that there is a lack of uniformity. But MonoSol's own expert, Dr. Lin, stated "these data [in Figure 5] indicate that the test method used in the analysis is not reproducible ***and/or*** there is a lack of active agent uniformity between individual dosage units." Lin Declaration at ¶ 22; ACP at 88:11-14 (emphasis added). That is, MonoSol's expert admits that the release date in Figure 5 could indicate a test problem.

Indeed, Figure 5 itself proves that there is a test problem. For example, the solid circles (hydromorphone) fluctuate *down* between 8 and 10 minutes. Similarly, the open triangles (oxybutynin) go *down* between 6 and 8 minutes. But the total amount of active that has been released cannot decrease over time—no matter how irregular the film samples might be. The decrease in total release can only indicate a problem with the test itself, which may include human error in performing the test.

Furthermore, MonoSol claims uniformity per dosage unit, not active released over time. Thus, the most relevant measurement, if any, is the last or latest release measurement as the closest representation to the total amount. Here, at 10 minutes, there is only one error bar over MonoSol's hand-drawn line (allegedly 110%). The gap between that error bar and MonoSol's line is less than or equal to the variation from the test or human error, as shown for hydromorphone (between 4 and 5 minutes) and oxybutynin (between 6 and 8 minutes). Thus, the clear problems with Figure 5 kill MonoSol's argument.

2. *Reitman confirms the prima facie case*

Requester has provided conclusive evidence that the methods of *Chen* anticipate the claims. Specifically, the data provided in the Reitman Declaration demonstrates active uniformity per dosage unit within a 10% variance in films prepared according to *Chen*. Reitman Decl. at ¶¶ 5-7. Dr. Reitman confirmed active uniformity employing each of the three alternative, acceptable methods disclosed in the '080 patent: visual inspection, weight variance, and dissolution. Thus, the Reitman Declaration independently proves that *Chen*'s films satisfy the claimed desired result (uniformity of content in the amount of active varies by no more than 10%).

According to MonoSol, the Reitman Declaration is defective because "oxybutynin chloride" was substituted for "oxybutynin" and "Kolliphor EL" for "Cremophor EL40." Reply at 67:8-10. MonoSol has not explained why these standard ingredient substitutions would only be done by an expert or would provide superior results. MonoSol speculates that these and other parameters unspecified by *Chen* were deliberate and "expert" rather than "ordinary skill" substitutions, and thus Reitman's production of uniform films would be beyond one of ordinary skill. Reply at 67:11-14. But as demonstrated in paragraph 4, Dr. Reitman and her team followed every available guidance or instruction disclosed in *Chen*, as is easily seen in the point-to-point correspondence of the *Chen* disclosure to the methods employed by Reitman. MonoSol

has failed to point to a single instance of something that Dr. Reitman's team did (some step or condition) that is unusual.[3]

For the reasons stated above, the Specialist has met its burden to provide a proper *prima facie* case. MonoSol has failed to rebut this *prima facie* case by proving that films made according to *Chen* do not possess the desired uniformity limitation that is the foundation of MonoSol's patentability argument.

E. Undue experimentation is not relevant to the pending claims because MonoSol's problem had already been solved by the art

Undue experimentation is not relevant because the solution to MonoSol's problem was solved in the prior art well before MonoSol's alleged invention. Based on the *Leo* case, MonoSol argues that a proper *prima facie* case of obviousness has not been made because optimization is not possible without recognition of the problem. Reply at 57-58 MonoSol argues that the prior art failed to recognize that "there were problems with obtaining the higher degrees of uniformity of content of active in films …and that 'locking-in' by controlled drying… could successfully address the problems." Reply at 57. And specifically, MonoSol states that the solution is "forming a visco-elastic film that locks-in the substantially uniform distribution of active(s) within about the first 4 minutes of drying." Reply at 54, 70-71. Further MonoSol alleges that the prior art did not even attempt to solve this problem. *See* Reply at 60.

The real problem is that the prior art, *e.g., Chen*, already discloses the solution. That is, there was no problem to be solved—the solution already existed. *Chen* has already been shown to disclose a method that forms a visco-elastic film that locks-in the substantially uniform distribution of active within about the first 4 minutes of drying. ACP at 34-39. This was

[3] Notably, both the '080 specification and the '080 patent claims are more devoid of detail than *Chen*. Moreover, the process descrived in the Bogue Declarations is so devoid of detail that it would be impossible not only to reproduce the experiments but also to confirm which claims are exemplified or supported by the experiments. Having chosen this breadth and vagueness in its specification, its claims, and its declarations, MonoSol cannot complain that the methods cannot be practiced without undue experimentation.

confirmed in the Reitman Declaration. Reitman at ¶ 8 ("Within about 4 minutes after initiation of drying, the film was self-supporting, non-tacky and viscoelastic."). Therefore, there cannot be any undue experimentation required to arrive at the solution disclosed in *Chen*.

In addition—even if the problem were not already solved by *Chen*, and confirmed by the Reitman Declaration—the newly submitted 2001 article authored by *Liang & Chen* (Exhibit 3) does not support patentability. Exhibit 3 says nothing about an alleged uniformity problem. Nor does it rebut the conclusion that *Chen* teaches forming a visco-elastic film in less than 4 minutes. The portion quoted and bolded by MonoSol (Reply at 61-62) only discusses further work related to, *e.g.*, high stability, transportability, and taste-masking to achieve an "ideal fast-dissolving system." No connection is made by MonoSol as to how this relates to the alleged problem of uniformity or the solution. And none is discernible to Requester.

The Office has made a proper *prima facie* case for both anticipation and obviousness, MonoSol has failed to rebut it. If anything, *Leo* demonstrates that MonoSol has not met its burden to rebut the *prima facie* case of anticipation and obviousness

V. THE OUTSTANDING REJECTIONS ARE PROPER

A. Proper Rejection of claims 1-11, 13-15, 17-71, 82-90, 92-94, 96-150, 161-172, 174-176, 178-232, 243-253, 256, 258-271, 274, 276-289, 292 and 294-318 under 35 USC 103(a) as obvious over *Chen.*

The outstanding rejection recited in the title above was proper. The rejections should be maintained even if the new amendments and evidence are entered because the new material does nothing that could overcome *Chen*.

MonoSol proposes to amend all of the independent claims to require that tests demonstrate the resulting films are "self-supporting." Reply at 44:19-20. But *Chen* expressly teaches self-supporting films. *Chen* 17:15, 15:31. *Chen* states that the resulting films are "stand alone" and "self-supporting. " *Id.* Because *Chen* anticipates the proposed new limitation, the amendment does not further prosecution. MonoSol also proposes to remove the 60 ºC limitation from claim 318, but that amendment also does not further prosecution.

In its Reply, MonoSol largely repeats the arguments addressed above.[4] In the interest of brevity, Requester will refer back to the rebuttal above where appropriate and address any differences or new arguments.

At the outset, Requester notes that MonoSol does not refute the office's position that *Chen* teaches "the same materials and the same processes" as claimed by MonoSol. ACP at 34-39. "[W]here the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established." MPEP 2112.01(I).

1. *Visco-elastic*

MonoSol appears to argue that "visco-elastic" has a special definition that includes "having said active substantially uniformly distributed throughout, within about 4 minutes by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying [...] by locking-in or substantially preventing migration of said active within said viscoelastic film..." Reply at 77:16-23. This argument is addressed in Section (IV)(A) above. If MonoSol is arguing that "locking in" and "increasing viscosity" are limitations that are not taught by the prior art, this is addressed immediately below.

2. *Locking-in / preventing migration*

MonoSol repeatedly relies on *Chen's* failure to literally include the words "locking-in" and "preventing migration" to overcome the rejection. Reply at p. 78, lines 2-3, 7-9, 13-17, and 24-27; and p. 80, lines 1-4. However, as a matter of law, "locking-in" and "preventing migration" are scientific theories, scientific mechanisms, and/or desired results of the claimed process step(s)—each of which is not entitled to patentable weight. This is addressed in the discussion of the Supreme Court case Markman in introduction to Section IV and in Section (IV)(A)(2). There is nothing patentable about reciting what necessarily happens (solvent

[4] MonoSol presented no argument regarding Example M with respect to *Chen*. *Chen* discloses a dissolution test (*i.e.*, an analytical chemical test) at p. 16, lines 27-29 and shown in Figure 5. Thus, "analytical chemical tests" cannot distinguish *Chen*.

removal increases viscosity) when one takes the materials and follow the same process steps taught in *Chen*, as confirmed by Reitman.

3. *Chen Fig. 5*

MonoSol makes the same arguments regarding Figure 5 (Reply at 79-80) that have been addressed in Section (IV)(D) above.

4. *Quasi-burden/undue experimentation/Leo*

In the ACP at the paragraph bridging pages 79-80 and the first paragraph on page 80, MonoSol makes a quasi-burden/undue experimentation/*Leo* argument. To the extent that this argument can be parsed, MonoSol makes the same arguments addressed above in Section (IV)(D) for burden, (IV)(E) for undue experimentation, and Section (III)(A) for *Leo*.

5. *Misquote of ACP*

MonoSol distorts the rejection by taking a quote out of context. According to MonoSol, "the Specialist appears to be saying that *Chen* does not disclose or suggest that its viscoelastic film is formed within 4 minutes. Thus, *Chen* cannot inherently disclose or suggest or make obvious [MonoSol's] claim limitation that its invention locks-in or substantially locks-in the active…within the first four minutes of drying." Reply at 80:21-24.

In that very context, however, the ACP points out that *Chen* uses the same solvent, same polymer (which '080 describes as producing viscoelasticity) , and a viscosity that overlaps with the claimed viscosity range and even the preferred viscosity range. ACP at 34-35. Then the ACP states on page 35, lines 6-9 and 17-21:

> "Accordingly, *Chen*'s films … are inherently viscoelastic before drying. Within 4 minutes of the 9 minute drying in *Chen*'s Examples… a more dry viscoelastic film is obtained. As an even further alternative, if *Chen*'s viscoelastic film is formed after about the first 4 minutes but with *Chen*'s 9 minute drying time, then a skilled artisan would recognize that with a higher drying temperature, a shorter time than 9 minutes can be used. In other words, a higher drying temperature than the 50°C exemplified by

> *Chen* would result in a formation of *Chen*'s visco-elastic film product sooner."

Thus, the Specialist was clearly providing an alternative argument.

6. *A higher drying temperature will allow a shorter drying time*

According to MonoSol, "one skilled in the art would not necessarily recognize that a higher drying temperature and shorter drying time than 9 minutes could be used or would be desirable." Reply at 81:5-8. But the combination is a common sense prediction of a physical relationship. Anyone who uses a clothes dryer with two settings would understand that a higher drying temperature allows for a shorter drying time. As an illustrative example in the film prior art, *Strobush* clearly teaches several ways to dry films by raising the temperature without exceeding the threshold of heat transfer rate such that film defects are formed.

In view of the above, the outstanding rejection was proper and has not been overcome by MonoSol.

B. Proper Rejection of claims 2, 3, 32, 55, 72-81, 111, 134, 151-160, 193, 216 and 233-242 under 35 USC § 103(a) as obvious over *Chen* and *Staab*

The outstanding rejection recited in the title above was proper. It should be maintained even if the proposed amendments and new evidence are entered because they do nothing to overcome the rejection over *Chen* and *Staab*.

MonoSol proposes to amend all of the independent claims to require that tests demonstrate that the resulting films be "self-supporting." Reply at 44:19-20. But *Chen* expressly teaches self-supporting films. *Chen* at 17:15, 15:31. *Chen* states that the resulting films are "stand alone" and "self-supporting." *Id.* *Staab* also discloses films that are self-supporting. In particular, *Staab* discloses films that "serve as a barrier" (8:65-9:25); "are intended to remain in substantially solid form for shelf storage…and have the turgidity and shape…to be inserted by hand" (9:45-63); and films that are "released from the drying sheet [*i.e.*, no substrate backing] and rolled onto a spool" (11:5-7). Because *Chen* and *Staab* both teach

self-supporting films, the amendment cannot further prosecution. MonoSol also proposes to remove the 60 ℃ limitation from claim 318, but this amendment also does not further prosecution.

In rebutting this rejection, MonoSol only refers to the obviousness rejection over *Chen* alone and the anticipation/obviousness rejection over *Staab* alone. We address their arguments for *Chen* in Section (V)(A) above, and their arguments for *Staab* alone in Section (V)(E). MonoSol did not challenge the propriety of combining *Chen* and *Staab*.

In view of the above, the outstanding rejection was proper and has not been overcome by MonoSol.

C. Proper Rejection of claims 317 and 318 under 35 USC § 103(a) as obvious over *Chen* and *Arter*

The ACP properly rejects claims 317 and 318 as obvious over *Chen* in view of *Arter*. Even if the proposed amendments and new evidence are entered, the rejections should be maintained. MonoSol's arguments related to alleged deficiencies in *Chen* are addressed above in Sections IV and V(A).

The ACP relies on *Arter* to strengthen the teachings of *Chen* as to drying. ACP at 48-49. Based on the proposed addition of the term "self-supporting" to the rejected claims, MonoSol argues that *Arter*'s drying process and apparatus is inapplicable to "pharmaceutical films, . . . which are aqueous-based and self-supporting." Reply at 83:5-9. But the proposed addition of the term "self-supporting" to the claims does not render *Arter* "inapplicable." *See* Section (II)(B) above. For example, even with the proposed amendment, the drying steps in rejected claims 317 and 318 do not involve a "self-supporting" film. If anything, the proposed addition of "self-supporting" to the post-production testing steps of the rejected claims is inapplicable—because the rejected claims do not require that film to be self-supporting until after the drying steps are done.

Like its other "inapplicability" arguments, MonoSol's comparison of the thickness of the Suboxone® film with the thickness of *Arter*'s films is a confusing distraction. The rejected claims are not limited to the Suboxone® film. And neither of the rejected claims requires films to have a thickness within a particular range. Finally, the '080 patent specification indicates that the alleged invention concerns dry films with a thickness range between 3 and 250 microns, a range that encompasses *Arter*'s films. '080 patent at 28:58-64.

Arter discloses the conveyance of "polymeric film" through a drying zone with a foraminous shield to promote uniformity. *Arter* at Abstract. *Arter* teaches evaporation "from aqueous solutions of hydrophilic colloids." *Arter* at 9:8; *see* also Reply at 48:24 (MonoSol quoting *Arter*'s reference to "aqueous . . . compositions"). Like *Arter*, *Chen* teaches the use of "hydrocolloids" in the preparation of films. *Chen*, *e.g.*, at 4:1, 3, 11, and 25. *Chen* also discusses both coating and casting. *See Chen* at 13:27 ("the film is cast"), 15:25-27 ("the coating solution is coated on the non-siliconized side of a polyester film"). Thus, one of skill in the art would have been motivated to consider *Arter*'s drying methods and apparatus with respect to *Chen*.

MonoSol argues that *Arter* can be distinguished because it teaches slow drying rates, "contrary to the claims of the '080 Patent, which recite rapidly increasing viscosity, and hence the rate of evaporation." Reply at 83:13-16. But the exemplary drying times of *Arter* are well within the drying times recited in the rejected claims. *See Arter* at 16:59-61 (disclosing an exemplary drying time of 27 seconds).

MonoSol's also mischaracterizes *Arter* as addressing only surface defects. Reply at 83:12-14 (citing *Arter* as addressing "mottle or non-uniform density of surface features 'blotches'). Contrary to MonoSol's argument, *Arter* actually states that its objective is "to prevent mottle or non-uniform density." *Arter* at 2:22 (emphasis added).

In view of the above, the outstanding rejection was proper and has not been overcome by MonoSol.

D. Proper rejection of claims 317 and 318 under 35 USC § 103(a) as obvious over *Chen* and *Strobush*

The ACP rejects claims 317 and 318 as obvious over *Chen* in view of *Strobush*. Even if the proposed amendments and new evidence are entered, the rejections should be maintained. MonoSol's arguments related to alleged deficiencies in *Chen* are addressed above in Sections IV and V(A).

The ACP relies on *Strobush* to strengthen the teachings of *Chen* as to drying. ACP at 50-51. Based on the proposed addition of the term "self-supporting" to the rejected claims, MonoSol argues that *Strobush* is "inapplicable." Reply at 85. MonoSol is simply wrong. *See* Section (II)(B) above. For example, even with the proposed amendment, the drying steps in rejected claims 317 and 318 do not involve "self-supporting" film. If anything, the proposed addition of "self-supporting" to the post-production testing steps of the rejected claims is inapplicable—because the rejected claims do not require the film to be self-supporting until after the drying steps are done.

Like its other "inapplicability" arguments, MonoSol's comparison of the thickness of "the '080 patent's films" with the thickness of *Strobush*'s films is a confusing distraction. The '080 patent specification indicates that the alleged invention concerns dry films with a thickness range between 3 and 250 microns, a range that encompasses *Strobush*'s films. '080 patent at 28:58-64. And neither of the rejected claims requires films to have a thickness within a particular range.

In an appeal of a related application, rejecting MonoSol's similar arguments, the Board found that "*Strobush* may . . . reasonably be considered to be within the field of Appellants endeavor (as stated under the 'Field of the Invention' on page 1 of the Specification)." Board Decision regarding U.S. Application No. 10/074,272 which resulted in U.S. Patent No. 7,425,292, Feb. 21, 2008, at 13:21-24. The fields of invention of the '080 patent and of the related '292 patents are remarkably similar. Compare Fields of Invention in the '080 patent, at 1:37-47, and of the '292 patent, at 1:11-17 (each stating: "The even or uniform distribution [of

active ingredient throughout the film] is achieved by controlling one or more parameters, . . . and the use of a drying process that reduces aggregation or conglomeration of the components in the film as it forms into a solid structure."). Consistent with the Board decision, *Strobush* may reasonably be considered to be within the '080 patent's field of endeavor. Thus, one of skill in the art would have been motivated to consider *Strobush*'s drying methods and apparatus with respect to *Chen*.

"*Strobush* relates to drying aqueous systems to achieve more uniform distribution (uniform density) of the active component (the flavor ingredient), while distinguishing over the conventional drying oven systems of the prior art which produce surface and density defects such as mottle." Board Decision regarding U.S. Application No. 10/074,272 which resulted in U.S. Patent No. 7,425,292, Feb. 21, 2008, at 13:14-18. Although its arguments about *Strobush* have failed to convince the Board, MonoSol again mischaracterizes *Strobush* in an effort to create deficiencies where none actually exist and thereby exclude pertinent prior art. Reply at 86.

For example, *Strobush* teaches that top air velocity can contribute to film defects. *See Strobush* at 1:67-2:2; 6:24-27; and 12:65-67. *Strobush* teaches that film defects can be minimized by reducing top air velocity to approximately match the velocity of the coated substrate so that there is no differential top airflow. *See Strobush* at 16:14-26. Without differential top airflow, there can be no shearing force acting on the top of the polymer matrix, and the inherent viscosity or yield value of the wet matrix cannnot be overcome. *See Strobush* at 16:20-22. Thus, contrary to MonoSol's argument (Reply at 86:12-14), *Strobush* teaches controlling the force of the air so as not to exceed a yield value of the polymer matrix.

Indeed, the Board already found: "*Strobush* teaches that the use of conventional drying ovens for drying aqueous coated film systems results in non-uniform density defects, and the solution to this problem is to apply hot air currents to only the bottom side of the coated film." Board Decision regarding U.S. Application No. 10/074,272 which resulted in U.S. Patent No. 7,425,292, Feb. 21, 2008, at 15:15-19.

Contrary to MonoSol's argument, *Strobush* teaches how to maximize the heat transfer rate hΔT, and dry films rapidly. *See*, *e.g.*, *Strobush* at 14:30-36 ("FIGS. 21-22 show that by increasing the heat transfer rate to correspond to the increasing maximum allowable heat transfer rate, the rate of drying can be increased even more rapidly than the simplified case in FIGS 19-20 in which the maximum allowable heat transfer rate is assumed constant (emphasis added); 13:63-14:12 ("At all times, the heat transfer rate is at or below the maximum allowable heat transfer rate").

In view of the above, MonoSol has not overcome the rejection over *Chen* and *Strobush*, which was proper and should be maintained.

E. Proper rejection of claims 1-5, 10, 13-15, 21, 24, 25, 32, 44-46, 54, 55, 59, 63-70, 72-75, 78-84, 89, 92-94, 100, 103, 104, 111, 123-125, 133, 134, 138, 142-149, 151-154, 157-166, 171, 174-176, 182, 185, 186, 193, 205-207, 215, 216, 220, 224-231, 233-236, 239-242, 249-252, 258-260, 267-270, 276-278, 285-288 and 294-318 under USC § 102(b) as anticipated by or, in the alternative, under 35 USC § 103(a) as obvious over *Staab*

The outstanding rejection recited in the title above was proper. It should be maintained even if the proposed new amendments and new evidence are entered because they fail to overcome the rejection over *Staab*.

MonoSol proposes to amend each of the independent claims to require that tests demonstrate that the resulting films are "self-supporting." Reply at 44:19-20. But *Staab* expressly teaches self-supporting films. *Staab* also discloses films that "serve as a barrier" (8:65-9:25); "are intended to remain in substantially solid form for shelf storage…and have the turgidity and shape…to be inserted by hand" (9:45-63); and films that are "released from the drying sheet [*i.e.*, no substrate backing] and rolled onto a spool" (11:5-7). Because *Staab* teaches self-supporting films, the proposed amendment does not further prosecution. MonoSol also proposes to remove the 60 ℃ limitation from claim 318, but this amendment also does not further prosecution.

MonoSol wishes to claim a process for making any pharmaceutical film. Yet, MonoSol failed to identify a single claimed manipulative step (*e.g.*, mixing, casting, or evaporating) or claimed process condition (*e.g.*, temperature, time, speed, or pH) that is not taught by *Staab*. MonoSol has misunderstood the ACP and/or *Staab*, in two ways.

1. *Locking-in / preventing migration*

According to MonoSol, *Staab* does not teach that "locking in or prevention of migration of the active ingredient is occurring within the viscoelastic film within the first 4 minutes." Reply at ¶ bridging pp. 88-89. This argument is addressed in the discussion of the Supreme Court case Markman in the introduction to Section IV and in Section IV(A). *Staab* uses "the same materials as disclosed in the '080 patent, and the same basic process steps here claimed, and each dosage film has the same weight with the same amount of active agent." ACP at 95:7-11; *Staab* at 11:35-12:3. Again, there is nothing patentable about reciting what necessarily happens (solvent removal increases viscosity) when one takes the same materials and follow the same process steps taught in *Staab*. MonoSol has not pointed out which process claim limitation or condition has not been taught by *Staab*. The rejection should be affirmed because there is no basis for expecting a different result.

2. *Analytical tests*

Relying on *Staab's* alleged failure to disclose uniformity confirmation based on "assaying," MonoSol argues that *Staab* "does not and cannot inherently disclose or make obvious Patentee's resulting film having the claimed levels of uniformity of content…." Reply at 89:18-21. But none of the claims recite "assaying," and the Office found that *Staab* discloses an analytical chemical test. ACP at 57:1-3. MonoSol did not refute that finding. In any event, the state of uniformity in a film is an objective fact, *i.e.*, a result, that is not influenced by any post-manufacturing test step. Indeed, the ACP acknowledges that the films of *Staab* have a variation 0% in active content. ACP at 56:17-21 (referencing *Staab* 11:35-12:3).

Once again, there is nothing patentable about reciting a property that results from taking the same materials and following the same process steps taught in *Staab*. MonoSol has not

pointed out which process claim limitation or condition has not been taught by *Staab*. The rejection should be affirmed because there is no basis for expecting a different result.

MonoSol has not presented any arguments based on fact or law that would overcome the rejection, which should be affirmed.

F. Proper rejections of claims 82, 89, 90, 92, 161, 171, 172, 174, 274, 292, 304-311 and 313-318 under 35 USC § 103(a) as being obvious over *Le Person*

The outstanding rejection recited in the title above was proper. It should be maintained even if the proposed amendments and new evidence are entered because they do nothing to overcome the rejection over *Le Person*.

MonoSol proposes to amend each of the independent claims to require that tests indicate that the resulting film is "self-supporting." Reply at 44:19-20. In its Reply, MonoSol links self-supporting to thickness. *See e.g.,* Reply at 87:9-14 (*Strobush* is too thin to be self-supporting), 87:23-24 (contrasting thickness of one '080 embodiment with thinner photographic films of *Strobush*); and 83:5-8 (coatings like *Strobush* with thinner wet thicknesses "are not self-supporting"). The '080 patent teaches that the alleged invention concerns dry films with a thickness range between 3 and 250 microns. '080 patent at 28:58-64. That range encompasses *Le Person*'s films of, *e.g.*, a dry thickness of 50 microns. *Le Person* at Table 1, Fig. 5, p. 263. Again, the film thickness range disclosed in the '080 patent, which films MonoSol argues are "self-supporting," encompass *Le Person's* film thickness. Thus, *Le Person*'s pharmaceutical films are self-supporting. Moreover, the proposed addition of the "self-supporting" limitation cannot distinguish *Le Person* or further prosecution.

MonoSol also proposes to remove the 60 ºC limitation from claim 318, but this amendment also does not further prosecution.

1. *Locking-in / preventing migration*

According to MonoSol, "*Le Person* does not inherently disclose locking-in or substantially preventing migration of the active within the visco-elastic film within the first 4

minutes." Reply at 91:21-22. First, MonoSol has not challenged the Specialist's factual reading of *Le Person*, Fig. 5. In Figure 5, at about 4 minutes of drying, 98% of the water has been removed, and thus the viscosity of the films must necessarily have been increased. ACP at 66:11-13. In addition, after 5 minutes, "the system tends to re-equilibrate the mechanical stresses…the meshes are densely packed." In any event, MonoSol's repetition of the argument does not change the fact that it has already been found unpersuasive. ACP at 66. "Locking-in" is addressed in the discussion of the Supreme Court case Markman in introduction to Section IV and in Section (IV)(A). MonoSol has not pointed out which process claim limitation or condition has not been taught by *Le Person*. The rejection should be affirmed because there is no basis for expecting a different result.

2. *Locking in / Uniformity*

According to MonoSol, the displacement of active along the z-axis is evidence that *Le Person*'s films do not lock-in active and thus the active is not uniform. Reply at 92-93. But MonoSol claims uniformity of active per dosage unit, not uniformity along the z-axis. As pointed out by the Specialist, *Le Person*'s temporary displacement of active along the vertical z-axis is not relevant to the question of whether *Le Person*'s films are uniform (or locked-in or migration-resistant) per dosage unit, that is, in the x-y plane. *See* ACP at 64-69, especially 65:12-66-7; Reply at 92:3-12. Nowhere in the '080 patent or anywhere else in the record is there support for the theory that "locking in" and "substantially uniform" mean total immobilization along all three spatial axes. And even if there were, MonoSol's preferred method for measuring uniformity, by dissolution, could not distinguish films with z-axis migration from films without z-axis migration.

3. *Stresses*

According to MonoSol, *Le Person* teaches that the "stresses imposed by the early drying process and different reaction [sic] by the active to such stresses can cause the active to become unevenly distributed." Reply at 92:12-22. Again, temporary displacement along the z-axis does not affect the total amount of active per dosage unit (x-y plane).

4. *The importance of 4 minutes*

Strangely, MonoSol admits in its Reply that the resulting films of *Le Person* are homogeneous after 15 minutes, but that uniform distribution of active (along the z-axis) does not occur until well after 4 minutes. Reply at 93:1-7. Thus, their argument concedes that 4 minutes is not critical to obtaining a film with uniform content of active.

Finally, Requester notes that MonoSol did not challenge many of findings in the ACP and, therefore, has conceded them. In view of the above, the rejection over *Le Person* has not been overcome, and is proper.

G. Proper rejection of claim 318 under 35 USC 112, first paragraph.

For the same reasons discussed in detail in Sections (II)(E), this rejection is proper whether or not entry is granted for the proposed amendment deleting the 60 ℃ temperature recitation.

H. Proper rejection of claim 318 under 35 USC 112, second paragraph.

If the proposed amendments are not entered, then the rejection stands. MonoSol has not argued this rejection. Reply 75-76.

VI. CONCLUSION

Because the proposed amendments would raise new 112 rejections, would not overcome even one prior art rejection, and do not comply with Rule 116 for other reasons stated above, Requester requests non-entry at this late hour.

Because MonoSol has made no showing of good or sufficient reasons as to why the new evidence is necessary, nor a showing as to why the evidence—available before MonoSol's March 2013 response—was not earlier presented, and for the other reasons stated above, Requester requests non-entry.

In the event that these new amendments and evidence are entered, they accomplish nothing. MonoSol has failed to identify any factual or legal error made by the Office which would result in overcoming any art-based rejection. MonoSol has failed to identify one claimed process step, material, or condition that is not taught by the prior art. MonoSol has failed to identify or claim a film-making process that can be distinguished from the cited art. Finally, MonoSol has failed to identify what, if anything, is in the prior art processes that would prevent the production of films with the claimed desired results. Thus, MonoSol's Reply is ineffective to overcome all of the outstanding rejections with respect to even one of the 300+ claims in this proceeding, with or without the proposed claim amendments, and with or without the new evidence and opinions.

In view of the above, Requester respectfully requests that all of the outstanding rejections be affirmed, and a Right of Appeal Notice be issued.

Respectfully submitted,

McCarter & English LLP

Dated: October 3, 2013

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CERTIFICATE OF FIRST CLASS SERVICE

It is certified that a copy of the Inter Partes Reexamination Comments Under 37 CFR § 1.947 by the Third Party Requester and this certificate of first class service have been served, by first class mail, on October 3, 2013, in their entirety on the Patent Owner in accordance with 37 C.F.R. §§ 1.903 and 1.248. The name and address of the party served is:

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Electronic Acknowledgement Receipt

EFS ID:	17037785
Application Number:	95002170
International Application Number:	
Confirmation Number:	6418
Title of Invention:	POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM
First Named Inventor/Applicant Name:	7897080
Customer Number:	23869
Filer:	Danielle L. Herritt/Maureen Tierney
Filer Authorized By:	Danielle L. Herritt
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Filing Date:	10-SEP-2012
Time Stamp:	23:23:54
Application Type:	inter partes reexam

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		117744_000023__080_Requesters_Comments_ACP_2013OCT3.PDF	229218 c7190912b995e2a589719d1b0524fabaead358cb	yes	39

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Reexam Miscellaneous Incoming Letter	1	38
	Reexam Certificate of Service	39	39
Warnings:			
Information:			
	Total Files Size (in bytes):	229218	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patentee:	Yang et al.	Specialist:	Diamond, Alan D.
Patent No.:	U.S. 7,897,080	Group Art Unit:	3991
Reexamination Control No.:	95/002,170	Confirmation No.	6418
Filed:	September 10, 2012	H&B Docket:	1199-26 RCE/CON/REX
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Alexandria, VA 22313-1450

Certificate of EFS-Web Transmission
I hereby certify that this correspondence is being transmitted via the U.S. Patent and Trademark Office electronic filing system (EFS-Web) to the USPTO on September 3, 2013
Signed: Michael I. Chakansky /Michael I Chakansky/

RESPONSE BY PATENTEE TO ACTION CLOSING PROSECUTION

Madame:

Patent owner MonoSol Rx, LLC ("Patentee" and/or "MonoSol") hereby presents its response to the Action Closing Prosecution in the above-identified *Inter Partes* Reexamination of U.S. Patent No. 7,897,080 ("the '080 Patent"), dated July 31, 2013 ("ACP"), pursuant to 37 C.F.R. § 1.195(a). Please note that August 31, 2013 was a Saturday, September 1, 2013 a Sunday, and September 2, 2013 Labor Day. Please amend the '080 Patent as set forth hereinbelow. The present amendment(s) are being made in accordance with 37 C.F.R. §1.530(d)–(j) and 37 C.F.R. § 116. No claim fees are believed to be due with this submission. If, however, there are any fees due in connection with this submission, authorization to charge such fees, including any claim fees, and authorization to credit any overpayments, to Deposit Account No. 08-2461 are hereby provided.

Amendment to the Claims begins on page 2 of this paper.

Remarks begin on page 44 of this paper.

TABLE OF CONTENTS

TABLE OF AUTHORITIES

CASES

STATUTES

RULES & MPEP

LIST OF EXHIBITS

Exhibit No.	Exhibit Description
1	For ease of reference a copy of entered Declaration of B. Arlie Bogue, Ph.D. Under 37 C.F.R. § 1.132, dated March 13, 2013, earlier submitted by Patentee with March 13, 2013 Response to Office Action ("Bogue Declaration I")
2	Declaration of B. Arlie Bogue, Ph.D. Under 37 C.F.R. § 1.132, executed August 29, 2013 ("Bogue Declaration II").
3	*Leo Pharmaceutical Products, Ltd. v. Teresa Staneck Rea, Acting Director, USPTO*, 2012-1520 (Fed. Cir. August 12, 2013).
4	"Fast-dissolving intraoral drug delivery systems," Alfred C. Liang & Li-lan H Chen, Lavipharm Laboratories, Inc., *Expert Opin., Ther. Patents, **11**(6): 981-986* (2001 © Ashley Publications Ltd, ISSN 1354-3776).
5	Reckitt Benckheiser Group plc, 2012 Annual Report, Excerpts.
6	Suboxone Sales Data - U.S. Pharmaceutical Statistics (http://www.drugs.com/stats/suboxone, August 27, 2013).
7	For ease of reference a copy of Third-Party Requester's **Exhibit J** from its April 12, 2013 Comments, namely: Chapter <905> Uniformity of Dosage Units (2011) (arrows and brackets supplied)
8	For ease of reference a copy of Third-Party Requester's **Exhibit K** from its April 12, 2013 Comments, namely: Chapter <905> Uniformity of Dosage Units (2007) (arrows and brackets supplied)

AMENDMENT TO THE CLAIMS

1. (Twice Amended) A process for manufacturing a resulting film which is self-supporting and suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said [making a]film having a substantially uniform distribution of components comprising a substantially uniform distribution of said active in individual dosage units of said resulting film, comprising the steps of:

(a) forming a masterbatch pre-mix comprising a solvent and a polymer selected from the group consisting of water-soluble polymers, water-swellable polymers and combinations thereof;

(b) adding [an]said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, to a pre-determined amount of said masterbatch pre-mix to form a flowable polymer matrix, said matrix having a substantially uniform distribution of said active;

(c) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(d) controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus and evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first [10]4 minutes [or fewer]by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, wherein during said drying said flowable polymer matrix temperature is 100 °C or less; [and]

(e) forming [a]said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained; and

(f) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units sampled from different locations of said resulting film, said tests indicating that uniformity of content in the amount of the active varies by no more than 10% and said resulting film is self-supporting and suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration.

2. (Original) The process of claim 1, wherein said pre-determined amount of master batch pre-mix is controllably fed via a first metering pump and a control valve to a first mixer and a second mixer.

3. (Original) The process of claim 2, wherein said first mixer and said second mixer are arranged in parallel, series or a combination thereof.

4. (Original) The process of claim 1, wherein said water-soluble polymer comprises polyethylene oxide.

5. (Original) The process of claim 1, wherein said polymer comprises a polymer selected from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations

thereof, alone or in combination with polyethylene oxide.

6. (Original) The process of claim 5, wherein said polymer further comprises a water insoluble polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone and combinations thereof.

7. (Original) The process of claim 5, wherein said polymer further comprises a polymer selected from the group consisting of methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(ά-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof.

8. (Original) The process of claim 5, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

9. (Original) The process of claim 5, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic

acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(d-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

10. (Original) The process of claim 1, wherein said solvent is selected from the group consisting of water, polar organic solvent, and combinations thereof.

11. (Original) The process of claim 10, wherein said solvent is selected from the group consisting of ethanol, isopropanol, acetone, and combinations thereof.

12. (Canceled)

13. (Amended) The process of claim 1, wherein said active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants,

obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, [anti-tumor drugs,]anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, [anti-convulsants,]neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, [anti-asthmatics,]cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

14. (Amended) The process of claim 1, wherein said active is selected from the group consisting of [cosmetic actives,]antigens, allergens, spores, microorganisms, seeds, [mouthwash components, flavors, fragrances,]enzymes, [preservatives, sweetening agents, colorants, spices,]vitamins and combinations thereof.

15. (Original) The process of claim 1, wherein said active is a bioactive active.

16. (Canceled)

17. (Original) The process of claim 1, wherein said active is an opiate or opiate-derivative.

18. (Original) The process of claim 1, wherein said active is an anti-emetic.

19. (Original) The process of claim 1, wherein said active is an amino acid preparation.

20. (Original) The process of claim 1, wherein said active is selected from the group consisting of sildenafils, tadalafils, vardenafils, apomorphines, yohimbine hydrochlorides, alprostadils and combinations thereof.

21. (Original) The process of claim 1, wherein said active is a protein.

22. (Original) The process of claim 1, wherein said active is insulin.

23. (Original) The process of claim 1, wherein said active is an anti-diabetic.

24. (Original) The process of claim 1, wherein said active is an antihistamine.

25. (Original) The process of claim 1, wherein said active is an anti-tussive.

26. (Original) The process of claim 1, wherein said active is a non-steroidal anti-inflammatory.

27. (Original) The process of claim 1, wherein said active is an anti-asthmatics.

28. (Amended) The process of claim 1, wherein said active is an anti-diarrhea preparation.

29. (Original) The process of claim 1, wherein said active is an alkaloid.

30. (Original) The process of claim 1, wherein said active is an anti-psychotic.

31. (Original) The process of claim 1, wherein said active is an anti-spasmodic.

32. (Original) The process of claim 1, wherein said active is a biological response modifier.

33. (Original) The process of claim 1, wherein said active is an anti-obesity drug.

34. (Original) The process of claim 1, wherein said active is an H_2-antagonist.

35. (Original) The process of claim 34, wherein said H_2-antagonist is selected from the group consisting of cimetidine, ranitidine hydrochloride, famotidine, nizatidine, ebrotidine, mifentidine, roxatidine, pisatidine, aceroxatidine and combinations thereof.

36. (Original) The process of claim 1, wherein said active is a smoking cessation aid.

37. (Original) The process of claim 1, wherein said active is an anti-parkinsonian agent.

38. (Original) The process of claim 1, wherein said active is an anti-depressant.

39. (Original) The process of claim 1, wherein said active is an anti-migraine.

40. (Original) The process of claim 1, wherein said active is an anti-Alzheimer's agents.

41. (Original) The process of claim 1, wherein said active is a dopamine receptor agonist.

42. (Original) The process of claim 1, wherein said active is a cerebral dilator.

43. (Original) The process of claim 1, wherein said active is a psychotherapeutic agent.

44. (Original) The process of claim 1, wherein said active is an antibiotic.

45. (Original) The process of claim 1, wherein said active is an anesthetic.

46. (Original) The process of claim 1, wherein said active is a contraceptive.

47. (Original) The process of claim 1, wherein said active is an anti-thrombotic drug.

48. (Original) The process of claim 1, wherein said active is diphenhydramine.

49. (Original) The process of claim 1, wherein said active is nabilone.

50. (Original) The process of claim 1, wherein said active is albuterol sulfate.

51. (Original) The process of claim 1, wherein said active is an anti-tumor drug.

52. (Original) The process of claim 1, wherein said active is a glycoprotein.

53. (Original) The process of claim 1, wherein said active is an analgesic.

54. (Original) The process of claim 1, wherein said active is a hormone.

55. (Original) The process of claim 1, wherein said active is a decongestant.

56. (Original) The process of claim 1, wherein said active is a loratadine.

57. (Original) The process of claim 1, wherein said active is dextromethorphan.

58. (Original) The process of claim 1, wherein said active is chlorpheniramine maleate.

59. (Original) The process of claim 1, wherein said active is selected from the group consisting of an analgesic, an anti-inflammatory, an antihistamine, a decongestant, a cough

suppressant and combinations thereof.

60. (Original) The process of claim 1, wherein said active is an appetite stimulant.

61. (Original) The process of claim 1, wherein said active is a gastrointestinal agent.

62. (Original) The process of claim 1, wherein said active is a hypnotic.

63. (Original) The process of claim 1, wherein said active is taste-masked.

64. (Original) The process of claim 1, wherein said active is taste-masked using a flavor.

65. (Original) The process of claim 1, wherein said active is coated with a controlled release composition.

66. (Original) The process of claim 65, wherein said controlled release composition provides an immediate release.

67. (Original) The process of claim 65, wherein said controlled release composition provides a delayed release.

68. (Original) The process of claim 65, wherein said controlled release composition provides a sustained release.

69. (Original) The process of claim 65, wherein said controlled release composition provides a sequential release.

70. (Original) The process of claim 1, wherein said active is a particulate.

71. (Original) The process of claim 1, further comprising adding a degassing agent to said masterbatch premix.

72. (Original) The process of claim 1, further comprising a step of providing a second film layer.

73. (Original) The process of claim 72, wherein said second film layer is coated onto said resulting film.

74. (Original) The process of claim 72, wherein said second film layer is spread onto said resulting film.

75. (Original) The process of claim 72, wherein said second film layer is cast onto said resulting film.

76. (Original) The process of claim 72, wherein said second film layer is extruded onto said resulting film. .

77. (Original) The process of claim 72, wherein said second film layer is sprayed onto said resulting film.

78. (Original) The process of claim 72, wherein said second film is laminated onto said resulting film.

79. (Original) The process of claim 72, further comprising laminating said resulting film to another film.

80. (Original) The process of claim 72, wherein said second film layer comprises an active.

81. (Amended) The process of claim [72]80, wherein said active in said second film is different than said active in said resulting film.

82. (Twice Amended) A process for manufacturing resulting films which are self-supporting and suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said [making a]films having a substantially uniform distribution of components comprising a substantially uniform distribution of a desired amount of said active in individual dosage units of said resulting films, comprising the steps of:

(a) forming a flowable polymer matrix comprising a polymer selected from the group consisting of a water-soluble polymer, a water swellable polymer and combinations thereof, a solvent and [an]said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives[, drugs, medicaments] and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus and evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first [10]4 minutes [or fewer]by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said

active within said visco-elastic film, wherein during said drying said flowable polymer matrix temperature is 100 °C or less, and wherein uniformity of content of said active in substantially equal sized individual dosage units of said visco-elastic film is such that the amount of the active varies by no more than 10%; [and]

(d) forming [a]said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained;

(e) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units sampled from different locations of said resulting film, said tests indicating that uniformity of content in the amount of said active varies by no more than 10% and said resulting film is self-supporting and suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration; and

(f) repeating steps (a) through (e) to form additional resulting films, such that uniformity of content in the amount of said active in said resulting film and said additional resulting films varies no more than 10% from the desired amount of the active as indicated by said analytical chemical tests.

83. (Original) The process of claim 82, wherein said water-soluble polymer comprises polyethylene oxide.

84. (Original) The process of claim 82, wherein said polymer comprises a polymer selected from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium

alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.

85. (Original) The process of claim 84, wherein said polymer further comprises a water insoluble polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone and combinations thereof.

86. (Original) The process of claim 84, wherein said polymer further comprises a polymer selected from the group consisting of methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(ά-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof.

87. (Original) The process of claim 84, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

88. (Original) The process of claim 84, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol

copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(ά-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

89. (Original) The process of claim 82, wherein said solvent is selected from the group consisting of water, polar organic solvent, and combinations thereof.

90. (Original) The process of claim 89, wherein said solvent is selected from the group consisting of ethanol, isopropanol, acetone, and combinations thereof.

91. (Canceled)

92. (Amended) The process of claim 82, wherein the active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones,

hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, [anti-tumor drugs,]anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, [anti-convulsants,]neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, [anti-asthmatics,]cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

93. (Amended) The process of claim 82, wherein said active is selected from the group consisting of [cosmetic actives,]antigens, allergens, spores, microorganisms, seeds, [mouthwash components, flavors, fragrances,]enzymes, [preservatives, sweetening agents, colorants, spices,]vitamins and combinations thereof.

94. (Original) The process of claim 82, wherein said active is a bioactive active.

95. (Canceled)

96. (Original) The process of claim 82, wherein said active is an opiate or opiate-derivative.

97. (Original) The process of claim 82, wherein said active is an anti-emetic.

98. (Original) The process of claim 82, wherein said active is an amino acid preparation.

99. (Original) The process of claim 82, wherein said active is selected from the group consisting of sildenafils, tadalafils, vardenafils, apomorphines, yohimbine hydrochlorides, alprostadils and combinations thereof.

100. (Original) The process of claim 82, wherein said active is a protein.

101. (Original) The process of claim 82, wherein said active is insulin.

102. (Original) The process of claim 82, wherein said active is an anti-diabetic.

103. (Original) The process of claim 82, wherein said active is an antihistamine.

104. (Original) The process of claim 82, wherein said active is an anti-tussive.

105. (Original) The process of claim 82, wherein said active is a non-steroidal anti-inflammatory.

106. (Original) The process of claim 82, wherein said active is an anti-asthmatics.

107. (Amended) The process of claim 82, wherein said active is an anti-diarrhea preparation.

108. (Original) The process of claim 82, wherein said active is an alkaloid.

109. (Original) The process of claim 82, wherein said active is an anti-psychotic.

110. (Original) The process of claim 82, wherein said active is an anti-spasmodic.

111. (Original) The process of claim 82, wherein said active is a biological response modifier.

112. (Original) The process of claim 82, wherein said active is an anti-obesity drug.

113. (Original) The process of claim 82, wherein said active is an H_2-antagonist.

114. (Amended) The process of claim [82]113, wherein said H_2-antagonist is selected from the group consisting of cimetidine, ranitidine hydrochloride, famotidine, nizatidine, ebrotidine, mifentidine, roxatidine, pisatidine, aceroxatidine and combinations thereof.

115. (Original) The process of claim 82, wherein said active is a smoking cessation aid.

116. (Original) The process of claim 82, wherein said active is an anti-parkinsonian agent.

117. (Original) The process of claim 82, wherein said active is an anti-depressant.

118. (Original) The process of claim 82, wherein said active is an anti-migraine.

119. (Original) The process of claim 82, wherein said active is an anti-Alzheimer's agents.

120. (Original) The process of claim 82, wherein said active is a dopamine receptor agonist.

121. (Original) The process of claim 82, wherein said active is a cerebral dilator.

122. (Original) The process of claim 82, wherein said active is a psychotherapeutic agent.

123. (Original) The process of claim 82, wherein said active is an antibiotic.

124. (Original) The process of claim 82, wherein said active is an anesthetic.

125. (Original) The process of claim 82, wherein said active is a contraceptive.

126. (Original) The process of claim 82, wherein said active is an anti-thrombotic drug.

127. (Original) The process of claim 82, wherein said active is diphenhydramine.

128. (Original) The process of claim 82, wherein said active is nabilone.

129. (Original) The process of claim 82, wherein said active is albuterol sulfate.

130. (Original) The process of claim 82, wherein said active is an anti-tumor drug.

131. (Original) The process of claim 82, wherein said active is a glycoprotein.

132. (Original) The process of claim 82, wherein said active is an analgesic.

133. (Original) The process of claim 82, wherein said active is a hormone.

134. (Original) The process of claim 82, wherein said active is a decongestant.

135. (Original) The process of claim 82, wherein said active is a loratadine.

136. (Original) The process of claim 82, wherein said active is dextromethorphan.

137. (Original) The process of claim 82, wherein said active is chlorpheniramine maleate.

138. (Original) The process of claim 82, wherein said active is selected from the group consisting of an analgesic, an anti-inflammatory, an antihistamine, a decongestant, a cough suppressant and combinations thereof.

139. (Original) The process of claim 82, wherein said active is an appetite stimulant.

140. (Original) The process of claim 82, wherein said active is a gastrointestinal agent.

141. (Original) The process of claim 82, wherein said active is a hypnotic.

142. (Original) The process of claim 82, wherein said active is taste-masked.

143. (Original) The process of claim 82, wherein said active is taste-masked using a flavor.

144. (Original) The process of claim 82, wherein said active is coated with a controlled release composition.

145. (Original) The process of claim 144, wherein said controlled release composition provides an immediate release.

146. (Original) The process of claim 144, wherein said controlled release composition provides a delayed release.

147. (Original) The process of claim 144, wherein said controlled release composition provides a sustained release.

148. (Original) The process of claim 144, wherein said controlled release composition provides a sequential release.

149. (Original) The process of claim 82, wherein said active is a particulate.

150. (Original) The process of claim 82, further comprising adding a degassing agent to said flowable polymer matrix.

151. (Original) The process of claim 82, further comprising a step of providing a second film layer.

152. (Original) The process of claim 151, wherein said second film layer is coated onto said resulting film.

153. (Original) The process of claim 151, wherein said second film layer is spread onto said resulting film.

154. (Original) The process of claim 151, wherein said second film layer is cast onto said resulting film.

155. (Original) The process of claim 151, wherein said second film layer is extruded onto said resulting film.

156. (Original) The process of claim 151, wherein said second film layer is sprayed onto said resulting film.

157. (Original) The process of claim 151, wherein said second film layer is laminated onto said resulting film.

158. (Original) The process of claim 151, further comprising laminating said resulting film to another film.

159. (Original) The process of claim 151, wherein said second film comprises an active.

160. (Amended) The process of claim [151]159, wherein said active in said second film is different than said active in said resulting film.

161. (Twice Amended) A process for manufacturing a resulting film which is self-supporting and suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said[making a] film capable of being administered to a body surface and having a substantially uniform distribution of components comprising a substantially uniform distribution of said active in individual dosage units of said resulting film, comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and [an]said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus and evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film, having said active substantially uniformly

distributed throughout, within about the first [10]4 minutes [or fewer]by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, wherein during said drying said flowable polymer matrix temperature is 100 °C or less, and wherein uniformity of content of said active in substantially equal sized individual dosage units of said visco-elastic film is such that the amount of the active varies by no more than 10%;

(d) forming [a]said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained; [and]

(e) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units sampled from different locations of said resulting film, said tests indicating that uniformity of content in the amount of said active varies by no more than 10% and said resulting film is self-supporting and suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration, and

[(e)](f) administering said resulting film to a body surface.

162. (Original) The process of claim 161, wherein said body surface is a mucous membrane.

163. (Original) The process of claim 162, wherein said mucous membrane is oral, anal, vaginal or ophthalmological.

164. (Original) The process of claim 161, wherein said body surface is the surface of a wound.

165. (Original) The process of claim 161, wherein said water-soluble polymer comprises polyethylene oxide.

166. (Original) The process of claim 161, wherein said polymer comprises a polymer selected from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.

167. (Original) The process of claim 166, wherein said polymer further comprises a water insoluble polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone and combinations thereof.

168. (Original) The process of claim 166, wherein said polymer further comprises a polymer selected from the group consisting of methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(ά-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof.

169. (Original) The process of claim 166, wherein said polymer further comprises a polymer

selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

170. (Original) The process of claim 166, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(ά-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

171. (Original) The process of claim 161, wherein said solvent is selected from the group consisting of water, polar organic solvent, and combinations thereof.

172. (Original) The process of claim 161, wherein said solvent is selected from the group consisting of ethanol, isopropanol, acetone, and combinations thereof.

173. (Canceled)

174. (Amended) The process of claim 161, wherein said active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory

agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, [anti-tumor drugs,]anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, [anti-convulsants,]neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, [anti-asthmatics,]cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

175. (Amended) The process of claim 161, wherein said active is selected from the group consisting of [cosmetic actives,]antigens, allergens, spores, microorganisms, seeds, [mouthwash components, flavors, fragrances,]enzymes, [preservatives, sweetening agents, colorants, spices,]vitamins and combinations thereof.

176. (Original) The process of claim 161, wherein said active is a bioactive active.

177. (Canceled)

178. (Original) The process of claim 161, wherein said active is an opiate or opiate-derivative.

179. (Original) The process of claim 161, wherein said active is an anti-emetic.

180. (Original) The process of claim 161 wherein said active is an amino acid preparation.

181. (Original) The process of claim 161, wherein said active is selected from the group consisting of sildenafils, tadalafils, vardenafils, apomorphines, yohimbine hydrochlorides, alprostadils and combinations thereof.

182. (Original) The process of claim 161, wherein said active is a protein.

183. (Original) The process of claim 161, wherein said active is insulin.

184. (Original) The process of claim 161, wherein said active is an anti-diabetic.

185. (Original) The process of claim 161, wherein said active is an antihistamine.

186. (Original) The process of claim 161, wherein said active is an anti-tussive.

187. (Original) The process of claim 161, wherein said active is a non-steroidal anti-inflammatory.

188. (Original) The process of claim 161, wherein said active is an anti-asthmatics.

189. (Amended) The process of claim 161, wherein said active is an anti-diarrhea preparation.

190. (Original) The process of claim 161, wherein said active is an alkaloid.

191. (Original) The process of claim 161, wherein said active is an anti-psychotic.

192. (Original) The process of claim 161, wherein said active is an anti-spasmodic.

193. (Original) The process of claim 161, wherein said active is a biological response modifier.

194. (Original) The process of claim 161, wherein said active is an anti-obesity drug.

195. (Original) The process of claim 161, wherein said active is an H_2-antagonist.

196. (Original) The process of claim 195, wherein said H_2-antagonist is selected from the group consisting of cimetidine, ranitidine hydrochloride, famotidine, nizatidine, ebrotidine, mifentidine, roxatidine, pisatidine, aceroxatidine and combinations thereof.

197. (Original) The process of claim 161, wherein said active is a smoking cessation aid.

198. (Original) The process of claim 161, wherein said active is an anti-parkinsonian agent.

199. (Original) The process of claim 161, wherein said active is an anti-depressant.

200. (Original) The process of claim 161, wherein said active is an anti-migraine.

201. (Original) The process of claim 161, wherein said active is an anti-Alzheimer's agents.

202. (Original) The process of claim 161, wherein said active is a dopamine receptor agonist.

203. (Original) The process of claim 161, wherein said active is a cerebral dilator.

204. (Original) The process of claim 161, wherein said active is a psychotherapeutic agent.

205. (Original) The process of claim 161, wherein said active is an antibiotic.

206. (Original) The process of claim 161, wherein said active is an anesthetic.

207. (Original) The process of claim 161, wherein said active is a contraceptive.

208. (Original) The process of claim 161, wherein said active is an anti-thrombotic drug.

209. (Original) The process of claim 161, wherein said active is diphenhydramine.

210. (Original) The process of claim 161, wherein said active is nabilone.

211. (Original) The process of claim 161, wherein said active is albuterol sulfate.

212. (Original) The process of claim 161, wherein said active is an anti-tumor drug.

213. (Original) The process of claim 161, wherein said active is a glycoprotein.

214. (Original) The process of claim 161, wherein said active is an analgesic.

215. (Original) The process of claim 161, wherein said active is a hormone.

216. (Original) The process of claim 161, wherein said active is a decongestant.

217. (Original) The process of claim 161, wherein said active is a loratadine.

218. (Original) The process of claim 161, wherein said active is dextromethorphan.

219. (Original) The process of claim 161, wherein said active is chlorpheniramine maleate.

220. (Original) The process of claim 161, wherein said active is selected from the group consisting of an analgesic, an anti-inflammatory, an antihistamine, a decongestant, a cough suppressant and combinations thereof.

221. (Original) The process of claim 161, wherein said active is an appetite stimulant.

222. (Original) The process of claim 161, wherein said active is a gastrointestinal agent.

223. (Original) The process of claim 161, wherein said active is a hypnotic.

224. (Original) The process of claim 161, wherein said active is taste-masked.

225. (Original) The process of claim 161, wherein said active is taste-masked using a flavor.

226. (Original) The process of claim 161, wherein said active is coated with a controlled release composition.

227. (Original) The process of claim 226, wherein said controlled release composition provides an immediate release.

228. (Original) The process of 226, wherein said controlled release composition provides a delayed release.

229. (Original) The process of claim 226, wherein said controlled release composition provides a sustained release.

230. (Original) The process of claim 226, wherein said controlled release composition provides a sequential release.

231. (Original) The process of claim 161, wherein said active is a particulate.

232. (Original) The process of claim 161, further comprising adding a degassing agent to said flowable polymer matrix.

233. (Original) The process of claim 161, further comprising a step of providing a second film layer.

234. (Original) The process of claim 233, wherein said second film layer is coated onto said resulting film.

235. (Original) The process of claim 233, wherein said second film layer is spread onto said resulting film.

236. (Original) The process of claim 233, wherein said second film layer is cast onto said resulting film.

237. (Original) The process of claim 233, wherein said second film layer is extruded onto said resulting film.

238. (Original) The process of claim 233, wherein said second film layer is sprayed onto said resulting film.

239. (Original) The process of claim 233, wherein said second film layer is laminated onto said resulting film.

240. (Original) The process of claim 233, further comprising laminating said resulting film to another film.

241. (Original) The process of claim 233, wherein said second film comprises an active.

242. (Amended) The process of claim [233]241, wherein said active in said second film is different than said active in said resulting film.

243. (Original) The process of claim 1, said active is an anti-nauseant.

244. (Amended) The process of claim 1, said active is an erectile dysfunction drug.

245. (Original) The process of claim 1, said active is a vasoconstrictor.

246. (Original) The process of claim 1, said active is a stimulant.

247. (Original) The process of claim 1, said active is a migraine treatment.

248. (Original) The process of claim 1, said active is granisetron hydrochloride.

249. (Original) The process of claim 1, wherein said resulting film provides administration of said active to an individual through the buccal cavity of said individual.

250. (Original) The process of claim 1, wherein said resulting film provides administration of said active through gingival application of said individual.

251. (Original) The process of claim 1, wherein said resulting film provides administration of said active through sublingual application of said individual.

252. (Original) The process of claim 1, wherein said resulting film provides administration of said active to an individual through a mucosal membrane of said individual.

253. (Original) The process of claim 1, wherein said resulting film provides administration of said active to an individual by administration within the body of the individual during surgery.

254. (Canceled)

255. (Canceled)

256. (Original) The method of claim 1, wherein said resulting film contains less than about 6% by weight solvent.

257. (Canceled)

258. (Original) The method of claim 1, wherein said resulting film is orally administrable.

259. (Original) The method of claim 1, wherein said active is in the form of a particle.

260. (Original) The method of claim 1, wherein said matrix comprises a dispersion.

261. (Original) The process of claim 82, said active is an anti-nauseant.

262. (Amended) The process of claim 82, said active is an erectile dysfunction drug.

263. (Original) The process of claim 82, said active is a vasoconstrictor.

264. (Original) The process of claim 82, said active is a stimulant.

265. (Original) The process of claim 82, said active is a migraine treatment.

266. (Original) The process of claim 82, said active is granisetron hydrochloride.

267. (Original) The process of claim 82, wherein said resulting film provides administration of said active to an individual through the buccal cavity of said individual.

268. (Original) The process of claim 82, wherein said resulting film provides administration of said active through gingival application of said individual.

269. (Original) The process of claim 82, wherein said resulting film provides administration of said active through sublingual application of said individual.

270. (Original) The process of claim 82, wherein said resulting film provides administration of said active to an individual through a mucosal membrane of said individual.

271. (Original) The process of claim 82, wherein said resulting film provides administration of said active to an individual by administration within the body of the individual during surgery.

272. (Canceled)

273. (Canceled)

274. (Original) The method of claim 82, wherein said resulting film contains less than about 6% by weight solvent.

275. (Canceled)

276. (Original) The method of claim 82, wherein said resulting film is orally administrable.

277. (Original) The method of claim 82, wherein said active is in the form of a particle.

278. (Original) The method of claim 82, wherein said matrix comprises a dispersion.

279. (Original) The process of claim 161, said active is an anti-nauseant.

280. (Amended) The process of claim 161, said active is an erectile dysfunction drug.

281. (Original) The process of claim 161, said active is a vasoconstrictor.

282. (Original) The process of claim 161, said active is a stimulant.

283. (Original) The process of claim 161, said active is a migraine treatment.

284. (Original) The process of claim 161, said active is granisetron hydrochloride.

285. (Original) The process of claim 161, wherein said resulting film provides administration of said active to an individual through the buccal cavity of said individual.

286. (Original) The process of claim 161, wherein said resulting film provides administration of said active through gingival application of said individual.

287. (Original) The process of claim 161, wherein said resulting film provides administration of said active through sublingual application of said individual.

288. (Original) The process of claim 161, wherein said resulting film provides administration of said active to an individual through a mucosal membrane of said individual.

289. (Original) The process of claim 161, wherein said resulting film provides administration of said active to an individual by administration within the body of the individual during surgery.

290. (Canceled)

291. (Canceled)

292. (Original) The method of claim 161, wherein said resulting film contains less than about 6% by weight solvent.

293. (Canceled)

294. (Original) The method of claim 161, wherein said resulting film is orally administrable.

295. (Original) The method of claim 161, wherein said active is in the form of a particle.

296. (Original) The method of claim 161, wherein said matrix comprises a dispersion.

297. (Original) The method of claim 1, wherein said matrix comprises an emulsion, a colloid or a suspension.

298. (Original) The method of claim 82, wherein said matrix comprises an emulsion, a colloid or a suspension.

299. (Original) The method of claim 161, wherein said matrix comprises an emulsion, a colloid or a suspension.

300. (New) The process of claim 1, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 5%.

301. (New) The process of claim 1, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 2%.

302. (New) The process of claim 1, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 1%.

303. (New) The process of claim 1, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 0.5%.

304. (New) The process of claim 82, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 5%.

305. (New) The process of claim 82, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 2%.

306. (New) The process of claim 82, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 1%.

307. (New) The process of claim 82, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 0.5%.

308. (New) The process of claim 161, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 5%.

309. (New) The process of claim 161, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 2%.

310. (New) The process of claim 161, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 1%.

311. (New) The process of claim 161, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 0.5%.

312. (New) The process of claim 1, wherein said evaporating is conducted by applying radiant energy selected from the group consisting of hot air currents, heat, infrared radiation, radio frequency radiation and combinations thereof.

313. (New) The process of claim 82, wherein said evaporating is conducted by applying radiant energy selected from the group consisting of hot air currents, heat, infrared radiation, radio frequency radiation and combinations thereof.

314. (New) The process of claim 161, wherein said evaporating is conducted by applying radiant energy selected from the group consisting of hot air currents, heat, infrared radiation, radio frequency radiation and combinations thereof.

315. (New) A process for manufacturing resulting films which are self-supporting and suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said films having a substantially uniform distribution of components comprising a substantially uniform distribution of a desired amount of said active in individual dosage units of said resulting films, comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said polymer matrix through a drying apparatus and evaporating at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, wherein during said drying said flowable polymer matrix temperature is 100 °C or less;

(d) forming said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of said active by said locking-in or substantially preventing migration of said active is maintained, such that uniformity of content in the amount of the active in substantially equal sized individual dosage units, sampled from different locations of said resulting film, varies by no more than 10%;

(e) performing analytical chemical tests for uniformity of content of said active in said substantially equal sized individual dosage units of said sampled resulting film, said tests indicating that uniformity of content in the amount of the active varies by no more than 10% and said resulting film is self-supporting and suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration; and

(f) repeating steps (a) through (e) to form additional resulting films, such that uniformity of content in the amount of said active in said resulting film and said additional resulting films varies no more than 10% from the desired amount of said active as indicated by said analytical chemical tests.

316. (New) A process for manufacturing a resulting film which is self-supporting and suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said film having a substantially uniform distribution of components comprising a substantially uniform distribution of said active in individual dosage units of said resulting film, comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said polymer matrix through a drying apparatus and evaporating at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, wherein during said drying said flowable polymer matrix temperature is 100 °C or less;

(d) forming said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said resulting film, varies by no more than 10%; and

(e) performing analytical chemical tests for uniformity of content of said active in said substantially equal sized individual dosage units of said sampled resulting film, said tests indicating that uniformity of content in the amount of said active varies by no more than 10% and said resulting film is self-supporting and suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration.

317. (New) A process for manufacturing a resulting film which is self-supporting and suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said film having a substantially uniform

distribution of components comprising a substantially uniform distribution of said active in individual dosage units of said resulting film, comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus using air currents, which have forces below a yield value of said flowable polymer matrix during drying, to evaporate at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said visco-elastic film, varies by no more than 10%, and wherein during said drying said flowable polymer matrix temperature is 100 °C or less;

(d) forming said resulting film from said visco-elastic film by further controlling drying by continuing evaporation to a water content of said resulting film of 10% or less and wherein said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said resulting film, varies by no more than 10%; and

(e) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units of said sampled resulting film, said tests indicating that uniformity of content in the amount of said active varies by no more than 10% and said resulting film is self-supporting and suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration.

318. (New) A process for manufacturing a resulting film which is self-supporting suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said film having a substantially uniform distribution of components comprising a substantially uniform distribution of said active in individual dosage units of said resulting film, comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus using air currents, which have forces below a yield value of the polymer matrix during drying, to evaporate at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, such that uniformity of content in the amount of said active in substantially equal sized individual dosage

units, sampled from different locations of said visco-elastic film, varies by less than 5%, and wherein during said drying said flowable polymer matrix temperature is 100 °C or less;

(d) forming said resulting film from said visco-elastic film by further controlling by continuing evaporation to a water content of said resulting film of 10% or less and wherein said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said resulting film, varies by less than 5%; and

(e) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units of said sampled resulting film, said tests indicating that uniformity of content in the amount of said active varies by less than 5% and said resulting film is self-supporting and suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration.

REMARKS

I. Description of the '080 Patent and Patentee's Response

The '080 Patent is presently under reexamination. Claims 1-299 were issued in the '080 Patent; these claims, subject to reexamination, were rejected in the Office Action dated November 29, 2012 ("Office Action"). In Patentee's Response to Office Action dated March 13, 2013 ("Patentee's ROA"), claims 12, 16, 91, 95, 173, 177, 254, 255, 257, 272, 273, 275, 290, 291, and 293 were canceled and claims 300 through 318 were added. Patentee hereby explicitly maintains its arguments from Patentee's ROA.

In the ACP, the Patent Reexamination Specialist ("Specialist") rejected all pending claims. The Specialist's rejection of all the claims is respectfully traversed in all respects. Nevertheless, claims 1, 82, 161 and 315-318 have been amended in an effort to advance the prosecution of the present reexamination. Entrance of these amendments is respectfully requested and was necessitated by the additoin of new references and is believed to place the claims in condition for allowance and/or better condition for appeal.

Claims 1, 82, 161 and 315-318 have been amended in an effort to advance the prosecution of the present reexamination and to address rejections made by the Specialist based on new references. See ACP, pp. 3, 48-51. The new references namely, Arter (U.S. 4,365,423) and Strobush (U.S. 5,881,476), address non-self-supporting coatings and not the self-supporting films of the present invention. To address advance the prosecution, Patentee herein has amended all independent claims to require that the resulting films be self-supporting. In accordance with the '080 Patent, "[d]esirably, the films will also be self-supporting or in other words able to maintain their integrity and structure in the absence of separate support." '080 Patent, col. 26, ll. 4-7. Again, this amendment is being made to advance prosecution, since as is apparent, a coating by definition requires a substrate to which it is attached and the films of the present

invention are not coatings, but films from which pharmaceutical active containing unit dosages are made, such unit dosages must be self-supporting.

Hence, Patentee has amended claims 1, 82, 161 and 315-318, from that submitted in Patentee's ROA:

(i) in the preambles, on the first line by inserting after "resulting film(s)" the following "which is (are) self-supporting and";

(ii) in step (f) for claim 1, and step (e) for claims 82,161 and 315-318, by inserting before "suitable for commercial and regulatory approval" the following "self-supporting and ".

Finally, to address certain concerns, with which Patentee does not agree, as expressed by the Specialist at pages 26-28 of the ACP, Patentee has additionally amended paragraph (c) of claim 318 from that submitted in Patentee's ROA by deleting reference to "at a temperature of about 60 °C and".

Claims 1, 82, 161 and 315- 318 are hereby amended in accordance with 37 C.F.R. §1.530(d) (2) & (f) and 37 C.F.R. § 116. In accordance with 35 U.S.C. § 314(a), the amendments to the claims do not enlarge the scope of the claims of the '080 Patent. Explanation of the support for these claims appears below. Entry of this amendment and reconsideration is respectfully requested.

II. Status of Claims and Support for Claim Changes Pursuant to 37 C.F.R. §1.530(e)

The status of the claims as of the date of this amendment is as follows: Claims 1-11, 13-15, 17-90, 92-94, 96-172, 174-176, 178-253, 256, 258-271, 274, 276-289, 292, 294-318 are pending. Claims 12, 16, 91, 95, 173, 177, 254, 255, 257, 272, 273, 275, 290, 291, and 293 were Canceled. Patentee thanks the Specialist for correcting the amendment by underlining the comma after the word "thereof" in claim 161. *See* ACP, p. 2. The underline appears in claim 161 hereto.

In compliance with 37 C.F.R. § 1.530(j), the amendment to claims 1, 82, 161 and 315-318 do not enlarge its scope or the scope of the original claims or introduce new matter.

Support for this amendment may be found in the '080 Patent, including:

> Desirably, the films will also be self-supporting or in other words able to maintain their integrity and structure in the absence of a separate support. '080 Patent, col. 26, ll. 4-7.
>
> The films were flexible, self-supporting and provided a uniform distribution ofthe components within the film. '080 Patent, col. 31, ll. 34-36.
>
> These films were also flexible, self-supporting and provided a uniform distribution of active which permits accuracy in dosing. '080 Patent, col. 33, ll. 1-3.

In compliance with 37 C.F.R. § 1.530(j), the additional amendment to claim 318 does not enlarge its scope or the scope of the original claims or introduce new matter.

Support for the additional amendment to claim 318 may be found in the '080 Patent, including:

> The formation of agglomerates randomly distributes the film components and any active present as well. When large dosages are involved, a small change in the dimensions of the film would lead to a large difference in the amount of active per film. If such films were to include low dosages of active, it is possible that portions of the film may be substantially devoid of any active. Since sheets of film are usually cut into unit doses, certain doses may therefore be devoid of or contain an insufficient amount of active for the recommended treatment. Failure to achieve a high degree of accuracy with respect to the amount of active ingredient in the cut film can be harmful to the patient. For this reason, dosage forms formed by processes such as Fuchs, would not likely meet the stringent standards of governmental or regulatory agencies, such as the U.S. Federal Drug Administration ("FDA"), relating to the variation of active in dosage forms.

> Currently, as required by various world regulatory authorities, dosage forms may not vary more than 10% in the amount of active present. When applied to dosage units based on films, this virtually mandates that uniformity in the film be present." '080 Patent, col. 2, ll. 27-46 (emphasis supplied).
>
> "Consideration of the above discussed parameters, such as but not limited to rheology properties, viscosity, mixing method, casting method and drying method, also impact material selection for the different components of the present invention. Furthermore, such consideration with proper material selection provides the compositions of the present invention, including a pharmaceutical and/or cosmetic dosage form or film product having no more than a 10% variance of a pharmaceutical and/or cosmetic active per unit area. In other words, the uniformity of the present invention is determined by the presence of no more than a 10% by weight of pharmaceutical and/or cosmetic variance throughout the matrix. Desirably, the variance is less than 5% by weight, less than 2% by weight, less than 1% by weight, or less than 0.5% by weight. " '080 Patent, col. 15, ll. 28-43 (emphasis supplied).

III. The Action Closing Prosecution - References and Declarations Cited

In the ACP, all pending claims 1-11, 13-15, 17-90, 92-94, 96-172, 174-176, 178-253, 256, 258-271, 274, 276-289, 292 and 294-318 of the '080 Patent were rejected in connection with one or more of the following references: Chen (WO 00/42992) ("Chen"); Staab (U.S. 5,393,528) ("Staab"); Le Person (*Chemical Engineering and Processing*, Vol. 37, pp. 257-263 (1998)) ("Le Person"); Horstmann (U.S. 5,629,003) ("Horstmann"); Arter (U.S. 4,365,423) ("Arter"); and Strobush (U.S. 5,881,476) ("Strobush").

The Specialist in the ACP also relied on several Rule 1.132 declarations submitted by both parties. Third Party Requester submitted: the Declaration of Edward D. Cohen, dated September 6, 2012 ("Cohen Declaration"); the Declaration of Jason O. Clevenger, dated April 12, 2013 ("Clevenger Declaration"); and the Declaration of Maureen Reitman, dated February 28, 2013 ("Reitman Declaration"). Patentee submitted: the Declaration of Arlie Bogue, dated March 13, 2013 ("Bogue Declaration I"); and the Declaration of David T. Lin, dated March 13, 2013 ("Lin Declaration").

IV. Declarations Submitted With This Response

For ease of reference, Patentee is including with its response a copy of the earlier entered Declaration of B. Arlie Bogue, Ph.D. under 37 C.F.R. § 1.132, dated March 13, 2013, as submitted by Patentee with the March 13, 2013 Response to Office Action ("Bogue Declaration I", Ex. 1).

Along with this response, Patentee is submitting a Rule 1.132 Declaration of B. Arlie Bogue, executed August 29, 2013 (Bogue Declaration II, Ex. 2) in connection with the Court of Appeals for the Federal Circuit's post ACP August 13, 2013 decision *Leo Pharmaceutical Products, Ltd. v. Teresa Staneck Rea, Acting Director, USPTO*, 2012-1520 (Fed. Cir. August 12, 2013) regarding the requirement to consider secondary indicia of non-obviousness, also to address, new references, exhibits and arguments made in Third Party Requester's Comments and the ACP (see, *e.g.*, pp. 3, 48-51, 79) and also to advance the prosecution of the reexamination.

V. Background of the '080 Patent

The '080 Patent is a continuation of U.S. application Ser. No. 10/856,176, filed May 28, 2004 now U.S. Pat. No. 7,666,337 (" '337 Patent"), which claims the benefit of U.S. Provisional Application No. 60/473,902, filed May 28, 2003 and is a continuation-in-part of U.S. application Ser. No. 10/768,809, filed Jan. 30, 2004 now U.S. Pat. No. 7,357,891 (" '891 Patent"), which claims benefit to U.S. Provisional Application No. 60/443,741 filed Jan. 30, 2003 and is a continuation-in-part of:

(a) PCT/US02/32575 filed Oct. 11, 2002, which claims priority to: (1) U.S. application Ser. No. 10/074,272, filed Feb. 14, 2002 now U.S. Pat. No. 7,425,292, (" '292 Patent") which claims benefit to U.S. Provisional Application No. 60/328,868, filed Oct. 12,

2001 and (2) U.S. Provisional Application No. 60/386,937, filed Jun. 7, 2002;

(b) PCT/US02/32594, filed Oct. 11, 2002, which claims priority to: (1) U.S. Provisional Application No. 60/414,276, filed Sep. 27, 2002, (2) U.S. application Ser. No. 10/074,272, filed Feb. 14, 2002, which claims benefit to U.S. Provisional Application No. 60/328,868, filed Oct. 12, 2001 and (3) U.S. Provisional Application No. 60/386,937, filed Jun. 7, 2002; and

(c) PCT/US02/32542, filed Oct. 11, 2002, which claims priority to: (1) U.S. Provisional Application No. 60/371,940, filed Apr. 11, 2002, (2) U.S. application Ser. No. 10/074,272, filed Feb. 14, 2002, which claims benefit to U.S. Provisional Application No. 60/328,868, filed Oct. 12, 2001 and (3) U.S. Provisional Application No. 60/386,937, filed Jun. 7, 2002.

There are pending applications claiming the benefit of the priority of all and/or some of the above.

The '891 Patent is involved in a U.S. litigation wherein Patentee has alleged that the Third Party Requester, BioDelivery Sciences International, Inc. ("BDSI") has infringed its '891 Patent. The litigation is Civil Action No. 10-cv-5695 in the U.S. District Court in the District of New Jersey. In the litigation, Patentee also alleged that the Third Party Requester infringed two other of Patentee's patents, U.S. 7,425,292 (" '292 Patent") and U.S. 7,824,588 (" '588 Patent").

Third Party Requester requested reexamination of the '891 Patent (90/012,098), the '292 Patent (90/012,097) and the '588 Patent (95/001,753) as well. Both the '292 and the '891 Patent successfully exited reexamination. The Specialist issued a Right of Appeal Notice ("RAN") for the '588 Patent reexamination and Patentee filed a timely Notice of Appeal. Patentee filed its Appeal Brief on June 24, 2013, Third-Party Requester filed its Brief on July 24, 2013, and the

Specialist filed his Answer on August 8, 2013. Patentee's Rebuttal Brief is due September 8, 2013.

On June 12, 2013, Third-Party Requestor, improperly, more than one year after Patentee had brought its District Court action, petitioned for *Inter Partes* Review of the '891 Patent (IPR2013-00316) and the '292 Patent (IPR2013-00315) which had recently successfully exited reexamination. The petitions are outstanding, with Patentee's Preliminary Responses due September 13, 2013.

Third Party Requester requested reexamination of another of Patentee's related patents, namely U.S. Pat. No. 7,666,337 (Control No. 95/002,171), reexamination was ordered, an Office Action issued, Patentee Replied, Third Party Requester submitted its Comments, and the Specialist issued an Action Closing Prosecution on August 9, 2013. Patentee's Response is due September 9, 2013.

Finally, Third Party Requester requested the reexamination herein of the '080 Patent. The '080 Patent has not been and is not currently involved in litigation. *See* 37 C.F.R. §1.985(a).

VI. The Patented Invention

Patentee's instant claims recite additional details about its processes for manufacturing a resulting pharmaceutical film suitable for commercialization and regulatory approval. Some of the details include: forming a flowable polymer matrix comprising a polymer, a solvent and an active, said matrix having a substantially uniform distribution of said active; casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps; controlling drying through a process comprising conveying said polymer matrix through a drying apparatus and evaporating at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said polymer matrix upon initiation of

drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film wherein the polymer matrix temperature is 100 °C or less; forming said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of said active by said locking-in or substantially preventing migration of said active is maintained, performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units of said sampled resulting film, said tests indicating that uniformity of content in the amount of the active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration; and, in the case of more than one resulting film, repeating the process for forming one film such that uniformity of content in the amount of said active across all said resulting films varies no more than 10% from the desired amount of the active as indicated by said analytical chemical tests.

A. Bogue Declarations Demonstrate Uniformity of Content and Locking-In in 4 Minutes

The inventive methods and processes of the '080 Patent maintain the desired uniformity of content of active by, *inter alia*, controlling polymer matrix viscosity and controlling the drying processes so as to form a visco-elastic film that locks-in the substantially uniform distribution of active(s) during the first about 4 minutes of drying. This ability to lock-in the substantially uniform distribution of active(s) provides the novel and non-obvious processes for manufacturing pharmaceutical and bioactive active containing films, suitable for commercialization and U.S. Food and Drug Administration ("FDA") approval. As noted in Bogue Declaration I, Ex. 1, ¶ 4, one manufactured lot of such resulting film can contain 2,000,000 individual dosage units. The claimed processes accomplish this feat while providing the necessary narrow ranges in the amount of active in individual dosage units. As claimed, the '080 Patent, at least, requires a uniformity of content in amount of active (i) in individual dosage units sampled from a resulting film of 10% or less (independent claims 1, 161 and 316-318, see

Appendix A, Bogue Declaration I, Ex. 1), and (ii) in individual dosage units sampled from two or more resulting films of 10% or less as a percent difference from a desired amount (independent claims 82 and 315, see Appendix B, Bogue Declaration I, Ex. 1).

Patentee's claimed processes keep differences between individual dosage units from one manufactured lot very small-- e.g. smaller than 10% in amount of pharmaceutical active. *See*, independent claims 1, 161 and 316-318.

Patentee's claimed processes also keep differences between individual dosage units between different manufactured lots small as well, just not necessarily as small-- e.g. smaller than a 10% difference from the standard, i.e. desired amount. *See*, independent claims 82 and 315.

Thus, in the case of a resulting film from one manufacturing lot, the substantially uniform distribution of the active is indicated through analytical chemical tests which indicate that uniformity of content in the amount of the active in substantially equal sized individual dosage units sampled from the resulting film varies by no more than 10%. See Appendix A from Bogue Declaration I copied below and Bogue Declaration I, ¶ 9, where this is shown to be true for 73 separately manufactured lots of film, all manufactured by Patentee in accordance with the claimed invention.

B. Patentee's Films are Manufactured in Accordance with the Claimed Invention thus providing , *inter alia*, the novel, non-obvious degree of uniformity of content obtained by within about the first 4 minutes of initiation of drying locking-in migration of the active within said visco-elastic film

As set forth in Bogue Declaration I, ¶ 4 (emphasis supplied).

> 4. Each of the 73 lots of resulting films (Lots 1-73) containing approximately 2,000,000 individual dosage units per lot discussed herein were manufactured: (i) for commercial use and regulatory approval; (ii) in compliance with U.S. Food and Drug Administration ("FDA") standards and regulations, including those relating to analytical chemical

testing for variation in active in individual dosage units; and (iii) in accordance with the invention disclosed in the '080 Patent, and as claimed by the '080 Patent both as issued and as amended in the Patentee's Reply to the Office Action; by:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and a pharmaceutical active, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) **controlling drying through a process comprising conveying said polymer matrix through a drying apparatus and evaporating at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film** wherein the polymer matrix temperature is 100 °C or less;

(d) forming the resulting pharmaceutical film from said visco-elastic film, wherein said resulting pharmaceutical film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained, such that uniformity of content in the amount of the active in substantially equal sized individual dosage units, sampled from different locations of said resulting pharmaceutical film, varies by no more than 10%; and

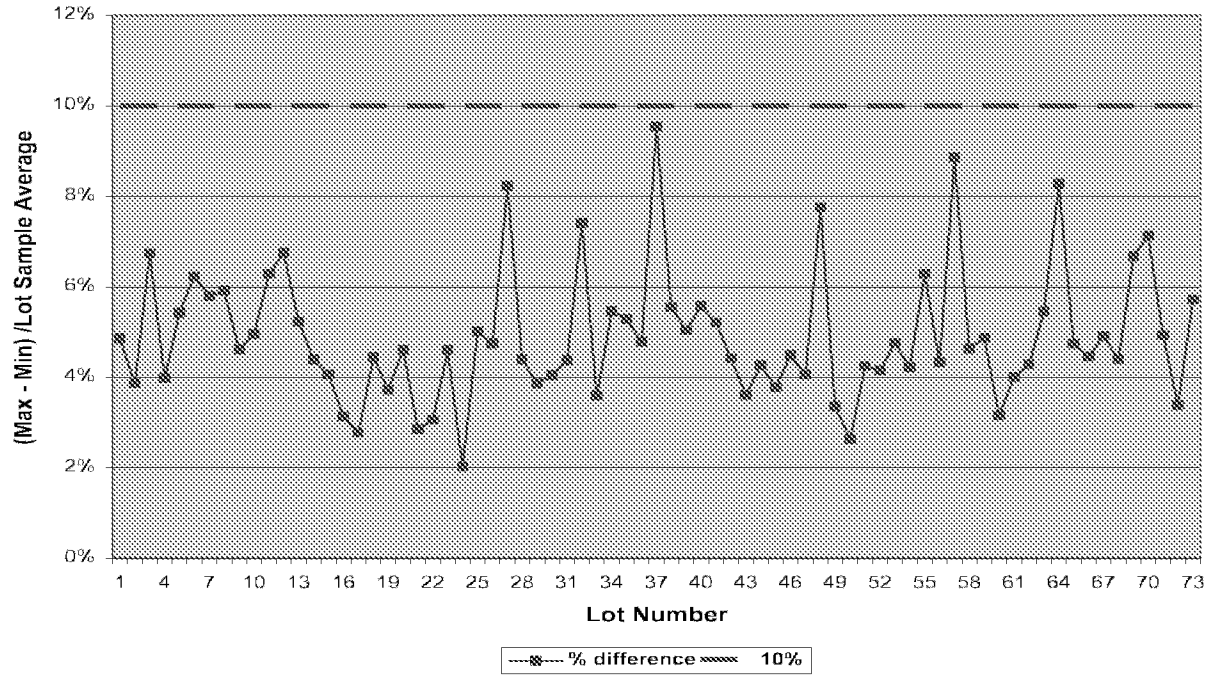
(e) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units of said sampled resulting pharmaceutical film, said tests indicating that uniformity of content in the amount of the active varies by no more than 10%, [see Appendix A] said resulting pharmaceutical film suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration.

Bogue Declaration I, ¶ 4 (emphasis supplied).

The uniformity of content of the active achieved by rapidly increasing the viscosity of said polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film is clearly demonstrated in the Appendices to the Bogue Declaration I, Ex. 1.

As claimed, the '080 Patent, at least, requires a uniformity of content in amount of active (i) in individual dosage units sampled from a resulting film of 10% or less (Appendix A), and (ii) in individual dosage units sampled from two or more resulting films of 10% or less from a desired amount (Appendix B).

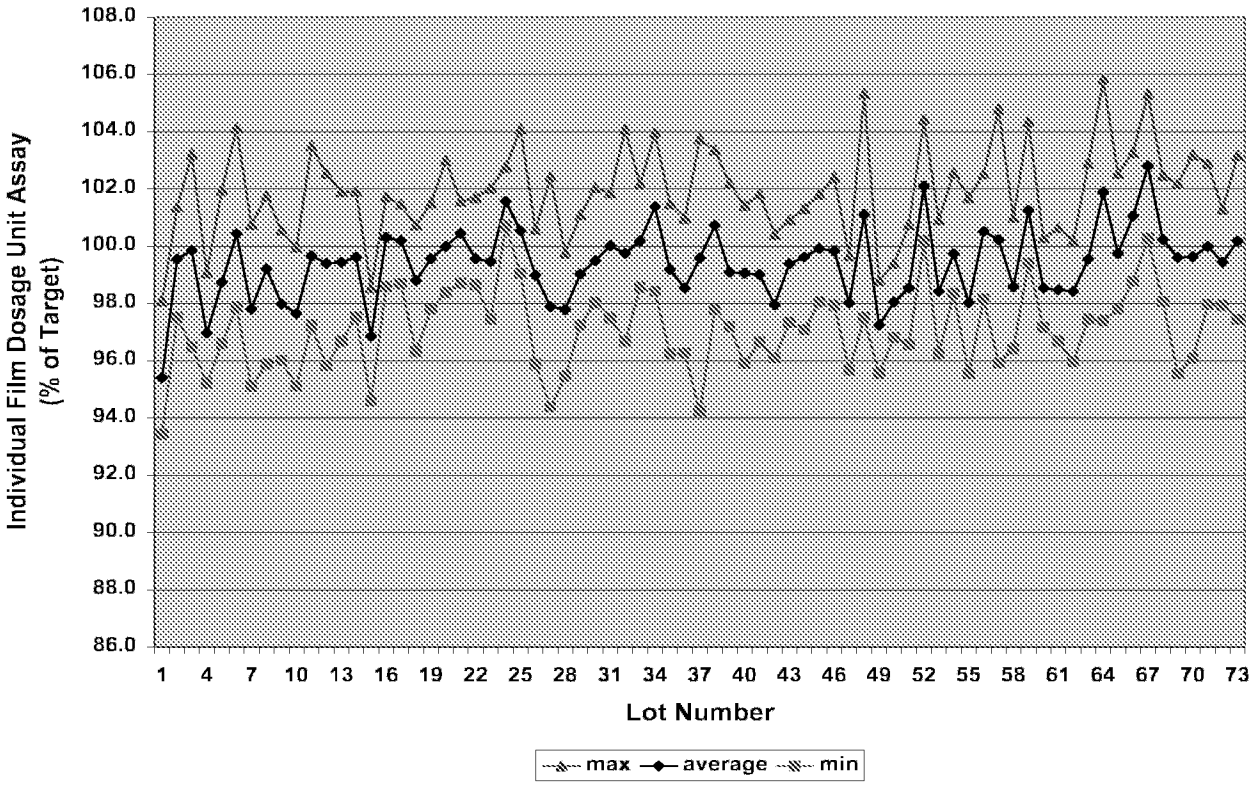
APPENDIX A (Bogue Declaration I)



Moreover, in the case of a resulting film from one manufacturing lot, the substantially uniform distribution of the active is indicated through analytical chemical tests which indicate

that uniformity of content in the amount of the active in substantially equal sized individual dosage units sampled from the resulting film varies by no more than 10%. See Appendix A from Bogue Declaration I copied above and Bogue Declaration I, ¶ 9, where this is shown to be true for 73 separately manufactured lots of film, all manufactured by Patentee in accordance with the claimed invention.

APPENDIX B (Bogue Declaration I)



In the case of resulting films from different manufacturing lots the substantially uniform distribution of the active is indicated through analytical chemical tests which indicate that uniformity of content in the amount of the active varies by no more than 10% from a desired amount. See Appendix B from Bogue Declaration I copied above and Bogue Declaration I, ¶ 10, where this is shown to be true across 73 separately manufactured lots of film, all manufactured

by Patentee in accordance with the claimed invention. The 100.0% of Appendix B above indicates the desired amount.

Hence, the manufacturing process of the '080 Patent as claimed is a commercially viable process which yields commercially viable products meeting FDA regulations, including active assaying requirements and accomplishes this, in significant part, by forming a visco-elastic film that locks-in the substantially uniform distribution of active(s) within the first 4 minutes of drying. Moreover, the film manufactured by Patentee and described in Bogue Declaration I is the commercial, FDA approved, Suboxone® sublingual unit dose film product, which Patentee manufactures exclusively for Reckitt Benckiser Pharmaceuticals Inc ("Reckitt Benckiser "). Bogue Declaration II, Ex. 2, ¶¶ 5-7. In 2012, Reckitt Benckiser had **almost one billion dollars in sales** of its Suboxone® sublingual unit dose film products manufactured in accordance with the claims of the '080 Patent. *See* full discussion below and Ex. 1, 2, 5 & 6.

C. *Leo,* a Post ACP Federal Circuit Decision, Clarifies Obviousness Determinations

Shortly after issuance of the ACP, the Court of Appeals for the Federal Circuit, in the context of an appeal in an *inter partes* reexamination, issued its opinion in *Leo Pharmaceutical Products, Ltd. v. Teresa Staneck Rea, Acting Director, USPTO*, 2012-1520 (Fed. Cir. August 12, 2013), Ex. 3 (*Leo*) clarifying obviousness determinations in cases like one involving the '080 Patent and strongly supporting Patentee's positions.

Leo concerns pharmaceutical compositions for the topical treatment treatment of psoriasis. The prior art disclosed that psoriasis can be treated through a combination of a Vitamin D analog and a corticosteroid. The *Leo* patent teaches the simultaneous treatment with vitamin D and corticosteroids can heal psoriasis faster and more effectively. The *Leo* patent taught that previous combination formulas were not storage stable because vitamin D and corticosteroids have different pH requirements. In an analogous manner, the '080 Patent

teaches that the prior art did not obtain the required level of uniformity of content because of many problems in processing.

After recognizing the problem, the Patentee in *Leo* found that a selection of solvents solved the stability problem by allow the Vitamin D and corticosteroid to coexist in a single product. Similarly, Patentee herein discovered the necessary parameter to adjust in order to obtain the required level of uniformity of content, including by drying the film so as to rapidly lock-in the required uniformity.

In reversing the PTAB (referred to as BPAI), the Federal Circuit made some holdings regarding obviousness determinations and secondary indicia of obviousness very relevant to this reexamination. This section discusses the obviousness determination, while secondary indica are discussed in the next section.

> As an initial matter, an invention can often be the recognition of a problem itself. *See Cardiac Pacemakers, Inc. v. St. Jude Med., Inc.*, 381 F.3d 1371, 1377 (Fed. Cir. 2004) ("There can of course arise situations wherein identification of the problem is itself the invention."). Here, the prior art either discouraged combining vitamin D analogs and corticosteroids in a single formulation, or attempted the combination without recognizing or solving the storage stability problems associated with the combination. *Leo*, Ex. 3, p. 11.

Prior to the '080 Patent there was no disclosure that anyone recognized there were problems with obtaining the higher degrees of uniformity of content of active in films claimed in the '080 Patent and that "locking-in" by controlled drying, among other things claimed in the '080 Patent, could successfully address the problems.

> Moreover, because neither Dikstein nor Serup [2 of the three prior art references cited against the *Leo* patent] recognized or disclosed the stability problem, the record shows no reason for one of ordinary skill in the art to attempt to improve

> upon either Dikstein or Serup using Turi. The ordinary artisan would first have needed to recognize the problem, i.e., that the formulations disclosed in Dikstein and Serup were not storage stable. To discover this problem, the ordinary artisan would have needed to spend several months running storage stability tests. *Leo*, Ex. 3, p. 13.

Moreover, since except for Le Person (and Le Person merely identified a problem, its complexity, the strict requirement for including assaying, but did not solve it (Le Person, *see e.g.*, p. 257)), none of the other prior art references Chen, Staab, Strobush, Horstmann and/or Arter recognized the problem with obtaining the higher levels of uniformity of content, the record shows no reason for one of ordinary skill in the art to attempt to improve upon each other by combining their disclosures. All these references merely assumed uniform content, and that is how they stated it. Moreover, none of Chen, Staab, Strobush, Horstmann and/or Arter refer to Le Person so they would not be aware of the problem by that means, but even if they had they failed to address it.

The *Leo* court goes on to discuss undue experimentation, see discussion below regarding this holding of *Leo* in connection with statements made by the Specialist in rejecting Patentee's claims as obvious for the skilled artisan to optimize the many parameters that needed to be adjusted to disclose the '080 Patent. Then *Leo* reiterates that without recognition of the problem, there could be no optimization, because they would not have known to even try to solve it.

> The problem was not known, the possible approaches to solving the problem were not known or finite, and the solution was not predictable. Therefore, the claimed invention would not have been obvious to try to one of ordinary skill in the art. **Indeed ordinary artisans would not have thought to try at all because they would not have recognized the problem.** *Leo*, Ex. 3, pp. 17-18 (emphasis supplied).

In the same way the claims of the '080 Patent are not obvious.

Finally the court noted:

> This court and obviousness law in general recognizes an important distinction between combining known options into "a finite number of identified, predictable solutions," *KSR*, 550 U.S. at 421, and "'merely throwing metaphorical darts at a board' in hopes of arriving at a successful result," *Cyclobenzaprine,* 676 F.3d at 1071 (quoting *In re Kubin*, 561 F.3d at 1359). While the record shows that, as early as 1995, the prior art indicated that both vitamin D analogs and corticosteroids were effective treatments for psoriasis, see J.A. 610, 6237, that same prior art gave no direction as to which of the many possible combination choices were likely to be successful. *Leo*, Ex. 3, p. 18.

Leo goes on to discuss secondary indica of non-obviousness. This discussion appears in the next section.

D. *Leo*, Commercial Success Demonstrates Non-Obviousness of '080 Patent

The Federal Circuit went further in its obviousness discussion to hold that objective indicia of non-obviousness must be given its proper weight and place and not treated as an afterthought.

> Whether before the Board or a court, this court has emphasized that consideration of the objective indicia is *part of* the whole obviousness analysis, not just an afterthought. *See Cyclobenzaprine*, 676 F.3d at 1075–76 (A fact finder "may not defer examination of the objective considerations until after the fact finder makes an obviousness finding." (quoting *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530 (Fed. Cir. 1983))). *Leo*, Ex. 3, p. 19.

> Objective indicia of nonobviousness play a critical role in the obviousness analysis. They are "not just a cumulative or confirmatory part of the obviousness calculus but constitute[] independent evidence of nonobviousness." *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1365 (Fed. Cir. 2008). This case illustrates a good reason for considering objective indicia as a critical piece of the obviousness analysis: Objective indicia "can be the most probative evidence of nonobviousness in the record,

> and enables the court to avert the trap of hindsight." *Crocs, Inc. v. Int'l Trade Comm'n*, 598 F.3d 1294, 1310 (Fed. Cir. 2010) (internal quotation marks omitted). Here, the objective indicia of nonobviousness are crucial in avoiding the trap of hindsight when reviewing, what otherwise seems like, a combination of known elements. *Leo*, Ex. 3, p. 20.
>
> Leo Pharmaceuticals provided other objective indicia of nonobviousness. For example, the commercial success of Leo Pharmaceutical's Taclonex® ointment is a testament to the improved properties of the '013 patent's claimed invention. Taclonex® is the first FDA-approved drug to combine vitamin D and corticosteroids into a single formulation for topical application. While FDA approval is not determinative of nonobviousness, it can be relevant in evaluating the objective indicia of nonobviousness. *See Knoll Pharm. Co., Inc. v. Teva. Pharm. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004). Here, FDA approval highlights that Leo Pharmaceutical's formulation is truly storage stable, something that the prior art formulations did not achieve. *Leo*, Ex. 3, p. 21.

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Patentee's patents, including the '080 Patent, all follow a path very similar to that in *Leo*, namely, the inventors recognized and solved the problem of how to achieve a high degree of uniformity of content, that the prior art neither recognized nor attempted to solve. Patentee's commercial success story and the long felt need are equally as compelling as *Leo*'s. **The FDA approval of the various Suboxone® sublingual unit dose film products highlights the uniformity of active content that prior art formulations did not achieve.**

Take as a starting point, Chen (WO 00/42992) cited in the ACP against the '080 Patent. Chen (WO 00/42992) was published July 27, 2000. The following year an article was published, it was entitled "Fast-dissolving intraoral drug delivery systems," *Expert Opin., Ther. Patents, 11(6): 981-986* (2001 © Ashley Publications Ltd, ISSN 1354-3776) ("Expert. Opin.", Ex. 4). It was authored by Alfred C. Liang & **Li-lan H Chen**, both of Lavipharm Laboratories, Inc. Li-lan H. Chen was also the lead co-inventor on the Chen reference (WO 00/42992), while Lavipharm Laboratories, Inc. was the applicant of record for the Chen reference. The '080 Patent was published in 2005. Importantly, Alfred C. Liang & Li-lan H Chen in their article

made several relevant points about the state of the technology, the state of technology **after** the Chen (WO 00/42992) was published.

> Fast-dissolving drug delivery is rapidly gaining interest in the pharmaceutical industry. . . . Finally, an emerging novel dosage form, a quick dissolving film, is discussed. . . . . Novel oral fast dissolving drug delivery systems . . . have generated tremendous business interest because of their potential to provide line extensions in the marketplace. . . . Fast-dissolving technology is growing, but there are very few published scientific articles discussing the technology. This is mainly because most technologies have been initiated and developed by the pharmaceutical industry and this proprietary information is only available in patent literature. Expert. Opin, Ex. 4, pp. 981-982.

> Besides the fast-dissolving tablets described above, there are also a few patents that disclose fast-dissolving thin films for pharmaceutical and cosmetic use. The advantage of a film . . . is that the risk of choking and the fear of taking solid tablets, which are still very much in existence with fast dissolving tablets, are completely eliminated in a film form. . . . Chen *et.al.* [reference 137 in the article, this is the Chen reference cited against the '080 Patent] described a simpler quick-dissolving film, which was suitable for both oral and mucosal delivery [137]. The film . . . was composed of highly water-soluble film-forming polymers with mucoadhesive properties, a plasticiser, and an active ingredient. It can be manufactured using conventional solvent coating, extrusion and semi-solid casting. Expert. Opin, Ex. 4, p. 985.

> Fast-dissolving drug delivery is no doubt a revolutionary and promising route of drug administration . . . . This explains the extensive research activity going on in this field. Each of the systems discussed in this review paper has its own limitations. A perfect fast-dissolving system does not exist as yet. . . . . In view of the above challenges associated with tablets, alternative dosage forms are being evaluated, and recently thin films became an option. . . . However, taste-masking remains a major challenge. Dose loading is also highly restricted, since rapid disintegration relies on the thickness of the film.

> **Although promising results have been achieved, a perfect fast-dissolving drug delivery system has not yet been developed. An ideal fast-dissolving drug delivery system should possess the following properties: high stability, transportability, good patient acceptability, ease of handling and administration, robustness in accommodating high dosage ranges and drug properties, and no specialized packaging and processing**

> **requirements. Undoubtedly, intense research is ongoing [2001] to achieve this ideal fast-dissolving system.** Expert. Opin, Ex. 4, pp. 985-986 (emphasis supplied).

However, it was Patentee who recognized the problems associated with achieving uniformity of content of active in film dosage units for use in commercially manufactured and FDA approvable pharmaceutical products, and it was Patentee who first solved these problems, now described in its inventions and patents, including the '080 Patent!

Currently, Patentee manufactures (among other products produced in accordance with the '080 Patent) Suboxone® sublingual unit dose film products. These FDA approved unit dose film drug products are manufactured for Reckitt Benckiser Pharmaceuticals Inc. ("Reckitt Benckiser ") in accordance with the '080 Patent. *See* Bogue Declaration II, ¶¶ 5-7.

As to the extraordinary commercial success of these products, by the end of 2012 Reckitt Benckiser's Suboxone® sublingual unit dose film products had 64% market share of the total Suboxone® drug products market which included Suboxone® tablets. In 2012 , sales in this market totaled $1,491,597,000. *See* Ex. 5&6.

Thus, assuming a 64% share of the $1,491,597,000 market or $954,622,000, **sales of the Reckitt Benckiser's Suboxone® sublingual unit dose film products manufactured by Patentee in accordance with the '080 Patent approached almost one billion dollars in 2012 alone**. *See* Ex. 5&6. Without the ability to make the Suboxone® unit dose film products using processes which achieve the uniformity of content as claimed, these products would not have been approved by the FDA, and no sales would be possible.

In light of the obvious commercial value, for example, of Suboxone® sublingual unit dose film products, if Chen, Staab, Le Person, Horstmann, Arter, and/or Strobush made the

process of manufacturing such film products inherent or obvious, why didn't anyone come out with the product before Patentee? Why didn't any of the many, well known pharmeceutical houses who have tremendous resources and tremendous experience in so many dosage forms do it? Why didn't anyone else become the exclusive manufacturer for Reckitt Benckiser? Why didn't Reckitt Benckiser make the film product it itself?

The answer is simple, it was **not obvious to do so.** Although film compositions were discussed in patents, no prior art discussed the uniformity of content problems nor the solutions to achieving uniformity of content of active, nor did they even have a hint of the difficulties involved. Making successful film drug products suitable for commercialization and regulatory approval was not obvious, but instead required the inventions of Patentee, including those claimed in the '080 Patent. Thus, objective secondary indicia firmly establish that the '080 Patent is neither inherent nor made obvious by any of the cited prior art.

VII. Arguments Made in Rejecting Claims are Unsupported

A. Visco-Elastic Film is defined in the '080 Patent

In the ACP, p. 76, the Specialist states that "[n]owhere does the '080 patent provide a special definition for the term 'visco-elastic film'." Respectfully, Patentee strongly disagrees. The visco-elastic film of the present invention is rapidly formed upon controlled drying of the flowable polymer matrix so as to lock-in the uniformity of content throughout the visco-elastic film.

> As mentioned above, the controlled drying process of the present invention allows for uniform drying to occur, whereby evaporative cooling and thermal mixing contribute to the rapid formation of viscoelastic film and the "locking-in" of uniformity of content throughout the film. '080 Patent, col. 44, ll. 9-14.

Thus, the '080 Patent's visco-elastic film is novel, for example, in that it is rapidly formed from the polymer matrix in accordance with the teachings of the '080 patent so as to lock-in the

desired degree of uniformity of content. Moreover, while a film may be in a visco-elastic state, and a fluid may be in a visco-elastic state, a visco-elastic fluid is NOT a visco-elastic film as disclosed and claimed in the '080 Patent. Further, while a film may be a visco-elastic film, nothing can be said about whether any actives or other components have been locked-in during the first about 4 minutes of its formation, so as to provide a specified degree of uniformity of pharmaceutical active content. Hence, the uniformity of active content present in the locking-in step(s) of the claims of the '080 Patent are directed to visco-elastic films. A visco-elastic material, let alone a visco-elastic film formed by any process which does not lock-in the content uniformity of the active cannot be compared to the '080 Patent's visco-elastic films, for purposes of inherency, novelty or obviousness.

B. Reliance on Third Party Requestor's Misrepresentations about being able to use Weight Variation instead of Assaying.

In the ACP, p. 79, the Specialist states:

> In fact, Patent Owner's Lin Declaration notes in ¶16 that "[t]esting to establish uniformity of dosage is defined in the USP under the general chapter <905>." As noted by Third Party Requester on pp. 13-14 of the Comments filed 04/12/13, "[i]f the amount of active is high enough, a Weight Variation Test is acceptable. See Exhibit K at pp. 6-7, Q&A5" Exhibit J of the Comments filed 04/12/13, which is the 2011 version of general chapter <905>, shows that weight variation involves weight measurement of dosages.

However, not withstanding Third Party Requester's or the Specialist's comments and arguments that weight variation is a method sufficient in and of itself for testing uniformity of content in the amount of pharmaceutical actives in a film drug product, these two documents actually stand for the requirement that **assays (analytical chemical testing) must always be made of film drug products**. As noted earlier, Third Party Requester's Exhibits J and K have been included as Exhibits 7 and 8 to this Response by Patentee to the Action Closing Prosecution and referred to as Chapter <905> Uniformity of Dosage Units (2011) (Ex. 7, Third Party

Requester's Ex. J) and Chapter <905> Uniformity of Dosage Units (2007) (Ex. 8, Third Party Requester's Ex. K). *See also* Bogue Declaration II, ¶¶ 10-15.

Staring with Exhibit 8, it is noted without qualification that **"Content Uniformity is the default test and may be applied in all cases. The test for Weight Variation is applicable for dosage forms specified as W1, W2, W3, and W4.**" Ex. 8, p. 1., Third Party Requester's Ex. K, p. 1 (emphasis supplied). Further, **Patentee's unit dose film** products manufactured in accordance with the '080 Patent, including its Suboxone® sublingual unit dose film products, **are not dosage forms W1, W2, W3 or W4** as disclosed in the box on page 1, first column, in Chapter <905> Uniformity of Dosage Units (2011), Ex. 7, Third Party Requester's Ex. J. Bogue Declaration II, ¶¶ 11-12.

Next, Patentee's pharmaceutical unit dose film products manufactured in accordance with the '080 Patent, including its **Suboxone® sublingual unit dose film products, are considered an "Others" dosage form for which CU or Content Uniformity with assaying is required.** See, Table 1, second column, Chapter <905> Uniformity of Dosage Units (2011), Ex. 7, Third Party Requester's Ex. J). Bogue Declaration II, ¶ 13. Importantly, **Patentee's pharmaceutical unit dose film products** manufactured in accordance with the '080 Patent, including its Suboxone® sublingual unit dose film products, **are not the "Tablets-Coated-with-a-Film" dosage forms in Table 1**, Chapter <905> Uniformity of Dosage Units (2011), Ex. 7, second column, 7, Third Party Requester's Ex. J, second column. Bogue Declaration II, ¶ 14.

Finally, Weight Variation always requires that the relevant party **"[c]arry out an assay for the drug substance(s) on a representative sample of the batch using an appropriate analytical method."** See Chapter <905> Uniformity of Dosage Units (2011), Ex. 7, p. 3, first column , Third Party Requester's Ex. J, p. 3, first column. Bogue Declaration II, ¶ 15 (emphasis supplied).

Both Chapter <905> Uniformity of Dosage Units (2011) (Ex. 7, Third Party Requester's Ex. J) and Chapter <905> Uniformity of Dosage Units (2007) (Ex. 8, Third Party Requester's Ex. K) require assaying (analytical chemical testing) for determining uniformity of "film" ("other") dosage units. Hence, prior art that does not diclose that they assayed to establish the uniformity of content of any active, cannot be relied upon to establish any level of degree of uniformity, let alone the '080 Patents claimed degrees of uniformity of content. This applies in particular to the references cited against the '080 Patent in the ACP, namely, Chen; Staab; Le Person; Horstmann; Arter; and Strobush.

Thus, Third Party Requester has not only misrepresented that weight variation may be substituted for content uniformity for pharmaceutical film dosage units, but it is clear that even weight variation requires assaying at some point and the Specialist's reliance on same to do away with the assaying (chemically analytical testing) requirement to determine the actual amount of pharmaceutical is misplaced and thus unsupported.

C. While '080 Patent Example M may not be an example of a Pharmaceutical Active, it does provide an example of an Active, in accordance with the '080 Patent.

In the ACP, at p. 79, *etc.*, the Specialist makes the distinction that "the example in the '080 patent cited by Patent Owner, *i.e.,* Example M at cols. 33-34, analytical chemical testing is used to test for the amount of one component, a red dye. However, red dye . . . is not a bioactive active or pharmaceutical active here claimed." Nevertheless, as set forth in the '080 Patent, in the section entitled Actives, no distinction is made between pharmaceutical actives and colorants actives, such as red dye. "The active components that may be incorporated into the films of the present invention include, without limitation pharmaceutical and cosmetic actives, . . . [and] colorants." '080 Patent, col. 19, ll. 40-48. Hence, it is improper to rely on the fact that the red dye active is not a pharmaceutical active to support an argument that in accordance with the '080 Patent analytical chemical testing is not required to establish the exact amount of active present.

D. Chen Figure 5 disproves any inherency argument that can be made about Chen.

The Specialist claims that Chen inherently discloses an active content of less than 10%, see, *e.g.*, ACP, pp. 36-37, 87-90. However, no proof has been provided that Chen's process examples when accurately followed by one of ordinary skill in the art and not an expert will inherently disclose or make obvious the '080 Patent as claimed. Importantly, Third Party Requester's Reitman Declaration suffers from many infirmities. The Reitman Declaration discloses that in its attempt to replicate a Chen example, they could not faithfully follow the Chen disclosure, but needed to rely on substitution of components (*e.g.*, substituing "Oxybutynin chloride" for "Oxybutynin", and "Kolliphor EL" for "Cremophor EL40") and drying conditions (*e.g.*, "backing was not looped", samples not "die cut in line"). Reitman Declaration, pp. 3-4.

In all likelihood, these substitutions were made because Reitman is declared to be an expert and not one ordinarily skilled in the art. Perhaps, other parameters of the process were also adjusted based on Reitman's inherent skill as an expert, perhaps even without any overt intention. Pointedly, Reitman does not conclude that the process she used to make the film was suitable for the commercial manufacture of pharmaceutical unit dosage films which are regulatory approvable by the FDA, and which exhibit the levels of uniformity of content in actual amount of active claimed by Patentee's processes. Moreover, as noted below in detail, Chen Figure 5 supports the opposite conclusion.

Getting back to Chen Figure 5, merely because Chen starts with a "coating solution that is a homogeneous mixture", does not mean that Chen's dry film will have a "substantially uniform content of therapeutic active composition per unit film" such that the variation of active is less than +/- 10% of the label amount of active. What happens during Chen's drying process, for example, is undisclosed and she fails to include any discussion or suggestions whatsoever on this point.

The '080 Patent teaches that achieving uniformity of content of the active in unit doses requires much more than simply producing a homogenous mixture of ingredients prior to casting and drying. For example, the Chen reference teaches a homogeneous mixture of ingredients (i.e., "a coating solution") that is then cast and dried to form a film. Chen, p. 15, ll. 19-30. However, the films of Chen do not achieve the uniformity of pharmaceutical active of +/- 10% of the deired/label amount claimed in the '080 Patent. As shown in Figure 5 of Chen, see below, which shows the amount of pharmaceutical active content of four different actives released from and therefore present in Chen's exemplary films, in six instances the amount of pharmaceutical active released from Chen's unit dose films is greater than 110% of the expected/desired amount of pharmaceutical active for that drug and thus outside the '080 Patent's claim limitations.

Indeed, notwithstanding arguments to the contrary, Chen Figure 5, shown below, supports Patentee's position that Chen does not and can not inherently disclose Patentee's uniformity of content claims. It is well settled that, "to establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. **Inherency, however, may not be established by probabilities or possibilities.** The mere fact that a certain thing may result from a given set of circumstances it not sufficient." *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999)(emphasis supplied); MPEP § 2112 IV.

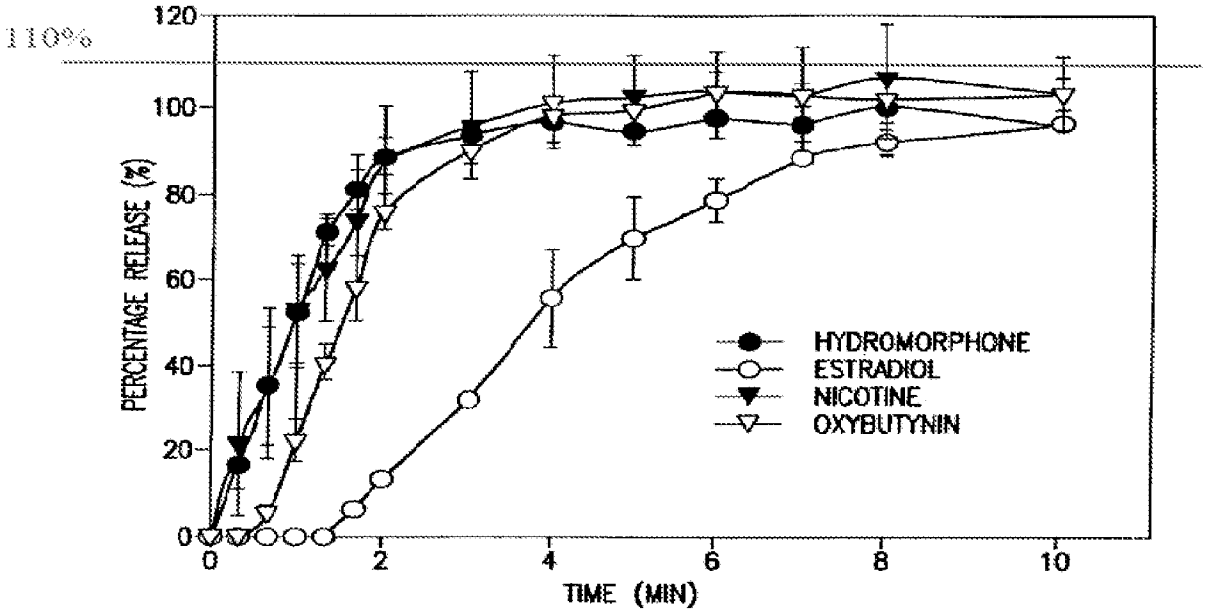

FIG.5

Chen, Figure 5 (110% line added by Patentee for clarity).

Likewise, the extrinsic evidence provided by Chen Figure 5, as noted in Patentee's Response to Office Action, demonstrates non-inherency by the non-zero probability or possibility reflected in the error bars of Figure 5, that Chen's drug dosage units unequivocally exceed the +/- 10% uniformity of drug content as claimed in the '080 Patent. Basically, it is improper to use Chen for inherency, when Chen's Figure 5 demonstrates this non-zero probability or possibility that Chen's drug dosage units exceed the '080 Patent's 10% claim limitation.

Patentee had earlier assumed a burden it did not have. Patentee had argued that Chen Figure 5 demonstrated that Chen's had drug dosage units containing more than 110% of the labeled amount for that drug active. But the burden is upon Third Party Requester and the

Specialist instead to demonstrate that Chen's Figure 5 absolutely and without possibility of error does not disclose any drug dosage units falling above the 110% line.

Pointedly, the Specialist and the Third Party Requester (or its experts) have not stated, nor can they state with absolute certainty, that there are no drug dosage units in Chen's Figure 5 which fall above the 110% line of the error bar. Again, it is their job to prove the non-existence of such drug dosage units falling above the 110% line. Understanding that any drug dosage units falling above the 110% line would necessarily have a drug content exceeding 110% of the label/desired amount of drug active.

They cannot prove this non-existence, because there is in fact a probability or possibility that Chen's Figure 5 drug samples fall in the greater than + 10% range as indicated by the error bars. Thus, no one can say with absolute certainty that there are no drug dosage units with active amounts greater than 110% of the desired amount produced by following the Chen disclosure. In other words, because there may be, and **it is highly probable** that there are drug dosage units with drug active amounts greater than 110%, Chen cannot support any claim of inherency with respect to any claim as a whole, or the steps relating to the +/-10% level of uniformity of active content or any narrower range levels.

E. Even a skilled artisan could not "minimize active content variation" or "obtain the variation of no more than 10% from the desired amount " without undue experimentation, nor could he/she ensure there was "locking-in uniformity of content within 4 minutes of initiation of drying"

The Specialist holds skilled artisans to a level of knowledge and experience to that of an expert, because only an expert could possibly "minimize active content variation" and "obtain the variation of no [more] than 10% from the desired amount," by somehow optimizing the parameters available in the prior art references, without undue experimentation. *See, e.g.*, ACP, pp. 38, 59, 69, 70, 96, 100. Importantly, none of these references discuss or even mention

"locking-in uniformity of content within 4 minutes of initiation of drying". Moreover, as discussed further below, in the case of inherency, even if the various parameters disclosed in the references cited could be manipulated to achieve such a result, their disclosure is not sufficient. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ 2d 1955, 1957 (Fed. Cir. 1993).

1. Any Chen optimization would require undue experimentation

In connection with the ability of optimizing Chen, the Specialist in the ACP asserted that:

> A skilled artisan would minimize active content variation by optimizing the available parameters in Chen's process, which are the same as or similar to those in the '337 patent specification. These include, [1]mixing/[2]degassing, [3]casting of the wet film, [4]viscosity of the wet film, [5]drying temperature, [6]drying time, [7]control of air flow in Chen's Fig. 2, [8]selection of appropriate colloid material, [9]etc. ACP, p. 38 (numbers in brackets added).
>
> It further would have been obvious to a skilled artisan at the time the invention was made to have prepared the multiple films such that the active content in each film does not vary by more than 10% from the amount of active the dosages are supposed to contain as required by various world regulatory authorities, in order to minimize dosage variation and commercialize the product. A skilled artisan would obtain the variation of no [more] than 10% from the desired amount by optimizing said available parameters in Chen's process. ACP, p. 39.

Thus, the Specialist is arguing that a "skilled artisan" could optimize at least nine (9) parameters to get the desired '080 Patent process and could do it without the teachings of the '080 Patent. But as held in *Leo*:

> In addition, the Board found that a person of ordinary skill in the art would have been capable of selecting the correct formulation from available alternatives. J.A. 12. Specifically, the Board found more than eight different classes of additives (e.g., diluents, buffers, thickeners, lubricants). J.A. 12; Serup col. 19, ll. 10–15. The Board also found more than ten different categories of composition forms (e.g., liniments, lotions, applicants, oil-in-water or water-in-oil emulsions such as creams, ointments, pastes, or gels). J.A. 12; Serup col. 19, ll. 5–9. "Based on these broad and general disclosures," the Board reasoned that an artisan would have

> been able to "mak[e] choices about what ingredients to include, and which to exclude" in formulating a composition with a vitamin D analog and steroid. J.A. 12. To the contrary, the breadth of these choices and the numerous combinations indicate that these disclosures would not have rendered the claimed invention obvious to try. *See Rolls-Royce PLC v. United Techs. Corp.*, 603 F.3d 1325, 1339 (Fed. Cir. 2010)(claimed invention was not obvious to try because the prior art disclosed a "broad selection of choices for further investigation"). *Leo*, Ex. 3, pp. 16-17.

Just consider a few of the above parameters with the range of values provided in Chen, *e.g.*: casting of a wet film with a solid content between 5 and 50% and a viscosity between 500 and 15000 cps (both at Chen, p. 15), a thickness between 1 and 20 mil (Chen, p. 13), dried under aeration at a temperature between 40 and 100°C (Chen, p. 15); and the hydrocolloid includes a polymer selected from the group consisting of a natural, semi-natural and synthetic biopolymer being exemplified by a polysaccharide and a polypeptide (Chen, p. 4).

With the above the solid content even if taken in 5 % increments gives rise to 9 variations, the thickness even if taken in 1 mil increments give rise to 20 variations, the viscosity even if taken in 500 cps increments gives rise to 29 variations, the temperature even if taken in 5°C increments gives rise to 12 variations, and the polymer even if only one from each of the three groups gives rise to 3 variations. With so many variations and potential combinations, the number of experiments potentially necessary to "minimize active content variation by optimizing the available parameters in Chen's process" is enormous, and by their sheer numbers demonstrate that such optimization would require undue experimentation. It is clear that even if, *arguendo*, Chen or the other prior art recognized the problems and attempted to solve them (which they did not), it would require a herculean effort, without Patentee's disclosure, to design and perform the experiments. Thus, the claimed '080 Patent is not obvious.

2. Any Staab optimization would require undue experimentation

In connection with the ability of optimizing Stabb, the Specialist in the ACP asserted that:

> A skilled artisan would minimize active content variation by optimizing the available parameters in Staab's process, which are the same as or similar to those in the '080 patent. These include the polymer material[1], drying temperature[2], hot air application[2], drying time[3], viscosity[4], etc.[5] . . . . ACP, pp. 59, 96.

> A skilled artisan would obtain the variation of no [more] than 10% from the desired amount by optimizing said available parameters in Staab's process. ACP, p. 59.

Again, with so many variations and potential combinations, the number of experiments potentially necessary to "minimize active content variation by optimizing the available parameters in Staab's process" is enormous, and by their sheer numbers demonstrate that such optimization would require undue experimentation. See *Leo*, Ex. 3, pp. 16-17, and discussion above.

3. Any Le Person optimization would require undue experimentation

In connection with the ability of optimizing Le Person, the Specialist in the ACP asserted that:

> A skilled artisan would minimize active content variation by optimizing the available parameters in Le Person's process, which are the same as or similar to those in the '080 patent. These include drying temperature[1], drying time[2], air velocity[3], humidity[4] etc [5] (see pp. 258-259 of Le Person). ACP, pp. 69, 100.

> A skilled artisan would obtain the variation of no [more] than 10% from the desired amount by optimizing said available parameters in Le Person's process. ACP, p. 70.

In fact Le Person comments on importance of drying to form the final thin film product and the necessity and difficulties involved in mastering the process variables and microscopic aspects of quality control.

> In the pharmaceutical industry some films are used in patches for transdermal drug delivery. Drying is the essential unit operation necessary to form the final product. In all cases, mastering of process variable and microscopic aspects of the product quality entails chemical and process engineering and transport phenomena as basic sciences. Le Person, page 257, first column.

Le Person went on to say:

> In the end, one must be sure that the selected process and its conditions is able to ensure the right product quality; a limited remanence of the process solvent (generally a mixture of volatile solvents) and a given quality product, i.e. physical and chemical homogeneity and an appropriate distribution of active substance.
>
> The tools to design the correct process are pilot plant experiments, bench scale experiments and modelisation of transfers. In this paper, small scale experiments were opted for and an experimental approach of internal transfers. Evidently, the diffusional approach of complex systems containing two immiscible solvents, a shrinking polymeric macromolecule network and an active substance, cannot be tracked from the basic text-book equations. What is modelisable is already intuitively and/or experimentally known. It would take a lot of basic investigation on simpler systems to make a substantial progress on the only problem of cross diffusivities. Le Person, page 257, first column-second columns.

Finally, Le Person went on to support Patentee's position that the only way to actually determine uniformity of content in the amount of active is through assaying (analytical chemical testing). "Adding an integral chemical analysis of the film, one is then able to quantify the absolute distribution for films produced under variable conditions." Le Person, p. 257, second column.

Hence, as explicitly acknowledged by Le Person, with so many variations and potential combinations, the number of experiments potentially necessary to "minimize active content variation by optimizing the available parameters in Le Person's process" is enormous, and by

their sheer numbers demonstrate that such optimization would require undue experimentation. *See Leo*, Ex. 3, pp. 16-17, and discussion above.

VIII. The Claim Rejections of Claim 318 under 35 U.S.C. § 112.

The Special made two rejections under § 112. In the first rejection, the Specialist rejected Claim 318 under 35 U.S.C. § 112(a) or 35 U.S.C. § 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement. The Specialist noting that "Claim 318 requires that the controlled drying is through a drying apparatus at a temperature of "about 60°C", and also requires uniformity of active varies by less than 5%. This combination of elements is found in unconnected passages of the specification and lacks adequate written description." ACP, p. 27.

In the second rejection, the Specialist rejected Claim 318 under 35 U.S.C. § 112(b) or 35 U.S.C. § 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention. The Specialist noting that "Claim 318 recites "during said drying said flowable polymer matrix temperature is 100°C or less". This is at odds with another requirement of claim 318 that the controlled drying is through a drying apparatus at a temperature of about 60°C. It is not clear how the matrix would ever reach a temperature that is 40° hotter than the drying apparatus." ACP, p. 28.

While Patentee does not agree with the reasoning or the rejections, and expressly disagrees with Third Party Requester's comments relied on by the Specialist, in order to advance prosecution, Patentee has amended paragraph (c) of claim 318 from that submitted in Patentee's ROA by deleting reference to "at a temperature of about 60 °C and". In compliance with 37 C.F.R. § 1.530(j), this amendment to claim 318 does not enlarge its scope or the scope of the

original claims or introduce new matter. Accordingly, these rejections should be withdrawn and the claim allowed to issue.

IX. The Claim Rejections under 35 U.S.C. §§ 102 and 103.

Patentee hereby incorporates the foregoing discussions into each of the following responses to the ACP rejection of claims. Moreover, due to obvious space limitations, while Patentee has for the most part addressed prior art references for the reasons they were asserted against the '080 Patent in the ACP, Patentee reserves the right to bring up the existing additional reasons why the references do not affect the patentability of the claims of the '080 Patent.

A. Rejections under 35 U.S.C. § 103(a) as being unpatentable over Chen

Claims 1-11, 13-15, 17-71, 82-90, 92-94, 96-150, 161-172, 174-176, 178-232, 243-253, 256, 258-271, 274, 276-289, 292 and 294-318 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Chen. Patentee respectfully traverses. To establish prima facie obviousness of a claimed invention, all the claim limitations much be taught or suggested by the prior art. *In re Royka*, 490 F 2d 981, 180 USPQ 580 (CCPA 1974). In this case, the Specialist has not even considered all of the elements of step (d) of Claim 1 or step (c) of Claims 82, 161 and 315-318, as required by MPEP § 2143.03.

The Specialist asserts that Chen teaches a dosage unit that includes a water-soluble hydrocolloid, mucosal surface-coat-forming film that includes an effective dose of a pharmaceutical or bioactive agent. The Specialist further asserts that the water-soluble polymer, solvent, and actives exemplified in Chen are the same as those exemplified in the `080 patent. The Specialist further asserts that, in the method of preparation of the film, Chen discloses that a hydrocolloid is dissolved in water under agitated mixing to form a uniform and viscous solution, and the additional ingredients are added under agitated mixing until they are uniformly disbursed

or dissolved in a hydrocolloid. The resultant mixture is degassed in a vacuum chamber and then cast on a polyester film. (ACP, p. 33).

With respect to steps (c) and (d) of Claims 82, 161 and 315-318, and with respect to steps (d) and (e) of Claim 1, the Specialist notes that Chen controls drying and evaporates water from the cast matrix in 9 minutes of drying in a hot air circulating oven at 50°C (citing page 17, lines 13-15 and Figure 2). The Specialist further asserts "[I]t is the Specialist's position that Chen's mixture before drying is viscoelastic." (ACP, p. 34). In particular, the Specialist notes that Chen adds the same hydrocolloid as in the `080 Patent and Chen's wet matrix before drying has a viscosity of 500-1500 cps which is within the instantly claimed range. Accordingly, the Specialist concludes, "Chen's films in Examples 1, 2 and 5-8 and the Example in Tables 7 and 8 are inherently viscoelastic before drying. Within 4 minutes of the 9 minutes of drying in Chen's Examples 1, 2, and 5-8 and Example in Tables 7 and 8, a more dry viscoelastic film is obtained." (ACP, p. 35). Thus, the Specialist concludes that steps (c) and (d) of Claims 82, 161 and 315-318 and steps (d) and (e) of Claim 1 are disclosed or suggested.

However, in making this assertion, the Specialist ignores key aspects of the elements set forth in step (d) of Claim 1 (and step (c) of Claims 82, 161 and 315-318). Step (d) of Claim 1 does not simply require that a visco-elastic state be formed. Rather, step (d) of Claim 1 also requires a visco-elastic film be formed "having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said viscoelastic film…." Thus, step (d) requires not only the creation of a **viscoelastic film** within the first 4 minutes of drying, but also rapidly increasing the viscosity upon the initiation of the drying process such that the active is locked-in or substantially prevented from migrating within the film. Chen does not teach, suggest or disclose this element. These important aspects of the claims cannot be ignored.

As indicated above, the Specialist cites page 17 and Figure 2 for the disclosure of the drying process in Chen. Figure 2 merely discloses the apparatus utilized in Chen's drying process and contains no disclosure whatsoever regarding "locking-in" or substantially preventing the migration of the active within the viscoelastic film within the first 4 minutes. Chen merely discloses on page 17, lines 13-15, "the formulation was then coated on the non-siliconized side of a polyester film at a wet thickness of 10 mil and dried in a hot air circulating oven at 50°C for 9 minutes". Thus, there is no disclosure at all in Chen of the "locking-in" element within the first 4 minutes necessary to achieve the recited the desired degree of uniformity of content of pharmaceutical active as verified by assaying unit dosages for the amount of active present.

Similarly, the Specialist cites Examples 1, 2 and 5-8 and the Example in Tables 7 and 8 to argue that the films disclosed therein are inherently viscoelastic before drying. However, even if this assertion were to be true (and there is no evidence in Chen that it is), it fails to satisfy the disclosure of the elements of step (d) of Claim 1. In other words, even if Chen disclosed a **viscoelastic film** before the end of the 9 minute drying period disclosed therein, there is no disclosure of a viscoelastic film forming within the first 4 minutes such that the active is substantially uniformly distributed throughout and locked-in to prevent subsequent migration of the active and achieve the desired level of uniformity of content of the active.

On page 35 of the ACP, the Specialist asserts that, "Alternatively, to the extent that Chen's wet film in Examples 1, 2, and 5-8 and the Example in Tables 7 and 8 before drying are not viscoelastic, then within about 4 minutes in the hot air circulating oven at 50°C, a viscoelastic film is inherently formed." Again, as indicated above, even assuming a viscoelastic state of one form or another is inherently formed, there is no disclosure or teaching in Chen that the active is "locked-in" within the first about 4 minutes by forming a viscoelastic film so as to substantially prevent the active from migrating within the film.

As discussed above, Figure 5 of Chen discloses various points of percentage release indicating the amounts of pharmaceutical active released from the drug dosage units as compared with a desired amount of drug released from the drug dosage units over time. Many of the points plotted for each of the actives, i.e., hydromorphone, estradiol, nicotine and oxybutynin; show ranges of pharmaceutical active release from the drug dosage forms well above 110% of the label/desired amount of drug active.

While, as noted above, it is not Patentee's burden to prove, these Chen prepared and tested films had present in them an amount of pharmaceutical active greater, by more than 10%, than the desired amount of pharmaceutical active. Moreover, since neither Third Party Requester nor the Specialist can prove that Chen's Figure 5 does not disclose drug dose units above the 110% line, Patentee can rely on the existence of Chen drug dosage units containing an amount of drug active exceeding the label/desired amount by more than 10%.

This additional amount of pharmaceutical active over the label/desired amount of drug active, clearly demonstrates the non-uniform distribution of the pharmaceutical active in these Chen films. *See* discussion *supra*. It is the uniform distribution of the active, locked-in during by forming a visco-elastic film within the first about 4 minutes of the drying period as set forth in the claims that permits the uniformity of content in the amount of active to vary by no more than 10% or +/- 10% of the desired amount. By Chen acknowledging a lack of uniformity content of pharmaceutical active of greater than 10% as demonstrated in Figure 5, Chen fails to lock-in or substantially prevent migration of the active within the first 4 minutes of drying. Thus, it cannot be argued that Chen inherently discloses the +/- 10 uniformity of content in amount of pharmaceutical active. *See* discussion above regarding Chen and inherency.

It is well settled that, "to establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be

established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances it not sufficient." *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999); MPEP § 2112 IV.

In view of the multitude of variations and potential combinations of processing parameters along with the excessive amounts of pharmaceutical active shown to be released and thus contained in the drug dosage units tested for content and shown in Figure 5 of Chen, it is abundantly clear that Examples 1, 2 and 5-6 and the Example in Tables 7 and 8 would **not necessarily** produce a viscoelastic film having the active substantially uniformly distributed throughout, within the first 4 minutes of drying by rapidly increasing the viscosity upon initiation of drying to maintain said substantially uniformed distribution of said pharmaceutical active by locking-in or substantially preventing migration of said active within said viscoelastic film, as claimed by the '080 Patent. Even if the various parameters disclosed in Chen et al. could be manipulated to achieve such a result, the disclosure is not sufficient. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ 2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily presented in the prior art).

The Specialist further argues that, "As an even further alternative, **if** Chen's viscoelastic film is formed after about the first 4 minutes but within Chen's 9 minute drying time, then a skilled artisan would recognize that with a higher drying temperature, a shorter time then 9 minutes can be used. In other words, a higher drying temperature then the 50°C exemplified by Chen would result in a formation of Chen's viscoelastic film product sooner." ACP, p. 35 (emphasis supplied). Significantly, the Specialist appears to be saying that Chen **does not** disclose or suggest that its viscoelastic film is formed within 4 minutes. Thus, Chen cannot inherently disclose or suggest or make obvious Patentee's claim limitation that its invention locks-in or substantially **locks-in the active in the visco-elastic films** within the first four minutes of drying. Thus, this argument again fails to consider the requirement that the active

uniformly distributed throughout the film is locked-in by rapidly increasing the viscosity upon initiation of drying within 4 minutes to maintain the substantially uniformed distribution of the active by **locking-in said active within said visco-elastic film**. Also, as described above, there is no indication that this "locking-in" would necessarily occur or even does occur in Chen. Lastly, contrary to what is stated by the Specialist, one skilled in the art would not necessarily recognize that a higher drying temperature and shorter drying time than 9 minutes could be used or would be desirable. As disclosed in the '080 Patent and known in the art, if the heat is increased too much and drying performed too quickly, the active may be destroyed, or the film may skin-over, causing the surface to be ruptured during evaporation, thereby leaving undesirable voids in the film.

All the above claims are allowable for all the reasons provided above and below where Chen is discussed. Chen does not render obvious the pending claims of this rejection.

B. Rejections under 35 U.S.C. §103(a) as being obvious over Chen and Staab

Claims 2, 3, 32, 55, 72-81, 111, 134, 151-160, 193, 216 and 232-242 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Chen and Staab. Patentee respectfully traverses. Patentee incorporates all its comments to Chen, above and Stabb, below. All the above claims are allowable for all the reasons provided in the sections dealing with Chen, above, and Staab, below and even combined Chen and Staab do not render obvious the pending claims of this rejection.

C. Rejections under 35 U.S.C. §103(a) as being obvious over Chen and Arter

Claims 317 and 318 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Chen and Arter. Patentee respectfully traverses. The Specialist relies on Chen for the reasons set forth in the rejection directly addressed in section A above. For the same reasons given by

Patentee regarding Chen above, Chen and Arter do not render obvious the pending claims of this rejection. Additionally, as noted above, Patentee has amended all independent claims to require that the resulting pharmaceutical active containing films be self-supporting. In accordance with the '080 Patent, "[d]esirably, the films will also be self-supporting or in other words able to maintain their integrity and structure in the absence of separate support." '080 Patent, col. 26, ll. 4-7. The coatings of Arter are coatings, not the self-supporting films of the '080 Patent and thus the disclosure is inapplicable. Moreover, the Specialist states at page 48 of the ACP that the "limitation in claims 317 and 318 of using air currents which have forces below a yield value of the polymer matrix during drying, the teachings of Arter strengthen the teachings of Chen." This is incorrect.

The Specialist has ignored key aspects of the step (c) in applying Chen to claims 317 and 318, namely, "to form a visco-elastic film, having said active substantially uniformly distributed throughout, **within about the first 4 minutes by rapidly increasing the viscosity** of said flowable polymer matrix **upon initiation of drying to maintain** said substantially uniform distribution of said active **by locking-in or substantially preventing migration of said active** within said visco-elastic film, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units . . . **varies by no more than 10%** . . . ". Emphasis supplied.

As previously noted, the Specialist has provided no evidence that Chen locks-in the uniformity within the about the first 4 minutes by increasing the visocosity upon initiation of drying in order to achieve the +/- 10% uniformity of content as measured by analytical chemical testing (assaying) the substantially equal sized dosage units. He merely concludes this because he assumes that Chen has achieved the +/- 10% uniformity. Chen provides no information as to what happens to his wet mixture at any point during the 9 minutes he is drying. *See* Chen, Examples 1-3. From the Chen disclosure there is no way of determining whether locking-in of the uniformity of content can or has been attained within the first 4 minutes of drying such that

when unit doses are assayed (analytical chemical testing) they do not vary by more than +/- 10% in active content.

The claim elements missing in Chen are not provided by Arter. Arter is cited for its disclosure of foraminous shields which form a "quiescent region" between the shields and the coated surface. Arter does not make or disclose films which can be used as self-supporting dosage units, instead Arter is a customized process and apparatus useful for making photographic coatings. Such a process and apparatus is not at all transferrable to drying methods for pharmaceutical films, and particularly pharmaceutical films which are aqueous-based and self-supporting.

There are several distinctions to be made between the Arter process and the present claims. First, Arter states that his objective is to prevent "mottle" or non-uniform density of surface features ("blotches"). Arter, col. 2, l. 22. Mottle is thus, an entirely different problem and characteristic from uniformity of active content expressed in the claims. Arter states, at col 4, ll. 55-60, that the shield "suppresses the evaporation rate . . . ." Evaporation which is too rapid will also disturb the surface and cause mottle. This is contrary to the claims of the '080 Patent which recite rapidly increasing the viscosity, and hence the rate of evaporation, upon initiation of drying, in order to lock-in the +/- 10 uniformity of active content as recited. Moreover, Arter states that "coating mottle" is distinct from "drying mottle", the former apparently being the appearance in the wet stage and the later being the appearance formed in drying the coating. Arter, col. 4, l. 44 - col. 5, l. 1.

Second, a coating by definition requires a substrate to which it is attached. The films of the present invention are not coatings but films from which pharmaceutical active-containing unit dosages are made, and such unit dosages must be self-supporting.

Third, the Specialist points to Examples 1 and 2 in Arter as films that are dried at 60°C for 3 and 5.2 seconds respectively. ACP, p. 49. The calculated wet thickness for Arter's Example 1 film has a wet thickness of 27 microns, and for the Example 2 film has a wet thickness of 75 microns. As stated above, Arter relates to exceptionally thin coatings, not films from which pharmaceutical dosage units can be made.

In Patentee's production of self-supporting unit dose film products, described in the '080 Patent, including its production of Suboxone® sublingual unit dose film products, the wet film thicknesses, from which the dry resulting products such as Suboxone® sublingual unit dose film products are produced, are always significantly greater in thickness than the dry resulting unit dose film products. Bogue Declaration II, ¶ 8.

Importantly, the Suboxone® sublingual unit dose film products made by Patentee, and described in Bogue Declarations I and II, have dry thicknesses ranging from approximately 110 to approximately 175 microns, depending on the particular Suboxone® sublingual unit dose film product. Hence, the wet films from which these products are made have wet film thicknesses significantly greater than approximately 110 to approximately 175 microns. Bogue Declaration II, ¶ 9.

Thus, the wet thicknesses of resulting films *(e.g.*, the self-supporting Suboxone® sublingual unit dose film products) made in accordance with the claims of the '080 Patent must be significantly greater than approximately 110 to approximately 175 microns. These wet thicknesses should be contrasted to Arter's substantially smaller wet thicknesses of 27 and 75 microns. **Hence, even dry, Patentee's films can be 5 to 7 times thicker than Arter's wet coatings.** Finally, Arter states at col. 6, ll. 30-37 that his method is most useful with relatively volatile materials and is designed for organic solvents. One skilled in the art would recognize that although Arter discloses that the coating can be an aqueous composition, his process is not

in fact designed for aqueous-based films of the thickness useful to obtain self-supporting pharmaceutical dosage units.

Again, assaying is required for demonstrating the level of content uniformity of pharmaceutical active in unit dosage films by measuring the actual amount of active present. Thus absent any determinations in Arter based on assaying, as required, *e.g.*, by Ex. 7 and Ex 8, see discussion above, Arter does not and cannot inherently disclose or make obvious Patentee's resulting film having the claimed levels of uniformity of content. Arter does not and cannot inherently form or make obvious a viscoelastic film within about the first 4 minutes, which locks-in the uniformity of content of active within the recited levels of uniformity of content. Finally, coatings such as Arter's with the disclosed wet thicknesses, are not self-supporting, while Patentee's dosage unit films must be self-supporting.

All the above claims are allowable for all the reasons provided herein and in connection with the Chen discussions above. Chen and Arter do not render obvious the pending claims of this rejection.

D. Rejections under 35 U.S.C. §103(a) as being obvious over Chen and Strobush

Claims 317 and 318 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Chen and Strobush. Patentee respectfully traverses. The Specialist relies on Chen for the reasons set forth in the rejection in section A, above. For the same reasons given by Patentee regarding Chen above, Chen and Strobush do not render obvious the pending claims of this rejection. Additionally, as noted above, Patentee has amended all independent claims to require that the resulting pharmaceutical active containing films be self-supporting. The coatings of Strobush are photographic coatings, not the self-supporting films of the '080 Patent and thus the disclosure is inapplicable. Moreover, the Specialist states at page 50 of the ACP that "limitation in claims 317 and 318 of using air currents which have forces below a yield value of the polymer

matrix during drying, the teachings of Strobush strengthen the teachings of Chen." This is incorrect.

The Specialist cites Strobush to "strengthen the teachings" but actually discloses another deficiency of Chen, that is, its failure to disclose let alone teach "using air currents which have forces below a yield value of the polymer matrix during drying". Strobush does not meet this deficiency and more importantly does not, either separately or when taken together with Chen disclose or make obvious same. At best, Strobush teaches that evaporation of the solvent must be performed very slowly (low $h\Delta T$), in multiple stages, so that the silver atoms lined up on the coating's surface are not disturbed so as to not cause a mottled appearance to the photographic coating. Strobush states "increasing the initial rate of heat transfer ($h\Delta T$), increases the severity of mottle." Strobush, col. 20, ll. 39-40. It is the $h\Delta T$ rate (heat transfer rate) which determines whether mottle will occur. Strobush, col. 20, ll. 34-37. Strobush suggests nothing about controlling the force of the air so as not to exceed a yield value of the polymer matrix during drying.

In fact, Strobush's teachings are completely contrary to Patentee's claims. The independent claims of the '080 Patent, in addition to requiring that the resulting films be "self-supporting", all require high heat transfer rates, as reflected in the language " rapidly increasing the viscosity . . . upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in . . . said active within said visco-elastic film".

Moreover, Strobush is directed to drying coatings on a substrate, wherein, *e.g*, an existing polyester substrate is coated with a photographic emulsion and top-coat solution, passed through a coating die and then dried. The coatings wet thicknesses were give in two examples:

> A polyester substrate having a thickness of 6.8 mil (173 μm) was simultaneously coated with the photothermographic emulsion and top-coat solutions at 75 ft/min (0.38 meters per second). The photothermographic emulsion layer was applied at a wet thickness of

> 3.2 mil (81.3 μm). The top-coat solution was applied at a wet thickness of 0.75 mil (19.1 μm). After passing the coating die, the coated substrate 16A traveled a distance of about 13 feet (4 meters) and passed through an entrance slot into a dryer composed of 3 zones. Strobush, col. 19, ll. 27-36 (emphasis supplied).
>
> Using the coating materials and oven described in Example 1, the photothermographic emulsion and top-coat solution were simultaneously coated at 3.6 mil (91.4 μm) and 0.67 mil (17.0 μm) respectively on 6.8 mil (173 μm) polyester substrate. Strobush, col. 20, ll. 57-58.

Thus, Strobush provides wet thicknesses if one adds both coating materials together of 100.4 microns and 108.4 microns. However, we know that the wet thickness of the '080 Patent's films which are dried into resulting films can be significantly greater than approximately 175 microns. Bogue Declaration II, ¶ 9. Thus, this wet thickness should be contrasted to Strobush's substantially smaller wet thickness of about 108.4 microns, a number which is probably even smaller once the coating passes under the coating die. **Hence, even dry, Patentee's films can be significantly thicker than Strobush's wet coatings.**

Again, assaying is required for demonstrating the level of content uniformity of pharmaceutical active in unit dosage films by measuring the actual amount of active present. Thus absent any determinations in Strobush based on assaying, as required, *e.g.*, by Ex. 7 and Ex 8, see discussion above, Strobush does not and cannot inherently disclose or make obvious Patentee's resulting film having the claimed levels of uniformity of content. Strobush does not and cannot inherently form or make obvious a viscoelastic film within about the first 4 minutes, which locks-in the uniformity of content of active within the recited levels of uniformity of content. Finally, coatings such as Strobush's with the disclosed wet thicknesses, are not self-supporting, while Patentee's dosage unit films must be self-supporting.

All the above claims are allowable for all the reasons provided herein and in connection with the Chen discussions above. Chen and Strobush do not render obvious the pending claims of this rejection.

E. Rejections under 35 U.S.C. §102(b) as anticipated by or, in the alternative, under 35 U.S.C. §103(a) as being obvious over Staab

Claims 1-5, 10, 13-15, 21, 24, 25, 32, 44-46, 54, 55, 59, 63-70, 72-75, 78-84, 89, 92-94, 100, 103, 104, 111, 123-125, 133, 134, 138, 142-149, 151-154, 157-166, 171, 174-176, 182, 185, 186, 193, 205-207, 215, 216, 220, 224-231, 233-236, 239-242, 249-252, 258-260, 267-270, 276-278, 285-288 and 294-318 stand rejected under 35 U.S.C. §102(b) as anticipated by or, in the alternative, under 35 U.S.C. §103(a) as being obvious over. This rejection is respectfully traversed. The Specialist asserts that Staab teaches the preparation of a film for local administration of an active agent in an internal body area that includes a polymer, active and solvent. With respect to steps (d) and (e) in Claim 1 and with respect to steps (c) and (d) in Claims 81, 161 and 315-318, the Specialist asserts that Staab exemplifies drying the film in a temperature regulated oven for approximately 20 minutes at 160° or for 20-40 minutes when using a continuously moving belt that enters a dryer. The Specialist concludes that "[S]ince Staab's film in the example at cols. 11-12 is inherently viscoelastic before drying, then within about the first 4 minutes of drying, a viscoelastic film having less water than before drying is formed." (ACP, p. 56).

In addition, as discussed above with regard to the Chen reference, the Specialist has failed to consider the element that the viscoelastic film, having the active substantially uniformly distributed throughout, is locked-in or substantially prevented from migrating within the viscoelastic film by rapidly increasing viscosity of the flowable polymer matrix upon initiation of drying within the first 4 minutes. Staab contains no disclosure whatsoever that such locking-in or prevention of migration of the active ingredient is occurring within the viscoelastic film

within the first 4 minutes. Thus, there is no evidence or suggestion at all in Staab of this claim requirement.

The Specialist alternatively asserts that to the extent that Staab's blended mixture before drying is not viscoelastic, then within about the first 4 minutes of the drying, a viscoelastic film is inherently formed. It is not understood on what basis the Specialist reaches this conclusion, because Staab is not only silent on this issue, it fails to suggest it. But even if, *arguendo*, Staab had disclosed or suggested it, this argument also fails to consider the "locking-in" of the active in order to maintain the substantially uniformly distribution of the active. In addition, similar to Chen, there is no indication that the parameters set forth in columns 11 and 12 of Staab would necessarily lock-in or substantially prevent migration of the active within the viscoelastic film within the first 4 minutes by rapidly increasing the viscosity of the flowable polymer matrix upon initiation of drying. To the contrary, the disclosure in Staab of an extended drying time of 20 minutes suggests that the viscosity of the matrix is not rapidly increased such that the uniform distribution of the active is locked-in and prevented from migrating within the film, as set forth in the pending claims.

Again, absent statements based on assaying, as required by by the references cited by Third Party Requester, to determine the actual uniformity of content in the amount of active present in the film, Staab does not and cannot inherently disclose or make obvious Patentee's resulting film having the claimed levels of uniformity of content, with respect to the amount of the active present in substantially equally sized individual dosage units sampled from different locations of the resulting film and/or of different resulting films. Again, Staab does not and cannot inherently form or make obvious a viscoelastic film within about the first 4 minutes, which locks-in the uniformity of content within the recited levels of uniformity of content. All the above claims are allowable for all the reasons provided herein. Stabb neither anticipates nor renders obvious the pending claims of this rejection.

F. Rejections under 35 U.S.C. §103(a) as being obvious over Staab

Claims 8, 9, 76, 77, 87, 88, 155, 156, 169, 170, 237 and 238 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Staab. Patentee respectfully traverses. The Specialist relies on Staab for the reasons set forth in the rejection in section E, above. For the same reasons given by Patentee regarding Staab above, Staab does not render obvious the pending claims of this rejection. All the above claims are allowable for all the reasons provided herein. Stabb does not render obvious the pending claims of this rejection.

G. Rejections under 35 U.S.C. §103(a) as being obvious over Le Person

Claims 82, 89, 90, 92, 161, 171, 172, 174, 274, 292, 304-311 and 313-318 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Le Person. Patentee respectfully traverses. The Specialist asserts that Le Person provides and compares several processes for the drying of pharmaceutical wet films. The films contain an acrylic adhesive polymer, solvents, and an active substance which is a pharmaceutical or drug. The Specialist further asserts that Le Person teaches that the constituents of the active phase, including the pharmaceutical drug, in the matrix are homogenously distributed citing page 262, column 2, lines 4-6. Le Person then discloses drying using infrared radiation. The Specialist further asserts that Le Person teaches a heated slab temperature of 60°C and a wind tunnel air temperature of 65°C.

Again, Patentee respectfully traverses the obviousness rejection under 35 U.S.C. §103(a). As with the Chen and Staab references, Le Person fails to teach or suggest all of the limitations of the rejected claim. More specifically, as with Chen and Staab, Le Person fails to disclose the the elements of step (d) of Claim 1 or step (c) of Claims 82, 161 and 315-318 that requires "having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of

drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film…."

The Specialist asserts Le Person discloses that after 5 minutes of drying, "the polymeric network is not turgescent and the meshes are densely packed. The polymer skeleton acts as a filter for the active substance [i.e., pharmaceutical or drug] when the system reequilibrates." (citing Le Person, p. 262, col. 2, 3rd full paragraph). The Specialist also asserts on page 65 of the ACP that Le Person also teaches "between the 5th and 10th min of drying the heavy solvent migrates…active substance, slowed down in its migration, stays in the bottom of the layer." (citing Le Person, p. 262, col. 2, last 4 lines). The Specialist asserts that the active material homogenizes and a quasi-equilibrium is obtained for the components of the active phase, taking into account evaporation of the heavy solvent (citing Le Person, p. 263, col.1, ll. 8-13). The Specialist further cites Figures 5 and 2 to demonstrate the evaporation rate of the solvents. Based upon the foregoing, the Specialist concludes on page 66 of the ACP, "Within about 4 minutes of drying, Le Person's film is inherently viscoelastic". With regard to the "locking-in" element, the Specialist asserts, "The claimed percent variation of active of no more than 10%, less than 5%, less than 2%, less than 1% and less than 0.5%, and thus also the claimed substantially uniform distribution and locking-in or substantially preventing migration are inherent in Le Person's films in view of the fact, as noted above, Le Person's active material homogenizes and a quasi-equilibrium is obtained for the components of the active phase, taking into account evaporation of the heavy solvent." ACP, pp. 67-68.

The Specialist has mischaracterized the disclosure of Le Person. Contrary to what is set forth in the ACP, Le Person, *inter alia*, does not inherently disclose locking-in or substantially preventing migration of the active within the visco-elastic film within the first 4 minutes. A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. den.*, 469 U.S. 851 (1984). In this particular

case, Le Person contains disclosure that shows that the active is not locked-in or substantially prevented from migrating within the visco-elastic film within the first 4 minutes.

For example, the Specialist cites Le Person, p. 261, col. 2, ll. 21-24 and 27-30 for the assertion that water is intensely removed from the film in the first 3 minutes of drying. However, that same paragraph of Le Person goes on to explain that the moisture removal produces a stress on the polymer skeleton. Le Person further indicates that this stress increases the water flow direction and the acrylic polymer becomes more dense. "This intense shrinkage coupled with the copolymer compaction causes a displacement of the active phase towards the bottom of the layer (Figure 7)." Le Person, p. 261, col. 2, last paragraph. Thus, contrary to any disclosure of locking-in or substantially preventing migration, Le Person discloses the drying process displacing the active ingredient within the film.

Similarly, the Specialist cites Le Person, p. 262, col. 2, ll. 4-6 for the disclosure that Le Person teaches that the constituents of the active phase, including the active, are homogenously distributed. However, the citation of page 64 of the ACP to this portion of Le Person omits the fact that the active is initially homogenously distributed. The full sentence on page 262, column 2, lines 4-6 actually states, "Initially, in the thin layer the constituents of the active phase are homogenously distributed." In the next sentence, Le Person goes on to state, "But the pharmaceutical active substance has a larger steric bulk then the heavy solvent and therefore might react differently to the stresses imposed by the skeleton of the acrylic polymer during the drying process." Thus, Le Person again is disclosing that, although the active may be initially homogenously distributed, the stresses imposed by the early drying process and different reaction by the active to such stresses can cause the active to become unevenly distributed.

In addition, the Specialist, on page 66 of the ACP, asserts that the active material homogenizes and a quasi-equilibrium is obtained for the components of the active phase, taking into account evaporation of the heavy solvent (citing Le Person, p. 263, col. 1, ll. 8-13).

However, this portion of Le Person again suggests that there is not any locking-in or substantially preventing migration of the active within the visco-elastic film within the first 4 minutes. This portion of Le Person states, "As the drying process proceeds, **the active substance**, from its strong affinity with the heavy solvent **migrates** and homogenizes in the enduction thickness. After 15 min of drying, a quasi-equilibrium is obtained for the components of the active phase, taking into account the evaporation of the heavy solvent." Emphasis supplied.

As discussed above, in order for the Specialist to satisfy inherency, he must demonstrate that the element must always and necessarily occur under the process conditions disclosed. In this case, Le Person not only fails to inherently disclosure the "locking-in" element, it suggests exactly the opposite. More specifically, Le Person indicates that although the active may initially be homogenous, it may migrate during the early drying process. This disclosed movement of the active component is contrary to what is set forth in the elements of step (d) of Claim 1 or step (c) of Claims 82, 161 and 315-318. All the above claims are allowable for all the reasons provided herein. Le Person does not render obvious the pending claims of this rejection.

X. CONCLUSION

The Specialist has cited Chen, Staab, Le Person, Strobush, Horstmann and Arter against the '080 Patent as claimed. As discussed above, none of these references however combined inherently or otherwise makes obvious the '080 Patent. None disclose inherently or make obvious the +/- 10% or better uniformity of active content levels claimed by the '080 Patent. Levels of uniformity which, based not only on Patentee's claims and disclosure, but also the national standards applicable to determining uniformity of content of unit dosage films (*See, e.g.*, Ex. 7 and Ex. 8), can only be established through the use of analytical chemical testing (assaying) to determine the actual amount of active present in the unit dosage film products.

While Staab, Arter and Strobush provide no disclosure or suggestion of assaying, Chen's disclosure (Figure 5), demonstrates the lack of +/- 10% or better uniformity of active content, and Le Person though stating that assaying as well as other technologies are needed to do an appropriate analysis, concludes that the films studied demonstrated the lack of uniformity of content. Importantly, there is no reason to combine these references. None even acknowledge there was a problem making self-supporting pharmaceutical unit dose film products; and none provided or suggested the solution, which includes, *inter alia*, drying in a manner such that the components are locked-in the visco-elastic film within the first 4 minutes of drying. None of these references, alone or in combination, make the claims of the '080 Patent non-patentable and they should be allowed to issue.

Entry of the amendment herein is respectfully requested. Patentee traverses all rejections of its claims. For at least the reasons set forth above, the pending independent claims 1, 82, 161, and 315-318 are allowable. The pending dependent claims 2-11, 13-15, 17-81, 83-90, 92-94, 96-160, 162-172, 174-176, 178-253, 256, 258-271, 274, 276-289, 292 and 294-314 are allowable at least based on their dependencies, whether direct or indirect, from independent Claims 1, 82, 161. Accordingly, Applicant respectfully requests that the Specialist reconsider and withdraw the rejections to same. Should the Specialist have any questions regarding this response, the undersigned would be pleased to address them.

Respectfully submitted,

/Daniel A. Scola, Jr./

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Attorneys for Patentee

HOFFMANN & BARON, LLP
6900 Jericho Turnpike
Syosset, New York 11791 (973) 331-1700

CERTIFICATE OF FIRST CLASS SERVICE

It is certified that a copy of this **RESPONSE BY PATENTEE TO ACTION CLOSING PROSECUTION**, including all Exhibits and Declarations, has been served, by first class mail, on September 3, 2013, in its entirety on the third party requester as provided in 37 CFR § 1.903 and 37 CFR § 1.248 at the address below.

DANIELLE L. HERRITT
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265 FRANKLIN STREET
BOSTON, MASSACHUSETTS 02110

/Michael I. Chakansky/
Michael I. Chakansky
Registration No.: 31,600
Attorney for the Patentee

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patentee:	Yang et al.	Specialist:	Diamond, Alan D.
Patent No.:	U.S. 7,897,080	Group Art Unit:	3991
Reexamination Control No.:	95/002,170	Confirmation No.	6418
Filed:	September 10, 2012	H&B Docket:	1199-26 RCE/CON/REX
Dated:	September 3, 2013	M&E Docket:	117744-00023

RESPONSE BY PATENTEE TO ACTION CLOSING PROSECUTION

EXHIBITS

DRL - EXHIBIT 1007
DRL995

Exhibit 1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patentee:	Yang et al.	Examiner:	Diamond, Alan D.
Patent No.:	U.S. 7,897,080	Group Art Unit:	3991
Reexamination Control No.:	95/002,170	Confirmation No.	6418
Filed:	September 10, 2012	H&B Docket:	1199-26 RCE/CON/REX
Dated:	March 13, 2013	M&E Docket:	117744-00023

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Central Reexamination Unit
Commissioner for Patents
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

Certificate of EFS-Web Transmission
I hereby certify that this correspondence is being transmitted via the U.S. Patent and Trademark Office electronic filing system (EFS-Web) to the USPTO on
March 13, 2013.
Signed: Michael I. Chakansky /Michael I Chakansky/

DECLARATION OF B. ARLIE BOGUE, PH.D. UNDER 37 C.F.R. § 1.132

Madame:

I, B. Arlie Bogue, Ph.D., do hereby make the following declaration:

I. Technical Background

1. I have worked in the field of pharmaceutical development, and particularly oral dosage form development, for 22 years. I am employed by MonoSol Rx, LLC. ("Patentee" and/or "MonoSol"), the assignee of issued patent U.S. 7,897,080 ("the '080 Patent"), as Senior Director for Manufacturing Strategy and Innovation.

2. I have a BS in Physical Chemistry from Colorado State University and a Ph.D. in Chemical and BioEngineering from Arizona State University. I have participated in postdoctoral studies in Biochemical Engineering at the University of Virginia. During my career, I have been named as an inventor on over 23 U.S. patents and numerous foreign patents directed to the formulation,

processing and/or packaging of pharmaceutical oral disintegrating unit doses (tablets and film strips). I have direct experience with the commercial scale processing of pharmaceutical film systems as well as an understanding of the uniformity of content of active and methods for testing the same.

3. I have read the '080 Patent and the Office Action issued on November 29, 2012 in the reexamination of the '080 Patent ("Office Action") and the references cited therein, and I have also reviewed the amendment as to the independent claims set forth in Patentee's Reply to the Office Action concurrently filed herewith.

II. Producing resulting films in accordance with the '080 Patent

4. Each of the 73 lots of resulting films (Lots 1-73) containing approximately 2,000,000 individual dosage units per lot discussed herein were manufactured: (i) for commercial use and regulatory approval; (ii) in compliance with U.S Food and Drug Administration ("FDA") standards and regulations, including those relating to analytical chemical testing for variation in active in individual dosage units; and (iii) in accordance with the invention disclosed in the '080 Patent, and as claimed by the '080 Patent both as issued and as amended in the Patentee's Reply to the Office Action; by:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and a pharmaceutical active, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said polymer matrix through a drying apparatus and evaporating at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film wherein the polymer matrix temperature is 100 °C or less;

(d) forming the resulting pharmaceutical film from said visco-elastic film, wherein said resulting pharmaceutical film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained, such that uniformity of content in the amount of the active in substantially equal sized individual dosage units, sampled from different locations of said resulting pharmaceutical film, varies by no more than 10%; and

(e) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units of said sampled resulting pharmaceutical film, said tests indicating that uniformity of content in the amount of the active varies by no more than 10%, [see Appendix A] said resulting pharmaceutical film suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration.

5. Additionally, the uniformity of content in the amount of active as sampled from the 73 lots of resulting film varies no more than 10% from the desired amount of the active as indicated by said analytical chemical tests from 4(e) above. [See Appendix B]

III. Analytical Chemical Testing for Uniformity of Content of Patentee's Resulting Films

6. To demonstrate the uniformity of individual dosage unit films, I compiled individual dosage unit assay data for individual Lots 1- 73, all of which were disclosed in MonoSol's 2012 Annual Product Review to the FDA.

7. Ten (10) individual dosage units all having the same dimensions were cut out from different locations of each of the 73 lots of resulting films using a commercial packaging machine, thus providing 730 randomly sampled individual dosage units, ten each from the 73 separate lots. All samples were analyzed by a validated method, in compliance with FDA guidelines and regulations regarding same, using analytical chemical testing, in which the pharmaceutical active

was extracted and analyzed by High Performance Liquid Chromatography (HPLC) against an external standard to quantify the amount of active present in each individual dosage unit.

8. According to the inventive process set forth and claimed in the '080 Patent, and in accordance with FDA nomenclature, I have prepared tables shown as Appendices A, B and C, reflecting the uniformity of content of active of individual dosage units within particular lots and across different lots.

9. First, the uniformity of content of active in a lot is determined through establishing the amount of active ($A_{N(i)}$) actually present in each sampled individual dosage unit from the same lot (N) as determined by taking the difference between the amount of active in the sample with the most active ($Max_{LOT(N)}$) minus the amount of active in the sample with the least amount of active ($Min_{LOT(N)}$) and dividing the difference by the average amount of active in the lot samples ($Lot_{(N)}$ Sample Average). That is: $(Max_{LOT(N} - Min_{LOT(N)}) / ((A_{N(1)} + A_{N(2)} + + + A_{N(10)})/10)$. The results are shown in Appendix A.

10. Second, the uniformity of content across different lots is determined through establishing the amount of active actually present in each sampled individual dosage unit from all 73 lots and comparing that amount of active with a "target" or "desired" amount of active contained therein. The target amount of active, when it is a pharmaceutical, is referred to as the "Label Claim", thus identifying the amount of pharmaceutical active in the film to a user. The desired amount is 100% of the target amount. Each individual dosage unit film cut from any individual lot must have the desired content of pharmaceutical active, varying no more that 10% from the target or desired amount. See Appendix B.

IV. <u>'080 Patent Process Produces Films With Required Uniformity of Content of Active</u>

11. The results shown in the appendices establish that the resulting films produced by the inventive method of the '080 Patent as disclosed and claimed have the required uniformity of content based on analytical chemical testing. First, the amount of active varies by no more than 10% between individual dosage units sampled from a particular lot of resulting film. See Appendix A.

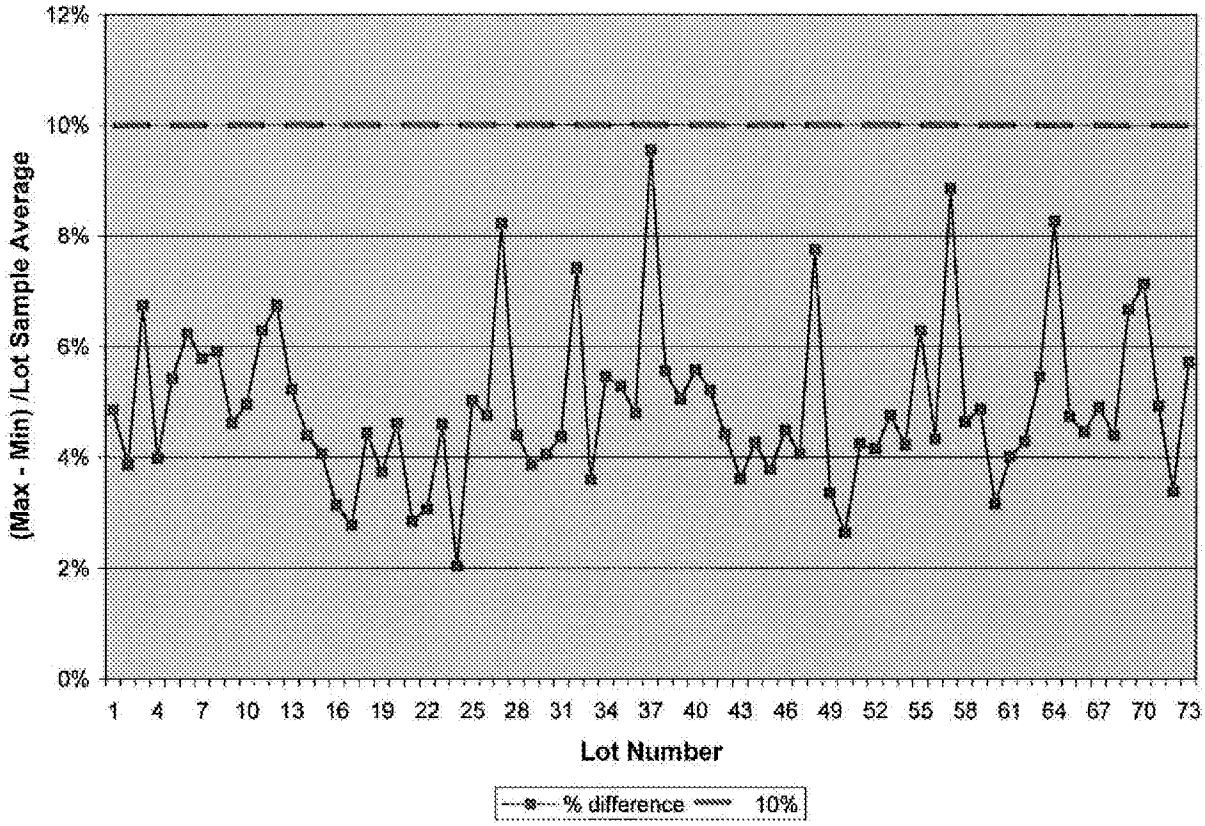
Second, the amount of active across different lots of resulting film varies no more than 10% from the desired amount of the active. See Appendix B. Finally, the uniformity of content of the 73 lots of resulting film meets even more stringent standards, for example, the data shows: (i) 46 lots of resulting film wherein the uniformity of content of active is shown with the amount of active varying by less than 5%; (ii) 15 lots of resulting film wherein the uniformity of content of active is shown with the amount of active varying by less than 4%; 4 lots of resulting film wherein the uniformity of content of active is shown with the amount of active varying by less than 3%; and 1 lot of resulting film wherein the uniformity of content of active is shown with the amount of active varying by only 2%. See Appendix C.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and. that such statements may jeopardize the validity of the application or any patents issued thereon.

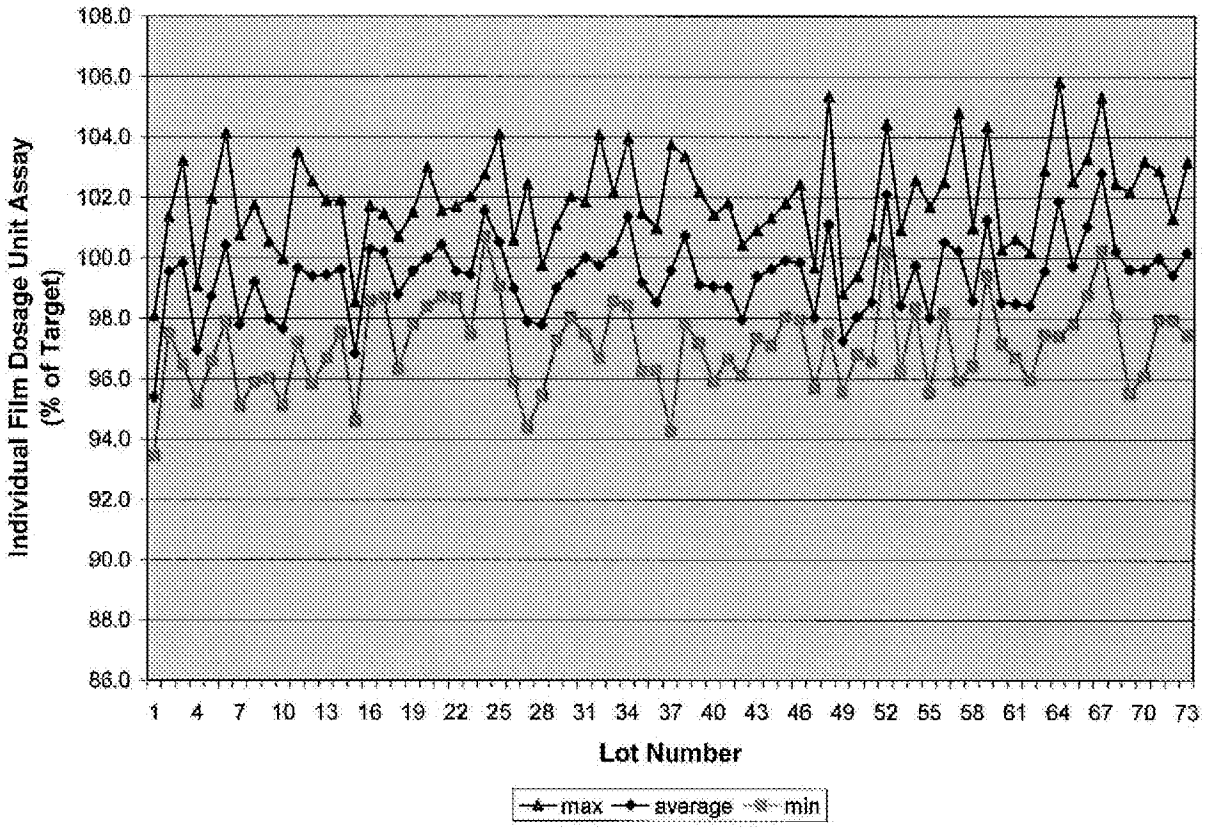
Dated this 13th day of March, 2013

B. Arlie Bogue

APPENDIX A


12%
10%
8%
6%
4%
2%
0%
(Max - Min) /Lot Sample Average
1 4 7 10 13 16 19 22 25 28 31 34 37 40 43 46 49 52 55 58 61 64 67 70 73
Lot Number
% difference
10%

APPENDIX B



APPENDIX C

Lots less than 5%			lots 5% to 10%	
Lot #	% Difference		Lot #	% Difference
24	2.0%		10	5.0%
45	2.6%		25	5.0%
17	2.8%		39	5.0%
21	2.8%		41	5.2%
22	3.1%		13	5.2%
16	3.1%		35	5.3%
60	3.2%		5	5.4%
50	3.4%		63	5.5%
72	3.4%		34	5.5%
33	3.6%		38	5.6%
43	3.6%		40	5.6%
19	3.7%		73	5.7%
46	3.8%		7	5.8%
29	3.9%		8	5.9%
2	3.9%		6	6.2%
4	4.0%		11	6.3%
61	4.0%		55	6.3%
30	4.0%		69	6.7%
48	4.1%		3	6.7%
15	4.1%		12	6.7%
52	4.2%		70	7.1%
54	4.2%		32	7.4%
51	4.2%		49	7.8%
44	4.3%		27	8.2%
62	4.3%		64	8.3%
56	4.3%		57	8.9%
31	4.4%		37	9.5%
28	4.4%			
14	4.4%			
68	4.4%			
42	4.4%			
18	4.4%			
66	4.5%			
47	4.5%			
23	4.6%			
20	4.6%			
9	4.6%			
58	4.6%			
65	4.7%			
26	4.8%			
53	4.8%			
36	4.8%			
1	4.9%			
59	4.9%			
67	4.9%			
71	4.9%			
total	46		total	27

CERTIFICATE OF FIRST CLASS SERVICE

It is certified that a copy of this **DECLARATION OF B. ARLIE BOGUE, PH.D. UNDER 37 C.F.R. § 1.132** has been served, by first class mail, on March 13, 2013, in its entirety on the third party requester as provided in 37 CFR § 1.903 and 37 CFR § 1.248 at the addess below.

DANIELLE L. HERRITT
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265 FRANKLIN STREET
BOSTON, MASSACHUSETTS 02110

/Daniel A. Scola, Jr./
Daniel A. Scola, Jr.
Registration No.: 29,855
Attorney for the Patentee

Exhibit 2

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patentee:	Yang et al.	Examiner:	Diamond, Alan D.
Patent No.:	U.S. 7,897,080	Group Art Unit:	3991
Reexamination Control No.:	95/002,170	Confirmation No.	6418
Filed:	September 10, 2012	H&B Docket:	1199-26 RCE/CON/REX
Dated:	September 3, 2013	M&E Docket:	117744-00023

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Central Reexamination Unit
Commissioner for Patents
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

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I hereby certify that this correspondence is being transmitted via the U.S. Patent and Trademark Office electronic filing system (EFS-Web) to the USPTO on September 3, 2013.
Signed: Michael I. Chakansky /Michael I Chakansky/

DECLARATION OF B. ARLIE BOGUE, PH.D. UNDER 37 C.F.R. § 1.132

Madame:

I, B. Arlie Bogue, Ph.D., do hereby make the following declaration:

I. Technical Background

1. I have worked in the field of pharmaceutical development, and particularly oral dosage form development, for 22 years. I am employed by MonoSol Rx, LLC. ("Patentee" and/or "MonoSol"), the assignee of issued patent U.S. 7,897,080 ("the '080 Patent"), as Senior Director for Manufacturing Strategy and Innovation.

2. I have a BS in Physical Chemistry from Colorado State University and a Ph.D. in Chemical and BioEngineering from Arizona State University. I have participated in postdoctoral studies in Biochemical Engineering at the University of Virginia. During my career, I have been named as an inventor on over 23 U.S. patents and numerous foreign patents directed to the formulation, processing and/or packaging of pharmaceutical oral disintegrating unit doses (tablets and film

strips). I have direct experience with the commercial scale processing of pharmaceutical film systems as well as an understanding of the uniformity of content of active and methods for testing the same.

3. My declaration dated March 13, 2013 was submitted in support of Patentee's response to the Office Action issued on November 29, 2012 in the reexamination of the '080 Patent ("Bogue Declaration I").

4. In Bogue Declaration I, I disclosed Patentee's method of producing resulting films in accordance with the '080 Patent and analytical chemical testing for uniformity of content thereof.

5. I hereby identify the resulting films in Bogue Declaration I as Suboxone® sublingual unit dose film products, and further declare that the Suboxone® sublingual unit dose film products were manufactured for Reckitt Benckiser Pharmaceuticals Inc. by Patentee, MonoSol.

6. Patentee is the exclusive source of Suboxone® sublingual unit dose film products for Reckitt Benckiser.

7. Suboxone® sublingual unit dose film products are FDA approved drug products.

8. In Patentee's production of unit dose film products, described in the '080 Patent, including its production of Suboxone® sublingual unit dose film products, the wet film thicknesses, from which the dry resulting products such as Suboxone® sublingual unit dose film products are produced, are always significantly greater in thickness than the dry resulting unit dose film products.

9. The Suboxone® sublingual unit dose film products made by MonoSol, and described in Bogue Declaration I, have dry thicknesses ranging from approximately 110 to approximately 175 microns, depending on the particular Suboxone® sublingual unit dose film product. Hence, the wet films from which these products are made have wet film thicknesses significantly greater than approximately 110 to approximately 175 microns.

10. I have reviewed the documents attached as Exhibits 7 and 8 to the Response by Patentee to the Action Closing Prosecution and referred to as Chapter <905> Uniformity of Dosage Units (2011) (Ex. 7) and Chapter <905> Uniformity of Dosage Units (2007) (Ex. 8).

11. Chapter <905> Uniformity of Dosage Units (2007), Ex. 8, specifies at p.1 that: "Content Uniformity is the default test and may be applied in all cases. The test for Weight Variation is applicable for dosage forms specified as W1, W2, W3, and W4.

12. Patentee's unit dose film products manufactured in accordance with the '080 Patent, including its Suboxone® sublingual unit dose film products are **not** dosage forms W1, W2, W3 or W4 as disclosed in the box on page 1, first column, in Chapter <905> Uniformity of Dosage Units (2011), Ex. 7.

13. Patentee's unit dose film products manufactured in accordance with the '080 Patent, including its Suboxone® sublingual unit dose film products are considered an "Others" dosage form for which CU or Content Uniformity with assaying is required. See, Table 1, second column, Chapter <905> Uniformity of Dosage Units (2011), Ex. 7.

14. Patentee's unit dose film products manufactured in accordance with the '080 Patent, including its Suboxone® sublingual unit dose film products, are **not** the "Tablets-Coated-with-a-Film" dosage forms in Table 1, Chapter <905> Uniformity of Dosage Units (2011), Ex. 7, second column.

15. **Weight Variation always requires that the relevant party "[c]arry out an assay for the drug substance(s) on a representative sample of the batch using an appropriate analytical method."** *See* Chapter <905> Uniformity of Dosage Units (2011), Ex. 7, p. 3, first column.

Dated this 29th day of August, 2013

B. Arlie Bogue

CERTIFICATE OF FIRST CLASS SERVICE

It is certified that a copy of this **DECLARATION OF B. ARLIE BOGUE, PH.D. UNDER 37 C.F.R. § 1.132** has been served, by first class mail, on September 3, 2013, in its entirety on the third party requester as provided in 37 CFR § 1.903 and 37 CFR § 1.248 at the addess below.

DANIELLE L. HERRITT
McCARTER & ENGLISH LLP
265 FRANKLIN STREET
BOSTON, MASSACHUSETTS 02110

/Michael I. Chakansky/
Michael I. Chakansky
Registration No.: 31,600
Attorney for the Patentee

Exhibit 3

United States Court of Appeals for the Federal Circuit

LEO PHARMACEUTICAL PRODUCTS, LTD.
Appellant,

v.

Teresa Stanek Rea, ACTING DIRECTOR, UNITED STATES PATENT AND TRADEMARK OFFICE,
Appellee.

2012-1520

Appeal from the United States Patent and Trademark Office, Board of Patent Appeals and Interferences in No. 95/000,153.

Decided: August 12, 2013

WILLIAM E. SOLANDER, Fitzpatrick, Cella, Harper & Scinto, of New York, New York, argued for appellant. On the brief were ANDREW D. MEIKLE , LEONARD R. SVENSSON and EUGENE T. PEREZ, Birch, Stewart, Kolasch & Birch, LLP, of Falls Church, Virginia.

AMY J. NELSON, Associate Solicitor, United States Patent & Trademark Office, of Alexandria, Virginia, argued for appellee. With her on the brief was FRANCES M.

LYNCH, Associate Solicitor. Of counsel was NATHAN K. KELLEY, Deputy Solicitor.

Before RADER, *Chief Judge,* O'MALLEY, and REYNA, *Circuit Judges.*

RADER, *Chief Judge*.

This appeal arises from an *inter partes* reexamination of U.S. Patent No. 6,753,013 (the '013 patent). The '013 patent is owned by Leo Pharmaceutical Products, Ltd. (Leo Pharmaceuticals) and challenged by third party requester Galderma R&D. While the "substantial evidence" standard of review for fact findings made by the Board of Patent Appeals and Interferences (Board)[1] makes Leo Pharmaceutical's burden on appeal a challenging one, after careful review, this court finds that Leo Pharmaceuticals has met that burden. Because the Board incorrectly construed the claim term "storage stable," this court reverses the Board's claim construction. *See Ex parte Leo Pharm. Prods., Ltd.*, No. 2012-003165 (B.P.A.I. Apr. 30, 2012). Furthermore, because the Board incorrectly found the claimed invention would have been obvious in view of the prior art and incorrectly weighed the objective indicia of nonobviousness, this court reverses the Board's obviousness determination.

I.

This case concerns pharmaceutical compositions for the topical treatment of certain skin conditions, *e.g.*,

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[1] Under the Leahy-Smith America Invents Act, Pub. L. No. 112-29 § 7(a)(1), 125 Stat. 284, 313 (2011), the Board changed its name from the Board of Patent Appeals and Interferences to the Patent Trial and Appeal Board. This court uses the prior designation for consistency with the decision below.

psoriasis. *See* '013 patent col. 1, ll. 8–10, 19–25. Psoriasis can be a painful and socially debilitating disease. The prior art discloses that psoriasis is commonly treated through a combination treatment of: (1) a vitamin D analog and (2) a corticosteroid. '013 patent col. 1, ll. 23–26.

The '013 patent teaches that simultaneous treatment with vitamin D and corticosteroids can heal psoriasis faster and more effectively. '013 patent col. 9, ll. 1–11. However, according to the '013 patent, a storage stable combination of vitamin D and corticosteroids in a single formulation did not exist in the prior art. '013 patent col. 1, ll. 29–31. The '013 patent teaches that previous combination formulations were not storage stable because vitamin D and corticosteroids have divergent pH requirements for optimum stability. '013 patent col. 1, ll. 31–36. Specifically, vitamin D analogs require basic environments with a higher pH value (above 8) for optimal stability, but corticosteroids are most stable in acidic environments with a lower pH value (in the range of 4–6). '013 patent col. 1, ll. 48–53. Because of the storage stability problem, physicians had to prescribe a two-drug regimen that required patients to apply one drug in the morning and another at night. '013 patent col. 1, ll. 61–67. This two-drug regimen generated patient compliance issues.

After recognizing the storage stability problem, Leo Pharmaceuticals began testing formulations that combined vitamin D analogs and corticosteroids. In testing formulations from the prior art, Leo Pharmaceuticals found that several ingredients—including almond oil, propylene glycol, and water—did not solve the problem. *See* J.A. 566–68 (aqueous alcohol-based solvents); J.A. 561–63, 570 (propylene glycol and almond oil). Leo Pharmaceuticals then discovered that a new set of solvents, including polyoxypropylene 15 stearyl ether (POP-15-SE), solved the storage stability problem by allowing

the vitamin D analog and the corticosteroid to coexist in a single pharmaceutical product.

The '013 patent claims a pharmaceutical composition comprising three components: a category A component (vitamin D analog); a category B component (corticosteroid); and a category C solvent. '013 patent col. 12, ll. 23–53. As amended during reexamination, independent claim 1 is representative:

> 1. A pharmaceutical composition for dermal use, said composition comprising:
>
> a first pharmacologically active *component A consisting of at least one vitamin D analogue* selected from the group consisting of seocalcitol, calcipotriol, calcitriol, tacalcitol, maxacalcitol, paricalcitol, falecalcitriol, 1α,24S-dihydroxy-vitamin D2, 1(S),3(R)-dihydroxy-20(R)-[((3-(2-hydroxy-2-propyl)-phenyl)-methoxy)-methyl]-9,10-seco-pregna-5(Z),7(E),10(19)-triene and mixtures thereof; and
>
> a second pharmacologically active *component B consisting of at least one corticosteroid*, wherein the difference between the maximum stability pH of said first component A and the maximum stability pH of said second component B is at least 1; and
>
> at least one *solvent component C* selected from the group consisting of:
>
> (i) compounds of the general formula $R^3(OCH_2C(R^1)H)_xOR^2$ (I) wherein x is in the range of 2-60, R^1 in each of the x units is CH_3, R^2 is straight chain or branched C_{1-20} alkyl or benzoyl, and R^3 is H or phenylcarbonyloxy;
>
> (ii) straight or branched C_{2-4}-alkyl esters of straight or branched C_{10-18}-alkanoic or -alkenoic acids;

(iii) propyleneglycol diesters with C_{8-14}-alkanoic acids; and

(iv) branched primary C_{18-24} alkanols,

wherein said pharmaceutical composition is *storage stable and non-aqueous*.

J.A. 3867 (emphases added).

Among other changes, Leo Pharmaceuticals amended claim 1 during reexamination to include the phrase "wherein said pharmaceutical composition is storage stable and non-aqueous." J.A. 3867. Leo Pharmaceuticals also added new claims 24–148, and amended and canceled other claims. Leo Pharmaceuticals contends that the commercial embodiment of the '013 patent, as amended, is the Taclonex® ointment.

The Board construed the term "storage stable" and "non-aqueous." J.A. 6. Then the Board—relying on the examiner's findings—rejected the claims of the '013 patent as obvious over three prior art references: U.S. Patent No. 4,083,974 (Turi); U.S. Patent No. 4,610,978 (Dikstein); and WO 94/13353 (Serup). J.A. 9.

Turi was filed in 1977 and is titled "Topical Steroidal Anti-Inflammatory Preparations Containing Polyoxypropyene 15 Stearyl Ether." Turi discloses pharmaceutical compositions comprising a steroid contained within a solvent, POP-15-SE, but it does not teach the use of vitamin D. Turi col. 1, ll. 58–63. Turi specifically discloses that the claimed invention *does not* contain water, gels, or alcohols. Turi col. 1, ll. 24–38. Instead, Turi discloses the use of POP-15-SE as "well known to those skilled in the art of formulating and compounding topical ointment like compositions and preparations." Turi col. 4, ll. 5–9. Turi teaches that POP-15-SE is antifungal, antibacterial, nonirritating, and lubricating. Turi col. 2, ll. 12–16. Turi further teaches that while these properties are not sufficient to provide therapeutic value, they are useful because they render additional preservatives unnecessary. Turi

col. 2, ll. 18–30. Turi's claimed invention thereby reduces exposure of tissue to chemical compounds and reduces manufacturing costs. Turi col. 2, ll. 18–30. Turi addresses neither stability concerns from combining vitamin D analogs and corticosteroids, nor the use of POP-15-SE or corticosteroids for the treatment of psoriasis.

The second prior art reference, Dikstein, was filed in 1984 and is titled "Compositions Containing 1α-Hydroxycholecalciferol for Topical Treatment of Skin Disorders and Methods Employing Same." Dikstein discloses dermatological compositions, including creams, ointments, and lotions, comprising a vitamin D analog and a corticosteroid. Dikstein col. 3, ll. 4–48. Dikstein teaches that vitamin D can treat psoriasis and that corticosteroids have side effects, but it does not teach using vitamin D to treat the side effects of corticosteroids. Dikstein col. 1, ll. 26–36; col. 2, ll. 55–60. Every example composition in Dikstein contains almond oil or propylene glycol and several also contain water. Dikstein col. 9, l. 40–col. 11, l. 60. Yet, Dikstein does not disclose or recognize the storage stability problems associated with using water, almond oil, or propylene glycol in the combination formulations. Nor does Dikstein disclose the use of POP-15-SE or any other solvent that could solve the storage stability concerns.

The third prior art reference, Serup, was filed in 1993 and is titled "Hydroxy Vitamin D3 Compounds for Treating Skin Atrophy." Serup describes a composition containing a vitamin D analog and a steroid. Serup col. 1, ll. 7–13. Serup further teaches the use of vitamin D analogs to treat skin atrophy, a well-known side effect of steroid treatment. Serup col. 1, ll. 14–15; col. 2, ll. 8–10. Atrophy is associated with reduced skin thickness—vitamin D can prevent atrophy and normalize skin thickness. Serup col. 3, ll. 3–6. Although Serup describes the benefits of using vitamin D to treat steroid-induced atrophy, Serup does not address any storage stability concerns associated with this combination. While Serup teaches that preparations

may include "creams, ointments, pastes, or gels," every example composition disclosed in Serup is aqueous, containing either purified or hot water. Serup col. 19, l. 34–col. 23, l. 15. Every example also contains almond oil, propylene glycol, or alcohol. Serup col. 19, l. 34–col. 23, l. 15. Thus, Serup does not recognize the stability problems associated with using water, almond oil, or propylene glycol in the combination formulations. Nor does Serup disclose the use of POP-15-SE or any other solvent that could solve the storage stability concerns.

Based on these three prior art references, the Board rejected claims 1, 2, 4–8, 14, 16–19, 21, 23, 39–91, and 143–146 of the '013 patent as obvious under 35 U.S.C. § 103(a). J.A. 19. The Board relied on Turi as the primary reference because Turi disclosed a category B corticosteroid and a category C solvent. J.A. 4. The Board then used Serup or Dikstein with Turi to reject various dependent claims concerning different vitamin D analogs. J.A. 9–14, 19–22.

Regarding the combination of Turi with Serup, the Board found that the reason for combining them was "for the [Turi] solvent's advantages and 'to obtain a more effective preparation without the potential of causing skin atrophy.'" J.A. 10 (quoting the examiner's reasoning). According to the Board, because both Serup and Turi describe compositions with corticosteroids, an artisan would have found the two references reasonably pertinent for the "same type of compositions with the same therapeutic purpose." J.A. 10. The Board concluded that adding vitamin D to Turi "would have been obvious to address the well-known side effects of topical steroid treatment." J.A. 10–11. The Board also found that because Serup discloses selecting ingredients that are "compatible" and "not deleterious," an artisan would have been familiar with selecting components by routinely "picking and choosing" from a list to achieve a compatible and non-deleterious preparation. J.A. 12.

Regarding the combination of Turi with Dikstein, the Board found that Dikstein "teaches the benefit of combining a vitamin D analog with a corticosteroid to achieve more complete skin healing," which was a reason to add a vitamin D analog to Turi's corticosteroid treatment. J.A. 22. The Board further concluded that the analysis for Serup also applied to Dikstein. J.A. 19–21.

The Board acknowledged that Leo Pharmaceuticals provided "extensive experimental evidence" that water, alcohol, and propylene glycol cause unacceptable degradation of vitamin D and steroid compositions. J.A. 14. However, the Board found that Turi provided explicit guidance to exclude these ingredients. J.A. 13. Specifically, the Board found that Turi excluded water, alcohol, and propylene glycol; taught that propylene glycol is "irritating to the skin" and "a nonlubricant;" and taught that POP-15-SE solved the problems associated with propylene glycol. J.A. 13 (quoting Turi col. 1, ll. 55–58). The Board also concluded that because Serup uses almond oil, but does not teach that almond oil is necessary, an artisan, at the time of the claimed invention, would have considered both compositions excluding or including almond oil to be obvious. J.A. 13–14, 23.

Addressing the objective indicia of nonobviousness, the Board found that the objective indicia did not overcome a prima facie case of obviousness. J.A. 15–17. The Board acknowledged that the claimed compositions were "adequately shown to be more storage stable than compositions formulated with certain ingredients that had been used in the prior art, such as water," "propylene glycol," and "alcohol." J.A. 15. However, the Board concluded that the "unexpected results" claimed by Leo Pharmaceuticals were not unexpected because Turi "provided explicit reason to use POP-15-SE as a solvent." J.A. 18–19. Therefore, the Board found that Leo Pharmaceuticals "did not establish that the improvement observed was unexpected to one of ordinary skill in the art in view of the strong reason to have utilized POP-15-SE." J.A. 19. Even

though the Board found that Turi did not teach POP-15-SE as a solvent to allow "vitamin D and corticosteroid to coexist," the Board nonetheless concluded that "the reason for utilizing the solvent does not have to be the same reason [the solvent] was employed by the inventors." J.A. 17 (citing *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 419–20 (2007)).

II.

This court reviews claim construction without deference. *Cybor Corp. v. FAS Techs., Inc.*, 138 F.3d 1448, 1455–56 (Fed. Cir. 1998) (en banc). "During reexamination, as with original examination, the PTO must give claims their broadest reasonable construction consistent with the specification." *In re Suitco Surface, Inc.*, 603 F.3d 1255, 1259 (Fed. Cir. 2010).

For claim construction, the portion of the representative claim at issue reads:

> 1. A pharmaceutical composition for dermal use, said composition comprising . . . [components A, B, & C] . . . wherein said *pharmaceutical composition is storage stable and nonaqueous.*

J.A. 3867 (emphasis added) (claim 1 of the '013 patent as amended during reexamination).

Although the claim term, "storage stable" is not defined in the '013 patent, the specification teaches a combination composition of a vitamin D analog, a corticosteroid, and a component C solvent, coexisting "without degradation." '013 patent col. 8, ll. 1–6. The Board construed "ability to resist degradation"—even though "ability to resist degradation" is not a claim term—to denote "that the composition is stable, i.e., not changing or fluctuating because it doesn't significantly degrade." J.A. 6 (citing http://www.merriam-webster.com/stable).

The Board then adopted a disclosure in the specification to define "storage stable." J.A. 6–7. Example two

discloses an accelerated chemical stability test "after storage for one month at 40°C and three months at 25°C and 40°C, respectively." '013 patent col. 10, ll. 54–56. This test "describes a specific stability test to determine the chemical stability of a composition comprising all three components stored for a period of time." J.A. 6; *see also* '013 patent col. 10, l. 50–col. 11, l. 56. The Board adopted this test because one of ordinary skill "would have reasonably looked to the described stability test as defining what was meant by 'storage stable.'" J.A. 6–7.

At the outset, the Board's construction of "storage stable" is impermissibly narrow because example two is just one disclosure of an accelerated stability test. Under its accepted and customary meaning, "storage stable" would include a composition that maintains its stability during its shelf life for its intended use as an approved pharmaceutical product for sale and home use by ordinary customers. *See* Appellant's Br. 30.

The Board erred by narrowing the definition of "storage stable" to something far short of its broadest reasonable meaning. The plain meaning of "storage stable" is broader than the disclosure in example two.

Accordingly, this court vacates the Board's construction. Because it is unnecessary for this court to adopt a specific alternative construction to resolve this appeal, this court declines to do so, leaving that question to a later forum where the issue is determinative.

III.

> Obviousness is a question of law based on underlying findings of fact. An analysis of obviousness must be based on several factual inquiries: (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the art at the time the invention was made; and (4) objective evidence of nonobviousness, if any.

In re Kubin, 561 F.3d 1351, 1355 (Fed. Cir. 2009); *see also Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966). This court reviews the Board's fact findings for substantial evidence. *In re Mouttet*, 686 F.3d 1322, 1330 (Fed. Cir. 2012). Based on the underlying fact findings, whether a claimed invention would have been obvious under 35 U.S.C. § 103(a) is a question of law reviewed de novo. *Id.*

As the Board acknowledges, this record does not present unresolved issues of fact. J.A. 9. Thus, at bottom, this court confronts a question of law: whether, in light of the prior art references and objective indicia of nonobviousness, the claimed invention would have been obvious to a person of ordinary skill in the art at a time just before the time of invention.

A.

Relying on Turi, Dikstein, and Serup, the Board concluded that "a skilled worker familiar with a wide range of possible ingredients to incorporate into a composition comprising a steroid and vitamin D analog" would have arrived at the '013 patent's claimed invention. J.A. 14.

The '013 patent, however, is not simply a combination of elements found in the prior art. The inventors of the '013 patent recognized and solved a problem with the storage stability of certain formulations—a problem that the prior art did not recognize and a problem that was not solved for over a decade.

As an initial matter, an invention can often be the recognition of a problem itself. *See Cardiac Pacemakers, Inc. v. St. Jude Med., Inc.*, 381 F.3d 1371, 1377 (Fed. Cir. 2004) ("There can of course arise situations wherein identification of the problem is itself the invention."). Here, the prior art either discouraged combining vitamin D analogs and corticosteroids in a single formulation, or attempted the combination without recognizing or solving the storage stability problems associated with the combination.

During reexamination, Leo Pharmaceuticals presented several medical research articles published as early as 1995 discouraging the combination of a vitamin D analog with a corticosteroid because of the stability problems of vitamin D analogs at lower pHs. *See* J.A. 612 (Knud Kragballe, *Vitamin D3 Analogues*, 13 DERMATOLOGICAL CLINICS 835, 838 (1995)); J.A. 6237 (Mark G. Lebwohl, *The Evolution of Vitamin D Analogs for the Treatment of Psoriasis*, ARCHIVES OF DERMATOLOGY, 285 (Nov. 1995)). These articles taught away from mixing topical vitamin D formulations with other drugs. *See, e.g.,* J.A. 612. Even though studies in the prior art compared the effectiveness of treating psoriasis with vitamin D versus corticosteroid, those studies did not describe combining the two into one formulation. *See id.* Researchers noted that it was "only natural" for clinicians to attempt to try combinations of vitamin D with other ingredients, but warned that vitamin D should not be combined with other drugs requiring a low pH (*e.g.*, corticosteroids). *See* J.A. 6237. These researchers recognized possible advantages from combining a vitamin D treatment with topical corticosteroids, but nevertheless they recommended a two-drug regimen where patients applied the drugs at different times of a day or on alternating days. *See id.*

Although Dikstein and Serup attempt the combination of a vitamin D analog with a corticosteroid, neither discloses or addresses the stability problems of combining vitamin D analogs and corticosteroids into one pharmaceutical formulation. As evidenced by the experiments Leo Pharmaceuticals conducted, the prior art does not teach any composition that exhibits storage stable properties. Every example disclosed in Dikstein contains either almond oil or propylene glycol. Similarly, the examples disclosed in Serup contain not only water, but also almond oil, alcohol, or propylene glycol.

Leo Pharmaceuticals presented experimental evidence to the Board that each of these ingredients harmed the storage stability of the vitamin D analog and cortico-

steroid combination. *See* J.A. 562–64, 570 (Hoy Decls. discussing propylene glycol and almond oil); J.A. 566–68 (Didriksen Decl. discussing aqueous alcohol-based solvents). For example, the use of propylene glycol as a solvent resulted in 100% degradation of the vitamin D analog. J.A. 562–564, 692–702. Similarly, the use of aqueous solvents resulted in almost complete degradation of the vitamin D analog after three months of storage—98.3% degradation in one formulation and 100% degradation in another. J.A. 710–16, 1025–26. And, when almond oil was used as a solvent, vitamin D analogs degraded 13–29% after three months of storage. J.A. 570, 723–24. The vitamin D analogs were not the only components at risk for degradation. When commercial ointments with vitamin D analogs or corticosteroids were combined, one corticosteroid degraded by 10% after four weeks and another degraded by almost 50% within 24 hours. J.A. 563; *see also* J.A. 723–24 (range of 5–12% corticosteroid degradation after 6 months of storage in combination with a vitamin D analog).

Moreover, because neither Dikstein nor Serup recognized or disclosed the stability problem, the record shows no reason for one of ordinary skill in the art to attempt to improve upon either Dikstein or Serup using Turi. The ordinary artisan would first have needed to recognize the problem, i.e., that the formulations disclosed in Dikstein and Serup were not storage stable. To discover this problem, the ordinary artisan would have needed to spend several months running storage stability tests. *See* '013 patent col. 10, l. 50–col. 11, l. 56; *see also* J.A. 545, 563–68. Only after recognizing the existence of the problem would an artisan *then* turn to the prior art and attempt to develop a new formulation for storage stability. If these discoveries and advances were routine and relatively easy, the record would undoubtedly have shown that some ordinary artisan would have achieved this invention within months of Dikstein or Serup. Instead this invention does not appear for more than a decade.

Although the Board acknowledges "compositions within the scope of the ['013 patent claims] were adequately shown to be more storage stable than compositions formulated with certain ingredients that had been used in the prior art," the Board went on to find this evidence insufficient "to overcome the strong case of obviousness." J.A. 15. By brushing aside the storage stability issue, the Board erred by collapsing the obviousness analysis into a hindsight-guided combination of elements. This record, however, discloses several reasons that a person of ordinary skill in the art would not have been motivated to try, let alone make, the claimed invention of the '013 patent.

First, the Board found motivation to combine Dikstein or Serup with Turi because one of ordinary skill would have used vitamin D to solve the well-known side effects of steroid treatment. However, combining Turi and vitamin D to address the side effects of a steroid treatment is only straightforward in hindsight. Turi was publicly available in the prior art for twenty-two years before the '013 patent was filed, yet there is no evidence that anyone sought to improve Turi with vitamin D. According to the record, even when Serup published the well-known side effects of steroid-induced atrophy in 1994, no one—including Serup—sought to improve Turi by adding vitamin D to Turi's corticosteroid composition. Serup even targeted the precise side effects that the Board believed would have motivated the addition of a vitamin D analog to Turi's corticosteroid composition, yet Serup did not seek to improve Turi by adding vitamin D.

Moreover, focusing on the "non-aqueous" claim element, the Board found "there was a strong reason to have made a non-aqueous composition with POP-15-SE." J.A. 15. The Board believed an artisan would have "add[ed] the Vitamin D analog of Serup [or Dikstein] to Turi's POP-15-SE containing steroid composition for the solvent's advantages and to obtain a more effective steroid preparation." J.A. 10 (internal quotations marks omitted). However, substantial evidence does not support the

Board's finding that an ordinary artisan would have deviated from the aqueous composition of Serup or the composition of Dikstein—plucking the vitamin D analog from those two references and incorporating the analog into Turi. The Board found that statements in Turi exclude the solvents used by Serup and Dikstein. J.A. 13 ("Turi provides explicit guidance to exclude water, alcohol, and propylene glycol . . . ."). Thus, Turi's guidance actually teaches *away* from the Board's posited combination or, at a minimum, provides no evidence of motivation to combine Turi with those prior solvents.

For example, Turi distinguishes its compositions from aqueous compositions: "The pharmaceutical compositions of the present invention contain no water." Turi col. 1, ll. 26–27. Indeed, all of Turi's examples are non-aqueous. Turi col. 8, l. 40–col. 10, l. 54. Yet, Serup's list of preparations are all aqueous, Serup col. 19, ll. 5–9, and Serup's examples are all aqueous, Serup col. 19, l. 34–col. 24, l. 17. Similarly, Dikstein discloses that dermatological creams are preferably formulated with, among other ingredients, water. Dikstein col. 3, ll. 14–26. And, five of Dikstein's examples include water. Dikstein col. 9, l. 40–col. 11, l. 21.

Moreover, Turi specifically disclaims the use of propylene glycol because of its "very undesirable qualities from a pharmacological point of view." Turi col. 1, ll. 24–61. Despite Turi's teaching away from that solvent, four of Dikstein's examples, Dikstein Exs. 7, 8, 15, 16, and five of Serup's examples, Serup Exs. 4–8, involve propylene glycol. Further, Dikstein discloses that propylene glycol is a convenient solvent in the preparation of dermatological lotions. Dikstein col. 3, ll. 14–26.

Even with the differing solvents taught by the prior art, the Board explained that, because Turi provided a reason to exclude water and propylene glycol, POP-15-SE would have been a logical non-aqueous choice to use for improving upon Serup and Dikstein. However, Serup "surprisingly observed that certain vitamin D analogues

can prevent and/or treat skin atrophy induced by topical steroid treatment." Serup col. 2, ll. 8–10. Similarly, when Dikstein combined a corticosteroid and vitamin D analog, it noted that "[s]urprisingly" the combination "led to more complete healing." Dikstein col. 6, ll. 48–54. With surprisingly successful results, an ordinary artisan would not have been motivated to change the solvents Serup or Dikstein relied upon and use the different solvent disclosed in Turi.

Thus, in the face of such divergent compositions with express disclaimers of the other's contents, the record showing that Turi, Serup, and Dikstein describe compositions for the same therapeutic purpose does not rise to the level of a motivation to combine. Without more, and especially in the face of such strong objective indicia of nonobviousness discussed *infra*, the Board erred by using hindsight to determine that the addition of Serup's or Dikstein's vitamin D analog to Turi's formulation would have been obvious.

In addition, the Board found that a person of ordinary skill in the art would have been capable of selecting the correct formulation from available alternatives. J.A. 12. Specifically, the Board found more than eight different classes of additives (*e.g.*, diluents, buffers, thickeners, lubricants). J.A. 12; Serup col. 19, ll. 10–15. The Board also found more than ten different categories of composition forms (*e.g.*, liniments, lotions, applicants, oil-in-water or water-in-oil emulsions such as creams, ointments, pastes, or gels). J.A. 12; Serup col. 19, ll. 5–9. "Based on these broad and general disclosures," the Board reasoned that an artisan would have been able to "mak[e] choices about what ingredients to include, and which to exclude" in formulating a composition with a vitamin D analog and steroid. J.A. 12. To the contrary, the breadth of these choices and the numerous combinations indicate that these disclosures would not have rendered the claimed invention obvious to try. *See Rolls-Royce PLC v. United Techs. Corp.*, 603 F.3d 1325, 1339 (Fed. Cir. 2010)

(claimed invention was not obvious to try because the prior art disclosed a "broad selection of choices for further investigation").

The '013 patent's claimed combination would not have been obvious to try. "[W]here the prior art, at best gives only general guidance as to the particular form of the claimed invention or how to achieve it, relying on an obvious-to-try theory to support an obviousness finding is impermissible." *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litigation*, 676 F.3d 1063, 1073 (Fed. Cir. 2012) (internal citations and quotation marks omitted). Further, "KSR did not create a presumption that all experimentation in fields where there is already a background of useful knowledge is 'obvious to try,' without considering the nature of the science or technology." *Abbot Labs. v. Sandoz, Inc.*, 544 F.3d 1341, 1352 (Fed. Cir. 2008).

Here, the "background of useful knowledge"—including the prior art relied on by the Board—was published decades before the '013 patent: Turi issued in 1978, Dikstein issued in 1986, and Serup was published in 1994. The elapsed time between the prior art and the '013 patent's filing date evinces that the '013 patent's claimed invention was not obvious to try. Indeed this considerable time lapse suggests instead that the Board only traverses the obstacles to this inventive enterprise with a resort to hindsight. It took over a decade—after Dikstein's disclosure of the benefits of combining vitamin D and corticosteroid treatments into one formulation—for Dikstein's formulations to be tested for storage stability. And, until the advancement made by the inventors of the '013 patent, no one had proposed a new formulation that would be storage stable. The problem was not known, the possible approaches to solving the problem were not known or finite, and the solution was not predictable. Therefore, the claimed invention would not have been obvious to try to one of ordinary skill in the art.

Indeed ordinary artisans would not have thought to try at all because they would not have recognized the problem.

And, even if it was obvious to experiment with these options, "there is nothing to indicate that a skilled artisan would have had a reasonable expectation that such an experiment would succeed in being therapeutically effective." *See Cyclobenzaprine*, 676 F.3d at 1070. There is no indication in the prior art which of these possible formulations would be the most promising to try. And, according to the '013 patent, the storage stability of these formulations cannot be determined based on a few days of work—testing would likely take one to three months per formulation. *See* '013 patent col. 10, l. 50–col. 11, l. 55. Without a reasonable expectation of success or clues pointing to the most promising combinations, an artisan could have spent years experimenting without success.

This court and obviousness law in general recognizes an important distinction between combining known options into "a finite number of identified, predictable solutions," *KSR*, 550 U.S. at 421, and "'merely throwing metaphorical darts at a board' in hopes of arriving at a successful result," *Cyclobenzaprine*, 676 F.3d at 1071 (quoting *In re Kubin*, 561 F.3d at 1359). While the record shows that, as early as 1995, the prior art indicated that both vitamin D analogs and corticosteroids were effective treatments for psoriasis, *see* J.A. 610, 6237, that same prior art gave no direction as to which of the many possible combination choices were likely to be successful. Instead, the prior art consistently taught away from combining vitamin D analogs and corticosteroids.

This court recognizes that the record need only supply "substantial evidence" to support the Board's finding. *In re Gartside*, 203 F.3d 1305, 1316 (Fed. Cir. 2000). In this case, however, with no material factual disputes, this court cannot share the Board's analysis and application of the law to those facts. In light of the lack of expectation of a successful result, the failure of the prior art to provide direction, and the substantial number of intervening

years between the publication of the prior art and the '013 patent's filing date, this invention is not simply a case of "'picking and choosing' from a list in order to achieve a compatible and non-deleterious preparation" as the Board suggests. J.A. 12. Because the problem was not known, the possible approaches to solving the problem were not known or finite, and the solution was not predictable, it would not have been obvious for a person of ordinary skill to make the claimed invention.

B.

The court now turns to the Board's analysis of the objective indicia of nonobviousness. The Board reasoned that "the strong case of obviousness outweighs the experimental evidence and testimony about the advantages of the claimed composition." J.A. 17. Contrary to the Board's conclusion, this court finds the objective indicia, in concert with the entire obviousness analysis, present a compelling case of nonobviousness. In fact, the objective indicia of nonobviousness highlight that the Board's analysis regarding the combination of Serup or Dikstein with Turi was colored by hindsight.

Whether before the Board or a court, this court has emphasized that consideration of the objective indicia is *part of* the whole obviousness analysis, not just an afterthought. *See Cyclobenzaprine*, 676 F.3d at 1075–76 (A fact finder "may not defer examination of the objective considerations until after the fact finder makes an obviousness finding." (quoting *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530 (Fed. Cir. 1983))). When an applicant appeals an examiner's objection to the patentability of an *application's* claims for obviousness, the PTO necessarily has the burden to establish a prima facie case of obviousness which the applicant then rebuts. *In re Mouttet*, 686 F.3d at 1330. However, during *inter partes* reexamination, the Board is reviewing evidence of obviousness—including objective indicia—submitted by two adversarial parties for the claims of an issued *patent*. Thus, the Board should give the objective indicia its

proper weight and place in the obviousness analysis, and not treat objective indicia of nonobviousness as an afterthought.

Objective indicia of nonobviousness play a critical role in the obviousness analysis. They are "not just a cumulative or confirmatory part of the obviousness calculus but constitute[] independent evidence of nonobviousness." *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1365 (Fed. Cir. 2008). This case illustrates a good reason for considering objective indicia as a critical piece of the obviousness analysis: Objective indicia "can be the most probative evidence of nonobviousness in the record, and enables the court to avert the trap of hindsight." *Crocs, Inc. v. Int'l Trade Comm'n*, 598 F.3d 1294, 1310 (Fed. Cir. 2010) (internal quotation marks omitted). Here, the objective indicia of nonobviousness are crucial in avoiding the trap of hindsight when reviewing, what otherwise seems like, a combination of known elements.

Unexpected results are useful to show the "improved properties provided by the claimed compositions are much greater than would have been predicted." *See In re Soni*, 54 F.3d 746, 751 (Fed. Cir. 1995) (internal quotation marks omitted). This record shows "extensive experimental evidence" of unexpected results that contradict the Board's obviousness finding. J.A. 14. The Board concluded that the "unexpected results" claimed by Leo Pharmaceuticals were not surprising or unexpected. J.A. 19. However, substantial evidence does not support the Board's conclusion.

During reexamination, the inventors of the '013 patent submitted test results that analyzed the Dikstein and Serup formulations. The inventors found that the formulations disclosed by Dikstein and Serup result in significant degradation of the vitamin D analog and corticosteroid. *See* J.A. 1041–46 (testing formulations in Serup); J.A. 1625–27, 2152–2154 (testing formulations in Dikstein). The inventors also tested an improvement of Serup using Turi, by replacing Serup's solvent with POP-

15-SE, and still found significant degradation of the corticosteroid component. *See* J.A. 1045–46. These test results are a strong indication that the '013 patent's combination of known elements yields more than just predictable results.

In addition to evidence of unexpected results, Leo Pharmaceuticals provided other objective indicia of nonobviousness. For example, the commercial success of Leo Pharmaceutical's Taclonex® ointment is a testament to the improved properties of the '013 patent's claimed invention. Taclonex® is the first FDA-approved drug to combine vitamin D and corticosteroids into a single formulation for topical application. While FDA approval is not determinative of nonobviousness, it can be relevant in evaluating the objective indicia of nonobviousness. *See Knoll Pharm. Co., Inc. v. Teva. Pharm. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004). Here, FDA approval highlights that Leo Pharmaceutical's formulation is truly storage stable, something that the prior art formulations did not achieve.

The record also shows evidence of *long* felt but unsolved need, *i.e.*, the need for a single formulation to treat psoriasis. The length of the intervening time between the publication dates of the prior art and the claimed invention can also qualify as an objective indicator of nonobviousness. *See Ecolochem, Inc. v. S. Cal. Edison Co.*, 227 F.3d 1361, 1376–77 (Fed. Cir. 2000). Here, the researchers were aware of the benefits of using both vitamin D and corticosteroids in the treatment of psoriasis as early as 1986. *See, e.g.,* Dikstein col. 1, ll. 9–16. And Turi, upon which the Board relied to make its case, issued in 1978. Yet, it was not until the '013 patent's filing in 2000—*twenty-two years* after Turi and *fourteen years* after Dikstein—that the solution to the long felt but unsolved need for a combined treatment of vitamin D and corticosteroid was created. The intervening time between the prior art's teaching of the components and the eventual

preparation of a successful composition speaks volumes to the nonobviousness of the '013 patent.

Here, the objective indicia—taken in sum—are the most "probative evidence of nonobviousness . . . enabl[ing] the court to avert the trap of hindsight." *Crocs, Inc.*, 598 F.3d at 1310. Viewed through the lens of the objective indicia, as opposed to the hindsight lens used by the Board, the '013 patent would not have been not obvious over Turi in combination with Dikstein or Serup. Therefore, this court reverses the Board's obviousness determination.

IV.

For the foregoing reasons, this court reverses the Board's claim construction of the term "storage stable" and its obviousness determination.

REVERSED

Exhibit 4

Expert Opinion

Fast-dissolving intraoral drug delivery systems

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Fast-dissolving drug delivery is rapidly gaining interest in the pharmaceutical industry. These delivery systems either dissolve or disintegrate in the mouth rapidly, without requiring any water to aid in swallowing. Such technologies offer a convenient way of dosing medications, not only to special population groups with swallowing difficulties, but also to the general population. They also impart unique product differentiation, thus enabling use as line extensions for existing commercial products. This review discusses the various technologies in recent patents used to achieve quick dissolution/dispersion in the oral cavity. They are categorised based on either processing or formulation variables. Processing techniques, such as lyophilisation, tablet moulding, sublimation and spray drying, are discussed in this article. Review of the formulation techniques includes addition of sugar-based ingredients, foaming agents and disintegrants. Finally, an emerging novel dosage form, a quick-dissolving film, is discussed.

Keywords: drug delivery, fast-disintegrating, fast-dissolving, film, intraoral, lyophilisation, oral, spray-drying, tablets

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1. Introduction

The oral route remains the most convenient way of drug administration for patients. Conventional oral dosage forms include suspensions, solutions, powder, granules, tablets and capsules, with the latter two being the most popular dosage forms used today. However, many patients approach drug administration with apprehension, and therefore do not take their medications as prescribed by physicians [1]. The elderly, who constitute a large portion of the worldwide population due to increased life expectancy, have difficulties taking conventional oral dosage forms because of hand tremors and dysphagia from deterioration in their physiological abilities. Paediatric patients, owing to their underdeveloped muscular and nervous systems, are often fearful of taking solid oral dosage forms [2]. Other groups that may experience problems using conventional oral dosage forms include the mentally ill, the developmentally disabled, patients who are uncooperative, on reduced liquid-intake plans or nauseated, and travelers who may not have access to water [3,4]. According to a recent survey, it is estimated that > 25% of the 1,576 outpatients involved had problems in swallowing tablets. A prominent complaint was the size of the tablet, followed by its surface contour, shape and taste [5].

Novel oral fast-dissolving drug delivery systems, which dissolve/disintegrate rapidly after placing in the mouth without the need for drinking water, will alleviate the problem of swallowing tablets. Such drug delivery systems have generated tremendous business interest because of their potential to provide line extensions in the marketplace. Worldwide, there are over a dozen fast-dissolving products on the market, nine of which have been launched in the last three years [6]. There has also been a large increase in the number of new chemical entities under development. Fast-dissolving technology is growing, but there are very few published scientific articles discussing the technology. This is mainly because most technologies have been initiated and developed by the pharmaceutical industry and

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Box 1. Benefits of fast dissolve technology.

- Rapid disintegration
- No tablet or capsule to swallow or chew
- No water needed
- Accurate dosing compared to liquid products
- Greater safety and efficacy
- Better patient compliance
- Unique product differentiation
- Product line extension with value added

this proprietary information is only available in patent literature. This article serves to provide a comprehensive review of the patents relating to fast-dissolving technologies and is structured based on the various techniques used to achieve fast-dissolving properties.

2. Benefits of a fast-dissolving drug delivery system

Fast-dissolving dosage forms offer substantial advantages over conventional oral dosage forms. The primary benefit is improved patient compliance due to ease of swallowing without drinking any water, a better taste, more accurate dosing as compared to liquid dosage form, and improved safety and efficacy. They may also offer superior clinical profiles with potential oramucosal absorption, thus improving bioavailability. From a commercial point of view, fast-dissolving drug delivery systems can be effectively used in the life-cycle management of a product. A fast-dissolving delivery system imparts unique product differentiation with value-added benefits and therefore can be used either as a primary formulation or as a line extension for an existing product. Box 1 lists the benefits of fast-dissolving drug delivery systems.

3. Recent patents

During the last 3 to 4 years, there have been more than 20 patents filed which relate to fast-dissolving drug delivery. Detailed descriptions of these patents are presented in the following sections.

3.1 Tablets

Most fast-dissolving drug delivery systems are in tablet form, and their rapid disintegrating properties are achieved through special processes or formulation modifications.

3.1.1 Process based technologies

Lyophilisation. Lyophilisation or freeze-drying, can be used to create an open matrix network with drugs entrapped within, which enables a liquid medium to penetrate through, thus exposing both the interior and exterior of the network to the liquid, thereby enhancing disintegration. Early work by Gregory *et al.* from John Wyeth & Brother who used highly water-soluble or water-dispersible polypeptides, polymers and/or saccharides as the matrix-forming carrier material, led to RP Scherer's Zydis® system in the late 1980s [7,101,102]. Partially hydrolysed gelatin, hydrolysed dextran, dextrin and alginates or mixtures with each other or with other carrier materials such as polyvinylpyrrolidone, polyvinyl alcohol or acacia, are commonly used in the Zydis® systems. Although the resulting products exhibit very rapid disintegration (< 10 s), lyophilisation is a long and expensive process. Other major limitations of the Zydis® systems are their fragility and moisture sensitivity, resulting in poor stability during storage under stressful conditions. Hence, special moisture-resistant and peelable blister packs are required. Okada *et al.* improved the hardness and moisture resistance of lyophilised rapidly dissolvable products by using a saccharide (trehalose, mannitol or dextrin) at high concentration (10 - 30 % wt) [103]. Resulting tablets had better hardness (> 1 kg) while still maintaining rapid disintegration time (< 10 seconds).

Another limitation of lyophilisation is that the active should be relatively water-insoluble, since incomplete freezing or collapse may occur with soluble drugs having low eutectic freezing temperatures. Therefore, soluble drugs are rendered less soluble by ion exchange resins [104], conversion to base form or change in the polymorphic forms [105]. At the same time such approaches may also provide taste masking capabilities. Brideau *et al.* first disclosed use of adsorbate (silicate clays, acrylic polymers) to provide non-rupturable taste-masking compositions to be incorporated into the lyophilised matrix [106]. Such compositions resist breakage and maintain an immediate release profile, as opposed to coating and barrier. Grother *et al.* disclosed another method of associating bitter tasting drugs with lipids to improve palatability [107]. The association might be a result of partitioning, direct binding or adsorption, depending on the physicochemical properties of the drug. This method again eliminated the gradual release of drugs over time commonly associated with physical lipid coating and barrier. Solid state emulsions were used by Remon *et al.* to incorporate lipid soluble drugs [108]. Resulting lyophilised rapid-disintegrating tablets contained maltodextrins with dextrose equivalent (DE) values between 12 and 40 as matrix-forming agents, water-soluble thickening agents as binding agents, as well as an oil, a co-solvent and a surfactant.

Tablet moulding. Conventional tablets made from compression do not disintegrate or dissolve fast enough. Moulded tablets, which are made under low pressure, have more rapid disintegration or dissolution, albeit at the expense of mechanical strength. Although not as fragile as lyophilised products, moulded tablets in general have poor hardness and may not withstand stress during packaging, shipping and handling.

A number of past inventors have addressed such problems of low hardness, as well as the need for taste-masking of active ingredients in moulded tablets. To provide taste masking, besides using sweetening agents (MagnaSweet® and Sunnett®) and flavouring agents [109], Van Scoik encapsulated the

active in a triglyceride vehicle by spray congealing [110]. The resulting discrete particles were then wet blended and mixed with carbohydrates (monosaccharides, disaccharides or sugar alcohol), moulded and subsequently dried. Gowan, Jr. also described a taste-masking methodology where he coated drug particles with a 90:10 to 50:50 blend of two polymers (the first polymer selected from the group consisting of cellulose acetate and cellulose acetate butyrate, and the second polymer from PVP and HPC) using a fluidised-bed coating operation [111]. To improve mechanical strength, Masaki *et al.* used agar for their tablet matrix formed by lactose and/or mannitol [112]. The procedure involved filling a mould with a suspension of the ingredients (agar, active, and/or mannitol), solidifying into a jelly form and subsequent vacuum drying of the jelly. Hardness of the tablets was ~ 2 kg (max = 3.5 kg), while *in vivo* disintegration times in the buccal cavity were ~ 10 s. Pebley *et al.* also produced rapid-disintegrating tablets with enhanced structural integrity [109]. The matrix network consisted of a gum, a carbohydrate, and the active, which were moulded into the desired shape, frozen, and vacuum dried above its collapse temperature. A partially collapsed matrix network is thus formed that has a lower porosity and a greater density and strength than using lyophilisation to prepare a fast-dissolving tablet.

More recently, Makino *et al.* described a method to produce a highly porous tablet by compression-moulding a mixture of active and a carbohydrate in water (the amount of water being barely sufficient to wet the surface of particles of the carbohydrate) into tablets followed by drying [113]. The amount of water was carefully controlled to obtain a balance between adequate porosity and hardness. The tablets exhibited sufficient mechanical strength and good dissolution and disintegration.

Ohno *et al.* used a combination of erythritol, microcrystalline cellulose, a disintegrant such as crospovidone or croscarmellose and optionally mannitol, to obtain a moulded tablet preparation with fast disintegration, dissolution and improved hardness [114]. The ingredients were either directly moulded, or kneaded/granulated, dried and then compression-moulded. Moulding compression was from 1.5 - 3 tons/cm^2. The resulting tablets had *in vivo* buccal dissolution times in the range 0.1 - 0.5 min while maintaining hardness between 3 and 10 kg.

Liu modified the moulding process by introducing additional steps of humidification and drying after granulation and tablet moulding to produce rapid-dissolving tablets with sufficient hardness [115]. The formulation is comprised of water soluble polymers (such as PVP and agar) and saccharides of high mouldability (maltose and sorbitol) as binders, as well as saccharides of low mouldability (mannitol and erythritol) as fillers. In the humidification step, the water soluble binder swelled upon absorption of water, allowing a more thorough wetting of the other components and a deeper penetration of water into the interior. In general, extending the humidification duration increases the hardness of the tablets, regardless of the length of the drying time. The tablets that were disclosed in this invention had uniform and improved hardness (4 - 7 kg) while still maintaining a rapid *in vivo* disintegration time (10 - 15 s). Although certain organoleptic properties (smoothness and dryness) were good, no taste masking capabilities were indicated.

Sublimation. Sublimable materials (ammonium salts, camphor, urethane, urea, menthol etc.) have been used to increase the porosity of conventional compressed tablets. Volatilisation of these materials eliminates the long and complicated process associated with sublimation of frozen water in lyophilisation. Since compressed tablets are formed with great mechanical strength and stability, sublimation of volatile materials leaves behind hollow spaces without significant collapse. In general, the volatile salts are mixed with other tablet ingredients and removed by vacuum or heat. Inclusion of trehalose (anhydrous) has recently been described to produce tablets with high quality and homogeneity [116]. Anhydrous trehalose has excellent tabletting properties, is chemically inert, and can impart stability for moisture-sensitive active ingredients.

Spray-drying. Spray-drying provides a fast and economical way of removing solvents and recovering small particles. Allen *et al.* utilised this process to produce a tablet support matrix for their fast-dissolving tablets [117,118]. Two polymeric materials of the same net charge (preferably unmodified gelatin and hydrolysed gelatin), a bulking agent, and a volatilising agent were spray-dried to obtain the particulate support matrix. An acidifying or alkalinising agent may be included to maintain the net charges of the polymeric materials. The use of polymeric materials possessing the same charge resulted in molecules that repelled each other, even after spray-drying, thereby forming porous and low bulk density particles. Incorporation of a volatilising agent (in most cases, ethanol) further reduced the surface tension of the droplets during spray-drying and created more pores and channels, which produced particles with an even higher porosity and lower density. One polymeric material was preferably more soluble than the other, and when combined with a bulking agent, the solubility of the matrix was further increased (in a matter of seconds). Optionally, a minimal amount of effervescent agents may be included to further accelerate the dissolution rate. A thin coating of polymeric material may also be applied externally to aid in keeping the tablets intact during handling without Inhibiting the capillary uptake of water during dissolution. Such coating may also help to mask the taste of bitter drugs. Active ingredients may be additionally micro-encapsulated or nano-encapsulated to further achieve taste-masking.

Flash-heat process. Fuisz Technologies has filed numerous patents on their unique sugar-containing flosses or Shearform matrices using the flash-heat process, which form the basis of their technological platforms (Flash Dose®, EZ Chew, Soft Chew) [119-122]. Shearform matrices, which employ a blend of sugar alcohols and saccharides (preferably sucrose, sorbitol

and xylitol), are prepared under centrifugal force and temperature gradient (flash-heat process). The matrices are then partially crystallised using crystallisation promoters/modifiers (preferably surfactants) to form flowable and tablettable flosses. The flosses are mixed with other tablet ingredients and compressed using a conventional tabletting machine to form fast-dissolving tablets that disintegrate within 30 s. Additionally, a similar process can be utilised to form microspheres which provide taste-masking capabilities (Liquiflash process) which use pressure, temperature and centrifugal force to form spheroidal particles.

Solvent removal processes. Gole *et al.* disclosed a unique method of solvent removal using solid-state dissolution [123,124]. Matrix material solution, typically aqueous, containing gelatin, pectin, soy-fibre protein (either alone or in combination) with one or more amino acids (2 to 12 carbon atoms), together with sweeteners, was frozen. The frozen matrix was then introduced into a non-aqueous solvent (such as ethanol or acetone) where the solidified water dissolved and was then removed. The non-aqueous solvent was then removed by vacuum drying. The active must be post-loaded from non-aqueous solution after the solid matrix was formed. *In vitro* disintegration in water was < 10 s. Compared with lyophilisation, this solvent removal method was more robust and less moisture sensitive, and eliminated the problems of cracking and meltback.

Humbert-Droz *et al.* introduced the use of microwave radiation, with or without reduced pressure, as a solvent evaporation method [125]. Porous tablet matrix typically composed of filler (saccharides) and binder (PVP or PEG) with high drug loading (up to 1000 mg) was formed. Oral disintegration time was < 15 s.

3.1.2 Formulation modifications

Sugar-based ingredients. Sugar-based excipients (e.g. sorbitol, mannitol, dextrose, xylitol, fructose, maltose, isomalt, maltitol, lactitol, starch hydrolysate and polydextrose) have been widely used as bulking agents. Due to their high aqueous solubility and sweetness, which impart pleasant mouthfeel and good taste-masking, sugar-based materials are commonly used in fast-dissolving formulations. However, not all sugar-based materials have a fast dissolution rate and good compressibility and/or compactability [4].

Nakamichi *et al.* described a method which utilised a mixture of highly water-soluble sugar or sugar alcohol (perferably xylitol with lactose or mannitol) to produce tablets with short dissolution and high tensile strength [126]. In contrast to conventional wet granulation, the mixtures, together with the active and other tabletting ingredients, were kneaded and compressively-moulded before drying. The mechanical strength of the tablets was postulated to result from the cross-linking force of the sugars and/or sugar alcohols. The described method allowed for high throughout and produced strong (> 8 kg/cm^2) and quickly solubilised tablets (oral dissolution time was < 25 seconds).

Matsumoto *et al.* described a rather complicated method that involved surface modification of drug and diluent with silicic acid [127]. The resulting powder was then mixed with partially gelatinised starch or crospovidone and directly tabletted. A further, multi-layer surface modification was described whereby the surface-modified powder was further dry-coated with TiO_2 and combined with erythritol. Tablets had an improved taste, with hardness > 7 kg and disintegration times around 25 s.

Foaming agents. Solid foam compositions as vehicles for oral delivery of pharmaceuticals have rarely been described, yet these aerated compositions have a very low density and a fast dissolution rate. Gowan, Jr. *et al.* disclosed a dried foam composition for pharmaceutical and nutritional uses, comprising a polymeric foaming agent (either protein (casein) or cellulose derivatives (hydroxypropylmethylcellulose)) and optionally a non-cellulosic polysaccharide [128]. Foams of appropriate density were generated by controlled vigorous agitation of polymeric solution in the presence of air or other gases, and were subsequently shaped and dried. Alternatively, a foam generating unit may be used. Additional mechanical strength of the dried foam can be imparted by incorporating sugar or other carbohydrates (dextrose, trehalose or maltodextrin) as well as humectant materials (glycerol, propylene glycol) to reduce friability. Coated particles of pharmaceutical or nutritional materials were applied, preferably after the foam was formed to prevent breakage or fracture of the particles during the vigorous agitation process.

Watt *et al.* also described a very similar solid foam composition, made from albumin and polysaccharide (sucrose or carboxymethylcellulose), and optionally a non-ionic surfactant, by moulding [129].

Disintegrants. The use of disintegrants and/or effervescent ingredients are the basis of a number of commercial fast-dissolving technologies.

Flashtab® technology was developed and patented by Prographarm. Flashtab® is a rapidly disintegratable multiparticulate tablet which was designed to disintegrate in the mouth in < 60 s [130]. The tablets consist of actives, at least one disintegrating agent (such as carboxymethylcellulose or insoluble polyvinylpyrrolidone) and at least one swelling agent (starch, modified starch or microcrystalline cellulose). Taste-masking was fulfilled by microencapsulation. A slight modification was described by Chauveau *et al.*, who substituted the swelling agent with a water-soluble diluent agent with binding properties (polyol such as mannitol, xylitol, sorbitol or maltitol) [131]. Resulting tablets disintegrated in the mouth in < 40 s. Crospovidone and croscarmellose were the preferred disintegrants. The tablets also had sufficient mechanical strength.

Both OraSolv® and DuraSolv® technologies utilised the evolution of carbon dioxide as a disintegration mechanism and were developed by CIMA Labs. OraSolv® technology

was based on the patent of Wehling *et al.* and was composed of a mixture of saliva-activated effervescent agents (acid-base combinations) and actives in the form of microparticles [132]. Special packaging, however, was required for these tablets due to their fragility and sensitivity to moisture. DuraSolv® technology, a more robust second-generation technology of CIMA, was patented by Khankari *et al.* [133]. It was a matrix composition which contained non-directly compressible sugar or sugar alcohols and a hydrophobic lubricant. Sugar or sugar alcohols having mean particle sizes of 20 - 65 μm were utilised. The level of lubricants (1.5 - 2 %) and the lubricant blending times (10 - 25 min) were also higher than normally used. The composition was directly compressed under low pressure and might additionally include wicking and/or effervescent agents. The resulting tablets had good mechanical strength (15 - 50 N) and *in vitro* disintegration time of less than 45 s. Taste-masking was provided by encapsulation of the active ingredient in microparticles.

Acosta-Cuello *et al.* described a fast-melt tablet composition which melted and disintegrated in the mouth in a few seconds [134]. The tablet consisted of an effervescent couple starch and a starch degrading enzyme (α-amylase, β-amylase or amyloglucosidase). Starch provided a rapid disintegration of the tablet due to its porosity. The starch degrading enzyme, which converted the starch rapidly into highly water soluble and palatable monosaccharides and polysaccharides, produced a synergistic effect. The effervescent couple served as a supplemental disintegrating agent.

Bonadeo *et al.* also described a high-porosity, low-density granulate composition which might optionally be coupled with effervescence to produce rapidly disintegrating tablets [135]. The granules were prepared by fluidised-bed granulation. Disintegration time of the tablets in saliva was ~ 30 s.

3.2 Films

Besides the fast-dissolving tablets described above, there are also a few patents that disclose fast-dissolving thin films for pharmaceutical and cosmetic use. The advantage of a film, as compared to the aforementioned tablets, is that the risk of choking and the fear of taking solid tablets, which are still very much in existence with fast-dissolving tablets, are completely eliminated in a film form. Zerbe *et al.* described a rapidly dissolving film with instant wettability comprising water-soluble polymers, one or more polyalcohols, one or more surfactants or plasticisers and the active ingredients [136]. In order to achieve the desired effect of instant wettability, a binary surfactant mixture with specific hydrophilicity-lipophilicity balance (HLB) values was preferred.

Chen *et al.* described a simpler quick-dissolving film formulation, which was suitable for both oral and mucosal delivery [137]. The film can also be applied to ocular, dermal, vaginal and rectal sites for absorption. It was composed of highly water-soluble film-forming polymers with mucoadhesive properties, a plasticiser, and an active ingredient. It can be manufactured by conventional solvent coating, extrusion and semi-solid casting. The resulting film was tough, soft, flexible and safely secured to the site of application. Dissolution time was ~ 30 seconds. These films can be easily packaged in conventional pouches.

Leung *et al.* also described an orally consumable film containing pharmaceutical agents using pullulan as the film-forming polymer. Oral cleansing films using other water soluble polymers were also described [138].

4. Expert opinion

Fast-dissolving drug delivery is no doubt a revolutionary and promising route of drug administration to all population groups, specifically geriatric and pediatric patients, and patients with swallowing difficulties. This explains the extensive research actively going on in this field.

Each of the systems discussed in this review paper has its own limitations. A perfect fast-dissolving system does not exist as yet. Most of the existing technologies are in the form of tablets. The biggest challenge associated with tablets is maintaining mechanical strength without compromising the rapid dissolution/disintegration time, so that they can withstand the handling and stress the same way as conventional tablets. Much of the research mentioned in this review focuses on the aspect of formulation to overcome the difficulty, but there is usually a balance. Dissolution/disintegration times are either increased, or otherwise specialised packaging is required to overcome the problem with mechanical strength, which may increase manufacturing burden and cost.

Another challenge is taste-masking of the active ingredients. All basic drugs are bitter, unless they have extremely poor water solubility. Taste-masking is thus critical, since the taste of the final dosage form greatly affects patient acceptance. Taste-masking is achieved in most patents by drug particle coating. However, coating increases particle size, thus compromising ultimate smoothness and mouthfeel of the tablet. In addition, the amount of coating depends on the drug dose and the degree of bitterness. Thus, with fast-dissolving systems carrying high dose drugs, the tablet size becomes an additional challenge. Large tablet size increases the risk of choking despite the rapid disintegration. Besides, a tablet, as a hard solid article itself, may not completely eliminate patients' fear of choking. Finally, most excipients used in fast-dissolving tablets are highly hygroscopic and moisture sensitive during manufacturing and storage, and may present other challenges.

In view of the above challenges associated with tablets, alternative dosage forms are being evaluated, and recently thin films became an option. Patients' fear of tablets and the risk of choking are completely eliminated with films. Handling, packaging and manufacturing are simple, with no more concerns regarding mechanical strength. However, taste-masking remains a major challenge. Dose loading is also highly restricted, since rapid disintegration relies on the thickness of the film.

Although promising results have been achieved, a perfect

fast-dissolving drug delivery system has not yet been developed. An ideal fast-dissolving drug delivery system should possess the following properties: high stability, transportability, good patient acceptability, ease of handling and administration, robustness in accommodating high dosage ranges and drug properties, and no specialised packaging and processing requirements. Undoubtedly, intense research is ongoing to achieve this ideal fast-dissolving system.

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133. CIMA LABS, INC.: US6024981 (2000).

• Patent for DuraSolv®.

134. LAB PHARM. RES. INT., INC.: US5807578 (1998).
135. ELAN PHARM. INT. LTD.: US6149938 (2000).
136. LTS LOHMANN THERAPIE-SYSTEME GMBH: US5948430 (1999).
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Exhibit 5

HEALTH › HYGIENE › HOME

Healthier Happier Stronger

Reckitt Benckiser Group plc

Annual Report and Financial Statements 2012

Outperformance continues

RB has once again met or exceeded its targets.

- Like-for-like net revenue grew +5% to £9,567m.
- Excellent growth in emerging market areas of LAPAC[1] & RUMEA[1];
- ENA[1] performance improved progressively and now back to growth over the year. The last quarter was +3% growth like-for-like.
- Health & hygiene Powerbrands Durex, Gaviscon, Strepsils, Dettol, Lysol, Harpic and Finish led the growth.
- Suboxone film reached 64% volume share of the US market.
- Operating margins[2] increased by +70 bps, ahead of target.
- Adjusted net income[2] grew +7% (+10% constant); adjusted diluted earnings[2] per share of 264.4p (+7%).
- Strong cash flow took net debt to £2,426m after dividends, acquisitions and restructuring.

These results are very encouraging and give us confidence that we have the right business strategy, the right organisation, the right growth platforms and the right culture to deliver our long-term goals.

£9,567m

our net revenue in 2012

£2,570m

adjusted operating profit in 2012

2013 targets

- Net revenue growth of 5-6% at constant exchange rates, excluding RB Pharmaceuticals.
- Maintain operating margin[3], excluding RB Pharmaceuticals.

For 2012 our health and hygiene revenues were 68% of our core[3] geographic portfolio (67% in 2011) and LAPAC and RUMEA were 44% of our core[3] geographic portfolio (42% in 2011). This strategic reshaping of our portfolio is ahead of schedule and we have accelerated two of our medium-term KPIs from 2016 to 2015.

Medium-term KPIs

- Health and hygiene revenues to be 72% of core[3] net revenue by end of 2015.
- LAPAC and RUMEA combined to be equal in net revenue size to EtoA by end of 2015.
- Achieve 200 bps pa of net revenue growth on average above our market growth.
- Achieve moderate operating margin expansion (excluding RB Pharmaceuticals).

1 Latin America, North Asia, South East Asia, and Australia and New Zealand (LAPAC), Russia and CIS, Middle East, North Africa, Turkey and Sub-Saharan Africa (RUMEA), Europe and North America (ENA)

2 Adjusted to exclude the impact of exceptional items

3 Core includes health, hygiene, home and portfolio brands

CATEGORY KPI

72%

of core[1] Company net revenues from health and hygiene by end of 2015

GEOGRAPHIC KPI

50%

of core[1] Company net revenues from LAPAC and RUMEA (equal to ENA) by end of 2015

NET REVENUE GROWTH KPI

200bps

a year, on average, ahead of the global market growth across RB's categories and geographies

[1] Core is health, hygiene, home and portfolio brands.

RB PHARMACEUTICALS

RB Pharmaceuticals, as a pioneer of innovative prescription treatments for chronic diseases of addiction, introduced Suboxone sublingual film in 2010. The popularity of the sublingual film meant that by the end of 2012 it had a 64% market share. The sublingual film has patent protection until at least 2020. Based on the enhanced benefits of the sublingual film and the significant reduction in unintended paediatric exposure due to its unit-dose child resistant packaging, RB Pharmaceuticals are voluntarily withdrawing their Suboxone tablets from the US market on 18 March 2013.

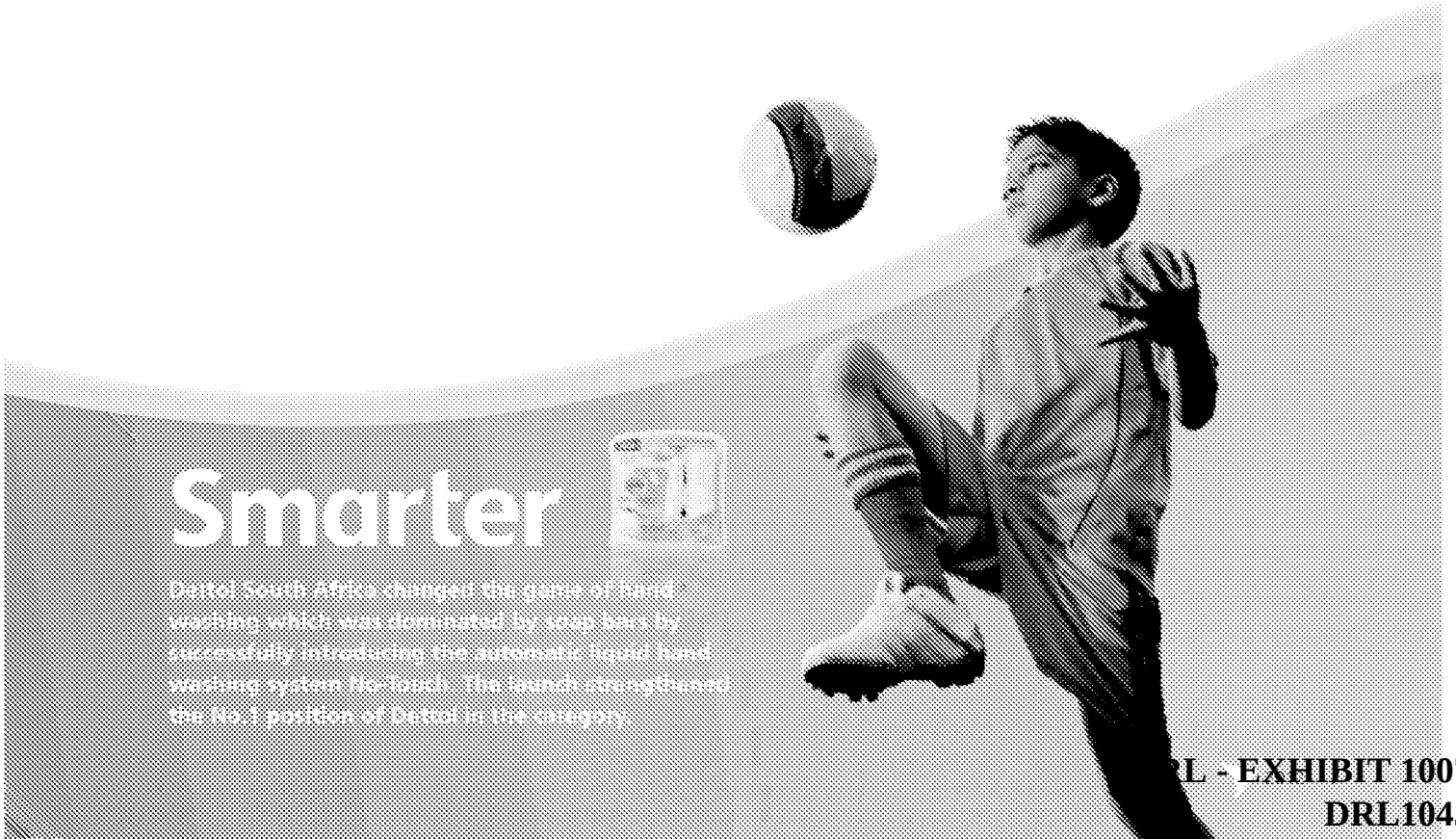
TALENTED, GLOBAL EMPLOYEES

Our strategy is supported by hugely talented and driven people from around the world. Their diverse backgrounds and mix of nationalities foster creativity and a culture of innovative thinking in every market. We have a highly geared, performance-driven remuneration structure for our leadership team.

Our people take a fresh view of what is possible in a market, what value they can create for consumers and how they can deliver healthier lives and happier homes.

Then they take often radically different approaches to deliver it. We grant them the freedom to operate, to decide and to create; entrepreneurship is in their blood. This is combined with a high drive for achievement, a strong sense of ownership and a willingness to partner with anyone who can help deliver for consumers.

My thanks go to all our employees and contractors all over the world who have contributed to our success in 2012.



Dettol South Africa changed the game of hand washing which was dominated by soap bars by successfully penetrating the universe liquid hand washing system no-touch. This launch strengthened the No.1 position of Dettol in the category.

achievement of planned cost savings. This has brought forward some of the planned cost savings originally targeted for 2013.

LAPAC. This area covers the markets of Latin America (including Brazil, Mexico, Chile, Argentina, the Andean Pact and Central America), North Asia (China, Korea, Japan, Taiwan, Hong Kong), South East Asia (India, Malaysia, Thailand, Singapore, Philippines, Indonesia, Sri Lanka) and Australia and New Zealand.

2012 total net revenue increased to £2,327m, with like-for-like growth of +11%. Growth came from Latin America, North Asia and South East Asia, driven by distribution expansion, innovation and increasing penetration. In health, all Powerbrands grew, with exceptionally strong performances from Durex in China, Scholl in Japan, Paras brands in India and Gaviscon roll outs in a number of markets. In hygiene, Dettol, Lysol, Harpic and Veet delivered strong growth from initiatives such as Dettol Daily Care and Re-energize, and Power Plus in Harpic. Vanish and Air Wick performed well in the home category.

Adjusted operating profit increased +17% to £464m. Adjusted operating margin was +100 bps higher at 19.9%. Increased investment behind BEI was more than offset by good gross margin, volume leverage and fixed cost containment.

RUMEA. This area covers the regions of Russia and CIS, Middle East, North Africa, Turkey and Sub-Saharan Africa.

2012 net revenue of £1,404m was ahead +8% on like-for-like basis (+7% total), driven by strong growth in Russia and CIS. In health, growth was driven by Durex, Gaviscon, and Strepsils. Hygiene Powerbrands Dettol, Finish, Harpic and Veet performed particularly well supported by initiatives such as Dettol Daily Care and Re-Energize. Air Wick performed well in the home category with growth driven by Freshmatic and Aqua Mist.

The second half saw the upscheduling of certain Nurofen products in Russia, an increased promotional environment and some operational and socio-political challenges in certain markets. These headwinds will continue through 2013 but we remain confident about the underlying strength of the business.

Adjusted operating profit increased by +3% to £290m. This resulted in a -80 bps decline in the adjusted operating margin to 20.7%. This was due to adverse FX impacting gross margin and increased investment in both BEI and the new area structure, to support the business and to drive future growth.

The Group also has two non core businesses: RB Pharmaceuticals and Food.

Pharmaceuticals. RB Pharmaceuticals is responsible for the development of the Group's Subutex and Suboxone prescription drug business. Both products are based on Buprenorphine for treatment of opiate dependence. Suboxone is a more advanced product compared to Subutex, as it has substantially better protection against abuse by the opioid-dependent population. In the US, Suboxone lost the exclusivity afforded by its orphan drug status on 8 October 2009.

On 31 August 2010, the Group announced that it had received approval from the US Food and Drug Administration for its New Drug Application to manufacture and market Suboxone sublingual film. Suboxone sublingual film has been developed through an exclusive agreement with MonoSol Rx, utilising its proprietary PharmFilm® technology, to deliver Suboxone in a fast-dissolving sublingual film.

As with all prescription drugs, the protection of the business has a finite term unless replaced with new treatments or forms.

RB Pharmaceuticals recently announced its voluntary discontinuation of Suboxone tablets in the US due to increasing concerns with paediatric exposure. The Group has recently been made aware that two manufacturers have received approval to produce generic Suboxone tablets in the US. The approval of generic tablets has been anticipated since the loss of orphan status in October 2009. Whilst the Group remains confident in the success of its patient-preferred Suboxone film, we do expect that increased price pressure will lead to a material reduction in sales revenue in the US.

2012 net revenue increased +10% to £837m. Growth came from continued strong volume growth in the US. This was offset by dilution from the increased film penetration, which is a lower priced product, and government price reductions in a number of European markets. Conversion from tablets to film in the US continued to increase with market volume share at the end of 2012 of 64%, up from 48% at the end of 2011, creating a significantly more sustainable business.

Operating profit increased +3% (constant) to £536m. The operating margin was down -400 bps to 64.0%, due to lower margins of the film variant, downward pricing pressure in Europe, and second half increase in BEI for advertising and marketing programmes to increase patient awareness about the film and treatment. We also increased investment in the clinical pipeline. We expect this gradual increase in investment to continue into 2013 and beyond as we build a strong, sustainable growth business.

Food. The Group owns a largely North American food business, the principal brands of which are the Powerbrand French's Mustard (the No.1 mustard), and Frank's Red Hot Sauce (the No.1 hot sauce and wing sauce in North America).

2012 net revenue increased +2% to £321m underpinned by continued growth in French's Mustard and Frank's Red Hot Sauce. The second half was flat due to weaker US market conditions and increased private label activity, particularly around French's Fried Onions. Our core French's Mustard and Frank's Red Hot franchises remain strong.

Operating margins fell by -80 bps to 28.7% due to adverse mix and input costs.

THE GROUP'S BRAND PORTFOLIO, MARKET POSITION AND PERFORMANCE

The Group benefits from many very strong market positions for its brand portfolio and has leading positions in selected health, hygiene and home categories. These positions derive from the strength of the Group's leading brands, described as Powerbrands, which are the flagship brands in the Group's three major categories and on which the Group focuses the majority of its efforts and investment. The Group also has other portfolio brands which play a role as builders of scale in local markets.

These leading positions include:

Health

The health category consists of products that relieve or solve common health problems.

- No 1 worldwide in medicated sore throat products with the Powerbrand Strepsils.
- No.1 worldwide in condoms for both safe and more pleasurable sex, with the Powerbrand Durex.
- No.2 worldwide in cold and flu (including decongestants) with the Powerbrand Mucinex.
- Leading positions in analgetics and upper gastro-intestinal products in Europe and Australia with the Powerbrands Nurofen and Gaviscon.
- Leading positions in footcare and comfort footwear in many markets outside North America and Latin America, with the Powerbrand Scholl.
- The Group also has local leading positions in denture care, dry skin care and cold and flu products.

2012 Results excluding RB Pharmaceuticals

In light of the announcement of generic competition to Suboxone in the US, the Group provides the following information relating to the performance of the business in 2012 excluding RB Pharmaceuticals.

	RB ex RB Pharmaceuticals		RB Pharmaceuticals		Total RB	
	£m	%	£m	%	£m	%
Net revenue	8,730	+5%*	837	+10%*	9,567	+5%*
Adjusted operating profit	2,034	+7%**	536	+3%**	2,570	+6%**
Adjusted operating margin		+23.3%		64.0%		+26.9%

* like-for-like at constant exchange rates ** at constant exchange rates

This report is part of an integrated approach to reporting our total performance. Our family of reports also includes the Annual Report Highlights, the Sustainability Report on our social and environmental responsibilities, and regularly updated corporate responsibility information at www.rb.com

Left: Annual Report Highlights 2012

Right: Sustainability Report 2011 (2012 report to be published at www.rb.com)

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Printed by The Colourhouse
The paper used for this report is produced using a Elemental Chlorine Free (ECF) bleaching process with FSC (Forest Stewardship Council) Mix Credit certified pulp from sustainable forests with a verifiable chain of custody. The envelope used for postal distribution of this report is made from FSC certified sustainable forest stocks.

Exhibit 6

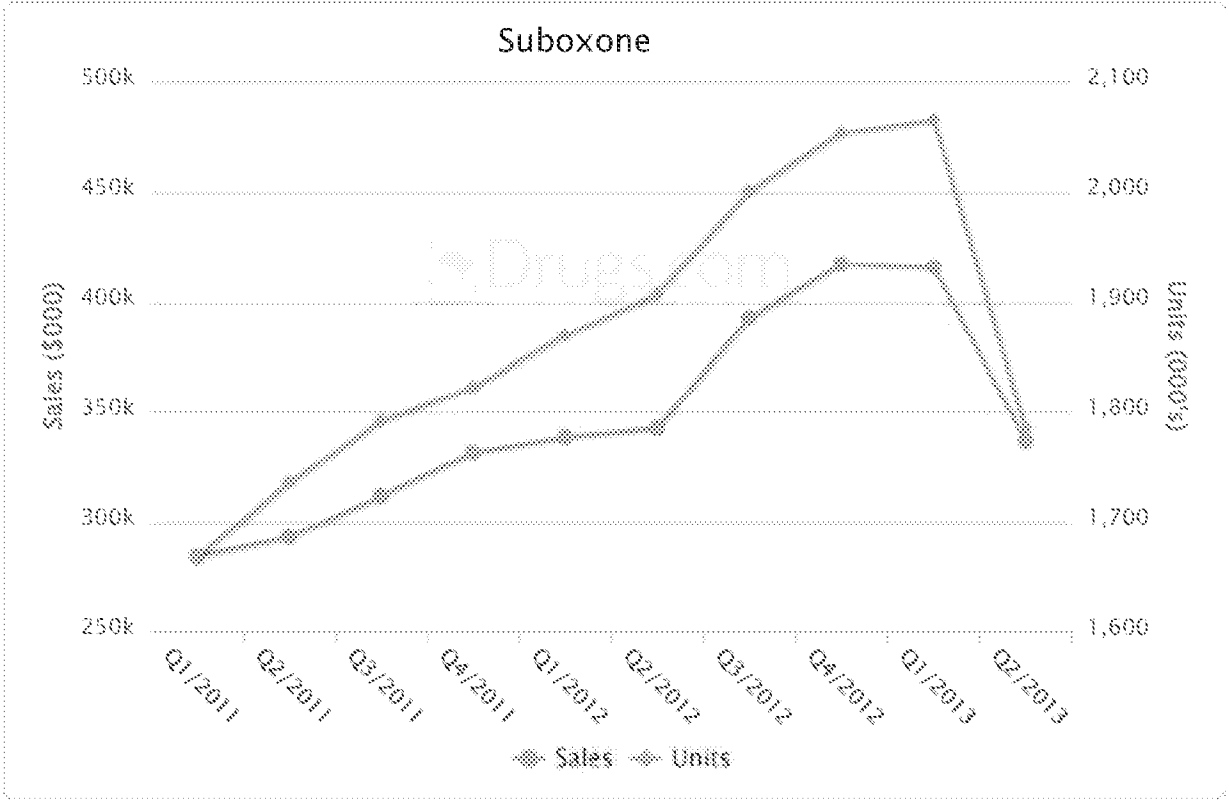
Drug Information Online
Drugs.com

Suboxone Sales Data

Last updated: August 2013 (updated quarterly).
The following data shows Suboxone U.S. retail sales in Q2 2013 compared to previous quarters.

Rank
37

Current sales rank, all U.S. Pharmaceuticals.



Date Range	Sales Rank	Sales ($000)		Units (000)	
Q2 2013	37 (▼9)	$337,109	-18.95%	1,785	-13.60%
Q1 2013	28 (▼1)	$415,929	-0.32%	2,066	0.58%
Q4 2012	27 (▲1)	$417,264	6.18%	2,054	2.65%
Q3 2012	28 (▲14)	$392,977	14.83%	2,001	4.93%
Q2 2012	42 (▲2)	$342,816	1.17%	1,907	1.98%
Q1 2012	44	$338,840	2.14%	1,870	2.58%
Q4 2011	44 (▼1)	$331,741	6.35%	1,823	1.73%
Q3 2011	43 (▲4)	$311,941	6.42%	1,792	3.23%
Q2 2011	47 (▲6)	$293,115	3.08%	1,736	4.08%

DRL - EXHIBIT 1007
DRL1049

Q1 2011	53	$284,350	[illegible]	1,668	[illegible]

* Units refer to the number of packages sold.

See Also

- Suboxone Consumer Information
- Suboxone Professional Monograph
- Search for Suboxone News
- Top 100 Prescription Sales

Exhibit 7

⟨905⟩ UNIFORMITY OF DOSAGE UNITS

Change to read:

This general chapter is harmonized with the corresponding texts of the *European Pharmacopoeia* and the *Japanese Pharmacopoeia*. Portions of the general chapter text that are national *USP* text, are not part of the harmonized text, are marked with symbols (✦✦) to specify this fact.

✦NOTE—In this chapter, *unit* and *dosage unit* are synonymous.✦

To ensure the consistency of dosage units, each unit in a batch should have a drug substance content within a narrow range around the label claim. Dosage units are defined as dosage forms containing a single dose or a part of a dose of drug substance in each unit. The uniformity of dosage units specification is not intended to apply to suspensions, emulsions, or gels in unit-dose containers intended for external, cutaneous administration.

The term "uniformity of dosage unit" is defined as the degree of uniformity in the amount of the drug substance among dosage units. Therefore, the requirements of this chapter apply to each drug substance being comprised in dosage units containing one or more drug substances, unless otherwise specified elsewhere in this Pharmacopeia.

The uniformity of dosage units can be demonstrated by either of two methods, *Content Uniformity* or ✦*Weight*✦*Variation* (see *Table 1*). The test for *Content Uniformity* of preparations presented in dosage units is based on the assay of the individual content of drug substance(s) in a number of dosage units to determine whether the individual content is within the limits set. The *Content Uniformity* method may be applied in all cases.

The test for ✦*Weight*✦*Variation* is applicable for the following dosage forms:

(W1)	Solutions enclosed in unit-dose containers and into soft capsules;
(W2)	Solids (including powders, granules, and sterile solids) that are packaged in single-unit containers and contain no active or inactive added substances;
(W3)	Solids (including sterile solids) that are packaged in single-unit containers, with or without active or inactive added substances, that have been prepared from true solutions and freeze-dried in the final containers and are labeled to indicate this method of preparation; and
(W4)	Hard capsules, uncoated tablets, or film-coated tablets, containing 25 mg or more of a drug substance comprising 25% or more, by weight, of the dosage unit or, in the case of hard capsules, the capsule contents, except that uniformity of other drug substances present in lesser proportions is demonstrated by meeting the requirements for *Content Uniformity*.

The test for *Content Uniformity* is required for all dosage forms not meeting the above conditions for the ✦*Weight*✦ *Variation* test.■ ■2s (USP34)

Table 1. Application of Content Uniformity (CU) and Weight Variation (WV) Tests for Dosage Forms

Dosage Form	Type	Subtype	Dose & Ratio of Drug Substance: ≥25 mg and ≥25%	Dose & Ratio of Drug Substance: <25 mg or <25%
Tablets	Uncoated		WV	CU
	Coated	Film	WV	CU
		Others	CU	CU
Capsules	Hard		WV	CU
	Soft	Suspension, emulsion, or gel	CU	CU
		Solutions	WV	WV
Solids in single-unit containers	Single component		WV	WV
	Multiple components	Solution freeze-dried in final container	WV	WV
		Others	CU	CU
Solutions in unit-dose containers ✦and into soft capsules✦			WV	WV
Others			CU	CU

Change to read:

CONTENT UNIFORMITY

Select not fewer than 30 units, and proceed as follows for the dosage form designated.

Where different procedures are used for assay of the preparation and for the *Content Uniformity* test, it may be necessary to establish a correction factor to be applied to the results of the latter.

Solid Dosage Forms—Assay 10 units individually using an appropriate analytical method. Calculate the acceptance value (see *Table 2*).

Liquid ■or Semi Solid■2s (USP34) Dosage Forms—■Assay 10 units individually using an appropriate analytical method.■2s (USP34) Carry out the assay on the amount of well-mixed material that is removed from an individual container

■ ✦European Pharmacopoeia and Japanese Pharmacopoeia text not accepted by the United States Pharmacopeia. Alternatively, products listed in them (4) above that do not meet the 25 mg/25% threshold limit may be tested for uniformity of dosage units by Mass Variation instead of the Content Uniform ity test if the concentration relative standard deviation (RSD) of the drug substance in the final dosage units is not more than 2%, based on process validation data and development data, and if there has been regulatory approval of such a change. The concentration RSD is the RSD of the concentration per dosage unit (w/w or w/v), where concentration per dosage unit equals the assay result per dosage unit divided by the individual dosage unit weight. See the RSD formula in Table 2.✦

in conditions of normal use, and express the results as delivered dose. Calculate the acceptance value (see *Table 2*).

Calculation of Acceptance Value—Calculate the acceptance value by the formula:

$$\left|M - \bar{X}\right| + ks$$

in which the terms are as defined in *Table 2*.

Table 2

Variable	Definition	Conditions	Value
$\bar{X}$	Mean of individual contents (χ_1, χ_2, … , χ_n), expressed as a percentage of the label claim		
χ_1, χ_2, … , χ_n	Individual contents of the units tested, expressed as a percentage of the label claim		
n	Sample size (number of units in a sample)		
k	Acceptability constant	If n = 10, then k =	2.4
		If n = 30, then k =	2.0
s	Sample standard deviation		$\left[\frac{\sum_{i=1}^{n}(\chi_i - \bar{X})^2}{n-1}\right]^{\frac{1}{2}}$
RSD	Relative standard deviation (the sample standard deviation expressed as a percentage of the mean)		$100s/\bar{X}$
M (case 1) to be applied when T ≤101.5	Reference value	If 98.5% ≤$\bar{X}$ ≤101.5%, then	M = $\bar{X}$ (AV = ks)
		If $\bar{X}$ <98.5%, then	M = 98.5% (AV = 98.5 – $\bar{X}$ + ks)
		If $\bar{X}$ >101.5%, then	M = 101.5% (AV = $\bar{X}$ – 101.5 + ks)
M (case 2) to be applied when T >101.5	Reference value	If 98.5 ≤$\bar{X}$ ≤T, then	M = $\bar{X}$ (AV = ks)
		If $\bar{X}$ <98.5%, then	M = 98.5% (AV = 98.5 – $\bar{X}$ + ks)
		If $\bar{X}$ >T, then	M = T% (AV = $\bar{X}$ – T + ks)
Acceptance value (AV)			general formula: $\left\|M - \bar{X}\right\| + ks$ (Calculations are specified above for the different cases.)
L1	Maximum allowed acceptance value		L1 = 15.0 unless otherwise specified

Table 2 *(Continued)*

Variable	Definition	Conditions	Value
L2	Maximum allowed range for deviation of each dosage unit tested from the calculated value of M	On the low side, no dosage unit result can be less than [1–(0.01)(L2)]M, while on the high side no dosage unit result can be greater than [1 + (0.01)(L2)]M. (This is based on an L2 value of 25.0.)	L2 = 25.0 unless otherwise specified
T	Target content per dosage unit at the time of manufacture, expressed as a percentage of the label claim. •Unless otherwise stated, T is 100.0 per cent, or T is the manufacturer's approved target content per dosage unit.•		

•WEIGHT• VARIATION

Carry out an assay for the drug substance(s) on a representative sample of the batch using an appropriate analytical method. This value is result A, expressed as percent of label claim (see *Calculation of Acceptance Value*). Assume that the concentration (weight of drug substance per weight of dosage unit) is uniform. Select not fewer than 30 dosage units, and proceed as follows for the dosage form designated.

Uncoated or Film-Coated Tablets—Accurately weigh 10 tablets individually. Calculate the content, expressed as % of label claim, of each tablet from the •weight• of the individual tablet and the result of the *Assay*. Calculate the acceptance value.

Hard Capsules—Accurately weigh 10 capsules individually, taking care to preserve the identity of each capsule. Remove the contents of each capsule by a suitable means. Accurately weigh the emptied shells individually, and calculate for each capsule the net •weight• of its contents by subtracting the •weight• of the shell from the respective gross •weight•. Calculate the drug substance content of each capsule from the •net weight• of the individual capsule •content• and the result of the *Assay*. Calculate the acceptance value.

Soft Capsules—Accurately weigh 10 intact capsules individually to obtain their gross •weights•, taking care to preserve the identity of each capsule. Then cut open the capsules by means of a suitable clean, dry cutting instrument such as scissors or a sharp open blade, and remove the contents by washing with a suitable solvent. Allow the occluded solvent to evaporate from the shells at room temperature over a period of about 30 minutes, taking precautions to avoid uptake or loss of moisture. Weigh the individual shells, and calculate the net contents. Calculate the drug substance content in each capsule from the •weight• of product removed from the individual capsules and the result of the assay. Calculate the acceptance value.

Solid Dosage Forms Other Than Tablets and Capsules—Proceed as directed for *Hard Capsules*, treating each unit as described therein. Calculate the acceptance value.

Liquid Dosage Forms—Accurately weigh the amount of liquid that is removed from each of 10 individual containers in conditions of normal use. If necessary, compute the equivalent volume after determining the density. Calculate the drug substance content in each container from the mass of product removed from the individual containers and the result of the assay. Calculate the acceptance value.

Calculation of Acceptance Value—Calculate the acceptance value as shown in *Content Uniformity*, except that the individual contents of the units are replaced with the individual estimated contents defined below.

$\chi_1, \chi_2, \ldots, \chi_n$	=	individual estimated contents of the units tested, where $\chi_i = w_i \times A/\overline{W}$
$w_1, w_2, \ldots, w_n$	=	individual •weights• of the units tested
A	=	content of drug substance (% of label claim) obtained using an appropriate analytical method
$\overline{W}$	=	mean of individual •weights• $(w_1, w_2, \ldots, w_n)$

Change to read:

CRITERIA

Apply the following criteria, unless otherwise specified.

Solid, •Semi-Solid,• (USP34) and Liquid Dosage Forms—The requirements for dosage uniformity are met if the acceptance value of the first 10 dosage units is less than or equal to L1%. If the acceptance value is > L1%, test the next 20 units, and calculate the acceptance value. The requirements are met if the final acceptance value of the 30 dosage units is ≤ L1%, and no individual content of •any• dosage unit is less than [1 – (0.01)(L2)]M nor more than [1 + (0.01)(L2)]M •as specified• in the *Calculation of Acceptance Value* under *Content Uniformity* or under •*Weight* *Variation*. Unless otherwise specified, L1 is 15.0 and L2 is 25.0.

Exhibit 8

U.S. PHARMACOPEIAL CONVENTION

USP–NF General Chapter <905> Uniformity of Dosage Units

Type of Posting Explanatory Note
Posting Date20–Apr–2007

This explanatory note is intended to clarify the steps taken by USP to address issues regarding the harmonization of <905> Uniformity of Dosage Units. It includes current chapter revision status, background information, testing requirements, statistical basis, information about the upcoming revision, and frequently asked questions.

Status of General Chapter <905>

As of January 1, 2007, the updated, harmonized revision of General Chapter <905> published as an Interim Revision Announcement in Pharmacopeial Forum 32(6) [November–December 2006] is official. This version also is published in the 1st Supplement to USP 30–NF 25.

Revision History and Rationale

The ICH Steering Committee considers international harmonization of about 10 specific compendial test chapters as critical to attaining full utility of the ICH Q6A guideline. ICH Q6A recommended the harmonization of certain tests for dosage forms, including General Chapter <905>.

- USP published a revised, harmonized General Chapter <905> on pages 2505–2510 of USP 28–NF 23 with an implementation date of April 1, 2006. This chapter contains the global harmonized text approved by the Pharmacopeial Discussion Group (PDG) as well as USP–specific national text. The PDG consists of USP, the Japanese Pharmacopeia, and the European Pharmacopeia.
- In Pharmacopeial Forum 31(6) [November–December 2005], USP postponed the implementation date of the revised, harmonized General Chapter <905> to January 1, 2007, to allow USP to consider comments received on Weight Variation as a test alternative in certain cases.
- In USP 29–NF 24, both the official and the revised, harmonized versions of <905> appeared. The revised, harmonized version (pages 2760–2765) was to become official on January 1, 2007, but was superseded by the subsequent revision in the Sixth Interim Revision Announcement to USP 29–NF 24 in Pharmacopeial Forum 32(6) [November–December 2006].

Official Harmonized Chapter <905>

The revision of General Chapter <905> that became official on January 1, 2007, was initially proposed in Pharmacopeial Forum 32(4) [July–August 2006] and made official through the Sixth Interim Revision Announcement to USP 29–NF 24 in Pharmacopeial Forum 32(6) [November–December 2006]. The official text includes changes based on the comments received.

Harmonized Chapter Testing Requirements

<905> includes Content Uniformity and Weight Variation procedures and acceptance criteria to evaluate uniformity of dosage units. These apply to both newly registered and existing products.

Content Uniformity is the default test and may be applied in all cases. The test for Weight Variation is applicable for dosage forms specified as W1, W2, W3, and W4.

- The requirements for dosage uniformity are met if the acceptance value of the first 10 dosage units is less than or equal to L1%.
- If the acceptance value is greater than L1%, test the next 20 units and calculate the acceptance value. The requirements are met if the final acceptance value of the 30 dosage units is less than or equal to L1% and all individual dosage units fall within the ranges calculated using L2 factor.

Statistical Basis of the New Content Uniformity Criteria

The primary concept underlying the criteria in the revised <905> Uniformity of Dosage Units is that of statistical tolerance intervals. The general idea of tolerance intervals is to use the available data to form an interval that covers a specified proportion of the distribution underlying the data. For content uniformity, this would be the distribution of content and the intent is to form an interval about the label claim within which a specified proportion of units would fall. Technically, an interval (a, b) is a 95% (the "confidence") tolerance interval for 90% of the distribution (the "coverage") if 95% of such intervals with repeated sampling would cover at least 90% of the distribution. The tolerance intervals can be parametric or nonparametric. Parametric intervals are based on an assumed distribution, usually the normal. When assuming the normal distribution, two–sided tolerance intervals are of the form, , where is the average, S the standard deviation, and k depends on the coverage,

confidence, and sample size. (The multiplier, k, becomes smaller as sample size increases, but never to 0. For 95% coverage, for example, it will decrease to 1.96.) This is the form of the criteria used in General Chapter <905>.

The basic tolerance interval has been modified in four ways in constructing the criteria of General Chapter <905>:

1. The tolerance interval is modified to correspond to the standard two-stage testing of content uniformity; i.e., where 10 units are tested and then, if needed, an additional 20 are tested. This requires a k1 after the first stage and then a different k2 after the second stage, if needed, where the sample is larger.
2. The acceptance interval is allowed to be asymmetric with respect to the label claim in those cases where the potency range specified in the monograph is not symmetric. The T of General Chapter <905> is the center of the potency range.
3. A 1.5% interval about the label claim is included so deviations of the mean content from the label claim count only to the extent they are greater than this percentage. This is reflected in the calculation of M.
4. The k's are chosen so that the new procedure has operating characteristics similar to those of the prior General Chapter <905> criteria. Having similar operating characteristics does NOT mean that data that would pass by the prior criteria will pass by the new criteria and similarly for data that would fail. What it means is that is for data drawn from a distribution that is acceptable for content uniformity, the probability of passing is similar with the old and new criteria.

Statistical References

Further information regarding the statistical basis of the chapter is available in the references noted below.

1. Ketori, N, Aoyagi N, Kojima S, A Proposal for Revision of the Content Uniformity Test and Weight Variation Test, PF 23(6), 5325–5333, 1997.
2. Content Uniformity—Evaluation of the USP Pharmacopeial Preview, Members of the Statistics Working Group PhRMA, PF 24(5), 7029–7044, 1998.
3. Content Uniformity—Alternative to the USP Pharmacopeial Preview, Members of the Statistics Working Group PhRMA, PF 25(2), 7939–7946, 1999.
4. Recommendation for a Globally Harmonized Uniformity of Dosage Units Test, Members of the Statistics Working Group PhRMA, PF 25(4), 8609–8624, 1999.
5. Recommendations for a Globally Harmonized Uniformity of Dosage Units Test, Members of the Statistics Working Group PhRMA, PF 25 (4), 8609–8624, 1999.

Calculation Examples

On the following pages are 3 examples involving different outcomes.

Please submit comments or further inquiries on this topic to William Brown, Senior Scientist at web@usp.org or +1-301-816-8380.

Example 1: Pass on First			
95	lower monograph limit		
110	upper monograph limit	**102.5**	T value
15.0	L1 (use 15.0 unless monograph specifies a different value)		
25.0	L2 (use 25.0 unless monograph specifies a different value)		
Step 1 --- content (or weight) of 10 units --- X1, ..., X10			
102.00000	Average of the 10 values expressed as % of the label claim (do not round) --- AVERAGE(X1, ..., X10)		

4.60000	Standard deviation of the 10 values expressed as % of the label claim (do not round) — STDEV(X1, ..., X10)		
102.00000	M value		
11.04000	AV		
Result:	Pass, stop here		
	(USP rounding applied)		
Step 2 — content (or weight) of 20 additional units — X11, –, X30			
	Average of the 30 values expressed as % of the label claim (do not round) — AVERAGE(X1, –, X30)		
	Standard deviation of the 30 values expressed as % of the label claim (do not round) — STDEV(X1, –, X30)		
	Minimum value of the 30, expressed as % of the label claim		
	Maximum value of the 30, expressed as % of the label claim		
	M value		
	AV		
	Minimum allowed value of 30, expressed as % of label claim		
	Maximum allowed value of 30, expressed as % of label claim		
Result:			
	(USP rounding applied)		

Example 2: Fail–Pass		

90	lower monograph limit		
110	upper monograph limit	100.0	T value
15.0	L1 (use 15.0 unless monograph specifies a different value)		
25.0	L2 (use 25.0 unless monograph specifies a different value)		
Step 1 ---- content (or weight) of 10 units ---- X1, ..., X10			
107.00000	Average of the 10 values expressed as % of the label claim (do not round) ---- AVERAGE(X1, ..., X10)		
4.60000	Standard deviation of the 10 values expressed as % of the label claim (do not round) ---- STDEV(X1, ..., X10)		
101.50000	M value		
16.54	AV		
Result:	Does not pass; proceed to step 2		
	(USP rounding applied)		
Step 2 ---content (or weight) of 20 additional units ---- X11, --, X30			
106.50000	Average of the 30 values expressed as % of the label claim (do not round) ---- AVERAGE(X1, --, X30)		
4.60000	Standard deviation of the 30 values expressed as % of the label claim (do not round) ---- STDEV(X1, --, X30)		
78.00000	Minimum value of the 30, expressed as % of the label claim		
118.20000	Maximum value of the 30, expressed as % of the label claim		
101.50000	M value		
14.20000	AV		

76.1	Minimum allowed value of 30, expressed as % of label claim		
126.9	Maximum allowed value of 30, expressed as % of label claim		
Result:	Passes		
	(USP rounding applied)		

Example 3: Fail–Fail			
90	lower monograph limit		
110	upper monograph limit	100	T value
15.0	L1 (use 15.0 unless monograph specifies a different value)		
25.0	L2 (use 25.0 unless monograph specifies a different value)		
Step 1 — content (or weight) of 10 units — X1, ..., X10			
107.00000	Average of the 10 values expressed as % of the label claim (do not round) — AVERAGE(X1, ..., X10)		
4.60000	Standard deviation of the 10 values expressed as % of the label claim (do not round) — STDEV(X1, ..., X10)		
101.50000	M value		
16.54000	AV		
Result:	Does not pass; proceed to step 2		
	(USP rounding applied)		
Step 2 — content (or weight) of 20 additional units — X11, ..., X30			

100.50000	Average of the 30 values expressed as % of the label claim (do not round) — AVERAGE(X1, –, X30)		
5.20000	Standard deviation of the 30 values expressed as % of the label claim (do not round) ---- STDEV(X1, –, X30)		
94.70000	Minimum value of the 30, expressed as % of the label claim		
127.10000	Maximum value of the 30, expressed as % of the label claim		
101.50000	M value		
15.40000	AV		
75.1	Minimum allowed value of 30, expressed as % of label claim		
125.9	Maximum allowed value of 30, expressed as % of label claim		
Result:	Fails		
	(USP rounding applied)		

Frequently Asked Questions

Question: What is meant by the term "special procedure" as found under Content Uniformity in the official chapter?

Answer: Typically, the Content Uniformity determination is made on individual dosage units using the procedure found in the Assay. For certain products, a separate procedure is given in the monograph. Where that is the case, the monograph procedure would be considered a special procedure for content uniformity. Theophylline Extended–Release Capsules is an example of a monograph requiring a special procedure for content uniformity.

Question: The harmonized <905> Uniformity of Dosage Units became official on January 1, 2007. Does the harmonized chapter completely replace the current text?

Answer: Yes. As of January 1, 2007, only the revised, harmonized chapter text is official.

Question: I have heard from European colleagues that existing products may be exempt from the requirements of the harmonized chapter and that it will only apply to new formulations. Will the USP allow such grandfathering?

Answer: The harmonized chapter text applies to any monograph, new or existing, that includes a test for Uniformity of Dosage Units.

Question: What is the maximum allowable acceptance value for Content Uniformity testing at level 2, where a total of 30 dosage units have been tested? Our confusion is in the use of the L1 and L2 values (15.0 and 25.0, respectively).

Answer: Content Uniformity testing can be performed in two stages. The first stage has a total of 10 dosage units tested, and an additional 20 dosage units are tested to complete testing at the second stage. L1 is used as the limit for the acceptance value for both stages of test. L2 is used only in the second stage of testing where a total of 30 dosage units have been tested, and it is only used in the calculation of the allowed limits for individual dosage unit content.

Question: Weight Variation is allowed for hard capsules, uncoated tablets, and film–coated tablets containing 25 mg or more of the drug substance comprising 25% or more of the weight of the dosage unit. If a product, such as an uncoated tablet, contains two drug substances but only one of them meets the requirement for weight variation, how can the requirement be met?

Answer: Weight Variation is generally seen as requiring less lab work than the procedure for Content Uniformity. Thus, the allowance to substitute Weight Variation for Content Uniformity may be seen as offering a benefit to manufacturers. In the case of a two-component tablet, the Uniformity of Dosage Units test requirement will be met by the Weight Variation procedure for the component that is present at 25 mg or more and also comprising 25% of the total dosage unit mass. The other component will require the Content Uniformity procedure.

CERTIFICATE OF FIRST CLASS SERVICE

It is certified that a copy of the foregoing **EXHIBITS**, has been served, by first class mail, on September 3, 2013, in its entirety on the third party requester as provided in 37 CFR § 1.903 and 37 CFR § 1.248 at the address below.

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BOSTON, MASSACHUSETTS 02110

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Electronic Acknowledgement Receipt

EFS ID:	16754045
Application Number:	95002170
International Application Number:	
Confirmation Number:	6418
Title of Invention:	POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM
First Named Inventor/Applicant Name:	7897080
Customer Number:	23869
Filer:	Michael I. Chakansky
Filer Authorized By:	
Attorney Docket Number:	117744-00023
Receipt Date:	03-SEP-2013
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Application Type:	inter partes reexam

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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		080REPLYTOACPPTO.pdf	789960 b8906f6f7527c81c3460a8c0f0bfcf84a9c0c36a	yes	100

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Patent Owner Comments after Action Closing Prosecution	1	99
	Reexam Certificate of Service	100	100

Warnings:					
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2		080ACPRESPONSEEXHIBITSPTO3.pdf	8446150 aefb103d54aa60db6f57381cb1088c46e455678e	yes	69

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Reexam Miscellaneous Incoming Letter	1	68
	Reexam Certificate of Service	69	69

Warnings:	
Information:	
Total Files Size (in bytes):	9236110

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
95/002,170	09/10/2012	7897080	117744-00023	6418

23869 7590 07/31/2013

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EXAMINER
DIAMOND, ALAN D

ART UNIT	PAPER NUMBER
3991	

MAIL DATE	DELIVERY MODE
07/31/2013	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

DRL - EXHIBIT 1007
DRL1066

ACTION CLOSING PROSECUTION (37 CFR 1.949)	**Control No.** 95/002,170	**Patent Under Reexamination** 7897080
	Examiner Alan Diamond	**Art Unit** 3991

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address. --

Responsive to the communication(s) filed by:
Patent Owner on 13 March, 2013
Third Party(ies) on 12 April, 2013

Patent owner may once file a submission under 37 CFR 1.951(a) within 1 month(s) from the mailing date of this Office action. Where a submission is filed, third party requester may file responsive comments under 37 CFR 1.951(b) within 30-days (not extendable- 35 U.S.C. § 314(b)(2)) from the date of service of the initial submission on the requester. **Appeal cannot be taken from this action.** Appeal can only be taken from a Right of Appeal Notice under 37 CFR 1.953.

All correspondence relating to this inter partes reexamination proceeding should be directed to the **Central Reexamination Unit** at the mail, FAX, or hand-carry addresses given at the end of this Office action.

PART I. THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892
2. ☒ Information Disclosure Citation, PTO/SB/08
3. ☐ _____

PART II. SUMMARY OF ACTION:

1a. ☒ Claims See Continuation Sheet are subject to reexamination.
1b. ☐ Claims _____ are not subject to reexamination.
2. ☒ Claims See Continuation Sheet have been canceled.
3. ☐ Claims _____ are confirmed. [Unamended patent claims]
4. ☐ Claims _____ are patentable. [Amended or new claims]
5. ☒ Claims See Continuation Sheet are rejected.
6. ☐ Claims _____ are objected to.
7. ☐ The drawings filed on _____ ☐ are acceptable ☐ are not acceptable.
8 ☐ The drawing correction request filed on _____ is: ☐ approved. ☐ disapproved.
9 ☐ Acknowledgment is made of the claim for priority under 35 U.S.C. 119 (a)-(d). The certified copy has:
☐ been received. ☐ not been received. ☐ been filed in Application/Control No _____
10. ☐ Other _____

Continuation of SUMMARY OF ACTION: 1a. Claims subject to reexamination are 1-11,13-15,17-90,92-94,96-172,174-176,178-253,256,258-271,274,276-289,292 and 294-318.

Continuation of SUMMARY OF ACTION: 2. Claims have been canceled are 12,16,91,95,173,177,254,255,257,272,273,275,290,291 and 293.

Continuation of SUMMARY OF ACTION: 5. Claims rejected are 1-11,13-15,17-90,92-94,96-172,174-176,178-253,256,258-271,274,276-289,292 and 294-318.

Summary of Proceedings

A Request pursuant to 37 CFR 1.913 for inter partes reexamination of claims 1-299 of U.S. Patent 7,897,080 (hereinafter "the '080 patent") was filed September 10, 2012 by Third Party Requester. Accompanying the request was a Rule 1.132 declaration of Edward D. Cohen ("Cohen Declaration"). An Order granting inter partes reexamination and a non-final Office action rejecting claims 1-299 of the '080 patent were mailed October 22, 2012. The Office action was re-mailed November 29, 2012.

On March 13, 2013, Patent Owner filed a response including an amendment which amends claims 1, 13, 14, 28, 81, 82, 92, 93, 107, 114, 160, 161, 174, 175, 189, 242, 244, 262 and 280; cancels claims 12, 16, 91, 95, 173, 177, 254, 255, 257, 272, 273, 275, 290, 291 and 293; and adds new claims 300-318. The response further includes a Rule 1.132 declaration by Arlie Bogue (hereafter "Bogue Declaration") and a Rule 1.132 declaration by David T. Lin (hereafter "Lin Declaration").

On April 12, 2013, Third Party Requester filed comments including Rule 1.132 declarations by Jason O. Clevenger (hereafter "Clevenger Declaration") and Maureen Reitman (hereafter "Reitman Declaration").

Claim Amendment

With respect to the claim amendment filed March 13, 2013, in claim 161 at the third line on page 21, the comma after the word "thereof" must be underlined since it is not part of issued claim 161. The Examiner has underlined the comma, and the corrected amendment has been scanned into the electronic file.

Art Cited in Rejections in this Action Closing Prosecution

Chen et al, WO 00/42992, hereafter "Chen".

Staab, U.S. Patent 5,393,528.

Le Person et al, "Near infrared drying of pharmaceutical thin films: experimental analysis of internal mass transport," Chemical Engineering and Processing, Vol. 37, pp. 257-263, (1998), hereafter "Le Person".

Horstmann et al, U.S. Patent 5,629,003, hereafter "Horstmann".

U.S. Patent 4,365,423 to Arter et al, hereafter "Arter". Arter was made of record in the instant reexamination proceeding by Patent Owner in an IDS filed 01/29/13.

U.S. Patent 5,881,476 to Strobush et al, hereafter "Strobush". Strobush is of record in grandparent U.S. Patent 7,357,891, as well as being made of record in the instant reexamination proceeding by Patent Owner in an IDS filed 01/29/13.

Scope of Claims

In reexamination, patent claims are construed broadly. *In re Yamamoto*, 740 F.2d 1569, 1571, 222 USPQ 934, 936 (Fed. Cir. 1984) (claims given "their broadest reasonable interpretation consistent with the specification"). This reexamination proceeding contains claims 1-11, 13-15, 17-90, 92-94, 96-172, 174-176, 178-253, 256, 258-271, 274, 276-289, 292 and 294-318 directed to a process for manufacturing a resulting film(s) suitable for commercialization and regulatory approval. Claim 1 is representative:

1. (Amended) A process for manufacturing a resulting film suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said [making a]film having a

substantially uniform distribution of components comprising a substantially uniform distribution of said active in individual dosage units of said resulting film, comprising the steps of:

(a) forming a masterbatch pre-mix comprising a solvent and a polymer selected from the group consisting of water-soluble polymers, water-swellable polymers and combinations thereof;

(b) adding [an]said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, to a pre-determined amount of said masterbatch pre-mix to form a flowable polymer matrix, said matrix having a substantially uniform distribution of said active;

(c) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(d) controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus and evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first [10]4 minutes [or fewer]by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, wherein during said drying said flowable polymer matrix temperature is 100 ℃ or less; [and]

(e) forming [a]said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained; and

(f) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units sampled from different locations of said resulting film, said tests indicating that uniformity of content in the amount of the active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration.

Claims 1, 82, 161 and 315-318 recite a step of forming a flowable polymer matrix comprising a recited polymer, a solvent and a recited active, said matrix having a substantially uniform distribution of said active. With respect to the “matrix”, the ‘080 patent, for example, states the following:

> When the active is combined with the polymer in the solvent, the type of matrix that is formed depends on the solubilities of the active and the polymer. If the active and/or polymer are soluble in the selected solvent, this may form a solution. However, if the components are not soluble, the matrix may be classified as an emulsion, a colloid, or a suspension (see col. 22, lines 22-28).
>
> After the desired components are combined to form a multi-component matrix, including the polymer, water, and an active or other components as desired … (see col. 25, lines 55-57).

Accordingly, the "matrix” is taken to be the material that results from mixing the polymer, solvent and active.

With respect to viscoelasticity in steps (d) and (e) of claim 1 and in steps (c) and (d) of claims 82, 161 and 315-318, it is noted that the matrix prior to evaporating the solvent (water) may be viscoelastic, and the viscoelasticity is present due, for example, to the fact that a hydrocolloid has been added. In particular, the '080 patent teaches the following (bold emphasis added):

> The viscosity of the liquid phase is critical and is desirably modified by customizing the liquid composition to a **viscoelastic** non-Newtonian fluid with low yield stress values .... Formation of a **viscoelastic** or a highly structured fluid phase provides additional resistive forces to particle sedimentation. (Col. 8, lines 32-38).
>
> The addition of hydrocolloids to the aqueous phase of the suspension increases viscosity, may produce **viscoelasticity**, and can impart stability depending on

> the type of **hydrocolloid**, its concentration and the particle composition, geometry, size and volume fraction. (Col. 8, lines 42-46).
>
> For **viscoelastic** fluid systems, a rheology that yields stable suspensions for extended time period, such as 24 hours, must be balanced with the requirements of high-speed film casting operations. (Col. 8, line 66 through Col. 9, line 2).
>
> The rheology requirements for the inventive compositions and films are quite severe. This is due to the need to produce a stable suspension of particles, for example 30-60 wt. %, in a **viscoelastic** fluid matrix with acceptable viscosity values throughout a broad shear rate range...
>
> In film casting or coating, rheology is also a defining factor with respect to the ability to form films with the desired uniformity. Shear viscosity, extensional viscosity, **viscoelasticity**, structural recovery will influence the quality of the film. (Col. 9, lines 9-20).
>
> Desirably, the films or film-forming compositions of the present invention have a very rapid structural recovery, i.e. as the film is formed during processing, it doesn't fall apart or become discontinuous in its structure and compositional uniformity. Such very rapid structural recovery retards particle settling and sedimentation. Moreover, the films or film-forming compositions of the present invention are desirably shear-thinning pseudoplastic fluids. Such fluids with consideration of properties, such as **viscosity and elasticity**, promote thin film formation and uniformity. (Col. 9, lines 31-40).
>
> Compositions P-R show the effects of **visco-elastic** properties on the ability to coat the film composition mixture onto the substrate for film formation .... This product coated the substrate but would not stay level due to the change in the **visco-elastic** properties of the wet foam. (Col. 35, lines 55-57, and 61-63).

While the ‘080 does not state what is an example of a hydrocolloid, a well-known hydrocolloid in the art is the water-soluble polymer hydroxypropyl methylcellulose (HPMC), which is used in most of the examples of the ‘080 patent. The Chen reference teaches that HPMC is a hydrocolloid (see p. 14, lines 22-27).

Each of the independent claims recites the newly added term “analytical chemical tests”. This term is not stated or defined in the '080 patent specification.

However, the '080 patent teaches that "[i]t may be desirable to test films of the present invention for chemical and physical uniformity during the manufacturing process"; and that “[a]ny conventional means for examining and testing the film pieces may be employed, such as, for example, visual inspection, use of analytical equipment, and any other suitable means known to those skilled in the art (see col. 28, line 66 through col. 29, line 1; and col. 29, lines 35-39). The '080 patent teaches checking film thickness, overall appearance, examination by the naked eye or under slight magnification, cutting the films into dosage forms and weighing the doses, or dissolving individual doses and testing for the amount of active therein (see col. 29, lines 3-47; and col. 31, line 37 through col. 32, line 39). It is clear that when the '080 patent refers to “physical” uniformity it is referring to, for example, uniformity based on the appearance of the film or the weight of individual doses cut from the film. Likewise, it is clear that when the '080 patent refers to “chemical” uniformity, it is referring to uniformity with respect to the actual amount of active, i.e., chemical, present in the sample. Accordingly, the term “analytical chemical tests” when read in light of the ‘080 patent specification means analytical tests for determining the amount of active content in the recited sample. Pages 56-57 of the Remarks filed 03/13/13 state that physical tests do not determine the actual amount of active in the sample, and that with "chemical uniformity type tests involving analytical equipment … [there is] actual testing of the uniformity of content of the amount of active."

It is noted the ‘080 patent teaches at col. 31, lines 37-44, that a “uniform distribution of components” can be determined by examination by either the naked eye

or under slight magnification, and that "by viewing the films it was apparent that they were substantially free of aggregation, i.e. the carrier and the actives remained substantially in place and did not move substantially from one portion of the film to another … [t]herefore, there was substantially no disparity among the amount of active in any portion of the film." An alternative means for evaluating uniformity is to cut the film into individual doses and measure the weight of the doses (col. 31, line 46 through col. 32, line 45). The '080 patent notes that "films of substantially similar size cut from different locations of the same film contain substantially the same amount of active." (col. 32, lines 37-39).

Proposed Claim Rejection - 35 U.S.C. § 314(a)

On pages 9-11 of the Comments filed 04/12/13, Third Party Requester proposes that all the claims be rejected under 35 USC 314(a) as enlarging the scope of the patent claims. This proposed rejection **is not adopted** for the reasons that follow.

Third Party Requester argues the following on pp. 9-10 of the Comments filed 04/12/13:

> Applicant amends every independent claim to broaden the term "flowable" to encompass viscosities that are not flowable. Step (c) of issued claim 1 and step (b) of issued claims 82 and 161 have been amended as follows:
>
> > casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;
>
> Each and every new independent claim also includes this recitation. Exhibit E provides the viscosity of common materials. As Exhibit E indicates, a viscosity of 100,000 cps corresponds to mincemeat. Materials having the viscosity of mincemeat are not flowable. The new recitation expands the polymer matrix cast in this step beyond that claimed in issued claims 1, 82, and 161--i.e., to include a

> polymer matrix that is not flowable--and thereby impermissibly broadens the scope of the claims beyond those issued in the '080 Patent.

This is unpersuasive. Exhibit E of the Comments filed 04/12/13 shows the viscosities of "common liquids", and mincemeat as well as toothpaste are in the list and can have a viscosity as high as 100,000 cps. Viscosity is equal to shear stress/shear rate, and is a measure of resistance to flow. The higher the viscosity, the more resistance to flow. While mincemeat and toothpaste have more resistance to flow compared to other liquids in Table E, such as milk (viscosity of 1 or 2 cps) and mayonnaise (viscosity of 20,000 cps), mincemeat and toothpaste are flowable. Accordingly, contrary to Third Party Requester's argument, a flowable polymer matrix as here claimed can have a viscosity of about 400 to about 100,000 cps (paragraph bridging cols. 16-17 of the '080 patent) and the instant claims are not broadened.

Third Party Requester argues the following on pp. 10-11 of the Comments filed 04/12/13:

> The issued claims referred to forming a visco-elastic film in less than 10 minutes. The only discussion in the specification, including the examples, for drying for 10 minutes is referring to total drying time:
>
> > For instance, the films of the present invention desirably are dried for 10 minutes or less. Drying the films at 80 °C for 10 minutes produces a temperature differential of about 5 °C. This means that after 10 minutes of drying, the temperature of the inside of the film is 5 °C less than the outside exposure temperature.
> >
> > '080 Patent 13:23-28.
>
> The '080 Patent teaches in this passage that keeping the total drying time short, allows the films to be dried at higher temperatures without heat degradation.

Applicants amends every independent claim to broaden the drying step to require only that viscosity be increased in the first 4 minutes. Step (d) of issued claim 1 and step (c) of issued claims 82 and 161 have been amended as follows:

> ...evaporating at least a portion of said solvent.., to form a visco-elastic film...within about the first [10] 4 minutes [or fewer] by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution...of said film ....

Each and every new independent claim also includes this recitation.

This amendment attempts to "redefine" the evaporating step by shifting from what would be construed as a total drying requirement to what is now merely an initial drying requirement. This amendment thus broadens the step. As newly recited, this step now is accomplished "by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying." This new claim does not require 10 minutes drying time, but only requires an increase in viscosity in the first 4 minutes.

This is unpersuasive. In issued independent claims 1, 82 and 161, the evaporating of at least a portion of the solvent was done "to form a visco-elastic film within about 10 minutes or fewer to maintain said substantially uniform distribution...of said film ....". This is not a total drying requirement. In fact, the '080 patent expressly teaches the following at col. 13, lines 53-59 (bold emphasis added):

> The resulting dried film is a visco-elastic solid. The components desirably are locked into a uniform distribution throughout the film. Although minor amounts of liquid carrier, i.e., water, may remain subsequent to formation of the visco-elastic, the film may be **dried further** without movement of particles, if desired.

Accordingly, the "within about the first 4 minutes" does not broaden the "within about 10 minutes or fewer" time period in the issued independent claims.

Proposed Claim Rejections - 35 USC § 112

The following is a quotation of 35 U.S.C. 112(a):
(a) IN GENERAL.—The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), first paragraph:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of 35 U.S.C. 112(b):
(b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Proposed 35 USC 112 rejections not adopted:

On pages 11-23 of the Comments filed 04/12/13, Third Party Requester proposes several rejections under 35 USC 112, first and second paragraphs. For the following reasons, Third Party Requester's proposed 35 USC 112 rejections **are not adopted**. The lettering used below is consistent with the lettering used by Third Party Requester on pp. 11-23.

A. Third Party Requester proposes that all pending claims be rejected as lacking enablement, clarity and written description due to the recitation "suitable for commercialization and regulatory approval including analytical chemical testing which

meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units" (Comments of 04/12/13, pp. 11-14).

With respect to enablement, Third Party Requester argues the Patent Owner has taken the position that Chen lacks an enabling disclosure because it "lacks sufficient information contained within to allow regulatory FDA approval" of its films; and that if FDA approvability is the standard for enablement, then the '080 patent specification is similarly lacking (Comments of 04/12/13, pp. 11-13). Third Party Requester cites ¶ 8 of the Clevenger Declaration and argues that "[e]ven the Bogue Declaration fails to provide evidence that its "lots" meet the recited standards." (Comments of 04/12/13, p. 13). ¶ 6 of the Clevenger Declaration states the following:

> 6. The analysis in the Bogue Declaration is not consistent with the currently adopted definition of content uniformity as described in USP <905> Uniformity of Dosage Units. The calculation in paragraphs 9 and 10 of the Bogue Declaration are not included within the definition of content uniformity as described in USP <905> Uniformity of Dosage Units.

With respect to lack of clarity, Third Party Requester argues the recitation is ambiguous and unclear because there is no set chemical tests or standards required; and that USP General Chapter <905> which is cited in ¶ 16 of the Lin Declaration "sets forth a number of standards, each of which is entirely different from anything claimed, argued or described in the '080 Patent." (Comments of 04/12/13, pp.13-14)

With respect to written description, Third Party Requester argues the following on p. 14 of the Comments filed 04/12/13:

> Finally, because the new "suitable..." recitation in the pending claims extends beyond what was disclosed or referenced in the specification, the claims lack written description. That is, even if the FDA did have one standard that would apply to all of the films manufactured by the methods claimed in the '080

> Patent--which it does not--the standards have changed over time. For example, in order to harmonize with international standards, the USP General Chapter <905> cited by Applicant in the Lin Declaration, was updated at least twice (i.e., on April 20, 2007, and again on December 1, 2011). See Exhibit J and Exhibit K, and Clevenger Decl. ¶ 4. Accordingly, this new recitation appears to reference something that did not exist when the application was filed, and therefore the claims lack written description.

This proposed rejection **is not adopted** for the following reasons. Said recitation is enabled and definite in view of the recitation in each of the independent claims of a process step of performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units sampled from different locations of said resulting film, said tests indicating that uniformity of content in the amount of the active varies by no more than 10% in independent claims 1, 82, 161, and 315-317, or less that 5% in claim 318. The claims do not require commercialization and regulatory approval, they set forth suitability for commercialization and regulatory approval. The bright line test for such suitability is based on performing analytical chemical tests for uniformity of content of active, said tests showing a particular variation of active, for example, not more than 10%.

The fact that no specific tests are mentioned in the claims is of no consequence since one of ordinary skill in the art knows what tests can be used. The '080 patent teaches testing the films for physical and chemical uniformity (col. 28, lines 6-67) and that "[a]ny conventional means for examining and testing the film pieces may be employed, such as, for example … the use of analytical equipment, and any other suitable means known to those skilled in the art." (col. 29, lines 35-38). In fact, ¶ 7 of Third Party Requester's Reitman Declaration uses a well-known technique, i.e., HPLC.

The Clevenger Declaration argues that the calculations in paragraphs 9 and 10 of the Bogue Declaration are not included within the definition of content uniformity as described in USP <905> Uniformity of Dosage Units. However, the instant claims do not state that any calculation has to meet the definition of content uniformity as described in USP <905> Uniformity of Dosage Units. The claims require a resulting film "suitable" for commercialization and regulatory approval which meets FDA standards. The bright line test in the claims for such suitability, as seen, for example, in step (f) of claim 1, is an active content that varies by no more than a particular percentage. In claim 1, the active content varies by no more than 10%.

Said recitation has written description in the '080 patent. The desire to prepare films that are suitable for commercialization and regulatory approval is noted in the Background of the Related Technology section of the '080 patent at col. 3, lines 58-60. Likewise, the Background of the Related Technology section teaches the following at col. 2, lines 36-46:

> Failure to achieve a high degree of accuracy with respect to the amount of active ingredient in the cut film can be harmful to the patient. For this reason, dosage forms formed by processes such as Fuchs, would not likely meet the stringent standards of governmental or regulatory agencies, such as the U.S. Federal Drug Administration ("FDA"), relating to the variation of active in dosage forms. Currently, as required by various world regulatory authorities, dosage forms may not vary more than 10% in the amount of active present. When applied to dosage units based on films, this virtually mandates that uniformity in the film be present."

Even further, col. 15, lines 37-42 of the '080 patent teach "the uniformity of the present invention is determined by the presence of no more than a 10% by weight of pharmaceutical and/or cosmetic variance throughout the matrix. Desirably, the variance

is less than 5% by weight, less than 2% by weight, less than 1% by weight, or less than 0.5% by weight."

B. Third Party Requester proposes that all pending claims be rejected as lacking clarity and written description due to the recitation "chemical analytical tests" (Comments of 04/12/13, pp. 14-15). In particular, Third Party Requester argues the following on pp. 14-15 of the Comments filed 04/12/13:

> 1. *Lack of Clarity*
>
> Independent claims 1, 82, 161 and 315-318 newly recite the term "analytical chemical tests." The term "analytical chemical tests" is vague and unclear. What is an "analytical chemical test" and how does it differ from a non-chemical test or a non-analytical test? Applicant does not disclose any analytical chemical tests or testing of active in the specification, but rather the desirability of testing for chemical and physical uniformity. Testing for chemical uniformity would include weight variation testing according to the FDA, but Applicant insists this is not an analytical chemical test. Compare Exhibit J at p. 1 to Reply at p. 58-59.
>
> Is a chemical transformation required? If so, HPLC testing would not be an analytical chemical test. And HPLC testing is commonly used to assess active content. The confusion is compounded by Applicant's statements that weighing cannot be relied upon to assess uniformity of content data. However, the FDA clearly provides that weight variation testing is a content uniformity test. Exhibit J at p. 1. In short, based upon the plain language in the '080 Patent and compounded by Applicant's arguments, it is not clear what is, and what is not, an analytical chemical test.
>
> 2. *Lack of Written Description*
>
> Nowhere in the '080 Patent does the Applicant describe the type, much less the amount, of analytical chemical testing required for regulatory approval. And even if it did, as discussed above, requirements for regulatory approval vary greatly, and change over time. Nowhere in the specification is the term "analytical chemical tests" written or described.

This proposed rejection **is not adopted** for the following reasons. As noted above in the Scope of Claims section, which cites to the '080 patent specification for support, the term “analytical chemical tests” means analytical tests for determining the amount of active content in the recited sample. The distinguishing point between analytical chemical tests as here claimed and physical testing (analytical or non-analytical) is not whether a chemical reaction occurs, but whether there is testing for the amount of active. Accordingly, the term “analytical chemical tests” is clear and has written description.

C. Third Party requester proposes that all pending claims be rejected as lacking clarity and enablement since the claims now recite that the individual dosage units vary by no more than 10%, 5%, 2%, 1% or 0.5% (Comments of 04/12/13, pp. 15-17).

In particular, with respect to lack of clarity, Third Party requester argues the following on p. 16 of the Comments filed 04/12/13:

> The data presented in the Bogue Declaration reflect "the uniformity of content of active of individual dosage units within particular lots and across different lots." Bogue Decl. ¶ 8 (emphasis added) and Appendices A, B and C. But "lots" are not equated to "resulting films." And there is also no reference to a "lot," "lots," or "lots of resulting films" in any of the claims. While Applicant may act as its own lexicographer in drafting the specification, it may not do so after the application has been filed. The fact is, Applicant's "uniformity" data--presented in the Bogue Declaration--fails to demonstrate individual dosage units where the active varies by no more than 10%, 5%, 2%, 1% or 0.5% as claimed.
>
> Moreover, Bogue' s Appendix A, which conceals lot variation by dividing it by the lot average, does not negate Bogue's Appendix B, which clearly shows that even the lot data does not satisfy the 10% variance limitation. It only introduces confusion with respect to the meaning of the claims.

With respect to lack of enablement, Third Party Requester argues the following on p. 16-17 of the Comments filed 04/12/13:

> Applicant's arguments also create an enablement problem as to the claimed uniformity. Applicant argues that the prior art does not demonstrate its claimed uniformity because "physically observable properties of the resulting film product, for example, its appearance and weight...do not indicate that the amount of active in individual dosage units varies by no more than 10%..." Reply pp. 54-55. "Even if the film appears uniform, analytical chemical tests must then be conducted to verify uniformity of content at the prescribed level." Reply p. 59. In short, Applicant argues that uniformity may only be determined by analytical chemical testing of film, not merely by physically observable properties of film. There is no indication or evidence in the '080 Patent that the disclosed methods result in a film with the claimed uniformity as determined by analytical chemical testing. In over 100 examples, the '080 Patent never demonstrates that any disclosed method results in a film that satisfies the recited active variation limitation as determined by analytical chemical testing. Applicant erroneously states that "analytical chemical testing is used in the '080 Patent to establish the actual amount of active in samples," citing Example M. Reply p. 59, last full ¶. The '080 Patent discloses no analytical chemical test for active with respect to Example M. '080 Patent 33:10-34:34. In fact, Example M contains no active. A red dye does not fall into the broadest reasonable interpretation of a bioactive or a pharmaceutical active.
>
> Applicant now improperly attempts to remediate its enablement problem by providing the data in the Bogue Declaration. First, a declaration cannot be used to provide enablement after the fact. This is particularly true when the declaration methods are not well-described, and what is described does not match even a single claim. Second, and most importantly, the data does not even meets [sic] its own recited requirement. Appendix B of the Bogue Declaration shows that the active in the individual dosage units does vary by more than 10%. Indeed, Applicant admits in the Bogue Declaration that only 46 of the 73 lots (i.e., only 63% of the lots) have active varying less than 5%, and only 1 lot (i.e., only 1% of the lots) has active varying less than 2%. Finally, absolutely no lots have active varying less than 1% or 0.5%.
>
> In short, none of these variation requirements are enabled in the '080 Patent specification. And the Bogue Declaration only serves to prove that its own commercial method--even if it were to fall within the claims--fails to produce films that meet the claimed variation requirements. By Applicant's own admission, without a demonstration of chemical tests, there is no indication that the disclosed methods met these requirements. Reply p. 67, lines 10-15. And physical tests are not enough, according to Applicant. *Id.*

This proposed rejection **is not adopted** for the following reasons. It is noted that issued claim 255, 273 and 291 (now cancelled), respectively, depended from issued independent claims 1, 82 and 161 and required a step of forming a plurality of individual dosage units of substantially the same size, wherein the active content of individual dosage units varies no more than 10%. Also, as discussed above, col. 15, lines 37-42 of the '080 patent teach "the uniformity of the present invention is determined by the presence of no more than a 10% by weight of pharmaceutical and/or cosmetic variance throughout the matrix. Desirably, the variance is less than 5% by weight, less than 2% by weight, less than 1% by weight, or less than 0.5% by weight." There is no requirement that a specification present working examples of a claimed invention. In any event, Example E of the 080 patent, a film is prepared containing loratadine as an active ingredient and is cut into dosage forms of substantially identical size (see col. 31-32). It was found that each dosage consistently weighed 0.04 grams, "which show the distribution of the components within the film was consistent and uniform. This is based on the simple principle that each component has a unique density. Therefore, when the components of different densities are combined in a uniform manner in a film, as in the present invention, individual dosages [sic] forms from the same film of substantially equal dimensions, will contain the same area." (See col. 32, lines 26-33). Likewise, the cut pieces in the example at col. 37, lines 52-67 weighed 70 mg $\pm$ 0.7 mg "demonstrating the uniformity of the composition of the film."

Patent Owner's Bogue Declaration is not part of the '080 patent specification, but supports non-adoption of the proposed lack of enablement and clarity rejections. ¶ 4 of

the Bogue Declaration states that each of 73 lots containing 2,000,000 individual dosage units per lot were manufactured according to the steps set forth in ¶ 4, which include forming a resulting pharmaceutical film and performing chemical analytical tests for uniformity of content of the active in substantially equally sized dosage units of the sampled resulting pharmaceutical film. As seen in Appendices A and C of the Bogue Declaration, a variation as low as 2% was obtained. The variation was calculated by taking the maximum active content of a lot minus the minimum active content of that lot, divided by the average active content of that lot (see ¶ 9). While the red dye of the '080 Patent's Example M is not a pharmaceutical active or bioactive active, a similar calculation is made in Example M at col. 34, lines 18-20 based on absorbance measurements, which are directly related to concentration of the red dye (see also col. 33, lines 49-51). Further, ¶¶ 10-11 of the Bogue Declaration, citing Appendix B, allege that "the amount of active across different lots of resulting film varies no more than 10% from the desired amount of the active."

D. Third Party Requester proposes that claims 82-90, 92-94, 96-160, 261-271, 274, 276-278, 298, 304-307, 313 and 315 be rejected as lacking clarity, written description and enablement due to the term "varies by no more than 10% from desired amount of active" (Comments of 04/12/13, pp. 17-19). In particular, Third Party Requester argues the following on pp. 18-19 of the Comments filed 04/12/13:

> In contrast to the maximum active variance limit recited in each of the independent claims and discussed directly above--step (f) of claims 82 and 315 includes the new recitation that "the amount of said active in said resulting film

and said additional resulting films varies no more than 10% from the desired amount of the active."

1. *Lack of clarity*

Whereas the previously discussed new recitation allows a larger maximum variation of active content, this new recitation allows a maximum variation of 20% (±10% around a target) in active content. Again, Applicant introduces clarity issues by attempting to amend its claims to match its new data. This new recitation in step (f) of claims 82 and 315 is particularly confusing because it appears to be broader than the uniformity recitation already present in step (e) of claims 82 and 315. The new language only appears to indicate that repeating the claimed method need not produce consistent films.

2. *Lack of written description*

The new language introduced into claims 82 and 315 allows a maximum variation of 20% (±10% around a desired amount or target) in the active content. Nowhere in the '080 Patent is this language found. Nor is this new definition of uniformity described or exemplified. Also there is absolutely no support for the idea that some uniformity is required within a resulting film and another is required between films. This language has been entirely fabricated in an attempt to retroactively support their claims with new data, but data in the specification does not support newly recited maximum variation of 20% in active content. As set forth in the MPEP: "If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from...the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application." MPEP 2163.02. The claims lack written description because nowhere in the specification are these new limitation [sic] described.

3. *Lack of enablement*

Applicant's arguments also create the same enablement problem as to the maximum variation of active as discussed above. That is, there is no evidence in the '080 Patent that the disclosed methods result in a film with the claimed uniformity--as determined by analytical chemical testing. And a declaration cannot be used to provide enablement after the fact.

This proposed rejection **is not adopted** for the following reasons. There is no lack of clarity because "the amount of said active in said resulting film and said additional resulting films varies no more than 10% from the desired amount of the active" means that the amount of active is in said resulting film and said additional

resulting films is ± 10% around the desired amount. In fact, the '080 patent teaches that "as required by various world regulatory authorities, dosage forms may not vary more than 10% in the amount of active present." (See col. 2, lines 42-45). It is well-known and conventional in the art that active content of a dosage is allowed to be ± 10% from the desired amount, e.g., the amount of active the dosage is supposed to have.

Further, there is no requirement that a specification present working examples of a claimed invention. In any event, as discussed above, in Example E at col. 30, line 64 through col. 32, line 44, a film is prepared containing loratadine as an active ingredient, then cut into substantially identical size dosage forms that are weighed and shown to have a consistent weight of 0.04 gm. This is evidence that the distribution of components within the film is consistent and uniform. The '080 patent teaches an alternative method of determining uniformity of the active is to cut the film into individual doses, and then dissolve and test the doses for amount of active (see col. 32, lines 34-39). This alternative type of testing is the analytical chemical testing here claimed.

E. Third Party Requester proposes that all pending claims be rejected as lacking clarity due to the term "rapidly increasing the viscosity of said flowable polymer matrix" (Comments of 04/12/13, p. 19). In particular, Third Party Requester argues that "rapidly" is a relative term with no benchmark; it only refers to the timing at which a desired result is obtained; and there is no indication of the degree to which the viscosity must be increased (Comments of 04/12/13, p. 19).

This proposed rejection **is not adopted** for the following reasons. The rapid increase in viscosity takes place during the step of evaporating the solvent from the flowable polymer matrix, and each of the independent claims sets forth the time period during evaporation in which the rapid increase takes place, i.e., within the first 4 minutes. Thus, the rapid increase occurs within this time frame. The claims also set forth the reason for such an evaporation time, i.e., "to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film." Accordingly, it is unnecessary to set forth a degree of viscosity increase for "rapidly increasing the viscosity".

F. Third Party Requester proposes that all claims be rejected as lacking clarity due to the recitation "during said drying said flowable polymer matrix temperature is 100 °C or less" (Comments of 04/12/13, pp. 19-20). In particular, Third Party Requester argues the limitation describes the temperature of the flowable polymer matrix (i.e., the matrix before it has been dried to a film), not the visco-elastic film; and that it is unclear whether the limitation may be satisfied if the flowable polymer matrix began the drying at a temperature of 100°C or less, or if it requires the temperature to be less than 100°C throughout the drying step (Comments of 04/12/13, p. 19).

This proposed rejection **is not adopted** for the following reasons. The recitation states "during drying" the flowable polymer matrix temperature is 100°C or less. The claims specify that the flowable polymer matrix has a viscosity of about 400 to about

100,000 cps. As long as the polymer matrix has this viscosity during drying, it is a flowable polymer matrix and its temperature must be 100°C or less.

Third Party Requester argues that "[s]ince every single recited solvent has a boiling point of 100 °C or less, it is not clear how the matrix would reach a temperature above the boiling point of the solvent contained therein"; and it is not clear what the recitation excludes "[s]ince the oven temperatures utilized in the Examples of the '080 patent are less than 100 °C." (Comments of 04/12/13, p. 20).

This argument is unpersuasive because the instant claims do not specify an oven temperature or specific solvent, and the '080 patent is not limited to its examples. The '080 patent specification teaches drying temperatures of "about 100°C or less" (col. 27, lines 53-55), which includes temperatures slightly above 100°C.

H. Third Party Requester proposes that all pending claims be rejected as lacking clarity, written description and enablement for the following reasons which are set forth on pp. 21-23 of the Comments filed 04/12/13 and reproduced below:

> 1. *Lack of clarity*
>
> Applicant adds so many new and different recitations regarding variation limitations to its independent claims, with multiple distinct variation levels, even within the same claim, that the claims are mired in ambiguity and uncertainty.
>
> Taking independent claim 82 as a representative claim, the problem with Applicant' s approach is readily apparent. The preamble recites that the film must be suitable for regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the FDA relating to variation of an active in individual dosage units. Later in step (e), claim 82 requires that the film is suitable for FDA approval without connecting the suitability to analytical chemical tests or the standards of the FDA relating to variation of active content recited in the preamble. Are analytical chemical tests required to show the FDA standards are met? Must the film meet the FDA

standards relating to variation of an active? Those limitations are not recited in the body of the claim. Then, to add more confusion, analytical chemical tests are required in a different part of step (e) to "indicate" that the active varies by no more than 10% in individual dosage units. First, this is not the FDA standard for approval. As discussed above, the standard is defined in USP General Chapter <905>. See Exhibit J. Second, what does it mean to "indicate" that the active varies by no more than 10%? Yet, there is one more layer of confusion. New step (f) requires that the amount of active varies no more than 10% from the desired amount of active. What is the desired active content? New step (f) also recites "said resulting film and said additional resulting films." How does a "resulting film" differ from "additional resulting films"? Where is that described in the specification? Or demonstrated for that matter? There is simply no discussion of $\pm$10% from a target anywhere in the specification. And certainly not with respect to comparison of "resulting films." And why is the amount of variation so large? This new claim amendment, and the data presented in the Bogue Declaration, only serve to demonstrate that repeating the claimed method does not produce consistent films. The Applicant has neither described nor enabled the method it now seeks to claim.

Every single independent claim is similarly confusing, each with their own combination of the many shades of "uniformity" that individually and collectively create a hopeless morass of confusion.

2. *Lack of written description*.

As discussed above, there is absolutely no support for the recitation of "varying by no more an [sic] 10% from a desired target." And certainly none for this variation between "resulting films" and "additional resulting films." In addition, if Chen's disclosure is not enabling with respect to the various regulatory authority recitations, neither is its own. See Section above regarding the Lin Declaration.

3. *Lack of enablement*

Nowhere in any of the over 100 examples in the '080 Patent is any film demonstrated to meet any of the newly recited "uniformity" limitations. No analytical chemical tests are performed with respect to an active. No results of analytical chemical tests of active are provided. No demonstration is made that the active varies by no more than 10% in individual dosage units. No demonstration is made that "resulting films" and "additional resulting films" vary by no more than 10% from a desired target. It almost seems like Applicant is not familiar with the '080 Patent because every recitation added to distinguish claims from the cited art lacks written description and/or enablement in the '080 Patent specification.

This proposed rejection **is not adopted** for the following reasons. As noted above, the instant claims do not require a step of getting regulatory approval. Rather, they set forth suitability for regulatory approval based on performing analytical chemical tests for uniformity of content of active, said tests showing a particular variation of active. For example, in step (f) of claim 1 and step (e) of claim 82, the active content varies by no more than 10%. A skilled artisan, using known analytical chemical tests, knows how to measure active content and determine uniformity of active content in substantially equally sized dosage units sampled from different locations of the film. The "indicating" in step (f) of claim 1 and step (e) of claim 82 means that the analytical chemical test results show that uniformity of content in the amount of the active varies by no more than 10%. Accordingly, the film is suitable for commercialization and the recited regulatory approval.

The issue of $\pm$10% from a target or desired value is discussed above. The '080 patent teaches that "as required by various world regulatory authorities, dosage forms may not vary more than 10% in the amount of active present." (See col. 2, lines 42-45). It is well-known and conventional in the art that the active content of a dosage is allowed to be $\pm$ 10% from the desired amount, e.g., the amount of active the dosage is supposed to have. The '080 patent further teaches in the Abstract that "the films also contain a pharmaceutical and/or cosmetic active agent with no more than a 10% variance of the active agent pharmaceutical and/or cosmetic active agent per unit area of the film"; and teaches at col. 15, lines 32-40 that "[c]onsideration of the above discussed parameters, such as but not limited to rheology properties, viscosity, mixing

method, casting method and drying method, also impact material selection for the different components of the present invention. Furthermore, such consideration with proper material selection provides the compositions of the present invention, including a pharmaceutical and/or cosmetic dosage form or film product having no more than a 10% variance of a pharmaceutical and/or cosmetic active per unit area. In other words, the uniformity of the present invention is determined by the presence of no more than a 10% by weight of pharmaceutical and/or cosmetic variance throughout the matrix."

As also noted above, there is no requirement of a working example. In any event, as also discussed above, in Example E at col. 30, line 64 through col. 32, line 44, a film was prepared, then cut into substantially identical size dosage forms that were weighed and shown to have a consistent weight of 0.04 gm. The '080 patent teaches this is evidence that the distribution of components within the film is consistent and uniform "based on the simple principle that each component has a unique density." (col. 32, lines 26-39).

Proposed 35 USC 112 rejections that are adopted:

Claim 318 is rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor or a joint inventor, or for pre-AIA the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection was proposed by Third Party

Requester on pp. 20-21 of the Comments filed 04/12/13 and **is adopted** for the reasons that follow.

Claim 318 requires that the controlled drying is through a drying apparatus at a temperature of "about 60 °C", and also requires uniformity of active varies by less than 5%. This combination of elements is found in unconnected passages of the specification and lacks adequate written description. In particular, as noted by Third Party Requester on p. 21 of the Comments filed 04/12/13:

> There are only two instances in the '080 Patent where a temperature of "about 60 °C" appears. The first instance, Example CF, makes no reference whatsoever to: (i) the yield value of the film; (ii) control of air velocities; or (iii) visco-elasticity of film at 4 minutes. See '080 Patent 41:49-50. The second instance, Examples P1-P3 use a "second heater section" at 60 °C with no top air flow, but does not exemplify a method suitable for film formation. See '080 Patent 35:57-59 ("Composition P displayed a stringy elastic property. The wet film would not stay level, the coating was uneven, and the film did not dry.").
>
> Moreover, the desired property relating to variation in active content--"[d]esirably, the variance is less than 5% by weight, less than 2% by weight, less than 1% by weight, or less than 0.5% by weight" (see '080 Patent 15:40-43)--cannot be attributed to any one of the 60 °C temperature, the air currents, or the formation of a visco-elastic film within 4 minutes. Indeed, there are no examples showing a variation of less than 5% in active content.

Claim 318 is rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention. This rejection was proposed by Third Party Requester on pp. 19-20 of the Comments filed 04/12/13 and **is adopted** for the reasons that follow.

Claim 318 recites "during said drying said flowable polymer matrix temperature is 100°C or less". This is at odds with another requirement of claim 318 that the controlled drying is through a drying apparatus at a temperature of about 60°C. It is not clear how the matrix would ever reach a temperature that is 40° hotter than the drying apparatus.

Proposed Claim Rejections - 35 USC § 102 and § 103

In the Comments file 04/12/13, Third Party Requester proposes art rejections over claims that have been canceled by the amendment of 03/13/13. For example, on pages 28 and 39 of the Comments, rejections are proposed over claim 12, which has been canceled. Proposed rejections over canceled claims will not be further addressed in this Action Closing Prosecution.

The following is a quotation of the appropriate paragraphs of pre-AIA 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. Claims 1-11, 13-15, 17-71, 82-90, 92-94, 96-150, 161-172, 174-176, 178-232, 243-253, 256, 258-271, 274, 276-289, 292 and 294-318 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen.

On pages 28-36 of the Comments filed 04/12/13, Third Party Requester proposes that claims 1, 4, 5, 8-11, 13-15, 17, 18, 20-32, 34, 36-40, 44-47, 51, 53, 54, 59, 62-71, 82-84, 87-90, 92-94, 96, 97, 99-111, 113, 115-119, 123-126, 130, 132, 133, 138, 141-150, 161-166, 169-172, 174-176, 178, 179, 181-193, 195, 197-201, 205-208, 212, 214, 215, 220, 223-232, 243, 244, 246, 247, 249-253, 256, 258-262, 264, 265, 267-271, 274, 276-280, 282, 283, 285-289, 292 and 294-318 be rejected under 35 USC 102(b) as anticipated by, or alternatively, under 35 USC 103(a) as being unpatentable over Chen. Further, on p. 36 of the Comments filed 04/12/13, Third Party Requester proposes that claims 2, 3, 6, 7, 19, 33, 35, 41-43, 48-50, 52, 55-58, 60, 61, 85, 86, 98, 112, 114, 120-122, 127-129, 131, 134-137, 139, 140, 167, 168, 180, 194, 196, 202-204, 209-211, 213, 216-219, 221, 222, 245, 248, 263, 266, 281 and 284 be rejected under 35 USC 103(a) as being unpatentable over Chen. For the reasons that follow, the proposed anticipatory rejection under 35 USC 102(b) of claims 1, 4, 5, 8-11, 13-15, 17, 18, 20-32, 34, 36-40, 44-47, 51, 53, 54, 59, 62-71, 82-84, 87-90, 92-94, 96, 97, 99-111, 113, 115-119, 123-126, 130, 132, 133, 138, 141-150, 161-166, 169-172, 174-176, 178, 179, 181-193, 195, 197-201, 205-208, 212, 214, 215, 220, 223-232, 243, 244, 246, 247, 249-253, 256, 258-262, 264, 265, 267-271, 274, 276-280, 282, 283, 285-289, 292 and 294-318 **is not adopted**. For the reasons that follow, the proposed obviousness

rejection of claims 1-11, 13-15, 17-71, 82-90, 92-94, 96-150, 161-172, 174-176, 178-232, 243-253, 256, 258-271, 274, 276-289, 292 and 294-318 **is adopted**.

The proposed anticipatory rejection of claims 1, 4, 5, 8-11, 13-15, 17, 18, 20-32, 34, 36-40, 44-47, 51, 53, 54, 59, 62-71, 82-84, 87-90, 92-94, 96, 97, 99-111, 113, 115-119, 123-126, 130, 132, 133, 138, 141-150, 161-166, 169-172, 174-176, 178, 179, 181-193, 195, 197-201, 205-208, 212, 214, 215, 220, 223-232, 243, 244, 246, 247, 249-253, 256, 258-262, 264, 265, 267-271, 274, 276-280, 282, 283, 285-289, 292 and 294-318 is not adopted because independent claims 1, 82 and 161 have been amended to require, and newly added independent claims 315-318 require, performing analytical chemical tests for uniformity content. As noted above, such tests are analytical tests for determining the amount of active content in the recited sample. Chen exemplifies testing for uniformity as evidenced by Table 4 on p. 20 where the g/dosage of films is reported. However, Chen does not teach measuring the amount of active in the dosage films.

With respect to the obviousness rejection, Chen teaches a dosage unit including a water-soluble hydrocolloid, mucosal surface-coat-forming film, such film including an effective dose of a pharmaceutical or bioactive active agent (see p. 3, lines 30-32; and p. 10, line 22 through p. 11, line 12). In Examples 5-8, Chen prepares hydroxypropyl methylcellulose (HPMC, i.e., “Methocel E5”) based quick dissolving intraoral films containing active agents (see p. 20, lines 17-20 and Tables 5 and 7). In particular, the films in Examples 5-8 contain an active agent, e.g., nicotine, hydromorphone, oxybutynin or estradiol; HPMC; and a solvent, i.e., water (see Tables 5 and 7). Further,

the film in Tables 7 and 8 of Chen uses sildenafil citrate as an active ingredient and is prepared using HPMC, i.e. “Methocel E15”, and water as the solvent. The film in Chen’s Example 1 contains HPMC; peppermint, citric acid and aspartame as actives; and water as the solvent (see Tables 1 to 4). The film in Chen’s Example 2 contains "Pullalan (P-20) [sic, Pullulan (P-20)]” as the polymer; peppermint, citric acid and aspartame as actives; and water and ethanol as solvents (see Tables 1 and 2). Peppermint, citric acid and aspartame are also actives in Chen’s Examples 5-8, and peppermint and aspartame are actives in the film in Chen's Tables 7 and 8. Under the general category of "Actives", the '080 patent teaches flavors such as mint oil, flavor enhancers such as citric acid, and sweeteners such as aspartame (see col. 21, lines 35-63 and col. 22, lines 9-13). Peppermint has a high menthol content, is a breath freshener; and the ‘080 patent teaches that breath fresheners are drugs (col. 20, lines 35-38). Other taste modifying agents, i.e., taste masking agents, are disclosed at p. 10, lines 7-14 of Chen.

The specific water-soluble polymer, solvent and actives exemplified in Chen are identical to those exemplified in the ‘080 patent. HPMC is employed in almost every example of the ‘080 patent. HPMC and pullulan are taught by the ‘080 patent as being water soluble (col. 15, lines 45-57). The same solvent, i.e., water is employed in almost every example in the '080 patent. Sildenafil is exemplified in Examples CI and FB of the ‘080 patent (see Tables 16 and 30). Likewise, peppermint oil and/or sweetener are used in numerous examples in the '080 patent, such as Examples A, B, C, D, F, G, H, BA, BB, BC, etc (see Tables 1 and 9).

The following is a list of hydrocolloid polymers, including said HPMC and pullulan, disclosed by Chen for forming the film (see p. 14, line 12 through page 15, line 3):

> In embodiments of the invention, the hydrocolloid may be a water soluble non-gelling (at room temperature) natural polysaccharide or derivatives including pectin and derivatives, guar gum arabic, tragacanth gum, xanthan gum, gellan sodium salt, propyleneglycol alginate, starches (amylose, amylopectin), modified starches, hydroxyethyl starch, pullulan, carboxymethyl starch, gum ghatti, okra gum, karaya gum, dextrans, dextrins and maltodextrins, konjac, acemannan from aloe, locust bean gum, tara gum, quince seed gum, fenugreek seed gum, scleroglucan, gum arabic, psyllium seed gum, tamarind gum, oat gum, quince seed gum, carrageenans, scleraglucan, succinoglucan, larch arabinogalactan, flaxseed gum, chondroitin sulfates, hyaluronic acid, curdlan, chitosan, deacetylated konjac, and rhizobium gum.
>
> In embodiments of the invention, the hydrocolloid may be a water soluble non-gelling polypeptide or protein exemplified by gelatins, albumins, milk proteins, soy protein, and whey proteins. The hydrocolloid may further be selected from a group of synthetic hydrocolloids exemplified by any of the following: polyethylene-imine, hydroxyethyl cellulose, sodium carboxymethyl cellulose, carboxymethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, methyl cellulose, ethyl cellulose, polyacrylic acids, low molecular weight polyacrylamides and their sodium salts (carbomers), polyvinylpyrollidone, polyethylene glycols, polyethylene oxides, polyvinyl alcohols, pluronics, tetronics, and other block co-polymers, carboxyvinyl polymers, and colloidal silicon dioxide. A preferred embodiment of the invention utilizes a hydroxypropyl methyl cellulose having a methoxy content of about 19-30% and hydroxypropyl content of 7-12% and a molecular weight of approximately 50,000-250,000 daltons (Table 9).

In addition to the specific active materials noted above, i.e., nicotine, hydromorphone, oxybutynin, estradiol, sildenafil citrate, peppermint, citric acid and aspartame, the following is a list of active agents disclosed by Chen (see p. 10, line 22 through page 11, line 12):

> Active agents (for human and veterinary applications) include therapeutic agents, nutritional supplements and hygiene aids. The therapeutic agents are

exemplified by analgesics, a-adrenergic receptor blockers, anti-Alzheimer's disease medication, antianginal, antianxiety, antiarrythmics, antiarthritics, antibiotics, anticoagulants/thrombolytics, anticonvulsants/anti-Parkinson medication, anti-depressants, anti-diabetics, anti-diarrheal, anti-epileptics, anti-fungal, anti-gout, anti-heartworm medication for dogs, anti-histamines, anti-hypertensives, anti-inflammatories, anti-infectives, antimigraines, anti-nasuants/anti-emetics, anti-neoplastics/anti-tumor active agents, anti-pruitics, anti-psychotics, anti-pyretics, anti-spasmodics, anti-virals, bronchial dilators/anti-asthmatics, calcium antagonists, cardiac agents, cardiotonics, central nervous system actives, contraceptives, coronary vasodilators, cough/cold remedies, dietary supplements, including vitamins and minerals, diuretics, fertility active agents, flea control agents for animals (Ivermectin), H_2 receptor antagonists, herbal actives, hormones, hypoglycemics, hypolipidemics, muscle relaxants, ovulation stimulators, peptide active agents, polypeptide active agents, proteins such as insulin, calcitonin, LHRH and the like. Sedatives and hypnotics, sexual dysfunction active agents, sleep aids, smoking cessation aids, steroids and steroidals, tranquilizers, laxatives, ophthalmic preparations, nutritional supplements, breath fresheners, breath deodorants, saliva substitutes, antigingivitis agents, anti-cavity agents, anti-plaque agents, diagnostic indicators, and local anesthetics. Also included are active agents for treatment of osteoporosis, hormone replacement, treatment of periodontal disease, antiseptics, corticosteroids, non steroidal anti-inflammatory agents, antiviral agents and vaccines.

In the method of preparation of the films, the HPMC or pullulan, which Chen teaches is a hydrocolloid, is dissolved in water under agitated mixing to form a uniform and viscous solution which reads on the instant masterbatch pre-mix, and the additional ingredients are added under agitated mixing until they are uniformly dispersed (i.e., suspended) or dissolved in the hydrocolloid (see p. 14, line 22 through p. 15, line 3; and p. 17, lines 6-19). The resultant mixture, i.e. the instant flowable polymer matrix, which Chen teaches has a viscosity of 500 to 15,000 cps, is degassed in a vacuum chamber until trapped air bubbles are removed, and then coated, i.e., casted as per step (b) of claims 82, 161 and 315-318, and as per step (c) of claim 1, on the non-siliconized side of a polyester film (see p. 15, lines 24-29; and p. 17, lines 13-15).

With respect to steps (c) and (d) of claims 82, 161 and 315-318, and with respect to steps (d) and (e) of claim 1, Chen controls drying and evaporates water from the cast matrix in 9 minutes of drying in a hot air circulating oven at 50°C (see p. 17, lines 13-15 and Fig. 2). In particular, as seen schematically in the drying apparatus of Chen's Fig. 2, the air flow is less direct at the film surface at the beginning of the drying and becomes more direct as the film proceeds through the drying oven, which has an aeration controller (see also p. 5, line 31 through p. 6, line 3). Chen's Example 1 starts with 74.42% water content and is dried to 1.7% water content (see Tables 1 and 4). Chen's Examples 5 to 8 start with 73.03%, 71.51%, 70.72% and 72.94% water content and are dried to 2.93%, 2.42%, 2.32% and 2.31% water content, respectively. Chen's Example 2 starts with 10.6% ethanol and 67.025% water and, after drying for 9 minutes at 50°C, the water content is 8.5% (see Tables 1 and 2). Since the drying is at 50°C, the temperature of the flowable polymer matrix is "100°C or less" as here claimed. In fact, Chen's general drying temperature range of 40-100°C is entirely with the range of about 100°C or less taught at col. 27, lines 53-55 of the '080 patent.

Further with respect to steps (c) and (d) of claims 82, 161 and 315-318, and steps (d) and (e) of claim 1, and with respect to viscoelasticity, it is the Specialist's position that Chen's mixture before drying is viscoelastic. In particular, as noted above, the '080 patent teaches that "[t]he addition of hydrocolloids to the aqueous phase of the suspension increases viscosity, may produce viscoelasticity, and can impart stability depending on the type of hydrocolloid, its concentration and the particle composition, geometry, size and volume fraction" (see col. 8, lines 42-46). Chen adds the same

hydrocolloid as in the '080 patent, i.e. said HPMC, to water, and Chen's wet matrix before drying has a viscosity of 500-15,000 cps (p. 15, line 26), which is within the instantly claimed range of about 400-100,000 cps and overlaps the '080 patent specification's most preferred range of about 1,000-40,000 cps (see the paragraph bridging cols. 16 and 17 of the '080 patent). Accordingly, Chen's films in Examples 1, 2 and 5-8 and the Example in Tables 7 and 8 are inherently viscoelastic before drying. Within 4 minutes of the 9 minutes of drying in Chen's Examples 1, 2 and 5-8 and the Example in Tables 7 and 8, a more dry viscoelastic film is obtained.

Alternatively, to the extent that Chen's wet film in Examples 1, 2 and 5-8 and the example in Tables 7 and 8 before drying are not viscoelastic, then within about 4 minutes in the hot air circulating oven at 50°C, a viscoelastic film is inherently formed. In particular, in order to arrive at a dried film product as in Chen, which is made using the same materials as disclosed in the '080 patent and the same basic process steps here claimed, wherein the dried film is glossy and substantially transparent and has the gram per dosage, thickness, density and water content set forth in Chen's Table 4 for Example 1, then a viscoelastic film is inherently formed within about 4 minutes. The remaining time after the viscoelastic film is formed further dries the viscoelastic film.

As an even further alternative, if Chen's viscoelastic film is formed after about the first 4 minutes but within Chen's 9 minute drying time, then a skilled artisan would recognize that with a higher drying temperature, a shorter drying time than 9 minutes can be used. In other words, a higher drying temperature than the 50°C exemplified by Chen would result in formation of Chen's viscoelastic film product sooner. In fact, Chen

teaches that its drying temperature can be in the range of 40-100°C (see p. 15, line 28). It would have been obvious to one of ordinary skill in the art at the time the invention was made to have used a higher drying temperature than the 50°C exemplified by Chen because Chen teaches that the drying temperature can be as high as 100°C, and the resulting expectation of a shorter drying time using a higher temperature.

With respect to the claimed percent variation of active, and thus also the claimed substantial uniform distribution and locking-in or substantially preventing migration, Chen's ingredients are mixed until they are uniformly dispersed or dissolved in the hydrocolloid (p. 17, lines 8-11), and Chen uses the same criteria exemplified in the '337 patent specification for evaluation of uniformity, i.e., weight of dosages and visual inspection (see col. 31, line 38 through col. 32, line 34, and col. 38, lines 8-10 of the '337 patent). In particular, Chen's dried film product of Example 1 is cut into equal sized dosage units ready for packing (p. 17, lines 31-32; Table 4) and has a weight of 0.028 $\pm$ 0.001 g/dosage film, a density of 1.0485 $\pm$ 0.009 g/cm^2, a water content of 1.7 $\pm$ 0.24%, a thickness of 2.1 $\pm$ 0.12 mil (see Table 4); and the dried films are glossy and substantially transparent (p. 17, line 15), i.e., they are visually free of aggregation. The 0.028 $\pm$ 0.001 g/dosage film has variation of (0.001/0.028) x 100 = 3.6%. When film weight is rounded to two decimal places as in Table 2 at col. 31 of the '337 patent, then the weight is 0.03 gram/dosage film with a variation of 0%. Accordingly, the claimed percent variation of active of no more than 10%, less than 5%, less than 2%, less than 1% and less than 0.5% is inherent in Chen's films and thus, the films are suitable for

regulatory approval by the U.S. Food and Drug Administration (FDA) and commercialization, as here claimed.

Furthermore, as noted in the Cohen Declaration submitted with the request, when working with a homogeneous or completely dissolved coating mixture as in Chen, it would be difficult for a person of ordinary skill in the film art not to obtain a film that has a uniform content of active, and the drying method disclosed in Chen would not be expected to create any agglomeration, aggregation or otherwise non-uniform content of active (see ¶¶ 8-10).

Alternatively, to the extent the claimed percent variation of active is not inherent from Chen's process, then such would have been obvious. Chen also differs from the instant claims in that while Chen cuts its film into equal sized dosage units and checks for uniformity by weighing the units and comparing the weights which, as noted above, have 0% variation, Chen does not perform "analytical chemical tests" on the equal sized dosage units to determine the amount of active in the dosage units.

However, Chen's films are cut into dosage units intended for human use so as to deliver an effective dose of an active agent (p. 1, lines 8-22; p. 3, lines 30-33; p. 16, lines 2-8; p. 17, lines 31-32). It is well-known in the art that world regulatory authorities do not permit dosage forms to vary by more than 10% in the amount of active present. It is also well-known in the art that to verify such uniformity, the actual content of active in individual dosages is measured, i.e., conventional analytical testing is used.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to minimize the active content variation among Chen's dosages as

close to zero as possible, including the instantly claimed no more than 10%, less than 5%, less than 2%, less than 1%, and less than 0.5%, in view of the well-known goal of a skilled artisan to prepare dosages that do not vary by more than 10% in the amount of active present, in view of the 0.03 gram/dosage film with a variation of 0% for the dosages in Chen's Table 4, and a desire to obtain FDA approval and commercialize the product. A skilled artisan would minimize active content variation by optimizing the available parameters in Chen's process, which are the same as or similar to those in the '337 patent specification. These include, mixing/degassing, casting of the wet film, viscosity of the wet film, drying temperature, drying time, control of air flow in Chen's Fig. 2, selection of appropriate colloid material, etc.

Further, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have performed known analytical chemical tests on Chen's dosages so as to determine the actual amount of active in the dosages and thus, assure active content uniformity.

With respect to claim 82 and 315, Chen does not specifically teach repeating its process and said analytical chemical tests. Further, Chen does not specifically teach that the active content of the first film obtained from the process and additional films prepared by repeating the process varies no more than 10% from a desired amount as indicated by analytical chemical tests.

However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have repeated Chen's process and the analytical chemical tests for each film prepared by the process so as to prepare more films and dosages,

seek regulatory approval and commercialize the product. It further would have been obvious to a skilled artisan at the time the invention was made to have prepared the multiple films such that the active content in each film does not vary by more than 10% from the amount of active the dosages are supposed to contain as required by various world regulatory authorities, in order to minimize dosage variation and commercialize the product. A skilled artisan would obtain the variation of no than 10% from the desired amount by optimizing said available parameters in Chen's process.

With respect to claims 32, 111 and 193, which require that the active is a biological response modifier, it is noted that all of the actives listed by Chen at p. 10, line 22 through page 11, line 12 are biological response modifiers. Alternatively, biological response modifiers are well-known actives in the art. It would have been obvious to one of ordinary skill in the art to have used any well-known active, such as a biological response modifier, as the active in Chen's film with the resulting expectation of preparing a film for delivery of the agent and so as to take advantage of the agent's known function.

With respect to claims 25, 104 and 186, which require that the active is an anti-tussive, Chen, as noted above, teaches that its active can be a cough/cold remedy (see p. 10, line 32 through page 11, line 1). A cough/cold remedy encompasses and thus, renders obvious an anti-tussive, i.e., cough relieving/depressing, agent.

With respect to claims 65-69, 144-148 and 226-230, which require that the active is coated with a controlled release composition, Chen discloses that its films may release the active agent over a period of time that is determined by a number of

different factors (see page 6, line 30 through page 7, line 21). More specifically, Chen discloses: "Depending on the optimal program for a specific application of the invention, the disintegration time and the dissolution time can be controlled within a prescribed range by adjustment of the formulation and the thickness of the film. In some cases, it is desirable for release of the active agent to occur after dissolution of the film. For these applications, the active agent may be encapsulated in a material with dissolution properties that are different from those of the hydrocolloid. Encapsulation of the active agent may also be utilized to achieve masking of taste for active agents that are bitter. In some cases, two or more different active agents may be included in the film." (See page 9, lines 9-16). Slow release films are also discussed, e.g., at page 7, lines 16-21. Accordingly, immediate, delayed, sustained or sequential release of active as here claimed, if not disclosed by Chen, would have been obvious so as to obtain a desired release of the active(s).

With respect to claims 70, 149, 231, 259, 260, 277, 278 and 295-297, Chen teaches that the active material can be in the form of a particle, e.g., a colloid particle or microencapsulated (see p. 7, lines 17-21). As noted above, Chen's polymers such as HPMC are hydrocolloids (p. 14, line 24-31), and Chen's matrix has the ingredients uniformly dispersed, i.e., suspended, in the hydrocolloid (p. 17, lines 6-11).

With respect to claims 71, 150 and 232, which require the addition of a degassing agent, as noted above Chen teaches peppermint (see p. 10, line 9; Examples 1-8 and the example in Tables 7 and 8). During prosecution U.S. patent application Serial No. 11/858,214, Patent Owner admits that peppermint is a foam

reducing flavoring agent which “act[s] to both flavor the film and prevent and/or remove air from the film-forming compositions.” (See the last paragraph on p. 5 of the response filed 12/20/10 and claim 5 of the 11/858,214 application).

With respect to claims 162, 163, 249-252, 258, 267-270, 276, 285-288 and 294, Chen teaches that the films are suitable for administration of the active material through buccal, gingival, sublingual and mucosal surfaces (see p. 8, lines 4 and 9-10, and Fig. 1). With respect to claim 164, Chen teaches that the mucosal surface can be a wound (see p. 7, lines 31-32).

With respect to claim 253, 271 and 289, which require that the film provides administration of the active within the body of the individual during surgery, as noted above, Chen teaches that its films can be applied to a mucosal surface, which refers to any moist surface in the body, including a wound (see p. 7, lines 31-32 and p. 8, line 4). Accordingly, Chen's films can be administered at any time, including surgery. Chen discloses several active agents that are highly suitable for use "during surgery", including sedatives, local anesthetics, antiseptics, anti-inflammatory agents, anti-viral agents, muscle relaxants, and steroids (see p. 10, line 29 through p. 11, line 12). Further, Chen teaches that "[e]mbodiments of the invention include .... for a quick dissolving film for local and systemic delivery of pharmaceutical agents to a mucosal surface in a subject .... The dosage unit of the invention may be applied to any mucosal surface as deemed appropriate for the systemic or local delivery of an active agent including vaginal, rectal and ocular surfaces ... [e]mbodiments [may be administered easily by] physicians, parents, patients ..." (*see* p. 8, lines 2-4, 6-10, and 19-20). Chen

also teaches the application of films to a wound surface "where lymph fluid bathes the tissue surface" at p. 7, lines 32 through p. 8, line 1. Thus, Chen discloses or renders obvious that its film “provides administration of said active to an individual by administration within the body of the individual during surgery” as here claimed.

With respect to claims 2 and 3, Chen does not specifically teach that its premix of polymer and solvent, i.e., instant masterbatch premix, is controllably fed via a first metering pump and a control valve to a first mixer and a second mixer, and that the first and second mixers are arranged in parallel, series or a combination thereof.

However, metering pumps, mixing vessels and control valves are standard equipment in the art, and so is their arrangement in parallel, series or a combination thereof. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have used metering pumps, mixing vessels and control valves when preparing Chen's wet film because such equipment is standard in the art, and so as to mix Chen’s masterbatch premix and active.

With respect to claims 6, 7, 85, 86, 167 and 168, Chen does not specifically teach using combinations of its hydrocolloids, such as a mixture of the exemplified HPMC with any of the other hydrocolloids taught by Chen such as ethylcellulose, polyacrylic acid polymer, etc.

However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have used combinations of Chen’s hydrocolloids in place of a single hydrocolloid with the expectation that a film for mucosal delivery of active agent would be obtained. The rationale to use a combination of Chen's hydrocolloids flows

logically from their each having been individually taught as useful as the hydrocolloid component of Chen's film.

Claims 19, 33, 35, 41-43, 48-50, 52, 55-58, 60, 61, 98, 112, 114, 120-122, 127-129, 131, 134-137, 139, 140, 180, 194, 196, 202-204, 209-211, 213, 216-219, 221, 222, 245, 248, 263, 266, 281 and 284 are directed to particular active materials. These active agents are either well-known in the art or are species of the generic active agents taught by Chen at p. 10, line 22 through p. 11, line 12. See also the discussion of these claims in the claim chart of the request on pp. 77-82 and 84-89, which are hereby incorporated by reference.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have used the actives here claimed so as to prepare Chen's film because such actives are well-known in the art or are species of the generic active agents taught by Chen; the reasonable expectation of success in preparing a film for mucosal delivery of the active; and so as to take advantage of the active's known function.

Claim 318 further requires that the drying is at a temperature of “about 60°C”. As noted above, Chen exemplifies a drying temperature of 50°C (p. 17, line 15), and more generally teaches that drying can be done at a temperature between 40-100°C (p. 15, line 28). It would have been obvious to one of ordinary skill in the art at the time the invention was made to have used a higher temperature than 50°C within the temperature range of between 40-100°C taught by Chen so as to dry the film. It is expected that a higher drying temperature would permit a shorter drying time.

New claims 317 and 318 also require that the drying uses “air currents, which have forces below a yield value of the polymer matrix". The '080 Patent states that "air velocities are desirably below the yield values of the film, i.e., below any force level that can move the liquids in the film-forming compositions." (See col. 11, lines 21-23). Moving liquids in the matrix during drying could produce defects in the film. However, as noted above, Chen's Fig. 2 shows air flow is less direct at the film surface at the beginning of the drying and becomes more direct as the film proceeds through the drying oven, which has an aeration controller (see also p. 5, line 31 through p. 6, line 3). As also noted above, Chen produces a film that is glossy, substantially transparent, has a weight of 0.028 $\pm$ 0.001 g/dosage film, a density of 1.0485 $\pm$ 0.009 g/cm^2, a water content of 1.7 $\pm$ 0.24%, a thickness of 2.1 $\pm$ 0.12 mil (seep. 17, lines 15-16; and Table 4). The 0.028 $\pm$ 0.001 g/dosage film, when rounded to two decimal places as in Table 2 at col. 31 of the ‘080 patent, is 0.03 gram/dosage film with a variation of 0%. Accordingly, the air flow of Chen either inherently or obviously has forces below a yield value of the polymer matrix in order to arrive at the, glossy, substantially transparent, essentially uniform films exemplified therein.

2. Claims 2, 3, 32, 55, 72-81, 111, 134, 151-160, 193, 216 and 233-242 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teaching of Chen and Staab.

This rejection was proposed by Third Party Requester on p. 37 of the Comments filed 04/12/13 and **is adopted** for the reasons that follow.

With respect to claims 2 and 3, to the extent that Chen does not render obvious controllably feeding its master batch pre-mix via a metering pump and a control valve to a first mixer and a second mixer such that the first and second mixer are arranged in parallel, series or a combination thereof, then such is rendered obvious in combination with the teachings of Staab.

Staab teaches films made of dissolvable polymer material and/or complex carbohydrate material which are food grade materials, wherein the films also contain an agent such as a drug or medication (see abstract). Staab teaches that "[t]he agent material is evenly distributed throughout the film, so as the film slowly dissolves, it releases the agent material in the proper dosage ...." (see col. 5, line 68 through col. 6, line 3). Staab also discloses that “[t]he device of the invention thus is composed of a biologically compatible material that has been blended homogeneously" with the drug (see col. 6, lines 6-10). Staab teaches forming a pre-mix including a water soluble polymer and water in proper concentrations at a first temperature in a first vessel and then transferring to another vessel of a cooler temperature (in series with the first vessel), and then stirring in heat sensitive ingredients (see col. 7, lines 37-48). Staab’s Fig. 5 depicts three mixing vessels that can readily be employed for practicing the claimed method, the top two vessels being in parallel with each other, the lower vessel being in series with the top two vessels. Any transfer from one vessel to another would inherently or obviously involve a metering pump and control valve. Arrangement of the vessels in parallel would accommodate a choice of heat sensitive ingredients, such as those disclosed in Staab (see col. 7, lines 37-51).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have prepared Chen's matrix by forming a pre-mix including a water soluble polymer and water in proper concentrations at a first temperature, then to have transferred the contents of the vessel to another vessel of a cooler temperature, and then to have stirred in heat sensitive ingredients, e.g., drug(s) as in Staab, so as to protect the drug(s), which is usually the most expensive component.

With respect to claims 32, 111 and 193, to the extent that Chen does not teach or render obvious that its active can be a biological response modifier, then such is rendered obvious in combination with the teachings of Staab. Likewise, with respect to claims 55, 134 and 216, to the extent that Chen does not teach or render obvious that its active can be a decongestant, then such is rendered obvious in combination with the teachings of Staab.

Staab teaches that its active agent can be monoclonal antibodies, i.e., biological response modifiers, such as those useful against cell surface components or against pathogenic organisms such as HIV (see col. 6, lines 49-53). Likewise, Staab teaches that its active agent can be a decongestant (see col. 7, line 1).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have used a monoclonal antibody or decongestant for Chen's active because such actives are conventional in the art, as shown by Staab; so as to take advantage of the active material's known function; and the reasonable expectation of success.

With respect to claims 72-81, 151-160 and 233-242, Chen does not specifically teach, for example, providing a second film layer having a active. Staab teaches that its film may be a laminate of two or more layers (see col. 5, lines 30-31; col. 9, lines 28-43; and Fig. 2). Staab teaches that the laminates can be formed in the conventional manner, for example the mixture in liquid form is poured or cast onto a plate or into a mold and allowed to begin to set, at which time another liquid mixture with different composition is poured on the first mixture, and both mixtures are allowed to set up completely producing a laminate or layers of different materials (see col. 5, lines 51-58). The extruding and spraying of the second film in claims 76, 77, 155, 156, 237 and 238 are conventional methods that are obvious variants of the pouring and casting exemplified by Staab.

Staab teaches that the first and second layers can comprise an active. In particular, referring to Fig. 2, Staab teaches the following at col. 9, lines 28-43:

> A first film layer 13 is made of, for example, a faster dissolving polymer material for release of a drug material 14a. A second film layer 15 is made of slower dissolving polymer material for release of more drug or another drug material 14b in combination, for example, a spermicide and an anti-infective or anti-inflammatory medication. A third (and additional) layer(s) 16 with additional drug can also be employed for sustained release of the drug.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have laminated a second film to Chen's drug-containing film as per the teachings of Staab so as to control the release rate of the drug, provide for release of more drug, or provide for release of another drug in addition to the drug in Chen's film.

3. Claims 317 and 318 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Chen and Arter.

The rejection of claim 318 was proposed by Third Party Requester on pp. 37-38 of the Comments file 04/12/13 and **is adopted** for the reasons that follow. The rejection of claim 317 is Examiner-initiated.

Chen is relied upon for the reasons stated above in rejection No. 1. As discussed above, Chen renders obvious all the limitations of new claims 317 and 318. Nevertheless, with respect to the newly presented limitation in claims 317 and 318 of using air currents which have forces below a yield value of the polymer matrix during drying, the teachings of Arter strengthen the teachings of Chen.

Arter is directed, in general, to the drying of liquid coating compositions that have been coated in the form of a layer, or in the form of two more superposed layers, on a sheet material (see col. 1, lines 6-9). Arter teaches that "[o]ne of the most common and difficult problems that is encountered in the drying of coating compositions is the formation of mottle." (See col. 2, lines 18-20). In particular, Arter teaches "[i]t is a problem that is encountered under a wide variety of circumstances. For example, mottle, or non-uniform density, is frequently encountered when compositions consisting of solutions of a polymeric resin in an organic solvent are coated in layer form onto sheet materials, such as webs of synthetic organic plastic material. Mottle is an especially severe problem when the coating solvent is a volatile organic solvent but can occur to a significant extent even with aqueous coating compositions or with coating

compositions utilizing an organic solvent of low volatility. The mottle is an undesirable defect in some instances because it detracts from the appearance of the finished product … .” (See col. 2, lines 20-53).

Arter teaches drying wet films in a two zone dryer, as shown in Figs. 1-3. In the first zone, the film is dried while being protected by a shield that creates a quiescent zone above the top surface of the film in which there are no turbulent flow conditions and uniform drying is promoted (see col. 3, line 57 through col. 4, line 18). Accordingly, Arter teaches "using air currents, which have forces below a yield value of the polymer matrix during drying, to evaporate at least a portion of said solvent," as required by step (c) of claims 317 and 318. Following the first zone, the film is further dried in a second zone to remove residual liquid medium form the film (see col. 13, lines 24-29).

Arter exemplifies films that are dried in about 3 seconds at 60 ℃ (Example 1 and Table 1). In particular, in Test No. 1 in Example 1, the film velocity is 355 cm/sec (Table 1), the dryer length is 4 x 0.3 m = 1.2 m, and the drying time is (1200 cm)/(355 cm/sec) = 3 sec. In Example 2, the residence time for the web in each of the first and second sections of the drier is 5.2 seconds (see col. 17, lines 4-6).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have applied the drying method taught by Arter, which uses a quiescent zone above the top surface of the film in which there are no turbulent flow conditions and uniform drying is promoted, to the film formation method disclosed by Chen in order to avoid the formation of mottle.

4. Claims 317 and 318 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Chen and Strobush.

The rejection of claim 318 was proposed by Third Party Requester on pp. 38-39 of the Comments file 04/12/13 and **is adopted** for the reasons that follow. The rejection of claim 317 is Examiner-initiated.

Chen is relied upon for the reasons stated above in rejection No. 1. As discussed above, Chen renders obvious all the limitations of new claims 317 and 318. Nevertheless, with respect to the newly presented limitation in claims 317 and 318 of using air currents which have forces below a yield value of the polymer matrix during drying, the teachings of Strobush strengthen the teachings of Chen.

Strobush discloses an apparatus and method for evaporating a coating solvent from a coating on a first substrate surface of a substrate while minimizing formation of mottle during evaporation (Abstract; col. 1, lines 9-18 and 27-29). Strobush teaches that the process of applying a coating to and drying that coating on a substrate can inherently create defects such as mottle, where "mottle" is defined as "an irregular pattern or non-uniform density defect that appears blotchy when viewed," and the usual cause of mottle is air movement over the coating before it enters the dryer, as it enters the dryer, or in the dryer (col. 1, line 43 through col. 2, line 5). Strobush teaches that mottle is a problem when the coating solution contains a volatile organic solvent "but can also occur to a significant extent even with aqueous coating compositions" (col. 2, lines 10-15). Strobush teaches that the prior art substrates which have been coated are often dried using a drying oven which contains a drying gas such as air (col. 2, lines 20-

22). Strobush discloses the drying of coated substrates without introducing significant mottle while running at higher web speeds by supplying drying gas (heated air) toward the bottom surface of the coated substrate such that the substrate rides on a cushion of drying gas, while the top side receives little or no drying gas, and where the coating comprises any film-forming material dispersed in any evaporable liquid vehicle (col. 6, lines 20-27; col. 9, lines 1-11 and 47-50; col. 11, lines 1-6 and 16-27; col. 12, lines 14-21, 27- 31, and 48-55; and col. 19, lines 43-46). In other words, Strobush teaches "using air currents, which have forces below a yield value of the polymer matrix during drying, to evaporate at least a portion of said solvent," as required by step (c) of claims 317 and 318. In fact, Strobush teaches that “if desired, topside air bars (34) can be used such that no gas is supplied by the air bars when topside gas is not needed or desired." (See col. 11, lines 15-17 and 24-27).

Strobush teaches that its apparatus and method are suitable for a "wide variety of coatings" (col. 9, line 9), with materials particularly suited for drying by this apparatus including "[a]ny mottle-susceptible material" such as graphic arts materials, magnetic media, and photothermographic imaging constructions (col. 16, lines 60-66). In fact, the coating composition can comprise a film forming material or other solid material dissolved, dispersed or emulsified in an evaporable liquid (see col. 9, lines 1-4).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have applied the drying method taught by Strobush, which uses little of no drying gas on the top side of the coated substrate, to the film formation method disclosed by Chen in order to avoid the formation of mottle.

5. Claims 1-5, 10, 13-15, 21, 24, 25, 32, 44-46, 54, 55, 59, 63-70, 72-75, 78-84, 89, 92-94, 100, 103, 104, 111, 123-125, 133, 134, 138, 142-149, 151-154, 157-166, 171, 174-176, 182, 185, 186, 193, 205-207, 215, 216, 220, 224-231, 233-236, 239-242, 249-252, 258-260, 267-270, 276-278, 285-288 and 294-318 are rejected under 35 USC 102(b) as anticipated by or, in the alternative under 35 U.S.C. 103(a) as being obvious over Staab.

This rejection was proposed by Third Party Requester on pages 39-41 of the Comments filed 04/12/13 and **is adopted** for the reasons that follow.

Staab teaches the preparation of a film for local administration of an active agent in an internal body area (see col. 2, lines 34-62). Staab teaches films made of dissolvable polymer material, e.g., PEO and/or HPMC, both of which are identified as water soluble polymers in the '080 patent at col. 15, lines 50-51, and Staab's film also contains a drug or medication as the active agent (see Abstract; and col. 2, lines 34-46). Staab teaches that "[t]he agent material is evenly distributed throughout the film, so as the film slowly dissolves, it releases the agent material in the proper dosage..." (See col. 5, line 68 through col. 6, line 3). Staab teaches that "the polymer solids, water, or other solvent, contraceptive [i.e., an active]…, are admixed in the proper concentrations and the mixture heated to the appropriate temperature for dissolution and formation of a uniform blend to take place." (See col. 7, lines 37-41). In the Example at cols. 11-12, the ingredients are mixed together in a blender until just blended (see col. 11, lines 222-27). As such, Staab teaches formation of a flowable polymer matrix. A masterbatch

pre-mix as in instant claim 1 can be formed containing polymer and solvent, and the pre-mix is then transferred to a cooler vessel for addition of heat-sensitive pharmaceuticals or other agents (see col. 7, lines 37-51). Other polymers that can be used along with PEO and/or HPMC include polyvinyl alcohol (see col. 2, line 41; and col. 4, lines 22-61).

The active agents that can be used in Staab's film include spermicides for contraceptive use and/or drugs or medications (see col. 5, lines 66-68). The following is a list of active agents taught by Staab at col. 6, line 35 through col. 7, line 3:

> (1) anti-infectives such as antibiotics, sulfonamides, antivirals, antifungals, antiprotozoan and antibacterials;
>
> (2) anti-inflammatories, such as hydrocortisone, dexamethasone, triamcinolone, and various prednisolone compounds;
>
> (3) estrogenic steroids, such as estrone;
>
> (4) progestational agents, such as progesterone;
>
> (5) prostaglandins;
>
> (6) coronary vasodilators;
>
> (7) antitussives;
>
> (8) antihistamines;
>
> (9) anesthetics and
>
> (10) decongestants.
>
> Monoclonal antibodies [which are biological response modifiers] such as those useful against cell surface components or against pathogenic organisms such as the human-immuno-deficiency (HIV) family of viruses may be incorporated into the device of the present invention … . Other drugs include clotrimazole, miconazole, ticonazole, benzalkonium chloride, nystatin, dermally

active steroids, hormones, benzocaine, sulfas, biologically prepared actives, decongestants, cough/cold remedies, psychotropics, nitroglycerine, etc.

Staab also teaches the use of flavors, fragrances and coloring agents (see col. 7, lines 28-29). Thus, Staab's active material can be taste-masked.

Staab also discloses that "[t]he device of the invention thus is composed of a biologically compatible material that has been blended homogeneously" with the drug (see col. 6, lines 5-10). In the Example at cols. 11-12, Staab prepares a four-foot wide film which is then cut into two inch by two inch films each weighing 190 mg and containing 19 mg of benzalkonium chloride as the active agent (see col. 11, line 52 through col. 12, line 3).

With respect to step (c) in claim 1 and with respect to step (b) in claims 82, 161 and 315-318, Staab further discloses that "the mixture in liquid form will be poured or cast on to a plate or into a mold..." (See col. 5, lines 51-58 and the casting lines depicted in Fig. 5). In the Example at cols. 11-12, the blended mixture is poured onto a glass plate and spread to an even 3 mil thick film covering the surface of the glass (see col. 11, lines 41-44). Since Staab teaches a pourable polymer matrix containing the same components here claimed, it necessarily or obviously has a viscosity of within about 400 to about 100,000 cps, which is a viscosity ranging from thin castor oil to mincemeat. In fact, Staab teaches that “[t]he dissolution of the film can be readily adjusted by using different viscosities of the hydroxypropyl methyl cellulose ranging from less than 80 to more than 4,000 centipoises.” (See col. 5, lines 10-14).

With respect to steps (d) and (e) in claim 1 and with respect to steps (c) and (d) in claims 82, 161 and 315-318, Staab exemplifies drying the film in a temperature

regulated oven for approximately 20 minutes at 160°F, i.e., 71°C, or for 20 to 40 minutes when using a continuously moving belt that enters a drier (see col. 11, lines 45 and 65). Generally, Staab teaches drying at a controlled temperature of 130°F to 140°F (col. 11, lines 1-6), i.e. 54°C to 60°C, which either anticipates the "about 60°C" in claim 318 or encompasses and thus, renders obvious the "about 60°C". Since the temperature is regulated, and heat is applied by underbelt steam and overbelt hot air which are each adjustable (col. 10, lines 28-34), the drying is controlled as here claimed. Likewise, since the oven temperature is 71°C, or 54°C to 60°C, the polymer matrix temperature during drying is 100°C or less as here claimed. The ingredients blended to prepare the film are 52.5% HPMC, 37.5% glycerin and 10.0% of a 50% aqueous solution of the benzalkonium chloride (see col. 11, lines 30-34). Since the water content before drying is 5% (i.e., half of the 10% of the 50% aqueous solution of benzalkonium chloride), the dried film must have a water content of 10% or less as here claimed.

Further, either Staab's mixture in the Example at cols. 11-12 before drying is viscoelastic and thus, a more dry film that is also viscoelastic is obtained within about the first 4 minutes of drying. Alternatively, if the blended mixture before drying is not viscoelastic, then it becomes viscoelastic as the drying proceeds, and the film becomes viscoelastic within about the first 4 minutes of drying.

In particular, as noted above, the '080 patent teaches that "[t]he addition of hydrocolloids to the aqueous phase of the suspension increases viscosity, may produce viscoelasticity, and can impart stability depending on the type of hydrocolloid, its

concentration and the particle composition, geometry, size and volume fraction (see col. 8, lines 42-46). Staab uses the same hydrocolloid as in the '080 patent, i.e. said HPMC. As noted above, Staab teaches that "[t]he dissolution of the film can be readily adjusted by using different viscosities of the hydroxypropyl methyl cellulose ranging from less than 80 to more than 4,000 centipoises." (See col. 5, lines 10-14). Accordingly, since Staab's film in the Example at cols. 11-12 is inherently viscoelastic before drying, then within about the first 4 minutes of drying, a viscoelastic film having less water that before drying is formed.

Alternatively, to the extent that Staab's blended mixture before drying is not viscoelastic, then within about the first 4 minutes of the drying, a viscoelastic film is inherently formed. In particular, in order to arrive at a dried film product as in Staab, which is made using the same materials as disclosed in the '080 patent and the same basic process steps here claimed and each dosage film weighing 190 mg and containing 19 mg of benzalkonium chloride as the active agent (col. 11, line 35 through col. 12, line 3), i.e., a variation in active content of 0%, then a viscoelastic film is inherently formed within about the first 4 minutes of drying.

The claimed percent variation of active of no more than 10%, less than 5%, less than 2%, less than 1% and less than 0.5%, and thus also the claimed substantially uniform distribution and locking-in or substantially preventing migration are inherent in Staab's films in view of the fact that, as noted above, each dosage film contains 19 mg of benzalkonium chloride, i.e., a variation of 0%. Accordingly, Staab's films are suitable for regulatory approval by the FDA and commercialization, as here claimed.

Performing analytical chemical tests as here claimed is inherent in Staab's process because Staab reports the amount of active, e.g., 19 mg of benzalkonium chloride, in the 190 mg samples (see col. 11, line 35 through col. 12, line 3).

With respect to claims 82 and 315, Staab teaches repeating the process for producing larger quantities of film (see col. 11, lines 52-53). Thus, repeating said analytical chemical tests for each additional film that is prepared is inherent. Further, performing analytical chemical tests to show that all films prepared have a uniformity of active content that varies no more than 10% from a desired amount is inherent in view of the fact that Staab reports the amount of active, e.g., 19 mg of benzalkonium chloride, in the 190 mg samples, and in view of the fact that it is well-known and conventional in the art that active content of a dosage is allowed to be $\pm$ 10% from the desired amount, e.g., the amount of active the dosage is supposed to have.

While Staab does not discuss viscosity, viscoelasticity, the percent variation of active in the film, or performing analytical chemical tests, Staab, as cited above, discloses a process which reasonably appears to be either the same as or an obvious variation of the instantly claimed process. Accordingly, claims 1-5, 10, 13-15, 21, 24, 25, 32, 44-46, 54, 55, 59, 63-70, 72-75, 78-84, 89, 92-94, 100, 103, 104, 111, 123-125, 133, 134, 138, 142-149, 151-154, 157-166, 171, 174-176, 182, 185, 186, 193, 205-207, 215, 216, 220, 224-231, 233-236, 239-242, 249-252, 258-260, 267-270, 276-278, 285-288 and 294-318, if not anticipated under 35 USC 102(b), would be obvious under 35 USC 103(a).

In particular, to the extent the claimed flowable matrix viscosity of about 400 to about 100,000 cps is not inherent in Staab's matrix, then such would have been obvious. It would have been obvious to one of ordinary skill in the art at the time the invention was made to have optimized the viscosity of Staab's matrix, i.e., Staab's blended mixture, in order to be able pour the mixture onto a glass plate and obtain a film, after drying, that can be, for example, cut into dosages weighing 190 mg containing 19 mg of active (see col. 11, line 35 through col. 12, line 3 of Staab). In fact, as noted above, Staab teaches that "[t]he dissolution of the film can be readily adjusted by using different viscosities of the hydroxypropyl methyl cellulose ranging from less than 80 to more than 4,000 centipoises." (See col. 5, lines 10-14). Staab's viscosity range overlaps with and thus, renders obvious, the claimed viscosity range.

To the extent the claimed percent variation of active and performing analytical chemical tests are not inherent in Staab's process, then such would have been obvious.

Staab's films are intended for human use so as to deliver an effective dose of an active agent (col. 1, lines 10-64; col. 2, lines 34-46; and col. 11, line 52 through col. 12, line 50). As noted above, it is well-known in the art that world regulatory authorities do not permit dosage forms to vary by more than 10% in the amount of active present. It is also well-known in the art that to verify such uniformity, the actual content of active in individual dosages is measured, i.e., conventional analytical testing is used.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to minimize the active content variation among Staab's dosages as close to zero as possible, including the instantly claimed no more than 10%, less than

5%, less than 2%, less than 1%, and less than 0.5%, in view of the well-known goal of a skilled artisan to prepare dosages that do not vary by more than 10% in the amount of active present, in view of Staab's 19 mg of benzalkonium chloride per dosage film, and a desire to obtain FDA approval and commercialize the product. A skilled artisan would minimize active content variation by optimizing the available parameters in Staab's process, which are the same as or similar to those in the '080 patent. These include the polymer material, drying temperature, hot air application, drying time, viscosity, etc.

Further, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have performed known analytical chemical tests on Staab's dosages so as to determine the actual amount of active in the dosages and thus, assure the active content uniformity.

With respect to claims 82 and 315, it would have been obvious to one of ordinary skill in the art at the time the invention was made to repeat said analytical chemical tests which each additional film that is prepared by repeating Staab's process in order to seek regulatory approval and commercialize the product. It further would have been obvious to a skilled artisan at the time the invention was made to have prepared the multiple films such that the active content in each film does not vary by more than 10%, as determined by analytical chemical tests, from the amount of active the dosages are supposed to contain as required by various world regulatory authorities, in order to minimize dosage variation and so as to commercialize the product. A skilled artisan would obtain the variation of no than 10% from the desired amount by optimizing said available parameters in Staab's process.

Further, with respect to claims 2 and 3, as noted above, Staab teaches a masterbatch pre-mix can be formed containing polymer and solvent, and the pre-mix is then transferred to a cooler vessel, i.e., a second vessel in series, for addition of heat-sensitive pharmaceuticals or other agents (see col. 7, lines 37-51). Staab's Fig. 5 depicts three mixing vessels, the top two vessels being in parallel with each other, the lower vessel being in series with the top two vessels. Any transfer from one vessel to another would inherently or obviously involve a metering pump and control valve.

With respect to claims 65-69, 144-148 and 226-230 which require that the active is coated with a controlled release composition, and with respect to claims 72-75, 78-81, 151-154, 157-160, 233-236 and 239-242 which require providing a second film layer, Staab teaches that its film may be a laminate of two or more layers (see col. 5, lines 30-31; col. 9, lines 28-43; and Fig. 2). Staab teaches that the laminates can be formed in the conventional manner, for example the mixture in liquid form is poured or cast onto a plate or into a mold and allowed to begin to set, at which time another liquid mixture with different composition is poured on the first mixture, and both mixtures are allowed to set up completely producing a laminate or layers of different materials (see col. 5, lines 51-58). Staab teaches that the first and second film can comprise an active. In particular, referring to Fig. 2, Staab teaches the following at col. 9, lines 28-43:

> A first film layer 13 is made of, for example, a faster dissolving polymer material for release of a drug material 14a. A second film layer 15 is made of slower dissolving polymer material for release of more drug or another drug material 14b in combination, for example, a spermicide and an anti-infective or anti-inflammatory medication. A third (and additional) layer(s) 16 with additional drug can also be employed for sustained release of the drug.

Thus, the layers provide for controlled release of the drug material, i.e., a fast and slow release, and thus a sequential release, and also a sustained release. Staab also teaches immediate release since Staab teaches that "in case of medications to be administered via the oral cavity, it is advantageous that dissolution take place fairly rapidly." (See col. 4, lines 59-61). Immediate release and sustained release are also exemplified at col. 13, lines 13-41.

With respect to claims 70, 149, 231, 259, 260, 277, 278 and 295-297, Staab teaches many actives that are particulate, such as monoclonal antibodies (see col. 5, lines 49-53). The particulate monoclonal antibodies would be dispersed, i.e., suspended, in the matrix during the uniform blending (see col. 6, lines 5-10; col. 7, line 41; and col. 11, lines 26-35). Also, it is noted that polymers such as said PEO and HPMC are hydrocolloids.

With respect to claims 162, 163, 249-252, 258, 267-270, 276, 285-288 and 294, Staab teaches that if the drug can be applied on or in a moist area of the body, such as the mouth, vagina, rectum or eye, then the film can be used to deliver the drug effectively (see col. 7, lines 3-8). Application on or in the mouth either anticipates or renders obvious gingival, sublingual and buccal application. With respect to claim 164, Staab teaches the treatment of burn wounds with its films (see col. 7, lines 7-9).

With respect to claims 317 and 318, air currents which have forces below the yield value of the polymer matrix are inherent in Staab's process because, as noted above, Staab's cut films each contain 19 mg of active and thus, the variation of active in the dosage units is 0% and Staab obtains a consistent product. Alternatively, it would

have been obvious to one of ordinary skill in the art at the time the invention was made to have adjusted Staab's overbelt hot air (col. 10, lines 28-34) so that the film is not excessively blown and thus, a consistent product can be obtained.

6. Claims 8, 9, 76, 77, 87, 88, 155, 156, 169, 170, 237 and 238 are rejected under 35 U.S.C. 103(a) as being unpatentable over Staab.

This rejection was proposed by Third Party Requester on pages 41-42 of the Comments filed 04/12/13 and **is adopted** for the reasons that follow.

Staab is relied upon for the reasons stated above in rejection No. 5.

With respect to claims 8, 9, 87, 88, 169, and 170, Staab teaches that its polymer can be a dissolvable complex carbohydrate (col. 4, line 6 through col. 5, line 29), but does not specifically teach the complex carbohydrates here claimed, such as sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum and starch. However, these are conventional dissolvable polymers in the art. Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have used sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum and/or starch for the dissolvable complex carbohydrate to prepare Staab's film because these are conventional, dissolvable complex carbohydrates in the art and the reasonable expectation of success in preparing Staab's film.

With respect to claims 76, 77, 155, 156, 237 and 238, Staab does not specifically teach that its second film layer is extruded or sprayed onto its first film layer. As noted above, Staab teaches that the laminates can be formed in the conventional manner, for

example the mixture in liquid form is poured or cast onto a plate or into a mold and allowed to begin to set, at which time another liquid mixture with different composition is poured on the first mixture, and both mixtures are allowed to set up completely producing a laminate or layers of different materials (see col. 5, lines 51-58). The instantly claimed extrusion and spraying are well known alternative techniques to coating and casting for forming a layer.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have used extrusion or spraying in place of coating and casting to form Staab's second film layer because extrusion and spraying are well known alternative techniques to coating and casting, and the resulting reasonable expectation of success in preparing Staab's second film layer.

7. Claims 82, 89, 90, 92, 161, 171, 172, 174, 274, 292, 304-311 and 313-318 are rejected under 35 U.S.C. 103(a) as being unpatentable over Le Person.

On pages 42-44 of the Comments filed 04/12/13, Third Party Requester proposes that claims 82, 89, 90, 161, 171, 172, 274, 292 and 300-318 be rejected under 35 USC 102(b) as anticipated by, or alternatively, under 35 USC 103(a) as being unpatentable over Le Person. Further, on p. 44 of the Comments filed 04/12/13, Third Party Requester proposes that claims 92 and 174 be rejected under 35 USC 103(a) as being unpatentable over Le Person. For the reasons that follow, the proposed anticipatory rejection under 35 USC 102(b) of claims 82, 89, 90, 161, 171, 172, 274, 292 and 300-318 and the proposed obviousness rejection of claims 300-303 and 312

are not adopted. For the reasons that follow, the proposed obviousness rejection of claims 82, 89, 90, 92, 161, 171, 172, 174, 274, 292, 304-311 and 313-318 **is adopted**.

The proposed anticipatory rejection of claims 82, 89, 90, 161, 171, 172, 274, 292 and 300-318 is not adopted because independent claims 82 and 161 have been amended to require, and newly added independent claims 315-318 require, performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units sampled from different locations of the resulting film. Le Person does not teach such testing of the resulting film.

Further, the proposed anticipatory and obviousness rejections of claims 300-303 and 312 are not adopted because these claims depend from claim 1. Neither in the request for reexamination nor in the Comments filed 04/12/13 has Third Party Requester shown how Le Person alone teaches or renders obvious all the limitations in claim 1.

With respect to the obviousness rejection, Le Person provides and compares several processes for the drying of pharmaceutical wet films including drying by convection, conduction, and infrared drying (see p. 258, first sentences of § 2.2). The films of Le Person contain an acrylic adhesive polymer, its solvents, which include water, and an active substance which is a pharmaceutical or drug (see p. 258, line 5 and the first sentence of § 2.1; and Table 1). Le Person teaches that the constituents of the active phase, including the pharmaceutical or drug, in the matrix are homogeneously distributed (see p. 262, col. 2, lines 4-6). Le Person teaches that "[a]fter preparation, the coating mixture is spread on a web and submitted to drying in a tunnel or an oven.

Frequently, impinging jets and Infra-red Radiation accomplish the work in a short drying time (100 s as an order of magnitude)." (See p. 257, col. 1, lines 10-14). Using a short infrared drying process, Le Person teaches that in 10 minutes, 99% of the initial water from a 100 µm thick coating is evaporated (see p. 260, col. 2, lines 12-14 and Fig. 5). As seen in Le Person's Fig. 3, the average temperature of the film during drying stays well below 100°C. As seen in Table 2, Le Person teaches a heated slab temperature, T_c, of 60°C and a wind tunnel air temperature, $T_{\infty db}$ of 65°C (see also p. 258), which render obvious the drying apparatus temperature of about 60°C in claim 318. The drying is controlled since, for example, Le Person teaches "a conventional drying rig where temperature ($T_{\infty db}$), velocity (U_∞) and humidity (Y_∞) or air are controlled." (See p. 258, col. 2 and Fig. 1).

As noted above, Le Person teaches that the active substance is homogeneously distributed throughout the initially wet film (see p. 262, col. 2, lines 4-6). Le Person then studies the migration of the active material vertically, i.e. throughout the thickness, of the film throughout the drying process (see p. 262, col. 1, lines 11 to col. 2, line 3). Le Person discloses that after 5 min of the drying, "the polymeric network is not turgescent and the meshes are densely packed. The polymer skeleton acts as a filter for the active substance [i.e., pharmaceutical or drug] when the system reequilibrates." (See p. 262, col. 2, third full paragraph.) Le Person also teaches that "[b]etween the 5^{th} and 10^{th} min of drying the heavy solvent migrates… active substance, slowed down in its migration, stays in the bottom of the layer." (See the last four lines at page 262, col. 2). It is noted that the heavy solvent only accounts for 2% of the wet composition of the coating (see

page 258, Table 1). The active material homogenizes and a quasi-equilibrium is obtained for the components of the active phase, taking into account evaporation of the heavy solvent (p. 263, col. 1, lines 8-13). Le Person also teaches that the films are used in patches for transdermal drug delivery (see Abstract and p. 257, col. 1). Thus, plural dosage units of the same size, e.g., plural transdermal patches of the same size, are rendered obvious by Le Person.

As noted above, after 10 minutes of drying, 99% of the water has been evaporated (see p. 260, col. 2, lines 12-14 and Fig. 5). In fact, the water is intensely removed from the film in the first 3 minutes with the short infrared drying process (see p. 261, col. 2, lines 21-24 and 27-30). Also, as can be seen from Fig. 2 on p. 259, similar intense drying is seen using conduction, convention, etc. As seen in Fig. 5, after 4 minutes of drying, about 98% of the water, i.e., the major solvent as seen in Table 1, has been evaporated. Further, Le Person's Fig. 2 shows that at 4 minutes, or approximately 15 $s^{0.5}$, solvent content is less than 20% by weight in the films dried by MIR and SIR and less than 35 % by weight in all dried films.

Within about 4 minutes of drying, Le Person's film is inherently viscoelastic. In particular, a compact polymer skeleton, wherein the polymer network is not turgescent and the meshes are densely packed, has been formed. Le Person uses the same type of polymer as disclosed in the '080 patent, i.e., an acrylic polymer (see p. 258 of Le Person; and col. 15, lines 55-56 of the '080 patent). As the drying proceeds, the active substance homogenizes, and after 15 minutes of drying, a quasi-equilibrium is obtained

for the components of the active phase, taking into account evaporation of the heavy solvent (see pp. 262-263).

Le Person teaches the limitations of the instant claims, other than the differences discussed below.

Le Person does not teach the viscosity of its wet mixture of ingredients, whereas the instant claims require a viscosity from about 400 to about 100,000 cps. It would have been obvious to one of ordinary skill in the art at the time the invention was made to have prepared Le Person's coating mixture of acrylic polymer, solvents and active with an appropriate viscosity so that it can be spread on a substrate and dried to form a film useful for transdermal delivery of the active (see p. 257). The claimed viscosity from about 400 to about 100,000 cps corresponds to a viscosity ranging from thin castor oil to mincemeat. It would been obvious to one of ordinary skill in the art at the time the invention was made to prepare Le Person's mixture such that the viscosity is not too low, and thus, the mixture doesn't run like water, but not too high so the mixture is spreadable on a substrate; and so as to ultimately form a transdermal delivery film which is a quality product with physical and chemical homogeneity and an appropriate distribution of active substance (see the paragraph bridging the left and right columns on p. 257 of Le Person).

The claimed percent variation of active of no more than 10%, less than 5%, less than 2%, less than 1% and less than 0.5%, and thus also the claimed substantially uniform distribution and locking-in or substantially preventing migration are inherent in Le Person's films in view of the fact that, as noted above, Le Person's active material

homogenizes and a quasi-equilibrium is obtained for the components of the active phase, taking into account evaporation of the heavy solvent. Accordingly, Le Person's films are suitable for regulatory approval by the FDA and commercialization, as here claimed.

Alternatively, to the extent the claimed percent variation of active is no inherent from Le Person's process, then such would have been obvious. Le Person also differs from the instant claims in that while Le Person teaches the active material homogenizes and a quasi-equilibrium is obtained for the components of the active phase, taking into account evaporation of the heavy solvent, Le Person does not perform "analytical chemical tests" on the equal sized dosage units.

However, Le Person's films are intended for human use for delivery of pharmaceuticals, such as transdermal drug delivery (see p. 257). It is well-known in the art that world regulatory authorities do not permit dosage forms to vary by more than 10% in the amount of active present. It is also well-known in the art that to verify such uniformity, the actual content of active in individual dosages is measured, i.e., conventional analytical testing is used.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to minimize the active content variation among Le Person's dosages, as measured by analytical chemical tests, as close to zero as possible, including the instantly claimed no more than 10%, less than 5%, less than 2%, less than 1%, and less than 0.5%, in view of the well-known goal of a skilled artisan to prepare dosages that do not vary by more than 10% in active, in view of the fact that Le

Person's active material homogenizes and a quasi-equilibrium is obtained for the components of the active phase, taking into account evaporation of the heavy solvent, and a desire to obtain FDA approval and commercialize the product. A skilled artisan would minimize active content variation by optimizing the available parameters in Le Person's process, which are the same as or similar to those in the '080 patent. These include drying temperature, drying time, air velocity, humidity etc (see pp. 258-259 of Le Person).

Further, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have performed known analytical chemical tests on Le Person's dosages so as to determine the actual amount of active in the dosages and thus, assure active content uniformity.

With respect to claim 82 and 315, Le Person does not specifically teach repeating its process and said analytical chemical tests. Further, Le Person does not specifically teach that the active content of the first film obtained from the process and additional films prepared by repeating the process varies no more than 10% from a desired amount as indicated by analytical chemical tests.

However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have repeated Le Person's process and the analytical chemical tests for each film prepared by the process so as to prepare more films and dosages, seek regulatory approval and commercialize the product. It further would have been obvious to a skilled artisan at the time the invention was made to have prepared the multiple films such that the active content in each film does not vary by

more than 10% from the amount of active the dosages are supposed to contain as required by various world regulatory authorities, in order to minimize dosage variation and commercialize the product. A skilled artisan would obtain the variation of no than 10% from the desired amount by optimizing said available parameters in Le Person's process.

With respect to claims 90 and 172, Le Person teaches that its coating mixture contains three light solvents (Sl_i) (see p. 258, section 2.1). Table 1 indicates that solvent Sl_2 has a molecular weight of 46, which is the molecular weight of ethanol. While dimethyl ether also has a molecular weight of 46, it cannot be used as a solvent due to its low boiling point of -24°C. Accordingly, the Le Person's light solvent of molecular weight 46 is either the same as or renders obvious ethanol as here claimed.

With respect to claims 274 and 292, which require that the resulting film contains less than about 6% by weight solvent, the solvent content in Le Person's dried films is far under about 6% as evidenced by Figs. 2 and 5. Le Person teaches that using a short-infrared drying process, in 10 minutes 99% of the initial water content from a 100 µm thick coating is evaporated (see § 3.1 at pp. 260-261, in particular Fig. 5 and the second paragraph of right col. at page 260). In view of the water and heavy solvent content in Fig. 5, the total solvent content is well under about 6%.

Le Person does not teach the pharmaceutical or drug active materials listed in claims 92 and 174. However, these materials are conventional pharmaceuticals and drugs.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have used the conventional pharmaceutical or drug materials here claimed as the pharmaceutical or drug material in Le Person's film so as to take advantage of the intended function of the pharmaceutical or drug, and because of a reasonable expectation of success.

With respect to claims 317 and 318, while Le Person does not specifically teach using air currents which have forces below the yield value of the polymer matrix such is either inherent or obvious. It's inherent because Le Person teaches air velocities of 2 m/s and 4 m/s (Table 2), which correspond to 4.5 miles/hr and 8.9 miles/hr, respectively. These are light winds that even with water (viscosity 1 cp) would produce only small wavelets.

Alternatively, since Le Person's resulting, dried films are homogeneous with respect to active material, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have adjusted Le Person's air velocity so that the film is not excessively blown and thus, a consistent product can be obtained.

8. On pages 45-46 of the Comments filed 04/12/13, Third Party Requester proposes that claims 1, 5, 7-10, 13, 14, 23, 63, 64, 82, 84, 86-89, 92, 93, 102, 142, 143, 161, 166, 168-171, 174, 175, 184, 224, 225, 249, 267, 285 and 300-317 be rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Horstmann.

9. On page 46 of the Comments filed 04/12/13, Third Party Requester proposes that claim 318 be rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Horstmann and Arter.

10. On pages 46-47 of the Comments filed 04/12/13, Third Party Requester proposes that claim 318 be rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Horstmann and Strobush.

These proposed rejection Nos. 8 to 10 **are not adopted** for the reasons that follow.

Independent claims 1, 82 and 161 have been amended to require, and new independent claims 315-318 require, performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units sampled from different locations of said resulting film, said tests indicating that uniformity of content in the amount of the active varies by no more than 10%. This requirement is similar to the imitation set forth in patented dependent claims 255, 273 and 291 (now canceled), which depended from claims 1, 82 and 161, respectively, and required the step of forming a plurality of individual dosage units of substantially the same size, wherein the active content of individual dosage units varies no more than 10%. Neither in the request for reexamination nor in the Comments filed 04/12/13 has Third Party Requester shown how Horstmann teaches or renders said requirement. Further, Horstmann is discussed in the Background of the Related Technology section of the '080 patent, where difficulty in achieving a uniform film after drying is discussed (col. 1,

line 52 through col. 4, line 23). Neither Arter nor Strobush solves Horstmann's deficiency.

Response to Arguments

Patent Owner's arguments filed March 13, 2013 have been fully considered but they are not persuasive.

It is noted that p. 61 of the Remarks filed 03/13/13 refers to "… the Bogue Declaration and the Fuller Declaration". There is no Fuller Declaration of record in the reexamination proceeding. As noted on p. 46 of the Remarks filed 03/13/13, the declarations accompanying Patent Owner's response of 03/13/13 are the Bogue Declaration and Lin Declaration.

General Arguments and the Bogue Declaration:

Patent Owner compares the claimed process to making bread on different days of the week (Remarks of 03/13/13, pp. 48-49). In particular, Patent Owner argues slices of bread from a loaf baked on a Monday would differ in taste by only 10%, and that slices from a Monday loaf and a Friday loaf have a difference in taste of about 10% from what the baker believes all his/her bread should be expected to taste like (Remarks of 03/13/13, pp. 48-49). Patent Owner cites the Bogue Declaration and argues that the "recipe" of Patent Owner's process keeps the difference between individual dosage units from one manufactured lot at smaller than 10% in amount of pharmaceutical active in claims 1, 82, 161 and 316-318, and keeps the difference between individual dosage

units between different manufactured lots smaller than 10% from a desired amount in claim 315 (Remarks of 03/13/13, pp. 48-52). The Bogue Declaration is cited in other portions of the Remarks of 03/13/13, including pp. 46, 60, 61, 63 and 64.

Patent Owner's arguments and the Bogue Declaration are unpersuasive. While a baker can follow a specific recipe with specific ingredients to bake the bread loaf, the instant claims are not so specific, but rather are broad and general. As noted above in the rejections, the prior art either explicitly, inherently and/or obviously performs the claimed generic manufacturing steps using the claimed generic ingredients.

In fact, as also noted above, Chen analyzes its resulting film using the same criteria exemplified in the '080 patent specification for evaluation of substantial uniform distribution, i.e., weight of dosages and visual inspection (see col. 31, line 37 through col. 32, line 34, and col. 37, lines 61-63 of the '080 patent). In particular, Chen's dried film product of Example 1 is cut into equal sized dosage units ready for packing (p. 17, lines 31-32; Table 4) and has a weight of 0.028 $\pm$ 0.001 g/dosage film, a density of 1.0485 $\pm$ 0.009 g/cm^2, a water content of 1.7 $\pm$ 0.24%, a thickness of 2.1 $\pm$ 0.12 mil (see Table 4); and the dried films are glossy and substantially transparent (p. 17, line 15), i.e., they are visually free of aggregation. The 0.028 $\pm$ 0.001 g/dosage film has variation of (0.001/0.028) x 100 = 3.6%. When film weight is rounded to two decimal places as in Table 2 at col. 31 of the '080 patent, then the weight is 0.03 gram/dosage film with a variation of 0%. Such small variation when following Chen's process was confirmed in the Reitman Declaration submitted by Third Party Requester.

Likewise, in the Example at cols. 11-12, Staab prepares a four-foot wide film which is then cut into two inch by two inch films each weighing 190 mg and containing 19 mg of benzalkonium chloride as the active agent (see col. 11, line 52 through col. 12, line 3). Le Person teaches the active material homogenizes and a quasi-equilibrium is obtained for the components of the active phase, taking into account evaporation of the heavy solvent (p. 263, col. 1, lines 8-13),

The Bogue Declaration is unpersuasive for several reasons. It does not make a comparison with the prior art of record, and thus, does not show anything unexpected with respect to the prior art of record. Other than the general process steps in the claims, which are performed by the prior art either explicitly, inherently or obviously, the Bogue Declaration lacks specific details about the film production. For example, it is not clear in the Bogue Declaration which materials, e.g., the specific polymers, actives and solvent, are used; it is not clear if other materials are present when preparing the films; it is not clear exactly what is done to form the flowable polymer matrix or how and on what it is casted, or how the controlled drying is performed and for what exact amount of time the drying is done, or which analytical chemical tests are used, etc. Accordingly, a definitive conclusion cannot be reached form the Bogue Declaration.

Patent Owner argues that "[a]s defined in the '080 patent, a visco-elastic film is one that has been controllably dried to lock its components into a substantially uniform distribution throughout the film while avoiding problems associated with conventional drying methods." (Remarks of 03/13/13, p. 53).

This argument is unpersuasive. Nowhere does the '080 patent provide a special definition for the term "visco-elastic film". As noted above in the Scope of Claims section, the matrix prior to evaporating the solvent (water) may be viscoelastic, and the viscoelasticity is present due, for example, to the fact that a hydrocolloid has been added. The instant claims have been amended to require "controlled drying … to form a visco-elastic film having said active substantially uniformly distributed throughout …". However, as noted in the rejections, Chen, Staab and Le Person use controlled drying and obtain the claimed substantial uniformity of active in a viscoelastic film.

Patent Owner argues that physical properties such as product film weight and appearance do not establish uniformity of content of components, and that in the Scope of Claims section of the Office action mailed 11/29/12, the Specialist mistakenly included physical uniformity type tests with chemical uniformity type tests (Remarks of 03/13/13, pp. 53-59). In particular, Patent Owner cites the following passage from the Scope of Claims:

> An alternative means for evaluating uniformity is to cut the film into individual doses and measure the weight of the doses (col. 31, line 46 through col. 32, line 45). The '080 patent notes that "films of substantially similar size cut from different locations of the same film contain substantially the same amount of active." (col. 32, lines 37-39).

and argues that the two sentences are not related to each other, other than that both deal with examples of cutting the film into dosage forms (Remarks of 03/13/13, pp. 57-58). Patent Owner cites col. 32, lines 35-40 of the '080 patent and argues that the '080 patent "discloses essentially that to demonstrate uniformity of content for active, the

amount of active in each substantially similarly sized sample must be determined." (Remarks of 03/13/13, pp. 58-59). Patent Owner argues that "it is one thing to have films which appear to be substantially free of aggregation and rely on that to say there is substantially no disparity among the amount of active in any portion of the film, and it is a totally different thing to demonstrate the presence of the required level of uniformity of content in the amount of active by analytical chemical testing and determining the actual amount of active in samples." (Remarks of 03/13/13, p. 58). Patent Owner argues that "[i]n one example, in the '080 Patent analytical chemical testing was used to test for the amount of one component, a red dye, and in so doing established that the uniformity of content of the component fell well within the 10% level, particularly, it was 4%. See, '080 Patent, col. 33, l. 10 through col. 34, l. 24 (example M)." (Remarks of 03/13/13, p. 59).

Patent Owner's arguments are unpersuasive. First, it is noted that the issued claims in the '080 patent do not recite "analytical chemical tests". This requirement was added by Patent Owner in the amendment dated 03/13/13 in response to the Office action mailed 11/29/12. Accordingly, in discussing the distribution of active in the Scope of Claims section in the first Office action, the Specialist was not mistaken in citing those portions of the '080 patent that deal with distribution of the active. In particular, the '080 patent teaches at col. 31, lines 37-44, that a "uniform distribution of components" can be determined by examination by either the naked eye or under slight magnification, and that "by viewing the films it was apparent that they were substantially free of aggregation, i.e. the carrier and the actives remained substantially in place and did not

move substantially from one portion of the film to another … [t]herefore, there was substantially no disparity among the amount of active in any portion of the film." An alternative means for evaluating uniformity is to cut the film into individual doses and measure the weight of the doses (col. 31, line 46 through col. 32, line 45). The '080 patent notes that "films of substantially similar size cut from different locations of the same film contain substantially the same amount of active." (col. 32, lines 37-39).

Further, contrary to Patent Owner's argument, said two sentences are related to each other, i.e., cutting the film into individual doses and measuring the weight of the doses is an analytical technique for determining uniformity of active, as discussed at col. 31, line 46 through col. 32, line 39 of the '080 patent. In particular, col. 31, line 46 through col. 32, line 39 of the '080 patent discusses measuring uniformity by cutting the film into individual dosage units and weighing them. In this example, i.e., Example E bridging cols. 30-32, the individual dosages weighed 0.04 grams, i.e., 40 mg, "which shows that the distribution of the components within the film was consistent and uniform. This is based on the simple principle that each component has a unique density. Therefore, when the components of different densities are combined in a uniform manner in a film, as in the present invention, individual dosages [sic] forms from the same film of substantially equal dimensions, will contain the same mass." (See col. 31, line 46 through col. 32, line 33). The '080 patent then goes on to teach that "[a]n alternative method of determining uniformity of the active is to cut the film into individual doses ... [which are then] dissolved and tested for the amount of active in films of particular size." (See col. 32, lines 34-39).

In fact, Patent Owner's Lin Declaration notes in ¶16 that "[t]esting to establish uniformity of dosage is defined in the USP under the general chapter <905>." As noted by Third Party Requester on pp. 13-14 of the Comments filed 04/12/13, "[i]f the amount of active is high enough, a Weight Variation Test is acceptable. See Exhibit K at pp. 6-7, Q&A5." Exhibit J of the Comments filed 04/12/13, which is the 2011 version of general chapter <905>, shows that weight variation involves weight measurement of dosages.

Further, in the example in the '080 patent cited by Patent Owner, i.e., Example M at cols. 33-34, analytical chemical testing is used to test for the amount of one component, a red dye. However, red dye, which footnote 4 of Table 4 notes is available from McCormick, is not a bioactive active or pharmaceutical active here claimed. In the examples of the '080 patent containing bioactive or pharmaceutical active, visual inspection and/or weight of dosage films are used as in Chen. In the '080 patent's Example E, which contains loratadine as an active, visual inspection is used, and so is weight of dosage films, which are consistently found to be 0.04 gm (see col. 31, line 37 through col. 32, line 33). In the example at col. 37, lines 52-67, loratadine is added to composition AA and a dried film is formed and then cut into 1 in. x 0.75 in. pieces. The pieces are measured to weigh 70 mg $\pm$ 0.7 mg "demonstrating the uniformity of the composition of the film."

Patent Owner argues the following on pp. 54-55 of the Remarks filed 03/13/13:

> Importantly, the process of forming a proper film product with the claimed levels of uniformity of content in, for example, the amount of active does not end

> at the mixing stage. Patentee has discovered that the various steps post-mixing play a very important role in ensuring that the resulting product complies with the stringent requirements for uniformity of content. For example, one key step in the formation of a film product is the drying step, particularly when heat and/or radiation is used to dry the film. Patentee has discovered that controlled drying methods is essential in meeting these claimed requirements. Controlled drying includes methods that avoid, for example, the formation of bubbles, or uncontrolled air currents that may cause movement of particles within the visco-elastic film forming matrix. Controlled drying, as required by the invention as claimed, may be effectuated through evaporating at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film wherein the polymer matrix temperature is 100 ℃ or less.

This argument is unpersuasive since, as noted above in the rejections, each of Chen, Staab and Le Person performs the claimed controlled drying. Using Chen as an example, it is the Specialist's position that Chen's mixture before drying is viscoelastic. In particular, as noted above, the '080 patent teaches that "[t]he addition of hydrocolloids to the aqueous phase of the suspension increases viscosity, may produce viscoelasticity, and can impart stability depending on the type of hydrocolloid, its concentration and the particle composition, geometry, size and volume fraction (see col. 8, lines 42-46). Chen adds the same hydrocolloid as in the '080 patent, i.e. said HPMC, to water, and Chen's wet matrix before drying has a viscosity of 500-15,000 cps (p. 15, line 26), which is within the '080 patent's disclosed range of about 400-100,000 cps and overlaps the most preferred range of about 1,000-40,000 cps (see the paragraph bridging cols. 16 and 17 of the '080 patent). Accordingly, Chen's films in Examples 1, 2 and 5-8 and the Example in Tables 7 and 8 are inherently viscoelastic before drying.

Within 4 minutes of the 9 minutes of drying in Chen's Examples 1, 2 and 5-8 and the Example in Tables 7 and 8, a more dry viscoelastic film is obtained.

Alternatively, to the extent that Chen's wet film in Examples 1, 2 and 5-8 and the example in Tables 7 and 8 before drying are not viscoelastic, then within about the first 4 minutes of the 9 minute drying in a hot air circulating oven at 50°C, a viscoelastic film is inherently formed. In particular, in order to arrive at a dried film product as in Chen, which is made using the same materials as disclosed in the '080 patent and the same basic process steps here claimed, wherein the dried film is glossy and substantially transparent and has the gram per dosage, thickness, density and water content in Chen's Table 4 for Example 1, then a viscoelastic film is inherently formed within about 4 minutes. The remaining time after the viscoelastic film is formed further dries the viscoelastic film.

As an even further alternative, if Chen's viscoelastic film is formed after about the first 4 minutes but within Chen's 9 minute drying time, then a skilled artisan would recognize that with a higher drying temperature, a shorter drying time than 9 minutes can be used. In other words, a higher drying temperature than the 50°C exemplified by Chen would result in formation of Chen's viscoelastic film product sooner. In fact, Chen teaches that its drying temperature can be in the range of 40-100°C (see p. 15, line 28). It would have been obvious to one of ordinary skill in the art at the time the invention was made to have used a higher drying temperature than the 50°C exemplified by Chen because Chen teaches that the drying temperature can be as high as 100°C, and the resulting expectation of a shorter drying time using a higher temperature.

Further, before controlled drying, Chen's mixture of ingredients, i.e., the instant flowable polymer matrix, which Chen teaches has a viscosity of 500 to 15,000 cps, is degassed in a vacuum chamber until trapped air bubbles are removed, and then coated on the non-siliconized side of a polyester film (see p. 15, lines 24-29; and p. 17, lines 13-15). Chen controls drying and evaporates water from the cast matrix in 9 minutes of drying in a hot air circulating oven at 50°C (see p. 17, lines 13-15 and Fig. 2). As seen schematically in the drying apparatus of Chen's Fig. 2, the air flow is less direct at the film surface at the beginning of the drying and becomes more direct as the film proceeds through the drying oven, which has an aeration controller (see also p. 5, line 31 through p. 6, line 3). According, Chen takes into account air bubbles and control of air currents.

Patent Owner argues that having a glossy surface does not equate to a uniform film, because the bottom side of a film product formed on a substrate will take the surface features of the substrate (Remarks of 03/13/13, p. 55).

This argument is unpersuasive. Apparently, this argument is referring to Chen, which teaches that its film is glossy (see p. 17, line 15). The argument ignores the fact that Chen further teaches its film is substantially transparent, has a weight of 0.028 $\pm$ 0.001 g/dosage film when cut into dosages, has a thickness of 2.1 $\pm$ 0.12 mil, has a density of 1.0485 $\pm$ 0.009 g/cm^2, and has a water content of 1.7 $\pm$ 0.24% (see p. 17, lines 15-16 and Table 4). The argument also ignores the fact that Chen uses essentially the same production steps, e.g., forming a masterbatch premix, adding

active, casting the flowable polymer matrix, controlled drying, and forming a resulting film, as in instant claim 1.

Patent Owner argues they were the first to identify and solve the problems associated with manufacture of commercially and pharmaceutically viable active containing film dosage units or forms (Remarks of 03/13/13, pp. 59-61). In particular, Patent Owner argues they discovered that conventional drying methods are not commercially viable to manufacture therapeutic-active-containing films, and argues they solved the problem by controlling polymer matrix viscosity and controlling the drying process (Remarks of 03/13/13, pp. 60-61).

These arguments are not persuasive. While the '080 patent states at col. 3, lines 33-37 that "[c]onventional drying methods generally include the use of forced hot air using a drying oven, drying tunnel, and the like" and that "[t]he difficulty in achieving a uniform film is directly related to the rheological properties and the process of water evaporation in the film-forming process", it is noted that none of the processes of Chen, Staab or Le Person, which are essentially the same as here claimed, with the exception of running conventional "analytical chemical tests", is addressed in the '080 patent.

Patent Owner argues the Cohen Declaration is "dead wrong on its face or does not apply to the '080 patent" because "Dr. Cohen does not discuss the degree of uniformity of content"; argues that Dr. Cohen provides no support for any prescribed

degree of uniformity; and cites case law for the proposition that inherency requires more than probabilities, possibilities or assumption (Remarks of 03/13/13, pp. 62-65).

This argument is unpersuasive. As noted above in the rejection over Chen, ¶¶ 8-10 of the Cohen Declaration are cited for the proposition that when working with a homogeneous or completely dissolved coating mixture as in Chen, it would be difficult for a person of ordinary skill in the film art not to obtain a film that has a uniform content of active, and the drying method disclosed in Chen would not be expected to create any agglomeration, aggregation or otherwise non-uniform content of active (see ¶¶ 8-10). This is supported by the results of Chen, who cuts a film into dosage units weighing 0.028 $\pm$ 0.001 g/dosage film (Table 4 of Chen) and thus, a variation of (0.001/0.028) x 100 = 3.6%. When film weight is rounded to two decimal places as in Table 2 at col. 31 of the '080 patent, then the weight is 0.03 gram/dosage film with a variation of 0%. As also noted above, the films have a density of 1.0485 $\pm$ 0.009 g/cm^2, a water content of 1.7 $\pm$ 0.24%, a thickness of 2.1 $\pm$ 0.12 mil (see Table 4); and the dried films are glossy and substantially transparent (p. 17, line 15), i.e., they are visually free of aggregation. The Cohen Declaration's assertions are further supported by the Reitman Declaration, which reproduced Chen's Example 7 and obtained films each weighing 0.034 grams/dosage unit, and having a variation of active content, i.e., oxybutynin content, of less than 10% as here claimed.

In rebutting Third Party Requester's position in the request that a "whereby" clause in a method claim is not given weight when it simply expresses the intended

result of a process step positively recited, Patent Owner argues that such clauses, including the "wherein" clauses of the instant independent claims, cannot be ignored (Remarks of 03/13/13, pp. 73-74).

This argument is moot since the rejections in the Office action mailed 11/29/12 and the instant Action Closing Prosecution address the "wherein" clauses of the claims. The requirements of the clauses are either taught by, inherent in, or rendered obvious by the prior art, as set forth in the rejections.

Arguments with respect to the rejections based on Chen; and Patent Owner's citation of the Lin Declaration:

Patent Owner argues the following on pp. 65-66 of the Remarks filed 03/13/13:

1. Chen's alleged inherency.

> "The claimed "substantially uniform distribution of components" and "locking-in or substantially preventing migration" of the active in independent claims 1, 82 and 161, and the variation of active content of 10% or less in dependent claims 254-255, 272-273 and 290-291, are inherent in Chen's exemplified films and process. Inherency is based on the following: As discussed above, Chen uses the same materials and method as here claimed. Chen's ingredients are mixed until they are uniformly dispersed or dissolved in the hydrocolloid (p. 17, lines 8-11). Chen uses the same criteria discussed above with respect to the '080 patent in the Scope of Claims section for evaluation of substantial uniform distribution, i.e., weight of dosages and visual inspection."
>
> Office Action, p. 13.
>
> The criteria used by Chen as cited by the Examiner for evaluation of "substantial uniform distribution" are physical observations. Such "observations" cannot be used, either inherently or otherwise, to establish the uniformity of content in the actual amount of active in equally sized samples in Chen's examples. Absent statements or data based on

> analytical chemical testing, not weighing or visual inspection, for the amount of active present in the film, Chen does not and cannot inherently disclose Patentee's resulting film having the claimed levels of uniformity of content. Moreover, even if Chen disclosed, which it does not, the use of the same materials and methods as the '080 Patent, the mere fact that a certain thing may result from a given set of circumstances is not sufficient to support inherency. *Crown, supra*, at 1378.

These arguments are unpersuasive. As noted above, Chen uses the same materials and method steps here claimed. Additionally, the criteria used by Chen to evaluate uniformity is the same as used in the examples of '080 patent, i.e., visual inspection and weight of dosage films. As noted above, Chen's dried film product of Example 1 is cut into dosage units ready for packing (p. 17, lines 31-32) and has a weight of 0.028 $\pm$ 0.001 g/dosage film, i.e., 0.03 gram/dosage film with a variation of 0%. Chen's films are glossy and substantially transparent (p. 17, line 15).

Likewise, at cols. 31-32, the '080 patent teaches that uniform distribution of components within the film was apparent by examination by either the naked eye or under slight magnification. Also, the individual dosages in Table 2 consistently weighed 0.04 grams, "which shows that the distribution of components within the film was consistent and uniform … based on the simple principle that each component has a unique density. Therefore, when the components of different densities are combined in a uniform manner in a film, as in the present invention, individual dosages [sic] forms from the same film of substantially equal dimensions, will contain the same area." (See col. 32, lines 26-33). Similarly, at col. 37, lines 52-67 of the '080 patent, the dried film was cut into 1 in. x 0.75 in. pieces weighing 70 mg $\pm$ 0.7 mg.

While the '080 patent teaches analytical chemical tests can be used as an alternative to visual inspection and weight of dosages films for determining uniformity (col. 31, line 37 through col. 32, line 39), no analytical chemical tests are done in any '080 patent example to determine the weight of a pharmaceutical active or bioactive active. The only analytical chemical tests exemplified in the '080 patent are in Example M at col. 33-34, and these tests are done for content of McCormick red dye, which is not a pharmaceutical active or bioactive active.

Patent Owner argues "Third Party Requester has not provided any proof that Chen's process examples when followed exactly, with all the components exactly as listed, and all other conditions of Chen exactly met, will provide a process suitable for commercial manufacture, a process which produces products which are regulatory approvable by the FDA, and which exhibit the levels of uniformity of content in actual amount of active claimed by Patentee's processes." (Remarks of 03/13/13, p. 66).

This argument is unpersuasive. The claims do not require FDA approval. Chen renders obvious the claimed invention and, as discussed above, shows the same level of uniformity, based on visual examination and weight of dosage units, as exemplified in the '080 patent. In any event, as also noted above, the Reitman Declaration submitted by Third Party Requester is further proof that when Chen's process example is followed exactly, with all the components exactly as listed, and all other conditions of Chen exactly met, provides a level of uniformity as here claimed.

On pp. 66-67 and 77 of the Remarks filed 03/13/13, Patent Owner points to ¶ 22 of the Lin Declaration, which argues the following:

> 22. Finally, Chen's patent discloses the release profiles of four active agents from films. See Chen, Figure 5. The release profile data presented in Figure 5 show a high degree of variability at each data point. For example, the release profile for nicotine containing film product show that the amount of nicotine released at the 5 minute and 8 minute time point can be as high as approximately 115-120%. This level of active agent is greater them the 110% level (from an expected amount of 100%) that is considered acceptable to FDA for regulatory approval of a product that purports to be manufactured consistently with acceptable content uniformity. These data indicate that the test method used in the analysis is not reproducible and/or there is a lack of active agent content uniformity between individual dosage units. These deficiencies demonstrate the lack of manufacturing consistency and lack of active agent content uniformity in the film.

This argument is unpersuasive. Nowhere does the '080 patent or USP general chapter <905> cited in ¶ 16 of the Lin Declaration (see also Exhibits J and K of the Comments filed 04/12/13) rely solely on a release profile to evaluate uniformity of content in the amount of active, as here claimed. Further, as noted by Third Party Requester on p. 7 of the Comments filed 04/12/13:

> Lin concludes his Declaration with a logical fallacy. Based on a possible relationship between data and a film problem, and despite evidence that indicates an alternative possibility is more likely, Lin illogically finds that the data necessarily shows a film problem. Lin states that Chen's interim release data indicates a problem with the test method "and/or" a variation in dosage unit active content. See Lin Decl. ¶ 20 [sic, ¶ 22] (emphasis added). Reduced to its logical components, Lin' s premise is that X (Chen' s interim release data) indicates A (test problem) and/or B (film problem). As an initial matter, the fact that Chen' s maximum release error bars decrease over time indicates that the error noted by Lin is an artifact of the test method--not a characteristic of the film. Nonetheless, without further support or explanation, Lin concludes that Chen's data demonstrates unacceptable variation in dosage unit active content (film problem). Reduced to its logical components, Lin's conclusion (X demonstrates B) does not follow from Lin's own premise (X indicates A and/or B). In other words, Lin's conclusion is logically invalid based on Lin' s own stated premise.

> Because it lacks viable support or explanation, Lin's conclusory allegation based on Chen's interim release data cannot overcome any rejections based on Chen. See MPEP 716.01 (C).III (requiring consideration of the absence of factual support for an expert opinion in assessing its probative value).

Patent Owner cites the Lin Declaration for the proposition that Chen's disclosure is insufficient to provide the manufacture of drug-containing films with the uniformity content in amount of drug (active) in individual dosage units to make FDA approvable film products (Remarks of 03/13/13, p. 67 and 78). Patent Owner argues that the claims now require analytical chemical testing and that the films have levels of uniformity in the amount of active which varies by no more than10% from film to film and/or no more than 10% from a desired amount across several films (Remarks of 03/13/13, p. 67).

These arguments and the Lin Declaration are unpersuasive. As noted by Third Party Requester on pp. 5-6 of the Comments filed 04/12/13, the issue here is not whether Chen provides the thousands of pages of documentation required for the FDA to approve a drug product for administration to humans. The issue here is one of meeting the well-known requirement of a variation in active content of no more than 10%. As noted in the Background of the Related Technology section of the '080 patent, it is well-known from various world regulatory authorities that dosage forms may not vary more than 10% in the amount of active present (col. 2, lines 38-45). The claims require a film has levels of uniformity in the amount of active which varies by no more than 10%, and claims 82 and 315 further require no more than 10% from a desired amount across additional films prepared by repeating the process. As discussed above,

while the '080 patent teaches analytical chemical tests can be used as an alternative to visual inspection and weight of dosages films for determining uniformity (col. 31, line 37 through col. 32, line 39), the only analytical chemical tests exemplified in the '080 patent are in Example M at col. 33-34, and these tests are done for content of McCormick red dye, which is not a pharmaceutical active or bioactive active.

As also discussed in detail above, the criteria used by Chen to evaluate uniformity is the same as used in the examples of '080 patent, i.e., visual inspection and weight of dosage films. Chen's dried film product of Example 1 is cut into dosage units ready for packing (p. 17, lines 31-32) and has a weight of 0.028 $\pm$ 0.001 g/dosage film, a density of 1.0485 $\pm$ 0.009 g/cm^2, a water content of 1.7 $\pm$ 0.24%, and a thickness of 2.1 $\pm$ 0.12 mil (see Table 4); and the dried films are glossy and substantially transparent (p. 17, line 15), i.e., they are visually free of aggregation and the weight is 0.028 $\pm$ 0.001 g/dosage, i.e., 0.03 gram/dosage with a variation of 0% when rounded to two decimal places as in Table 2 at col. 31 of the '080 patent.

Further, as noted in the rejection, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have performed known analytical tests on Chen's dosages so as to determine the actual amount of active in the dosages and assure active content uniformity.

Patent Owner argues that the terms "glossy" and "transparent" used to describe the films prepared in Chen are not interchangeable or equivalent with uniformity of content of components of a film (Remarks of 03/13/13., pp. 67-68 and 75-77).

This argument is unpersuasive. Chen uses the terms "glossy" and "transparent", i.e., visual characteristics of the film, along with measuring gram per dosage of a film cut into dosages (see p. 17, line 15; and Table 4). These are the same types of evaluations taught at col. 31, line 37 through col. 32, line 39 of the '080 patent.

Patent Owner argues the following on p. 75 of the Remarks filed 03/13/13:

> Chen does not disclose as claimed in the '080 patent: the recited controlled drying; the recited viscoelastic film; substantially uniform distribution of components; or locking-in or substantially preventing migration of the active; or said substantially uniform distribution of said active maintained by locking-in or substantially preventing migration of said active within said visco-elastic film, rapidly increasing the viscosity of the flowable polymer matrix upon initiation of drying within about 4 minutes to maintain said substantially uniform distribution of active, such that uniformity of content of the resulting film varies by no more than 10% in amount of the active present in substantially equally sized individual dosage units sampled from different locations of a lot of the resulting film, and by no more than 10% from the desired amount across different lots of resulting films, and is in compliance with FDA regulations governing same.

This argument is unpersuasive because, for all the reasons set forth above, the features argued by Patent Owner are either taught, inherent in, or rendered obvious by Chen.

Patent Owner argues the following on p. 75 of the Remarks filed 03/13/13:

> Chen also fails to disclose, explicitly or inherently, the additional elements found in Claim 317. Claim 317 generally adds, inter alia, conveying said flowable polymer matrix through a drying apparatus at a temperature of at least 60 °C and using air currents, which have forces below the yield value of the polymer matrix, to evaporate at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said visco-elastic film, varies by less

than 5%, and further controlling drying through a process comprising drying at a temperature differential ranging from 5 °C to 30 °C between polymer matrix inside temperature and outside exposure temperature.

Patent Owner's arguments are misguided because claim 317 does not recite a drying apparatus at a temperature of at least 60°C, nor does it recite a variance of less than 5%, or a temperature differential ranging from 5°C to 30°C between polymer matrix inside temperature and outside exposure temperature.

Claim 317 does recite using air currents, which have forces below the yield value of the polymer matrix. However, as noted above, Chen's Fig. 2 shows air flow is less direct at the film surface at the beginning of the drying and becomes more direct as the film proceeds through the drying oven, which has an aeration controller (see also p. 5, line 31 through p. 6, line 3). As also noted above, Chen produces a film that is glossy, substantially transparent, has a weight of 0.028 $\pm$ 0.001 g/dosage film, a density of 1.0485 $\pm$ 0.009 g/cm^2, a water content of 1.7 $\pm$ 0.24%, a thickness of 2.1 $\pm$ 0.12 mil (seep. 17, lines 15-16; and Table 4). The 0.028 $\pm$ 0.001 g/dosage film, when rounded to two decimal places as in Table 2 at col. 31 of the '080 patent, is 0.03 gram/dosage film with a variation of 0%. Accordingly, the air flow of Chen either inherently or obviously have forces below a yield value of the polymer matrix in order to arrive at the glossy, transparent, essentially uniform films which are exemplified therein.

Formation of a viscoelastic film is also recited in claim 317, but as discussed in the rejection, Chen's films in Examples 1, 2 and 5-8 and the example in Tables 7 and 8 before drying are already viscoelastic, the films become viscoelastic within the first 4

minutes of drying, or such would have been obvious using a higher drying temperature and shorter drying time.

Patent Owner argues that statements in Chen such as “dried under aeration” and “glossy, stand alone, self-supporting, non-tacky and flexible film” are general statements and cannot support either anticipation or obviousness (Remarks of 03/13/13, pp. 75-76).

This argument is unpersuasive because the rejection over Chen is based on much more in Chen that these statements, and Chen renders obvious the claimed invention for the reasons stated above.

Patent Owner argues that Chen’s drying process “is so general and devoid of detail so as to provide no guidance other than to dry a film in a conventional hot air circulating oven at temperatures of from 40-100°C and leaves it for a period of time”; that Chen does not disclose any other drying methods beyond drying under aeration; that Chen does not disclose any controlled drying process; and that Chen shows no recognition of complexities involved in commercial manufacturing of films. (Remarks of 03/13/13, p. 76).

These arguments are unpersuasive. As noted in the rejection, Chen’s processing steps are essentially the same as here claimed. Further, with respect to drying, as seen schematically in the drying apparatus of Chen's Fig. 2, the air flow is less direct at the film surface at the beginning of the drying and becomes more direct as the film proceeds through the drying oven, which has an aeration controller (see also p.

5, line 31 through p. 6, line 3). Chen exemplifies drying at 50℃ for 9 minutes, which is within the '080 patent's most desirable temperature range of about 80°C or less (col. 27, lines 53-55) and within the '080 patent's time range of about 10 minutes or fewer (col. 7, line 31).

With respect to the rejection over the combined teaching of Chen and Staab, Patent Owner relies on the same arguments set forth above (Remarks of 03/13/13, p. 78).

These arguments are unpersuasive for the reasons set forth above.

Arguments with respect to the rejections based on Staab:

Patent Owner argues that Staab does not and cannot inherently disclose the claimed levels of uniformity content or forming a viscoelastic film within about the first 4 minutes (Remarks of 03/13/13, pp. 69 and 79).

This argument is unpersuasive. The '080 patent teaches that "[t]he addition of hydrocolloids to the aqueous phase of the suspension increases viscosity, may produce viscoelasticity, and can impart stability depending on the type of hydrocolloid, its concentration and the particle composition, geometry, size and volume fraction (see col. 8, lines 42-46). Staab uses the same hydrocolloid as in the '080 patent, i.e. said HPMC. As noted above, Staab teaches that "[t]he dissolution of the film can be readily adjusted by using different viscosities of the hydroxypropyl methyl cellulose ranging from less than 80 to more than 4,000 centipoises." (See col. 5, lines 10-14). Staab's film in the

Example at cols. 11-12 is inherently viscoelastic before drying. Accordingly, within about the first 4 minutes of drying, a viscoelastic film having less water that before drying is formed.

Alternatively, to the extent that Staab's blended mixture before drying is not viscoelastic, then within about the first 4 minutes of the drying, a viscoelastic film is inherently formed. In particular, in order to arrive at a dried film product as in Staab, which is made using the same materials as disclosed in the '080 patent and the same basic process steps here claimed and each dosage film weighing 190 mg and containing 19 mg of benzalkonium chloride as the active agent (col. 11, line 35 through col. 12, line 3), i.e., a variation in active content of 0%, then a viscoelastic film is inherently formed within about the first 4 minutes of drying.

With respect to uniformity, the claimed percent variations as measured by analytical chemical tests, as well as the claimed "substantially uniform distribution of components" and "locking-in or substantially preventing migration" are inherent in Staab's films in view of the fact that each dosage film contains 19 mg of benzalkonium chloride, i.e., a variation of 0%. Alternatively, such would have been obvious to one of ordinary skill in the art at the time the invention was in view of the well-known goal of a skilled artisan to prepare dosages that do not vary by more than 10% in the amount of active present, in view of Staab's 19 mg of benzalkonium chloride per dosage film, and to commercialize the product. A skilled artisan would minimize active content variation by optimizing the available parameters in Staab's process, which are the same as or

similar to those in the '080 patent. These include the polymer material, drying temperature, hot air application, drying time, viscosity, etc.

Patent Owner argues that "Staab does not disclose testing to determine the amount of benzalkonium chloride present in the final product or even how each and every sample turned out to be 19 mg." (Remarks of 03/13/13, p. 69).

This argument is unpersuasive. It is not necessary for a patent to disclose what is very well-known in the art, e.g., analytical chemical testing. In fact, there are no examples in the '080 patent specification where analytical chemical testing is used to measure an amount of pharmaceutical active or bioactive active. With respect to how each and every sample turned out to be 19 mg, Staab uses essentially the same process steps as here claimed.

Patent Owner further argues that Staab does not disclose "the recited controlled drying" (Remarks of 03/13/13, p. 79).

This argument is unpersuasive. Generally, Staab teaches drying at a controlled temperature of 130°F to 140°F (col. 11, lines 1-6), 54°C to 60°C. Since the temperature is regulated, and heat is applied by underbelt steam and overbelt hot air which are each adjustable (col. 10, lines 28-34), the drying is controlled as here claimed.

Patent Owner argues "Staab starts with a composition having 10% by weight of benzalkonium chloride (50% aqueous) yet allegedly obtains a resulting film with 19 mg benzalkonium chloride in a 190 mg film, to once again obtain a 10% benzalkonium

chloride resulting composition" and that a perfect yield must always be considered suspect (Remarks of 03/13/13, p. 69).

This argument is unpersuasive. None of the examples in the '080 patent measures or reports a weight or weight percent of pharmaceutical active or bioactive in a cut dosage film. In fact, just as the example at cols. 31-32 in the '080 patent prepares dosage units weighing 0.04 grams, i.e., 40 mg, Staab's dosage units weigh 190 mg. Staab goes further and provides the active material weight in the dosage films, i.e., 19 mg. The argument that Staab's benzalkonium chloride content is suspect is unsupported by factual evidence.

Patent Owner argues the following on pp. 79-80 of the Remarks filed 03/13/13:

> Staab certainly does not disclose, explicitly or inherently, the additional claim elements of Claim 317. Claim 317 generally adds to the above, inter alia, conveying said flowable polymer matrix through a drying apparatus at a temperature of at least 60 °C and using air currents, which have forces below the yield value of the polymer matrix, to evaporate at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said visco-elastic film, varies by less than 5%, and further controlling drying through a process comprising drying at a temperature differential ranging from 5 °C to 30 °C between polymer matrix inside temperature and outside exposure temperature.

Patent Owner's arguments are misguided because claim 317 does not recite a drying apparatus at a temperature of at least 60°C, nor does it recite a variance of less than 5%, or a temperature differential ranging from 5°C to 30°C between polymer matrix inside temperature and outside exposure temperature.

Claim 317 does recite using air currents, which have forces below the yield value of the polymer matrix. However, as noted in the rejection, such is inherent in Staab's process because Staab's cut films each contain 19 mg of active and thus, the variation of active in the dosage units is 0%. Alternatively, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have adjusted Staab's overbelt hot air (col. 10, lines 28-34) so that the film is not excessively blown and thus, a consistent product can be obtained

Formation of a viscoelastic film is also recited in claim 317. However, as discussed in detail above, Staab's blended mixture before drying is already viscoelastic, or alternatively, within about the first 4 minutes of drying, a viscoelastic film is formed.

Patent Owner's arguments concerning a gas-formed film in Staab are addressed by Third Party Requester on p. 40 of the Comments filed 04/12/13, reproduced below:

> Applicant also discusses how Staab teaches the benefits of a gas-foamed film, which is "contraindicated in Patentee's invention." Reply [Remarks of 03/13/13] pp. 80-81. In fact, Applicant specifically states that "the '080 Patent teaches the use of anti-foaming agents to prevent gas bubble formation." Reply p. 80 (emphasis in original). Yet not one of the pending claims recites the presence of an anti-foaming agent, or the formation of a film with no bubbles.

Arguments with respect to the rejection based on Le Person:

Many of Patent Owner's arguments with respect to Le Person are addressed by Third Party Requester on pp. 42-43 of the Comments filed 04/12/13, reproduced below:

> Applicant argues that "Le Person allows for materials which may have such a low molecular weight that forming a visco-elastic film may not be possible" and "lacks sufficient enabling disclosure to be an effective reference." Reply [of 03/13/13] p. 70. But the claims do not require a high molecular weight. And again, Applicant

has not met its burden of providing facts rebutting the presumption that Le Person is operable. See MPEP 2121. Indeed, for all Le Person allegedly "lacks," it still includes a teaching of each and every manipulative drying step recited in the pending claims.

Applicant also argues that Le Person "discloses methods that result in a non-uniform product prior to and at 10 minutes." Reply [of 03/13/13] p. 82. Applicant argues:

> Le Person even states that "intense moisture removal through the exposed surface of the layer to the radiation, during the first 3 min of drying (Le Person, Fig. 7) produces a stress on the polymer skeleton ... and as a result the acrylic polymer becomes more and more dense in the upper part of the layer (exposed surface)." (Le Person, p. 261). As a result, this "intense" shrinkage results in displacement of the active phase.
>
> Reply page 83.

But what Le Person actually says is that "[t]his intense shrinkage coupled with the polymer compaction causes a displacement of the active phase towards the bottom of the layer." Le Person p. 26, col. 2, last ¶ (emphasis added). Changes in density in the upper and lower part of the layer and displacement of the active to the bottom of the film would have no effect on dose-to-dose variability.

Again, as with Staab, Applicant presents the basically identical conclusory argument that Le Person does not teach the claimed drying methods. Reply [of 03/13/13] pp. 81-82. But the Office Action already confirmed that Le Person teaches the claimed drying methods. Office Action [mailed 11/29/12], pp. 36-39 [as well as the rejection set forth above]. The addition of the word "controlled" does not distinguish the claims from Le Person, at least because Le Person teaches "a conventional drying rig where temperature ($T_{\infty db}$),Velocity (U_{∞}),and humidity (Y_{∞}), of air are controlled." See Le Person, p. 258, col. 2 and Fig. 1. Additionally, Le Person teaches a polymer matrix having a viscosity of from about 400 to about 100,000 cps, at least because this viscosity range encompasses any conceivable polymer solution that is capable of being cast. And Le Person teaches forming a viscoelastic film within about 4 minutes by increasing the viscosity of the polymer matrix upon initiation of drying. See Le Person, Figure 2, illustrating that, at 4 minutes (or 240 s - approximately 15 $s^{0.5}$), water content is less than 20% by weight in films dried by MIR and SIR and less than about 35% by weight in all dried films.

Patent Owner argues that Le Person does not teach the instantly claimed no more than 10% in amount of active in substantially equally sized dosage units sampled from different locations, and no more than 10% from the desired amount across different lots of resulting films, and in compliance with FDA regulations governing same (Remarks of 03/13/13, p. 82)

However, all of the claimed percent variation as measured by analytical chemical tests, as well as the claimed "substantially uniform distribution of components" and "locking-in or substantially preventing migration" are inherent in Le Person's films in view of the fact that, as noted above, Le Person's active material homogenizes and a quasi-equilibrium is obtained for the components of the active phase, taking into account evaporation of the heavy solvent.

Alternatively, such would have been obvious in view of the well-known goal of a skilled artisan to prepare dosages that do not vary by more than 10% in active, in view of the fact that Le Person's active material homogenizes and a quasi-equilibrium is obtained for the components of the active phase, taking into account evaporation of the heavy solvent, and to commercialize the product. A skilled artisan would minimize active content variation by optimizing the available parameters in Le Person's process, which are the same as or similar to those in the '080 patent. These include drying temperature, drying time, air velocity, humidity etc (see pp. 258-259 of Le Person).

Patent Owner argues the following on p. 83 of the Remarks filed 03/13/13:

> Le Person certainly does not disclose, either explicitly or inherently, the additional claim elements found in Claim 317. Claim 317 generally adds to the above, inter alia, conveying said flowable polymer matrix through a drying apparatus at a temperature of at least 60 °C and using air currents, which have

> forces below the yield value of the polymer matrix, to evaporate at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said visco-elastic film, varies by less than 5%, and further controlling drying through a process comprising drying at a temperature differential ranging from 5 °C to 30 °C between polymer matrix inside temperature and outside exposure temperature.

Patent Owner's arguments are misguided because claim 317 does not recite a drying apparatus at a temperature of at least 60°C, nor does it recite a variance of less than 5%, or a temperature differential ranging from 5°C to 30°C between polymer matrix inside temperature and outside exposure temperature.

Claim 317 does recite using air currents, which have forces below the yield value of the polymer matrix. However, as noted in the rejection, while Le Person does not specifically teach using air currents which have forces below the yield value of the polymer matrix such is either inherent or obvious. It's inherent because Le Person teaches air velocities of 2 m/s and 4 m/s (Table 2), which correspond to 4.5 miles/hr and 8.9 miles/hr, respectively. These are light winds that even with water (viscosity 1 cp) would produce only small wavelets.

Alternatively, since Le Person's resulting, dried films are homogeneous with respect to active material, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have adjusted Le Person's air velocity so that the film is not excessively blown and thus, a consistent product can be obtained.

Formation of a viscoelastic film is also recited in claim 317. However, as discussed in the rejection, within about 4 minutes of drying, Le Person's film is inherently viscoelastic.

Conclusion

The patent owner is reminded of the continuing responsibility under 37 CFR 1.985 to apprise the Office of any litigation activity, or other prior or concurrent proceeding, involving Patent No. 7,897,080 throughout the course of this reexamination proceeding. The third party requester is also reminded of the ability to similarly apprise the Office of any such activity or proceeding throughout the course of this reexamination proceeding. MPEP 2686.

This is an ACTION CLOSING PROSECUTION (ACP); see MPEP § 2671.02.

(1) Pursuant to 37 CFR 1.951(a), the patent owner may once file written comments limited to the issues raised in the reexamination proceeding and/or present a proposed amendment to the claims which amendment will be subject to the criteria of 37 CFR 1.116 as to whether it shall be entered and considered. Such comments and/or proposed amendments must be filed within a time period of 30 days or one month (whichever is longer) from the mailing date of this action. Where the patent owner files such comments and/or a proposed amendment, the third party requester may once file comments under 37 CFR 1.951(b) responding to the patent owner's submission within 30 days from the date of service of the patent owner's submission on the third party requester.

(2) If the patent owner does not timely file comments and/or a proposed amendment pursuant to 37 CFR 1.951(a), then the third party requester is precluded from filing comments under 37 CFR 1.951(b).

(3) Appeal **cannot** be taken from this action, since it is not a final Office action.

All correspondence relating to this *inter partes* reexamination proceeding should be directed:

By EFS: Registered users may submit via the electronic filing system EFS-Web at https://efs.uspto.gov/efile/myportal/efs-registered

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/Deborah D Jones/
Supervisory Patent Examiner, Art Unit 3991

PTO/SB/08a (03-08)
Approved for use through 07/31/2008. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	95002170
Filing Date	2012-09-10
First Named Inventor	Robert K. Yang
Art Unit	3991
Examiner Name	Diamond, Alan D.
Attorney Docket Number	1199-26 RCE/CON/REX

U.S.PATENTS

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
/A.D./	1	4515162		1985-05-07	Yamamoto et al	
/A.D./	2	4517173		1985-05-14	Kizawa et al	
/A.D./	3	4529601		1985-07-16	Broberg et al	
/A.D./	4	4529748		1985-07-16	Wienecke	
/A.D./	5	4562020		1985-12-31	Hijiya et al	
/A.D./	6	4569837		1986-02-11	Suzuki et al	
/A.D./	7	4593053		1986-06-03	Jevne et al	
/A.D./	8	4608249		1986-08-26	Otsuka et al	

/Alan Diamond/ (07/11/2013)

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/A.D./	9	4615697		1986-10-07	Robinson	
/A.D./	10	4623394		1986-11-18	Nakamura et al	
/A.D./	11	4652060		1987-03-24	Miyake	
/A.D./	12	4659714		1987-04-21	Watt-Smith	
/A.D./	13	4675009		1987-06-23	Hymes et al	
/A.D./	14	4695465		1987-09-22	Kigasawa et al	
/A.D./	15	4704119		1987-11-03	Shaw et al	
/A.D./	16	4713239		1987-12-15	Babaian et al	
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/A.D./	19	4740365		1988-04-26	Yukimatsu et al	

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/A.D./	20	5028632		1991-07-02	Fuisz	
/A.D./	21	4748022		1988-05-31	Busciglio	
/A.D./	22	4765983		1988-08-23	Takayanagi et al	
/A.D./	23	4772470		1988-09-20	Inoue et al	
/A.D./	24	4777046		1988-10-11	Iwakura et al	
/A.D./	25	4789667		1988-12-06	Makino et al	
/A.D./	26	4849246		1989-07-18	Schmidt	
/A.D./	27	4860754		1989-08-29	Sharik et al	
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/A.D./	31	4888354		1989-12-19	Chang et al	
/A.D./	32	4894232		1990-01-16	Reul et al	
/A.D./	33	4900552		1990-02-13	Sanvordeker et al	
/A.D./	34	4900554		1990-02-13	Yanagibashi et al	
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/A.D./	36	4910247		1990-03-20	Haldar et al	
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/A.D./	39	4927634		1990-05-22	Sorrentino et al	
/A.D./	40	4927636		1990-05-22	Hijiya et al	
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/A.D./	42	4940587		1990-07-10	Jenkins et al	
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/A.D./	44	4958580		1990-09-25	Asaba et al	
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/A.D./	48	5023082		1991-06-11	Friedman et al	
/A.D./	49	5024701		1991-06-18	Desmarais	
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U.S.PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear

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/A.D./	1	20050037055		2005-02-17	Yang et al.	

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FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
/A.D./	1	0191721	WO	A2	2001-12-06	A.E. Staley Manufacturing Co.		☐
/A.D./	2	0170194	WO	A1	2001-09-27	Warner-Lambert Company		☐

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NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1		☐

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Examiner Signature	/Alan Diamond/ (07/11/2013)	Date Considered	

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[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ None

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Daniel A. Scola, Jr., Reg. No. 29,855/	Date (YYYY-MM-DD)	2013-01-29
Name/Print	Daniel A. Scola, Jr.	Registration Number	29,855

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

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9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Transmittal of Communication to Third Party Requester *Inter Partes* Reexamination	Control No.	Patent Under Reexamination	
	95/002,170	7897080	
	Examiner	Art Unit	
	Alan Diamond	3991	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address. --

(THIRD PARTY REQUESTER'S CORRESPONDENCE ADDRESS)

Danielle L. Herrit
McCarter & English LLP
265 Franklin Street
Boston, MA 02110

Enclosed is a copy of the latest communication from the United States Patent and Trademark Office in the above-identified reexamination proceeding. 37 CFR 1.903.

Prior to the filing of a Notice of Appeal, each time the patent owner responds to this communication, the third party requester of the *inter partes* reexamination may once file written comments within a period of 30 days from the date of service of the patent owner's response. This 30-day time period is statutory (35 U.S.C. 314(b)(2)), and, as such, it cannot be extended. See also 37 CFR 1.947.

If an *ex parte* reexamination has been merged with the *inter partes* reexamination, no responsive submission by any *ex parte* third party requester is permitted.

All correspondence relating to this inter partes reexamination proceeding should be directed to the **Central Reexamination Unit** at the mail, FAX, or hand-carry addresses given at the end of the communication enclosed with this transmittal.

PTO/SB/08a (01-10)
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/A.D./	1	4202966		1980-05-13	Misaki et al.	
/A.D./	2	7241411		2007-07-10	Berry et al.	
/A.D./	3	4365423		1982-12-28	Arter et al.	
/A.D./	4	4851394		1989-07-25	Kubodera	
/A.D./	5	5759599		1998-06-02	Wampler et al.	
/A.D./	6	6428825		2002-08-06	Sharma et al.	
/A.D./	7	6047484		2000-04-11	Bolland et al.	
/A.D./	8	5137729		1992-08-11	Kuroya et al.	

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/A.D./	9	6238700		2001-05-29	Donher et al.	
/A.D./	10	5028632		1991-07-02	Fuisz	

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/A.D./	1	20050170138	A1	2005-08-04	Berry	

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/A.D./	1	Endo and Ueda, FABAD J. PHARM. SCI., 29:27-38, 2004	☐
/A.D./	2	Dr. June V. Engel, "The Benefits of Eating Fibre" from http://www.diabetes.ca/Section_About/fibre.asp (dated 5/11/05)	☐

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	Attorney Docket Number	1199-26 RCE/CON/REX

/A.D./	3	ATRIDOX(R) (DOXYCYCLINE HYCLATE) product label (Date Unknown).	☐
/A.D./	4	Cholewinski et al., PHARMACEUTICA ACTA HELVETIAE, 71:405-419, 1996.	☐
/A.D./	5	Di Donato et al., J. BIOL. CHEM., 268(7): 4745-4751, 1993.	☐
/A.D./	6	Leathers, APPL. MICROBIOL. BIOTECHNOL., 62:468-473, 2003.	☐
/A.D./	7	Huus et al., "Thermal Dissociation and Unfolding of Insulin,' Biochemistry, Vol. 44, pp. 11171-11177, 2005.	☐

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EXAMINER SIGNATURE

Examiner Signature	/Alan Diamond/ (07/11/2013)	Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

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☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Daniel A. Scola, Jr., Reg. No. 29,855/	Date (YYYY-MM-DD)	2013-01-29
Name/Print	Daniel A. Scola	Registration Number	29,855

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PTO/SB/08a (03-08)
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/A.D./	4	5089307		1992-02-18	Ninomiya et al	
/A.D./	5	5158825		1992-10-27	Altwirth	
/A.D./	6	5166233		1992-11-24	Kuroya et al	
/A.D./	7	5186938		1993-02-16	Sablotsky et al	
/A.D./	8	5229164		1993-07-20	Pins et al	

/Alan Diamond/ (07/11/2013)

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	95002170
	Filing Date	2013-09-10
	First Named Inventor	Robert K. Yang
	Art Unit	3991
	Examiner Name	Diamond, Alan D.
	Attorney Docket Number	1199-26 RCE/CON/REX

/A.D./	9	5234957		1993-08-10	Mantelle	
/A.D./	10	5271940		1993-12-21	Cleary et al	
/A.D./	11	5272191		1993-12-21	Ibrahim et al	
/A.D./	12	5346701		1994-09-13	Heiber et al	
/A.D./	13	6660292		2003-12-09	Zerbe et al.	
/A.D./	14	5411945		1995-05-02	Ozaki et al	
/A.D./	15	5413792		1995-05-09	Ninomiya et al	
/A.D./	16	5433960		1995-07-18	Meyers	
/A.D./	17	5455043		1995-10-03	Fischel-Ghodsian	
/A.D./	18	5462749		1995-10-31	Rencher	
/A.D./	19	5472704		1995-12-05	Santus et al	

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/A.D./	20	5518902		1996-05-21	Ozaki et al	
/A.D./	21	5567431		1996-10-22	Vert et al	
/A.D./	22	5620757		1997-04-15	Ninomiya et al	
/A.D./	23	6284264		2001-09-04	Zerbe et al.	
/A.D./	24	5700478		1997-12-23	Biegajski et al	
/A.D./	25	5700479		1997-12-23	Lundgren	
/A.D./	26	5733575		1998-03-31	Mehra et al	
/A.D./	27	5766620		1998-06-16	Heiber et al	
/A.D./	28	5881476		1999-03-16	Strobush et al	
/A.D./	29	5948430		1999-09-07	Zerbe et al	
/A.D./	30	6153210		2000-11-28	Roberts et al	

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/A.D./	31	6177096		2001-01-23	Zerbe et al	
/A.D./	32	6231957		2001-05-15	Zerbe et al	

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U.S.PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
/A.D./	1	20010046511	A1	2001-11-29	Zerbe et al.	
/A.D./	2	20050118217		2005-06-02	Barnhart et al.	

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FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
/A.D./	1	2432925	DE	C3	1976-01-22	Schering AG		☐
/A.D./	2	2449865	DE	B2	1976-04-29	Schering AG Berlin and Bergkamen		☐
/A.D./	3	3630603	DE	C2	1988-03-10	Desitin Arzneimittel GmbH		☐

/Alan Diamond/ (07/11/2013)

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	Attorney Docket Number	1199-26 RCE/CON/REX

/A.D./	4	0200508	EP	B1	1986-12-10	Nitto Denko Corporation		☐
/A.D./	5	0219762	EP	A1	1987-04-29	Desitin Arzneimittel GmbH		☐
/A.D./	6	0241178	EP	B1	1987-10-14	Rohto Pharmaceutical Co., Ltd.		☐
/A.D./	7	0250187	EP	B1	1987-12-23	Johnson & Johnson Consumer Products, Inc.		☐
/A.D./	8	0259749	EP	B1	1988-03-16	Desitin Arzneimittel GmbH		☐
/A.D./	9	0273069	EP	B1	1988-07-06	Uni Colloid Kabushiki Kaisha		☐
/A.D./	10	0381194	EP	A2	1990-08-08	Nitto Denko Corporation		☐
/A.D./	11	0452446	EP	B1	1991-10-23	Desitin Arzneimittel GmbH		☐
/A.D./	12	0514691	EP	B1	1992-11-25	Euroresearch S.r.L.		☐
/A.D./	13	1110546	EP	A1	2001-06-27	Johnson & Johnson Consumer Companies, Inc.		☐
/A.D./	14	9105540	WO		1991-05-02	Desitin Arzneimittel GMBH		☐

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	Attorney Docket Number	1199-26 RCE/CON/REX

/A.D./	15	9215289	WO		1992-09-17	Noven Pharmaceuticals, Inc.		☐
/A.D./	16	9505416	WO		1995-02-23	Cygnus Therapeutic Systems		☐
/A.D./	17	9518046	WO		1995-07-06	Frank, Richard, D.		☐

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NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1		☐

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[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ None

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Daniel A. Scola, Jr., Reg. No. 29,855/	Date (YYYY-MM-DD)	2013-01-29
Name/Print	Daniel A. Scola, Jr.	Registration Number	29,855

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

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5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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Approved for use through 07/31/2008. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	95002170
Filing Date	2012-09-10
First Named Inventor	Robert K. Yang
Art Unit	3991
Examiner Name	Diamond, Alan D.
Attorney Docket Number	1199-26 RCE/CON/REX

U.S.PATENTS

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
/A.D./	1	0307537		1884-11-04	Foulks	
/A.D./	2	0688446		1901-12-10	Stempel	
/A.D./	3	2142537		1939-01-03	Tisza	
/A.D./	4	2277038		1942-03-24	Curtis	
/A.D./	5	2352691		1944-07-04	Curtis	
/A.D./	6	2501544		1950-03-21	Shrontz	
/A.D./	7	2980554		1961-04-18	Gentile et al	
/A.D./	8	3249109		1966-05-03	Maeth et al	

/Alan Diamond/ (07/11/2013)

DRL - EXHIBIT 1007
DRL1193

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	Attorney Docket Number	1199-26 RCE/CON/REX

/A.D./	9	3444858		1969-05-20	Russell	
/A.D./	10	3536809		1970-10-27	Applezweig	
/A.D./	11	3551556		1970-12-29	Kliment et al	
/A.D./	12	3598122		1971-08-10	Zaffaroni	
/A.D./	13	3632740		1972-01-04	Robinson et al	
/A.D./	14	3640741		1972-02-08	Etes	
/A.D./	15	3641237		1972-02-08	Gould et al	
/A.D./	16	3731683		1973-05-08	Zaffaroni	
/A.D./	17	3753732		1973-08-21	Boroshok	
/A.D./	18	3814095		1974-06-04	Lubens	
/A.D./	19	3892905		1975-07-01	Albert	

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/A.D./	20	3911099		1975-10-07	DeFoney et al	
/A.D./	21	3972995		1976-08-03	Tsuk et al	
/A.D./	22	3996934		1976-12-14	Zaffaroni	
/A.D./	23	3998215		1976-12-21	Anderson et al	
/A.D./	24	4029757		1977-06-14	Mlodozeniec et al	
/A.D./	25	4029758		1977-06-14	Mlodozeniec et al	
/A.D./	26	4031200		1977-06-21	Reif	
/A.D./	27	4123592		1978-10-31	Rainer et al	
/A.D./	28	4128445		1978-12-05	Sturzenegger et al	
/A.D./	29	4136145		1979-01-23	Fuchs et al	
/A.D./	30	4136162		1979-01-23	Fuchs et al	

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/A.D./	31	4139627		1979-02-13	Lane et al	
/A.D./	32	4226848		1980-10-07	Nagai et al	
/A.D./	33	4251400		1981-02-17	Columbus	
/A.D./	34	4292299		1981-09-29	Suzuki et al	
/A.D./	35	4294820		1981-10-13	Keith et al	
/A.D./	36	4302465		1981-11-24	AF Ekenstam et al	
/A.D./	37	4307075		1981-12-22	Martin	
/A.D./	38	4325855		1982-04-20	Dickmann et al	
/A.D./	39	4373036		1983-02-08	Chang et al	
/A.D./	40	4406708		1983-09-27	Hesselgren	
/A.D./	41	4432975		1984-02-21	Libby	

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/A.D./	42	4438258		1984-03-20	Graham	
/A.D./	43	4460562		1984-07-17	Keith et al	
/A.D./	44	4466973		1984-08-21	Rennie	
/A.D./	45	4478658		1984-10-23	Wittwer	
/A.D./	46	4503070		1985-03-05	Eby, III	

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U.S.PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
/A.D./	1	20010022964	A1	2001-09-20	Leung et al	
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/A.D./	1	XP-002298105, Poluethylenglykole; Internet www.roempp.com (09/20/2004).	☐

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☒ None

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Name/Print	Daniel A. Scola, Jr.	Registration Number	29,855

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	95002170
Filing Date	2012-09-10
First Named Inventor	Robert K. Yang
Art Unit	3991
Examiner Name	Diamond, Alan D.
Attorney Docket Number	1199-26 RCE/CON/REX

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
/A.D./	1	5656297		1997-08-12	Bernstein et al.	
/A.D./	2	5045445		1991-09-03	Schultz	
/A.D./	3	5380529		1995-01-10	Heusser et al.	
/A.D./	4	5506046		1996-04-09	Andersen et al.	
/A.D./	5	5605698		1997-02-25	Ueno	
/A.D./	6	5653993		1997-08-05	Ghanta et al.	
/A.D./	7	5679145		1997-10-21	Andersen et al.	
/A.D./	8	5681873		1997-10-28	Norton et al.	

/Alan Diamond/ (07/11/2013)

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/A.D./	9	5750145		1998-05-12	Patell	
/A.D./	10	5750157		1998-05-12	Grosswald et al.	
/A.D./	11	5766839		1998-06-16	Johnson et al.	
/A.D./	12	5792494		1998-08-11	Kanca et al.	
/A.D./	13	5264024		1993-11-23	Bosvot et al.	
/A.D./	14	5906742		1999-05-25	Wang et al.	
/A.D./	15	5316717		1994-05-31	Koepff et al.	
/A.D./	16	3237596		1966-03-01	Grass et al.	
/A.D./	17	4562020		1985-21-31	Hijiya et al.	
/A.D./	18	5891461		1999-04-06	Jona et al.	
/A.D./	19	6103266		2000-08-15	Tapolsky et al.	

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/A.D./	20	6667060		2003-12-23	Vandecruys et al.	
/A.D./	21	5881476		1999-03-16	Strobush et al.	
/A.D./	22	4136145		1979-01-23	Fuchs et al.	
/A.D./	23	6552024		2003-04-22	Chen et al.	

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Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
/A.D./	1	20040156901	A1	2004-08-12	Thakur et al.	
/A.D./	2	20030124176	A1	2003-07-03	Hsu et al.	

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FOREIGN PATENT DOCUMENTS Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
/A.D./	1	0440462	EP	A1	1991-08-07	Merck & Co., Inc.		☐

/Alan Diamond/ (07/11/2013)

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/A.D./	2	1061557	GB		1967-03-15	Ashe Chemical Limited		☐
/A.D./	3	741362	AU		2001-11-29	LTS Lohmann Therapie Systeme GmbH		☐
/A.D./	4	196465392	DE		1998-04-14	LTS Lohmann Therapie Systeme GmbH		☐
/A.D./	5	1997031621	WO		1997-09-04	Warner-Lambert Company		☐
/A.D./	6	2005102287	WO		2005-11-03	Duo-Cort AB		☐

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NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T5
/A.D./	1	Stella, V., et al., "Gliadin Films. I: Preparation and in vitro evaluation as a carrier for controlled drug release", Int., J. Pharmaceutics, 121: pp 117-121 (1995).	☐
/A.D./	2	Bodmeier, Roland, "Evaluation of Drug-Containing Polymer Films Prepared from Aqueous Latexes", Pharmaceutical Research, Vol. 6, No. 8 (1989).	☐
/A.D./	3	Senel, S., et al., "Chitosan films and hydrogels of chlorhexidine gluconate for oral mucosal delivery", Int. J. Pharmaceutics, 193: pp 197-203 (2000).	☐
/A.D./	4	Peh et al., "Polymeric Films as Vehicle for Buccal Delivery: Swelling, Mechanical, and Bioadhesive Properties", J. Pharm Pharmaceut Sci 2(2): pp. 53-61 (1999)	☐

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EXAMINER SIGNATURE			
Examiner Signature	/Alan Diamond/ (07/11/2013)	Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Daniel A. Scola, Jr., Reg. No. 29,855/	Date (YYYY-MM-DD)	2013-01-29
Name/Print	Daniel A. Scola, Jr.	Registration Number	29,855

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

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2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	95002170	7897080
	Examiner	Art Unit
	ALAN DIAMOND	3991

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	10/08/2012	07/11/2013							
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CLAIM		DATE								
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	254	✓	-							
	255	✓	-							
	256	✓	✓							
	257	✓	-							
	258	✓	✓							
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	263	✓	✓							
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	267	✓	✓							
	268	✓	✓							
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	271	✓	✓							
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	273	✓	-							
	274	✓	✓							
	275	✓	-							
	276	✓	✓							
	277	✓	✓							
	278	✓	✓							
	279	✓	✓							
	280	✓	✓							
	281	✓	✓							
	282	✓	✓							
	283	✓	✓							
	284	✓	✓							
	285	✓	✓							
	286	✓	✓							
	287	✓	✓							
	288	✓	✓							

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	95002170	7897080
	Examiner	Art Unit
	ALAN DIAMOND	3991

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	10/08/2012	07/11/2013							
	289	✓	✓							
	290	✓	-							
	291	✓	-							
	292	✓	✓							
	293	✓	-							
	294	✓	✓							
	295	✓	✓							
	296	✓	✓							
	297	✓	✓							
	298	✓	✓							
	299	✓	✓							
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	316		✓							
	317		✓							
	318		✓							

Amendment to the Claims

1. (Amended) A process for manufacturing a resulting film suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said [making a]film having a substantially uniform distribution of components comprising a substantially uniform distribution of said active in individual dosage units of said resulting film, comprising the steps of:

(a) forming a masterbatch pre-mix comprising a solvent and a polymer selected from the group consisting of water-soluble polymers, water-swellable polymers and combinations thereof;

(b) adding [an]said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, to a pre-determined amount of said masterbatch pre-mix to form a flowable polymer matrix, said matrix having a substantially uniform distribution of said active;

(c) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(d) controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus and evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first [10]4 minutes [or fewer]by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, wherein during said drying said flowable polymer matrix temperature is 100 °C or less; [and]

(e) forming [a]said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained; and

(f) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units sampled from different locations of said resulting film, said tests indicating that uniformity of content in the amount of the active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration.

2. (Original) The process of claim 1, wherein said pre-determined amount of master batch pre-mix is controllably fed via a first metering pump and a control valve to a first mixer and a second mixer.

3. (Original) The process of claim 2, wherein said first mixer and said second mixer are arranged in parallel, series or a combination thereof.

4. (Original) The process of claim 1, wherein said water-soluble polymer comprises polyethylene oxide.

5. (Original) The process of claim 1, wherein said polymer comprises a polymer selected from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.

6. (Original) The process of claim 5, wherein said polymer further comprises a water insoluble polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl

cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone and combinations thereof.

7. (Original) The process of claim 5, wherein said polymer further comprises a polymer selected from the group consisting of methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(ά-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof.

8. (Original) The process of claim 5, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

9. (Original) The process of claim 5, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(d-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

10. (Original) The process of claim 1, wherein said solvent is selected from the group

consisting of water, polar organic solvent, and combinations thereof.

11. (Original) The process of claim 10, wherein said solvent is selected from the group consisting of ethanol, isopropanol, acetone, and combinations thereof.

12. (Cancelled)

13. (Amended) The process of claim 1, wherein said active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, [anti-tumor drugs,]anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, [anti-convulsants,]neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-

spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, [anti-asthmatics,]cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

14. (Amended) The process of claim 1, wherein said active is selected from the group consisting of [cosmetic actives,]antigens, allergens, spores, microorganisms, seeds, [mouthwash components, flavors, fragrances,]enzymes, [preservatives, sweetening agents, colorants, spices,]vitamins and combinations thereof.

15. (Original) The process of claim 1, wherein said active is a bioactive active.

16. (Cancelled)

17. (Original) The process of claim 1, wherein said active is an opiate or opiate-derivative.

18. (Original) The process of claim 1, wherein said active is an anti-emetic.

19. (Original) The process of claim 1, wherein said active is an amino acid preparation.

20. (Original) The process of claim 1, wherein said active is selected from the group consisting of sildenafils, tadalafils, vardenafils, apomorphines, yohimbine hydrochlorides, alprostadils and combinations thereof.

21. (Original) The process of claim 1, wherein said active is a protein.

22. (Original) The process of claim 1, wherein said active is insulin.

23. (Original) The process of claim 1, wherein said active is an anti-diabetic.

24. (Original) The process of claim 1, wherein said active is an antihistamine.

25. (Original) The process of claim 1, wherein said active is an anti-tussive.

26. (Original) The process of claim 1, wherein said active is a non-steroidal anti-inflammatory.

27. (Original) The process of claim 1, wherein said active is an anti-asthmatics.

28. (Amended) The process of claim 1, wherein said active is an anti-diarrhea preparation.

29. (Original) The process of claim 1, wherein said active is an alkaloid.

30. (Original) The process of claim 1, wherein said active is an anti-psychotic.

31. (Original) The process of claim 1, wherein said active is an anti-spasmodic.

32. (Original) The process of claim 1, wherein said active is a biological response modifier.

33. (Original) The process of claim 1, wherein said active is an anti-obesity drug.

34. (Original) The process of claim 1, wherein said active is an H_2-antagonist.

35. (Original) The process of claim 34, wherein said H_2-antagonist is selected from the group consisting of cimetidine, ranitidine hydrochloride, famotidine, nizatidine, ebrotidine, mifentidine, roxatidine, pisatidine, aceroxatidine and combinations thereof.

36. (Original) The process of claim 1, wherein said active is a smoking cessation aid.

37. (Original) The process of claim 1, wherein said active is an anti-parkinsonian agent.

38. (Original) The process of claim 1, wherein said active is an anti-depressant.

39. (Original) The process of claim 1, wherein said active is an anti-migraine.

40. (Original) The process of claim 1, wherein said active is an anti-Alzheimer's agents.

41. (Original) The process of claim 1, wherein said active is a dopamine receptor agonist.

42. (Original) The process of claim 1, wherein said active is a cerebral dilator.

43. (Original) The process of claim 1, wherein said active is a psychotherapeutic agent.

44. (Original) The process of claim 1, wherein said active is an antibiotic.

45. (Original) The process of claim 1, wherein said active is an anesthetic.

46. (Original) The process of claim 1, wherein said active is a contraceptive.

47. (Original) The process of claim 1, wherein said active is an anti-thrombotic drug.

48. (Original) The process of claim 1, wherein said active is diphenhydramine.

49. (Original) The process of claim 1, wherein said active is nabilone.

50. (Original) The process of claim 1, wherein said active is albuterol sulfate.

51. (Original) The process of claim 1, wherein said active is an anti-tumor drug.

52. (Original) The process of claim 1, wherein said active is a glycoprotein.

53. (Original) The process of claim 1, wherein said active is an analgesic.

54. (Original) The process of claim 1, wherein said active is a hormone.

55. (Original) The process of claim 1, wherein said active is a decongestant.

56. (Original) The process of claim 1, wherein said active is a loratadine.

57. (Original) The process of claim 1, wherein said active is dextromethorphan.

58. (Original) The process of claim 1, wherein said active is chlorpheniramine maleate.

59. (Original) The process of claim 1, wherein said active is selected from the group consisting of an analgesic, an anti-inflammatory, an antihistamine, a decongestant, a cough suppressant and combinations thereof.

60. (Original) The process of claim 1, wherein said active is an appetite stimulant.

61. (Original) The process of claim 1, wherein said active is a gastrointestinal agent.

62. (Original) The process of claim 1, wherein said active is a hypnotic.

63. (Original) The process of claim 1, wherein said active is taste-masked.

64. (Original) The process of claim 1, wherein said active is taste-masked using a flavor.

65. (Original) The process of claim 1, wherein said active is coated with a controlled release composition.

66. (Original) The process of claim 65, wherein said controlled release composition provides an immediate release.

67. (Original) The process of claim 65, wherein said controlled release composition provides a delayed release.

68. (Original) The process of claim 65, wherein said controlled release composition provides a sustained release.

69. (Original) The process of claim 65, wherein said controlled release composition provides a sequential release.

70. (Original) The process of claim 1, wherein said active is a particulate.

71. (Original) The process of claim 1, further comprising adding a degassing agent to said masterbatch premix.

72. (Original) The process of claim 1, further comprising a step of providing a second film layer.

73. (Original) The process of claim 72, wherein said second film layer is coated onto said resulting film.

74. (Original) The process of claim 72, wherein said second film layer is spread onto said resulting film.

75. (Original) The process of claim 72, wherein said second film layer is cast onto said resulting film.

76. (Original) The process of claim 72, wherein said second film layer is extruded onto said resulting film.

77. (Original) The process of claim 72, wherein said second film layer is sprayed onto said resulting film.

78. (Original) The process of claim 72, wherein said second film is laminated onto said resulting film.

79. (Original) The process of claim 72, further comprising laminating said resulting film to another film.

80. (Original) The process of claim 72, wherein said second film layer comprises an active.

81. (Amended) The process of claim [72]80, wherein said active in said second film is different than said active in said resulting film.

82. (Amended) A process for manufacturing resulting films suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said [making a]films having a substantially uniform distribution of components comprising a substantially uniform distribution of a desired amount of said active in individual dosage units of said resulting films, comprising the steps of:

(a) forming a flowable polymer matrix comprising a polymer selected from the group consisting of a water-soluble polymer, a water swellable polymer and combinations thereof, a solvent and [an]said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives[, drugs, medicaments] and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus and evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first [10]4 minutes [or fewer]by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, wherein during said drying said flowable polymer matrix temperature is 100 °C or less, and wherein uniformity of content of said active in substantially equal sized individual dosage units of said visco-elastic film is such that the amount of the active varies by no more than 10%; [and]

(d) forming [a]said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained;

(e) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units sampled from different locations of said resulting film, said tests indicating that uniformity of content in the amount of said active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration; and

(f) repeating steps (a) through (e) to form additional resulting films, such that uniformity of content in the amount of said active in said resulting film and said additional resulting films varies no more than 10% from the desired amount of the active as indicated by said analytical chemical tests.

83. (Original) The process of claim 82, wherein said water-soluble polymer comprises polyethylene oxide.

84. (Original) The process of claim 82, wherein said polymer comprises a polymer selected

from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.

85. (Original) The process of claim 84, wherein said polymer further comprises a water insoluble polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone and combinations thereof.

86. (Original) The process of claim 84, wherein said polymer further comprises a polymer selected from the group consisting of methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(ά-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof.

87. (Original) The process of claim 84, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

88. (Original) The process of claim 84, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol

copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(ά-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

89. (Original) The process of claim 82, wherein said solvent is selected from the group consisting of water, polar organic solvent, and combinations thereof.

90. (Original) The process of claim 89, wherein said solvent is selected from the group consisting of ethanol, isopropanol, acetone, and combinations thereof.

91. (Cancelled)

92. (Amended) The process of claim 82, wherein the active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management

agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, [anti-tumor drugs,]anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, [anti-convulsants,]neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, [anti-asthmatics,]cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

93. (Amended) The process of claim 82, wherein said active is selected from the group consisting of [cosmetic actives,]antigens, allergens, spores, microorganisms, seeds, [mouthwash components, flavors, fragrances,]enzymes, [preservatives, sweetening agents, colorants, spices,]vitamins and combinations thereof.

94. (Original) The process of claim 82, wherein said active is a bioactive active.

95. (Cancelled)

96. (Original) The process of claim 82, wherein said active is an opiate or opiate-derivative.

97. (Original) The process of claim 82, wherein said active is an anti-emetic.

98. (Original) The process of claim 82, wherein said active is an amino acid preparation.

99. (Original) The process of claim 82, wherein said active is selected from the group consisting of sildenafils, tadalafils, vardenafils, apomorphines, yohimbine hydrochlorides, alprostadils and combinations thereof.

100. (Original) The process of claim 82, wherein said active is a protein.

101. (Original) The process of claim 82, wherein said active is insulin.

102. (Original) The process of claim 82, wherein said active is an anti-diabetic.

103. (Original) The process of claim 82, wherein said active is an antihistamine.

104. (Original) The process of claim 82, wherein said active is an anti-tussive.

105. (Original) The process of claim 82, wherein said active is a non-steroidal anti-inflammatory.

106. (Original) The process of claim 82, wherein said active is an anti-asthmatics.

107. (Amended) The process of claim 82, wherein said active is an anti-diarrhea preparation.

108. (Original) The process of claim 82, wherein said active is an alkaloid.

109. (Original) The process of claim 82, wherein said active is an anti-psychotic.

110. (Original) The process of claim 82, wherein said active is an anti-spasmodic.

111. (Original) The process of claim 82, wherein said active is a biological response modifier.

112. (Original) The process of claim 82, wherein said active is an anti-obesity drug.

113. (Original) The process of claim 82, wherein said active is an H_2-antagonist.

114. (Amended) The process of claim [82]113, wherein said H_2-antagonist is selected from the group consisting of cimetidine, ranitidine hydrochloride, famotidine, nizatidine, ebrotidine, mifentidine, roxatidine, pisatidine, aceroxatidine and combinations thereof.

115. (Original) The process of claim 82, wherein said active is a smoking cessation aid.

116. (Original) The process of claim 82, wherein said active is an anti-parkinsonian agent.

117. (Original) The process of claim 82, wherein said active is an anti-depressant.

118. (Original) The process of claim 82, wherein said active is an anti-migraine.

119. (Original) The process of claim 82, wherein said active is an anti-Alzheimer's agents.

120. (Original) The process of claim 82, wherein said active is a dopamine receptor agonist.

121. (Original) The process of claim 82, wherein said active is a cerebral dilator.

122. (Original) The process of claim 82, wherein said active is a psychotherapeutic agent.

123. (Original) The process of claim 82, wherein said active is an antibiotic.

124. (Original) The process of claim 82, wherein said active is an anesthetic.

125. (Original) The process of claim 82, wherein said active is a contraceptive.

126. (Original) The process of claim 82, wherein said active is an anti-thrombotic drug.

127. (Original) The process of claim 82, wherein said active is diphenhydramine.

128. (Original) The process of claim 82, wherein said active is nabilone.

129. (Original) The process of claim 82, wherein said active is albuterol sulfate.

130. (Original) The process of claim 82, wherein said active is an anti-tumor drug.

131. (Original) The process of claim 82, wherein said active is a glycoprotein.

132. (Original) The process of claim 82, wherein said active is an analgesic.

133. (Original) The process of claim 82, wherein said active is a hormone.

134. (Original) The process of claim 82, wherein said active is a decongestant.

135. (Original) The process of claim 82, wherein said active is a loratadine.

136. (Original) The process of claim 82, wherein said active is dextromethorphan.

137. (Original) The process of claim 82, wherein said active is chlorpheniramine maleate.

138. (Original) The process of claim 82, wherein said active is selected from the group consisting of an analgesic, an anti-inflammatory, an antihistamine, a decongestant, a cough suppressant and combinations thereof.

139. (Original) The process of claim 82, wherein said active is an appetite stimulant.

140. (Original) The process of claim 82, wherein said active is a gastrointestinal agent.

141. (Original) The process of claim 82, wherein said active is a hypnotic.

142. (Original) The process of claim 82, wherein said active is taste-masked.

143. (Original) The process of claim 82, wherein said active is taste-masked using a flavor.

144. (Original) The process of claim 82, wherein said active is coated with a controlled release composition.

145. (Original) The process of claim 144, wherein said controlled release composition provides an immediate release.

146. (Original) The process of claim 144, wherein said controlled release composition provides a delayed release.

147. (Original) The process of claim 144, wherein said controlled release composition provides a sustained release.

148. (Original) The process of claim 144, wherein said controlled release composition provides a sequential release.

149. (Original) The process of claim 82, wherein said active is a particulate.

150. (Original) The process of claim 82, further comprising adding a degassing agent to said flowable polymer matrix.

151. (Original) The process of claim 82, further comprising a step of providing a second film layer.

152. (Original) The process of claim 151, wherein said second film layer is coated onto said resulting film.

153. (Original) The process of claim 151, wherein said second film layer is spread onto said resulting film.

154. (Original) The process of claim 151, wherein said second film layer is cast onto said resulting film.

155. (Original) The process of claim 151, wherein said second film layer is extruded onto said resulting film.

156. (Original) The process of claim 151, wherein said second film layer is sprayed onto said resulting film.

157. (Original) The process of claim 151, wherein said second film layer is laminated onto said resulting film.

158. (Original) The process of claim 151, further comprising laminating said resulting film to another film.

159. (Original) The process of claim 151, wherein said second film comprises an active.

160. (Amended) The process of claim [151]159, wherein said active in said second film is different than said active in said resulting film.

161. (Amended) A process for manufacturing a resulting film suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said[making a] film capable of being administered to a body surface and having a substantially uniform distribution of components comprising a substantially uniform distribution of said active in individual dosage units of said resulting film, comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and [an]said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus and evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first [10]4 minutes [or fewer]by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, wherein during said drying said flowable polymer matrix temperature is 100 °C or less, and wherein uniformity of content of said active in substantially equal sized individual dosage units of said visco-elastic film is such that the amount of the active varies by no more than 10%;

(d) forming [a]said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained; [and]

(e) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units sampled from different locations of said resulting film, said tests indicating that uniformity of content in the amount of said active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration, and

[(e)](f) administering said resulting film to a body surface.

162. (Original) The process of claim 161, wherein said body surface is a mucous membrane.

163. (Original) The process of claim 162, wherein said mucous membrane is oral, anal, vaginal or ophthalmological.

164. (Original) The process of claim 161, wherein said body surface is the surface of a wound.

165. (Original) The process of claim 161, wherein said water-soluble polymer comprises polyethylene oxide.

166. (Original) The process of claim 161, wherein said polymer comprises a polymer selected from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.

167. (Original) The process of claim 166, wherein said polymer further comprises a water insoluble polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone and combinations thereof.

168. (Original) The process of claim 166, wherein said polymer further comprises a polymer selected from the group consisting of methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic

acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(ά-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof.

169. (Original) The process of claim 166, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

170. (Original) The process of claim 166, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(ά-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

171. (Original) The process of claim 161, wherein said solvent is selected from the group consisting of water, polar organic solvent, and combinations thereof.

172. (Original) The process of claim 161, wherein said solvent is selected from the group consisting of ethanol, isopropanol, acetone, and combinations thereof.

173. (Cancelled)

174. (Amended) The process of claim 161, wherein said active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, [anti-tumor drugs,]anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, [anti-convulsants,]neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, [anti-asthmatics,]cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

175. (Amended) The process of claim 161, wherein said active is selected from the group consisting of [cosmetic actives,]antigens, allergens, spores, microorganisms, seeds, [mouthwash components, flavors, fragrances,]enzymes, [preservatives, sweetening agents, colorants, spices,

]vitamins and combinations thereof.

176. (Original) The process of claim 161, wherein said active is a bioactive active.

177. (Cancelled)

178. (Original) The process of claim 161, wherein said active is an opiate or opiate-derivative.

179. (Original) The process of claim 161, wherein said active is an anti-emetic.

180. (Original) The process of claim 161 wherein said active is an amino acid preparation.

181. (Original) The process of claim 161, wherein said active is selected from the group consisting of sildenafils, tadalafils, vardenafils, apomorphines, yohimbine hydrochlorides, alprostadils and combinations thereof.

182. (Original) The process of claim 161, wherein said active is a protein.

183. (Original) The process of claim 161, wherein said active is insulin.

184. (Original) The process of claim 161, wherein said active is an anti-diabetic.

185. (Original) The process of claim 161, wherein said active is an antihistamine.

186. (Original) The process of claim 161, wherein said active is an anti-tussive.

187. (Original) The process of claim 161, wherein said active is a non-steroidal anti-inflammatory.

188. (Original) The process of claim 161, wherein said active is an anti-asthmatics.

189. (Amended) The process of claim 161, wherein said active is an anti-diarrhea preparation.

190. (Original) The process of claim 161, wherein said active is an alkaloid.

191. (Original) The process of claim 161, wherein said active is an anti-psychotic.

192. (Original) The process of claim 161, wherein said active is an anti-spasmodic.

193. (Original) The process of claim 161, wherein said active is a biological response modifier.

194. (Original) The process of claim 161, wherein said active is an anti-obesity drug.

195. (Original) The process of claim 161, wherein said active is an H_2-antagonist.

196. (Original) The process of claim 195, wherein said H_2-antagonist is selected from the group consisting of cimetidine, ranitidine hydrochloride, famotidine, nizatidine, ebrotidine, mifentidine, roxatidine, pisatidine, aceroxatidine and combinations thereof.

197. (Original) The process of claim 161, wherein said active is a smoking cessation aid.

198. (Original) The process of claim 161, wherein said active is an anti-parkinsonian agent.

199. (Original) The process of claim 161, wherein said active is an anti-depressant.

200. (Original) The process of claim 161, wherein said active is an anti-migraine.

201. (Original) The process of claim 161, wherein said active is an anti-Alzheimer's agents.

202. (Original) The process of claim 161, wherein said active is a dopamine receptor agonist.

203. (Original) The process of claim 161, wherein said active is a cerebral dilator.

204. (Original) The process of claim 161, wherein said active is a psychotherapeutic agent.

205. (Original) The process of claim 161, wherein said active is an antibiotic.

206. (Original) The process of claim 161, wherein said active is an anesthetic.

207. (Original) The process of claim 161, wherein said active is a contraceptive.

208. (Original) The process of claim 161, wherein said active is an anti-thrombotic drug.

209. (Original) The process of claim 161, wherein said active is diphenhydramine.

210. (Original) The process of claim 161, wherein said active is nabilone.

211. (Original) The process of claim 161, wherein said active is albuterol sulfate.

212. (Original) The process of claim 161, wherein said active is an anti-tumor drug.

213. (Original) The process of claim 161, wherein said active is a glycoprotein.

214. (Original) The process of claim 161, wherein said active is an analgesic.

215. (Original) The process of claim 161, wherein said active is a hormone.

216. (Original) The process of claim 161, wherein said active is a decongestant.

217. (Original) The process of claim 161, wherein said active is a loratadine.

218. (Original) The process of claim 161, wherein said active is dextromethorphan.

219. (Original) The process of claim 161, wherein said active is chlorpheniramine maleate.

220. (Original) The process of claim 161, wherein said active is selected from the group consisting of an analgesic, an anti-inflammatory, an antihistamine, a decongestant, a cough suppressant and combinations thereof.

221. (Original) The process of claim 161, wherein said active is an appetite stimulant.

222. (Original) The process of claim 161, wherein said active is a gastrointestinal agent.

223. (Original) The process of claim 161, wherein said active is a hypnotic.

224. (Original) The process of claim 161, wherein said active is taste-masked.

225. (Original) The process of claim 161, wherein said active is taste-masked using a flavor.

226. (Original) The process of claim 161, wherein said active is coated with a controlled release composition.

227. (Original) The process of claim 226, wherein said controlled release composition provides an immediate release.

228. (Original) The process of 226, wherein said controlled release composition provides a delayed release.

229. (Original) The process of claim 226, wherein said controlled release composition

provides a sustained release.

230. (Original) The process of claim 226, wherein said controlled release composition provides a sequential release.

231. (Original) The process of claim 161, wherein said active is a particulate.

232. (Original) The process of claim 161, further comprising adding a degassing agent to said flowable polymer matrix.

233. (Original) The process of claim 161, further comprising a step of providing a second film layer.

234. (Original) The process of claim 233, wherein said second film layer is coated onto said resulting film.

235. (Original) The process of claim 233, wherein said second film layer is spread onto said resulting film.

236. (Original) The process of claim 233, wherein said second film layer is cast onto said resulting film.

237. (Original) The process of claim 233, wherein said second film layer is extruded onto said resulting film.

238. (Original) The process of claim 233, wherein said second film layer is sprayed onto said resulting film.

239. (Original) The process of claim 233, wherein said second film layer is laminated onto said resulting film.

240. (Original) The process of claim 233, further comprising laminating said resulting film to another film.

241. (Original) The process of claim 233, wherein said second film comprises an active.

242. (Amended) The process of claim [233]241, wherein said active in said second film is different than said active in said resulting film.

243. (Original) The process of claim 1, said active is an anti-nauseant.

244. (Amended) The process of claim 1, said active is an erectile dysfunction drug.

245. (Original) The process of claim 1, said active is a vasoconstrictor.

246. (Original) The process of claim 1, said active is a stimulant.

247. (Original) The process of claim 1, said active is a migraine treatment.

248. (Original) The process of claim 1, said active is granisetron hydrochloride.

249. (Original) The process of claim 1, wherein said resulting film provides administration of said active to an individual through the buccal cavity of said individual.

250. (Original) The process of claim 1, wherein said resulting film provides administration of said active through gingival application of said individual.

251. (Original) The process of claim 1, wherein said resulting film provides administration of said active through sublingual application of said individual.

252. (Original) The process of claim 1, wherein said resulting film provides administration of said active to an individual through a mucosal membrane of said individual.

253. (Original) The process of claim 1, wherein said resulting film provides administration of said active to an individual by administration within the body of the individual during surgery.

254. (Cancelled)

255. (Cancelled)

256. (Original) The method of claim 1, wherein said resulting film contains less than about 6% by weight solvent.

257. (Cancelled)

258. (Original) The method of claim 1, wherein said resulting film is orally administrable.

259. (Original) The method of claim 1, wherein said active is in the form of a particle.

260. (Original) The method of claim 1, wherein said matrix comprises a dispersion.

261. (Original) The process of claim 82, said active is an anti-nauseant.

262. (Amended) The process of claim 82, said active is an erectile dysfunction drug.

263. (Original) The process of claim 82, said active is a vasoconstrictor.

264. (Original) The process of claim 82, said active is a stimulant.

265. (Original) The process of claim 82, said active is a migraine treatment.

266. (Original) The process of claim 82, said active is granisetron hydrochloride.

267. (Original) The process of claim 82, wherein said resulting film provides administration of said active to an individual through the buccal cavity of said individual.

268. (Original) The process of claim 82, wherein said resulting film provides administration of said active through gingival application of said individual.

269. (Original) The process of claim 82, wherein said resulting film provides administration of said active through sublingual application of said individual.

270. (Original) The process of claim 82, wherein said resulting film provides administration of said active to an individual through a mucosal membrane of said individual.

271. (Original) The process of claim 82, wherein said resulting film provides administration of said active to an individual by administration within the body of the individual during surgery.

272. (Cancelled)

273. (Cancelled)

274. (Original) The method of claim 82, wherein said resulting film contains less than about 6% by weight solvent.

275. (Cancelled)

276. (Original) The method of claim 82, wherein said resulting film is orally administrable.

277. (Original) The method of claim 82, wherein said active is in the form of a particle.

278. (Original) The method of claim 82, wherein said matrix comprises a dispersion.

279. (Original) The process of claim 161, said active is an anti-nauseant.

280. (Amended) The process of claim 161, said active is an erectile dysfunction drug.

281. (Original) The process of claim 161, said active is a vasoconstrictor.

282. (Original) The process of claim 161, said active is a stimulant.

283. (Original) The process of claim 161, said active is a migraine treatment.

284. (Original) The process of claim 161, said active is granisetron hydrochloride.

285. (Original) The process of claim 161, wherein said resulting film provides administration of said active to an individual through the buccal cavity of said individual.

286. (Original) The process of claim 161, wherein said resulting film provides administration of said active through gingival application of said individual.

287. (Original) The process of claim 161, wherein said resulting film provides administration of said active through sublingual application of said individual.

288. (Original) The process of claim 161, wherein said resulting film provides administration of said active to an individual through a mucosal membrane of said individual.

289. (Original) The process of claim 161, wherein said resulting film provides administration of said active to an individual by administration within the body of the individual during surgery.

290. (Cancelled)

291. (Cancelled)

292. (Original) The method of claim 161, wherein said resulting film contains less than about 6% by weight solvent.

293. (Cancelled)

294. (Original) The method of claim 161, wherein said resulting film is orally administrable.

295. (Original) The method of claim 161, wherein said active is in the form of a particle.

296. (Original) The method of claim 161, wherein said matrix comprises a dispersion.

297. (Original) The method of claim 1, wherein said matrix comprises an emulsion, a colloid or a suspension.

298. (Original) The method of claim 82, wherein said matrix comprises an emulsion, a colloid or a suspension.

299. (Original) The method of claim 161, wherein said matrix comprises an emulsion, a colloid or a suspension.

300. (New) The process of claim 1, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 5%.

301. (New) The process of claim 1, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 2%.

302. (New) The process of claim 1, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 1%.

303. (New) The process of claim 1, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 0.5%.

304. (New) The process of claim 82, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 5%.

305. (New) The process of claim 82, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 2%.

306. (New) The process of claim 82, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 1%.

307. (New) The process of claim 82, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 0.5%.

308. (New) The process of claim 161, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 5%.

309. (New) The process of claim 161, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 2%.

310. (New) The process of claim 161, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 1%.

311. (New) The process of claim 161, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 0.5%.

312. (New) The process of claim 1, wherein said evaporating is conducted by applying radiant energy selected from the group consisting of hot air currents, heat, infrared radiation, radio frequency radiation and combinations thereof.

313. (New) The process of claim 82, wherein said evaporating is conducted by applying radiant energy selected from the group consisting of hot air currents, heat, infrared radiation, radio frequency radiation and combinations thereof.

314. (New) The process of claim 161, wherein said evaporating is conducted by applying radiant energy selected from the group consisting of hot air currents, heat, infrared radiation, radio frequency radiation and combinations thereof.

315. (New) A process for manufacturing resulting films suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said films having a substantially uniform distribution of components comprising a substantially uniform distribution of a desired amount of said active in individual dosage units of said resulting films, comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said polymer matrix through a drying apparatus and evaporating at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes

by rapidly increasing the viscosity of said polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, wherein during said drying said flowable polymer matrix temperature is 100 °C or less;

(d) forming said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of said active by said locking-in or substantially preventing migration of said active is maintained, such that uniformity of content in the amount of the active in substantially equal sized individual dosage units, sampled from different locations of said resulting film, varies by no more than 10%;

(e) performing analytical chemical tests for uniformity of content of said active in said substantially equal sized individual dosage units of said sampled resulting film, said tests indicating that uniformity of content in the amount of the active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration; and

(f) repeating steps (a) through (e) to form additional resulting films, such that uniformity of content in the amount of said active in said resulting film and said additional resulting films varies no more than 10% from the desired amount of said active as indicated by said analytical chemical tests.

316. (New) A process for manufacturing a resulting film suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said film having a substantially uniform distribution of components comprising a substantially uniform distribution of said active in individual dosage units of said resulting film, comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said polymer matrix through a drying apparatus and evaporating at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, wherein during said drying said flowable polymer matrix temperature is 100 °C or less;

(d) forming said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said resulting film, varies by no more than 10%; and

(e) performing analytical chemical tests for uniformity of content of said active in said substantially equal sized individual dosage units of said sampled resulting film, said tests indicating that uniformity of content in the amount of said active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration.

317. (New) A process for manufacturing a resulting film suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said film having a substantially uniform distribution of components comprising a substantially uniform distribution of said active in individual dosage units of said resulting film, comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus using air currents, which have forces below a yield value of said flowable polymer matrix during drying, to evaporate at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said visco-elastic film, varies by no more than 10%, and wherein during said drying said flowable polymer matrix temperature is 100 °C or less;

(d) forming said resulting film from said visco-elastic film by further controlling drying by continuing evaporation to a water content of said resulting film of 10% or less and wherein said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained, such that uniformity of content in the amount of said

active in substantially equal sized individual dosage units, sampled from different locations of said resulting film, varies by no more than 10%; and

(e) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units of said sampled resulting film, said tests indicating that uniformity of content in the amount of said active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration.

318. (New) A process for manufacturing a resulting film suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said film having a substantially uniform distribution of components comprising a substantially uniform distribution of said active in individual dosage units of said resulting film, comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus at a temperature of about 60 °C and using air currents, which have forces below a yield value of the polymer matrix during drying, to evaporate at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-

elastic film, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said visco-elastic film, varies by less than 5%, and wherein during said drying said flowable polymer matrix temperature is 100 °C or less;

(d) forming said resulting film from said visco-elastic film by further controlling by continuing evaporation to a water content of said resulting film of 10% or less and wherein said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said resulting film, varies by less than 5%; and

(e) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units of said sampled resulting film, said tests indicating that uniformity of content in the amount of said active varies by less than 5% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration.

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95/002,170	10 September, 2012	7897080	117744-00023

Hoffmann & Baron LLP
6900 Jericho Turnpike
Syosset, NY 11791

EXAMINER	
Alan Diamond	
ART UNIT	PAPER
3991	20130405

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner for Patents

On March 13, 2013, Patent Owner filed a response to the Notice re Defective Paper in Inter Partes Reexamination mailed on February 26, 2013. The Third Party Requester response filed February 28, 2013 will be closed since the Patent Owner papers filed January 29, 2013 are not entered. Patent Owner's non-entered papers filed January 29, 2013 will likewise be closed.

Third Party Requester is given 30 days from the mail date of this notice to file comments to the Patent Owner response of March 13, 2013.

/Alan Diamond/
Patent Reexamination Specialist
Central Reexamination Unit 3991

PTO-90C (Rev.04-03)

Transmittal of Communication to Third Party Requester *Inter Partes* Reexamination	Control No.	Patent Under Reexamination	
	95/002,170	7897080	
	Examiner	Art Unit	
	Alan Diamond	3991	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address. --

(THIRD PARTY REQUESTER'S CORRESPONDENCE ADDRESS)

Danielle L. Herrit
McCarter & English LLP
265 Franklin Street
Boston, MA 02110

Enclosed is a copy of the latest communication from the United States Patent and Trademark Office in the above-identified reexamination proceeding. 37 CFR 1.903.

Prior to the filing of a Notice of Appeal, each time the patent owner responds to this communication, the third party requester of the *inter partes* reexamination may once file written comments within a period of 30 days from the date of service of the patent owner's response. This 30-day time period is statutory (35 U.S.C. 314(b)(2)), and, as such, it cannot be extended. See also 37 CFR 1.947.

If an *ex parte* reexamination has been merged with the *inter partes* reexamination, no responsive submission by any *ex parte* third party requester is permitted.

All correspondence relating to this inter partes reexamination proceeding should be directed to the **Central Reexamination Unit** at the mail, FAX, or hand-carry addresses given at the end of the communication enclosed with this transmittal.

EXHIBIT A

COMPARISON OF INDEPENDENT CLAIMS RELATIVE TO CLAIM 82

Claim 82 as Amended	*Claim 1 as Amended*
A process for manufacturing resulting films suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said films having a substantially uniform distribution of components, comprising a substantially uniform distribution of a desired amount of said active in individual dosage units of said resulting films, comprising the steps of:	A process for manufacturing a resulting film**s** suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said film**s** having a substantially uniform distribution of components comprising a substantially uniform distribution of ~~a desired amount of~~ said active in individual dosage units of said resulting film**s**, comprising the steps of:
(a) forming a flowable polymer matrix comprising a polymer selected from the group consisting of a water-soluble polymer, a water-swellable polymer and combinations thereof, a solvent and said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, said matrix having a substantially uniform distribution of said active;	(a) forming a masterbatch pre-mix ~~flowable polymer matrix~~ comprising a solvent and a polymer selected from the group consisting of ~~a~~ water-soluble polymer**s**, ~~a~~ water-swellable polymer**s** and combinations thereof~~, a solvent and said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, said matrix having a substantially uniform distribution of said active~~;
	(b) adding said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, to a pre-determined amount of said masterbatch pre-mix to form a flowable polymer matrix, said matrix having a substantially uniform distribution of said active;
(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;	(c) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;
(c) controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus and evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, wherein during said drying said flowable polymer matrix temperature is 100°C or less, and wherein uniformity of content of said active in substantially equal sized individual dosage units of said visco-elastic film is such that the amount of the active varies by no more than 10%;	(d) controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus and evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, wherein during said drying said flowable polymer matrix temperature is 100°C or less~~, and wherein uniformity of content of said active in substantially equal sized individual dosage units of said visco-elastic film is such that the amount of the active varies by no more than 10%~~;
(d) forming said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained;	(e) forming said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained; and
(e) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units sampled from different locations of said resulting film, said tests indicating that uniformity of content in the amount of said active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration; and	(f) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units sampled from different locations of said resulting film, said tests indicating that uniformity of content in the amount of the ~~said~~ active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration~~; and~~.
(f) repeating steps (a) through (e) to form additional resulting films, such that uniformity of content in the amount of said active in said resulting film and said additional resulting films varies no more than 10% from the desired amount of the active as indicated by said analytical chemical tests.	

Claim 82 as Amended	*Claim 161 as Amended*
A process for manufacturing resulting films suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said films having a substantially uniform distribution of components, comprising a substantially uniform distribution of a desired amount of said active in individual dosage units of said resulting films, comprising the steps of:	A process for manufacturing a resulting film**s** suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said film**s** capable of being administered to a body surface and having a substantially uniform distribution of components comprising a substantially uniform distribution of ~~a desired amount of~~ said active in individual dosage units of said resulting film**s**, comprising the steps of:
(a) forming a flowable polymer matrix comprising a polymer selected from the group consisting of a water-soluble polymer, a water swellable polymer and combinations thereof, a solvent and said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, said matrix having a substantially uniform distribution of said active;	(a) forming a flowable polymer matrix comprising ~~a polymer selected from the group consisting of~~ a water-soluble polymer~~, a water swellable polymer and combinations thereof~~, a solvent and said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, said matrix having a substantially uniform distribution of said active;
(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;	(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;
(c) controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus and evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, wherein during said drying said flowable polymer matrix temperature is 100°C or less, and wherein uniformity of content of said active in substantially equal sized individual dosage units of said visco-elastic film is such that the amount of the active varies by no more than 10%;	(c) controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus and evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, wherein during said drying said flowable polymer matrix temperature is 100°C or less, and wherein uniformity of content of said active in substantially equal sized individual dosage units of said visco-elastic film is such that the amount of the active varies by no more than 10%;
(d) forming said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained;	(d) forming said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained;
(e) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units sampled from different locations of said resulting film, said tests indicating that uniformity of content in the amount of said active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration; and	(e) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units sampled from different locations of said resulting film, said tests indicating that uniformity of content in the amount of said active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration; and
(f) repeating steps (a) through (e) to form additional resulting films, such that uniformity of content in the amount of said active in said resulting film and said additional resulting films varies no more than 10% from the desired amount of the active as indicated by said analytical chemical tests	
	(f) administering said resulting film to a body surface.

Claim 82 as Amended	*Claim 315 (New)*
A process for manufacturing resulting films suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said films having a substantially uniform distribution of components, comprising a substantially uniform distribution of a desired amount of said active in individual dosage units of said resulting films, comprising the steps of:	A process for manufacturing resulting films suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said films having a substantially uniform distribution of components comprising a substantially uniform distribution of a desired amount of said active in individual dosage units of said resulting films, comprising the steps of:
(a) forming a flowable polymer matrix comprising a polymer selected from the group consisting of a water-soluble polymer, a water swellable polymer and combinations thereof, a solvent and said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, said matrix having a substantially uniform distribution of said active;	(a) forming a flowable polymer matrix comprising ~~a polymer selected from the group consisting of~~ a water-soluble polymer~~, a water swellable polymer and combinations thereof~~, a solvent and said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, said matrix having a substantially uniform distribution of said active;
(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;	(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;
(c) controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus and evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, wherein during said drying said flowable polymer matrix temperature is 100°C or less, and wherein uniformity of content of said active in substantially equal sized individual dosage units of said visco-elastic film is such that the amount of the active varies by no more than 10%;	(c) controlling drying through a process comprising conveying said ~~flowable~~ polymer matrix through a drying apparatus and evaporating at least a portion of said solvent ~~from said flowable polymer matrix~~ to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said ~~flowable~~ polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, wherein during said drying said flowable polymer matrix temperature is 100°C or less~~, and wherein uniformity of content of said active in substantially equal sized individual dosage units of said visco-elastic film is such that the amount of the active varies by no more than 10%~~;
(d) forming said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained;	(d) forming said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of said active by said locking-in or substantially preventing migration of said active is maintained, such that uniformity of content in the amount of the active in substantially equal sized individual dosage units, sampled from different locations of said resulting film, varies by no more than 10%;
(e) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units sampled from different locations of said resulting film, said tests indicating that uniformity of content in the amount of said active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration; and	(e) performing analytical chemical tests for uniformity of content of said active in said substantially equal sized individual dosage units of said sampled ~~from different locations of said~~ resulting film, said tests indicating that uniformity of content in the amount of the active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration; and
(f) repeating steps (a) through (e) to form additional resulting films, such that uniformity of content in the amount of said active in said resulting film and said additional resulting films varies no more than 10% from the desired amount of the active as indicated by said analytical chemical tests.	(f) repeating steps (a) through (e) to form additional resulting films, such that uniformity of content in the amount of said active in said resulting film and said additional resulting films varies no more than 10% from the desired amount of said active as indicated by said analytical chemical tests.

Claim 82 as Amended	*Claim 316 (New)*
A process for manufacturing resulting films suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said films having a substantially uniform distribution of components, comprising a substantially uniform distribution of a desired amount of said active in individual dosage units of said resulting films, comprising the steps of:	A process for manufacturing a resulting film**s** suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said film**s** having a substantially uniform distribution of components comprising a substantially uniform distribution of ~~a desired amount of~~ said active in individual dosage units of said resulting film**s**, comprising the steps of:
(a) forming a flowable polymer matrix comprising a polymer selected from the group consisting of a water-soluble polymer, a water swellable polymer and combinations thereof, a solvent and said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, said matrix having a substantially uniform distribution of said active;	(a) forming a flowable polymer matrix comprising ~~a polymer selected from the group consisting of~~ a water-soluble polymer~~, a water swellable polymer and combinations thereof~~, a solvent and said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, said matrix having a substantially uniform distribution of said active;
(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;	(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;
(c) controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus and evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, wherein during said drying said flowable polymer matrix temperature is 100°C or less, and wherein uniformity of content of said active in substantially equal sized individual dosage units of said visco-elastic film is such that the amount of the active varies by no more than 10%;	(c) controlling drying through a process comprising conveying said ~~flowable~~ polymer matrix through a drying apparatus and evaporating at least a portion of said solvent ~~from said flowable polymer matrix~~ to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said ~~flowable~~ polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, wherein during said drying said flowable polymer matrix temperature is 100°C or less~~, and wherein uniformity of content of said active in substantially equal sized individual dosage units of said visco-elastic film is such that the amount of the active varies by no more than 10%~~;
(d) forming said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained;	(d) forming said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of ~~said~~ active by said locking-in or substantially preventing migration of said active is maintained, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said resulting film, varies by no more than 10%; and
(e) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units sampled from different locations of said resulting film, said tests indicating that uniformity of content in the amount of said active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration; and	(e) performing analytical chemical tests for uniformity of content of said active in said substantially equal sized individual dosage units of said sampled ~~from different locations of said~~ resulting film, said tests indicating that uniformity of content in the amount of said active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration~~; and~~.
(f) repeating steps (a) through (e) to form additional resulting films, such that uniformity of content in the amount of said active in said resulting film and said additional resulting films varies no more than 10% from the desired amount of the active as indicated by said analytical chemical tests	

Claim 82 as Amended	*Claim 317 (New)*
A process for manufacturing resulting films suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said films having a substantially uniform distribution of components comprising a substantially uniform distribution of a desired amount of said active in individual dosage units of said resulting films, comprising the steps of:	A process for manufacturing a resulting film~~s~~ suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said film~~s~~ having a substantially uniform distribution of components comprising a substantially uniform distribution of ~~a desired amount of~~ said active in individual dosage units of said resulting film~~s~~, comprising the steps of:
(a) forming a flowable polymer matrix comprising a polymer selected from the group consisting of a water-soluble polymer, a water swellable polymer and combinations thereof, a solvent and said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, said matrix having a substantially uniform distribution of said active;	(a) forming a flowable polymer matrix comprising ~~a polymer selected from the group consisting of~~ a water-soluble polymer, ~~a water swellable polymer and combinations thereof,~~ a solvent and said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, said matrix having a substantially uniform distribution of said active;
(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;	(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;
(c) controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus and evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, wherein during said drying said flowable polymer matrix temperature is 104°C or less, and wherein uniformity of content of said active in substantially equal sized individual dosage units of said visco-elastic film is such that the amount of the active varies by no more than 10%;	(c) controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus using air currents, which have forces below a yield value of ~~and evaporating at least a portion of said solvent from~~ said flowable polymer matrix during drying, to evaporate at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said visco-elastic film, varies by no more than 10%, and wherein during said drying said flowable polymer matrix temperature is 104°C or less ~~and wherein uniformity of content of said active in substantially equal sized individual dosage units of said visco-elastic film is such that the amount of the active varies by no more than 10%~~;
(d) forming said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained;	(d) forming said resulting film from said visco-elastic film ~~wherein said resulting film has~~ by further controlling drying by continuing evaporation to a water content of said resulting film of 10% or less and wherein said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said resulting film, varies by no more than 10%; and
(e) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units sampled from different locations of said resulting film, said tests indicating that uniformity of content in the amount of said active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration; and	(e) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units of said sampled ~~from different locations of said~~ resulting film, said tests indicating that uniformity of content in the amount of said active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration~~; and~~.
(f) repeating steps (a) through (e) to form additional resulting films, such that uniformity of content in the amount of said active in said resulting film and said	

additional resulting film varies no more than 10% from the desired amount of the active as indicated by said analytical chemical tests.	

Claim 82 as Amended	*Claim 318 (New)*
A process for manufacturing resulting films suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said films having a substantially uniform distribution of components, comprising a substantially uniform distribution of a desired amount of said active in individual dosage units of said resulting films, comprising the steps of:	A process for manufacturing a resulting film~~s~~ suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said film~~s~~ having a substantially uniform distribution of components comprising a substantially uniform distribution of ~~a desired amount of~~ said active in individual dosage units of said resulting film~~s~~, comprising the steps of:
(a) forming a flowable polymer matrix comprising a polymer selected from the group consisting of a water-soluble polymer, a water swellable polymer and combinations thereof, a solvent and said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, said matrix having a substantially uniform distribution of said active;	(a) forming a flowable polymer matrix comprising ~~a polymer selected from the group consisting of~~ a water-soluble polymer, ~~a water swellable polymer and combinations thereof,~~ a solvent and said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, said matrix having a substantially uniform distribution of said active;
(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;	(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;
(c) controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus and evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, wherein during said drying said flowable polymer matrix temperature is 100°C or less, and wherein uniformity of content of said active in substantially equal sized individual dosage units of said visco-elastic film is such that the amount of the active varies by no more than 10%;	(c) controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus at a temperature of about 60°C and using air currents, which have forces below a yield value of ~~and evaporating at least a portion of said solvent from~~ the ~~said flowable~~ polymer matrix during drying, to evaporate at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said visco-elastic film, varies by less than 5%, and wherein during said drying said flowable polymer matrix temperature is 100°C or less ~~and wherein uniformity of content of said active in substantially equal sized individual dosage units of said visco-elastic film is such that the amount of the active varies by no more than 10%~~
(d) forming said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained;	(d) forming said resulting film from said visco-elastic film ~~wherein said resulting film has~~ by further controlling by continuing evaporation to a water content of said resulting film of 10% or less and wherein said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said resulting film, varies by less than 5%; and
(e) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units sampled from different locations of said resulting film, said tests indicating that uniformity of content in the amount of said active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration; and	(e) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units of said sampled ~~from different locations of said~~ resulting film, said tests indicating that uniformity of content in the amount of said active varies by less than ~~10%~~ 5% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration~~; and~~.
(f) repeating steps (a) through (e) to form additional resulting	

films, such that uniformity of content in the amount of said active in said resulting film and said subsequent resulting films varies no more than 10% from the desired amount of the active as indicated by said analytical chemical tests.	

EXHIBIT C

Docket No.: 117744-00023
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Inter Partes Reexamination of:	)
US Patent No. 7,897,080	)
Issued: March 1, 2011	) Confirmation No.: 6418
Named Inventor: Robert K. Yang et al.	) Group Art Unit: 3991
Control No.: 95/002,170	) Examiner: Diamond, Alan D.
Filed: September 10, 2012	) M&E Docket: 117744-00023
Title: Polyethylene-oxide based RCE/CON/REX films and Drug delivery systems made therefrom	) H&B Docket: 1199-26

Mail Stop Inter Partes Reexam
Attn: Central Reexamination Unit
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Declaration of Jason O. Clevenger under 37 C.F.R. § 1.132

I, Jason O. Clevenger, Ph.D., declare:

1. I am a Principal Scientist at Exponent, a science and engineering consulting firm. My expertise focuses on materials characterization and process engineering for specialty manufacturing, including regulated products such as medical devices and pharmaceuticals. Specifically with regard to pharmaceuticals, my experience includes process engineering and method development for transdermal and solid oral formulations, regulatory compliance and CMC (Chemistry, Manufacturing, and Controls) related issues including root cause analysis, corrective and preventive action plans, and regulatory submissions. Attached is my *curriculum vitae*.

2. While Exponent is being paid for my time, I am not an employee of, nor do I have any financial interest in, BioDelivery Sciences International, Inc.

3. I have carefully reviewed U.S. Patent No. 7,897,080 ("the '080 Patent"), International Publication No. WO 00/42992 ("Chen"), the Declaration of B. Arlie Bogue, Ph.D. submitted to the U.S. Patent Office on March 13, 2013 ("Bogue Declaration") and the Declaration of David T. Lin, Ph.D. submitted to the U.S. Patent Office on March 13, 2013 ("Lin Declaration").

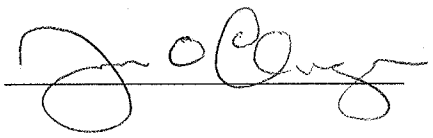
4. In my experience, the route to regulatory approval is an ongoing negotiation with the FDA through the New Drug Application (NDA) process. In this negotiation process, analytical testing and standards are determined for each product depending on its particular properties and characteristics. Different active agents and dosage forms have different properties, and would thus generally have different standards and testing requirements. Also, standardized test methods can change over time (e.g., USP <905> was revised in 2007 and 2011), so regulations from 2000 will not provide adequate information for present approval processes.

5. An FDA New Drug Application ("NDA") is a long and very detailed document. The CMC Section alone is often many hundreds to thousands of pages long. Patents are not intended to be part of an NDA and would not be expected to have the same disclosure, at least because the two documents have different requirements and very different purposes. To the extent that Chen does not provide sufficient information to comply with all of the information required in an NDA, neither does the '080 Patent.

6. The analysis in the Bogue Declaration is not consistent with the currently adopted definition of content uniformity as described in USP <905> Uniformity of Dosage Units. The calculation in paragraphs 9 and 10 of the Bogue Declaration are not included within the definition of content uniformity as described in USP <905> Uniformity of Dosage Units.

All statements herein of my own knowledge are true and all statements made on information and belief are believed to be true; and further these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon

Dated: 12 April 2013

Signature: 

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Professional Profile

Dr. Jason O. Clevenger is a Principal Scientist in Exponent's Polymer Science and Materials Chemistry practice. His expertise focuses on materials characterization and process engineering for specialty manufacturing, with a particular emphasis on regulated products such as medical devices and pharmaceuticals.

Dr. Clevenger's physical chemistry experience is applicable to problems involving materials such as semiconductors, MEMS, metal films, dielectrics, polymers, materials processing, materials characterization, pharmaceutical process chemistry, identification of trace contaminants including organics and particulates, and corrosion processes.

His pharmaceutical experience includes process engineering and optimization for transdermal and solid oral formulations, regulatory compliance and CMC (Chemistry, Manufacturing, and Controls) related issues involving root cause analysis, corrective and preventive action plans, quality assurance, and Quality by Design initiatives. His medical device experience includes method development for regulatory submissions, product development and manufacturing support, and technology due diligence assessment.

His characterization background encompasses a broad range of advanced technologies and techniques including laser spectroscopy, X-ray photoelectron spectroscopy (XPS), Auger spectroscopy, Raman, FTIR, solid/liquid-NMR, optical emission/absorption spectroscopy, energy dispersive spectroscopy (EDS), white-light interferometry, spectroscopic ellipsometry, atomic force microscopy (AFM), and secondary ion mass spectrometry (SIMS). In addition, he has extensive experience with plasma chemistry and spectroscopy, thin film metrology and reliability, high vacuum technology and semiconductor processing.

Academic Credentials and Professional Honors

Ph.D., Physical Chemistry, Massachusetts Institute of Technology, 2002
B.A., Chemistry, Vanderbilt University (*magna cum laude* with *high honors*), 1995

Phi Beta Kappa and Omicron Delta Kappa

High Honors in Chemistry for Undergraduate Thesis, 1995; Outstanding Senior in Chemistry Award, 1995; T.W. Martin Award and D.E. Pearson Award for Excellence in Undergraduate Research and Study of Physical Chemistry, 1995; J.M. Breckenridge Scholarship, 1994; Barry M. Goldwater Foundation Scholarship, Goldwater Excellence in Education Foundation, 1994;

Stephen H. Cook Summer Research Fellowship, 1994; Top-Tennessee Scholars Tuition Scholarship, 1993; Eastman Kodak National Merit Scholarship, 1991

Publications

Kou PM, Clevenger JO. A Coat for All Weathers: A Survey of the Hydrophilic Coatings Market. Med Device Develop 2012; May.

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Prior Experience

Process Technologist (Etch and CVD), Applied Materials, Inc., 2002–2004

Professional Affiliations

- American Association of Pharmaceutical Scientists—AAPS
- American Chemical Society—ACS
- Society of Photo-Optical Instrumentation Engineers—SPIE

EXHIBIT D

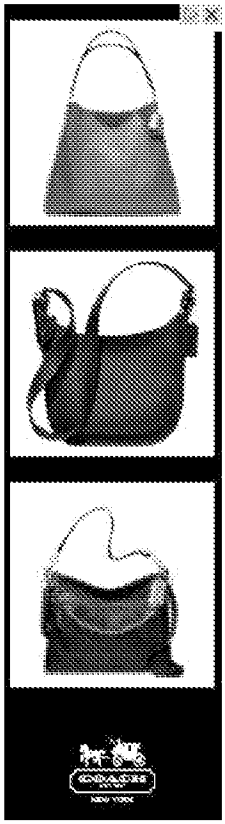
Name That Thing
Take Our 10-Question Quiz

Uniform

Save Popularity

9 ENTRIES FOUND

Uniform
uniform flow
uniform resource locator



Uniform

Definition of UNIFORM Like

—a communications code word for the letter *u*

First Known Use of UNIFORM

1956

Other Alphabet Terms

cuneiform, linear, minuscule, pictograph, rune, symbology, wedge

¹uni·form *adjective* \ˈyü-nə-ˌfȯrm\

Definition of UNIFORM

1 : having always the same form, manner, or degree : not varying or variable <*uniform* procedures>

2 : consistent in conduct or opinion <*uniform* interpretation of laws>

3 : of the same form with others : conforming to one rule or mode : CONSONANT

4 : presenting an unvaried appearance of surface, pattern, or color <*uniform* red brick houses>

5 : relating to or being convergence of a series whose terms are functions in such manner that the absolute value of the difference between the sum of the first *n* terms of the series and the sum of all terms can be made arbitrarily small for all values of the domain of the functions by choosing the *n*th term sufficiently far along in the series

··· uni·form·ly *adverb*
··· uni·form·ness *noun*

See uniform defined for English-language learners »

See uniform defined for kids »

Examples of UNIFORM

The museum is kept at a *uniform* temperature to protect the artifacts.

All departments have *uniform* training standards.

Origin of UNIFORM

Middle English *uniforme,* from Middle French, from Latin *uniformis,* from *uni-* + *-formis* -form

First Known Use: 15th century

Related to UNIFORM

Synonyms
even, invariant, steady, unchanging, undeviating, unvarying, unwavering

Antonyms
changing, deviating, nonuniform, unsteady, varying

Related Words
fixed, immutable, invariable, set, unalterable, unchangeable

more

Rhymes with UNIFORM

chloroform, cruciform, dendriform, dentiform, disciform, fungiform, funnelform, fusiform, land reform, letterform, microform, multiform, nonconform, racing form, thunderstorm, up a storm, vermiform

[2]uniform *transitive verb*

Definition of UNIFORM

1 : to bring into uniformity

2 : to clothe with a uniform

First Known Use of UNIFORM

circa 1681

[3]uniform *noun*

Definition of UNIFORM

: dress of a distinctive design or fashion worn by members of a particular group and serving as a means of identification; *broadly* : distinctive or characteristic clothing

See uniform defined for English-language learners »

Examples of UNIFORM

<the band *uniform* was brown with red and white stripes>

First Known Use of UNIFORM

1748

Related to UNIFORM

Synonyms
livery, outfit

Related Words

fatigues, full dress, regimentals, costume, finery, regalia

more

Other Clothing Terms

babushka, brogue, bumbershoot, cravat, dishabille, furbelow, layette, raiment, spectator

Browse

Next Word in the Dictionary: uniformal
Previous Word in the Dictionary: unifoliolate
All Words Near: Uniform

« Seen & Heard »

What made you want to look up *Uniform*? Please tell us where you read or heard it (including the quote, if possible).

6 comments

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Comment using...

Krishna Kumar Mangalam · New Delhi, India
wanted to know whether uniform has a plural form, 'uniforms'!
Reply · Like · March 21, 2011 at 8:42am

Alonzo D. Lotac III · General Santos City
SOMEONE PLS TELL ME WHAT IS THE MEANING OF UNIFORM!
Reply · Like · June 30, 2011 at 4:46am

Andrew Regan · Sparhawk School
balls
Reply · Like · October 5, 2011 at 2:34pm

Marilyn Tackett Wilson · George Washington High School, Indy
homework for thi.
rd grade
Reply · Like · January 6, 2012 at 4:12am

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EXHIBIT E

APPROXIMATE VISCOSITIES OF SOME COMMON LIQUIDS

Liquid	Specific Gravity at 16°c	Absolute Viscosity Cp	Temperature C°	Viscosity Type N = Newtonian T = Thixotropic
DAIRY PRODUCTS				
Butter Fat		42	43	N
Butter Fat		20	65	N
Butter Deodorised		45	50	N
Cottage Cheese		30,000	18	T
Cocoa Butter	0.92	50	60	N
Cocoa Butter	0.87	0.5	100	N
Condensed Milk		40-80	40-50	N
Condensed Milk 75% Solids	1.3	2160	20	T
Cream 30% Fat	1.0	14	16	N
Cream 45% Fat	0.99	48	16	N
Cream 50% Fat	0.98	112	16	N
Cream 50% Fat		55	32	N
Milk	1.02-1.05	2.0	18	N
Milk	1.02-1.05	1.0	52	N
Milk Whey 48% Sugar		800-1500	40	T
Process Cheese		6500	80	T
Process Cheese		30,000	18	T
Whole Egg		150	4.5	T
Yoghurt	1.15	152	40	T
FOOD PRODUCTS				
Batter		29,500	30	T
Baby Food		1400	93	T
Beet Sauce		1950	76	T
Biscuit Cream Premix		29,200	18	T
Brewers Yeast		368	18	T
Broth Mix		430	18	T
Carob Bean Sauce		1500	30	T
Chocolate		280	49	T
Citrus Fruit Pulp	1.27	600	20	T
Coffee Liquor 30-40%		10-100	20	T
Custard	1.6	1500	85-90	T
Edible Oil	0.9	65	20	N
Gelatine 37% Solids		1190	43	T
Glucose	1.3	4300-8600	25-30	T

Liquid	Specific Gravity at 16°c	Absolute Viscosity Cp	Temperature C°	Viscosity Type N = Newtonian T = Thixotropic
Gravy Slurry	1.0	110	80	T
Fruit Juice	1.04	55-75	18	N
Jam Garnish		8440	16	T
Malt Extract 80%		9500	18	T
Malt Extract	1.4	3000	60	T
Mayonnaise		20,000	20	T
Mincemeat		100,000	30	T
Mousse Mix		1200	5	T
Pectin		300	38	N
Pectin		345	27	N
Orange Juice Concentrate	30 Brix	630	20	N
Orange Juice Concentrate	30 Brix	91	80	N
Orange Juice Concentrate	50 Brix	2410	20	N
Orange Juice Concentrate	50 Brix	330	80	N
Rice Pudding		10,000	100	T
Salad Cream		1300-2600	18	T
Sauce – Apple	1.1	500	80	T
Sorbitol	1.29	200	20	N
Tomato Ketchup		1000	30	T
Tomato Paste 30%		195	18	T
Vinegar		12-15	20	N
Yeast Surry		20	18	T
Soya Bean Slurry		5000-10,000	50-90	T
PHARMACEUTICALS				
Detergents		1470	70	T
Hand Cream		780	18	T
Latex Emulsion	1.0	200	24	T
Latex Emulsion		48	65	T
Paraffin Emulsion	1.2	3000	18	T
Shampoos		3000	36	T
Soap Arylan	1.0 at 40°C	630	60	T
Soap Solution	1.03 at 60°C	82	60	T
Toothpaste		70,000-100,000	18	T
Wax	0.9	500	93	T
FISH AND ANIMAL OILS				
Bone Oil	0.92	48	54	N
Cod Oil	0.93	32	38	N
Lard	0.96	62	38	N

Liquid	Specific Gravity at 16°c	Absolute Viscosity Cp	Temperature C°	Viscosity Type N = Newtonian T = Thixotropic
Lard Oil	0.91-0.93	40-47	38	N
Sperm Oil	0.88	24	38	N
Whale Oil	0.93	25-39	38	N
VEGETABLE OILS				
Castor Oil	0.96	580	27	N
Castor Oil		36	80	N
Chinawood Oil	0.94	300	21	N
Coconut Oil	0.93	55	24	N
Coconut Oil		30	38	N
Corn Oil	0.92	28	57	N
Cotton Seed Oil	0.88	62	24	N
Cotton Seed Oil	0.93	24	52	N
Linseed Oil Raw	0.93-0.94	29	38	N
Olive Oil	0.91	40	38	N
Palm Oil	0.92	43	38	N
Peanut Oil	0.92	38	38	N
Soya Bean Oil	0.93	60	24	N
Soya Bean Oil		12	80	N
Turpentine	0.86	2.0	16	N
INDUSTRIAL PRODUCTS				
Acetate Glue		1200-1400	20	T
NaOH 20%	1.22	1.0	18	N
NaOH 30%	1.33	1.0	18	N
NaOH 40%	1.43	20	18	N
Cresol Crystals		10	18	T
Glycerine 100%	1.26 at 20°C	648	20	N
Glycerine 100%		176	38	N
Isopropyl Alcohol	1.11	1.9	85	N
Lacquer 25% Solids		3000	18	T
Polyester	1.1 at 30%	3000	30	T
Polypropylene		240,000	50	T
Polyisobutylene	1.09 at 85°	12,500	85	T
Plastisol	2.5	28,000	18	T
Printers Ink		550-2200	38	T
Printers Ink		238-660	54	T
Resin Solution		880	24	T
Resin Solution		975	21	T
Resin Solution		7140	18	T

Liquid	Specific Gravity at 16°c	Absolute Viscosity Cp	Temperature C°	Viscosity Type N = Newtonian T = Thixotropic
Sulphonic Acid	1.04	125	30	T
Triacetate Dope		48,000/60,000	40	T
GLYCOL PRODUCTS				
Propylene	1.04	52	21	N
Triethylene	1.12	40	21	N
Diethylene	1.12	32	21	N
Ethylene	1.12	18	21	N

EXHIBIT F

CROWN OPERATIONS INTERNATIONAL, LTD. and MARSHALL H. KRONE, Plaintiffs-Appellants, v. SOLUTIA INC., Defendant-Appellee.

01-1144

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

289 F.3d 1367*; *2002 U.S. App. LEXIS 9173*; *62 U.S.P.Q.2D (BNA) 1917

May 13, 2002, Decided

SUBSEQUENT HISTORY: [**1] As Corrected June 19, 2002. Rehearing Denied June 10, 2002, Reported at: *2002 U.S. App. LEXIS 13283*.

PRIOR HISTORY: Appealed from: United States District Court for the Western District of Wisconsin. Senior Judge John C. Shabaz.

DISPOSITION: AFFIRMED-IN-PART, REVERSED-IN-PART, AND REMANDED.

COUNSEL: Joseph T. Leone, DeWitt Ross and Stevens, S.C., of Madison, Wisconsin, argued for plaintiffs-appellants. With him on the brief was Joseph A. Ranney.

Gregory E. Upchurch, Thompson Coburn LLP, of St. Louis, Missouri, argued for defendant-appellee. With him on the brief were Kenneth R. Heineman, and Dudley W. Von Holt.

JUDGES: Before LOURIE, CLEVENGER, and GAJARSA, Circuit Judges.

OPINION BY: GAJARSA

OPINION

[*1370] GAJARSA, Circuit Judge.

Crown Operations International, Ltd., and Mr. Marshall H. Krone (collectively "Crown"), appeal the decision of the United States District Court for the Western District of Wisconsin denying Crown declaratory relief that Solutia's *U.S. Patent No. 4,973,511 ("the '511 patent")* is invalid for lack of novelty and non-obviousness, and that Solutia's *U.S. Patent No. 5,091,258 ("the '258 patent")* is invalid for lack of enablement and written description. Crown Operations Int'l, Ltd. v. Solutia, Inc., No. 99-C-802-S, slip op. at 8 (W.D. Wis. Aug. 30, 2000) (memorandum decision and order granting [**2] summary judgment) ("August 30 Order"); Crown Operations Int'l, Ltd. v. Solutia, Inc., No. 99-C-802-S, slip op. at 24, 27 (W.D. Wis. Aug. 22, 2000) (same) ("August 22 Order"). Because we find no error in the district court's opinion with respect to the *'511 patent*, we affirm that portion of the district court's decision. However, because the district court erred in its analysis of enablement for the *'258 patent*, and did not address the written description issue for the *'258 patent*, we reverse the district court's grant of summary judgment on that issue and remand for additional proceedings consistent with this opinion.

I. BACKGROUND

The patents at issue in this appeal relate to layered films used to create safety and solar control glass. An example is an automobile windshield. Most windshields have two layers of glass with a multi-layer film between the glass layers. The multi-layer film adds properties to

the glass assembly, such as impact resistance or providing a conductive layer that facilitates defrosting the windshield. An inner layer of the film has solar control properties to selectively reflect, absorb (and thus convert to heat) or transmit defined percentages [**3] of certain wavelengths of light. This inner layer is called the solar control film. It is made of a substrate coated by one or more layers of metal or metallic substances. *'511 patent*, col. 3, l. 64 to col. 4, l. 2. Typically, manufacturers laminate the solar control film between layers of plasticized polyvinyl butyral ("PVB") (sometimes called the "safety film") in a process known as encapsulation. Then, the encapsulated solar control film is sandwiched between two pieces of glass for a final assembly of multi-layer glass with safety and solar control properties.

A. The *'511 Patent*

The *'511 patent* is directed to the problem that the metal-coated substrate, i.e., solar control film, tends to wrinkle during encapsulation causing visual distortions. The *'511 patent* claims to mask the wrinkles from detection by the human eye by [*1371] limiting to two percent or less the visible light reflection contribution of the solar control film compared to reflection from a complete assembly of glass, PVB and solar control film. *'511 patent*, col. 4, ll. 46-49, col. 8, l. 66 to col. 9, l. 6, col. 14, l. 67 to col. 15, l. 2. Figure 1 from the *'511 patent*, set forth below, shows the layers in a complete [**4] assembly.

[SEE FIGURE 1 IN ORIGINAL]

The complete safety and solar control glass assembly 10 includes two outer glass layers 28 & 30, PVB layers 22 & 23, and the solar control film 20. The solar control film is comprised of a substrate layer 16 and solar control coating 18. *'511 patent*, col. 3, ll. 41-53, col. 7, ll. 2-4, col. 10, l. 15. Figure 3 from the *'511 patent*, set forth below, shows the sub-layers of the solar control coating 18.

[SEE FIGURE 3 IN ORIGINAL]

Layer 18 is made of multiple sub-layers. Layers 34 and 36 are metal oxide, and layer 38 is metal. *'511 patent*, col. 5, ll. 12-14. In addition, the *'511 patent* notes that "prior automotive windshields have visible light reflection contributions for their solar films of three percent or greater." Further, it relates that the primary method of achieving a low solar control film reflectance contribution is by providing a specially-designed solar coating. *'511 patent*, col. 4, ll. 56-65.

On December 16, 1999, Crown sued Solutia (the "Initial Complaint"), seeking, among various other relief, a declaration that the *'511 patent* was invalid for anticipation and obviousness. Upon the parties' cross-motions for summary judgment, [**5] the district court found the *'511 patent* not anticipated and not invalid for obviousness. August 22 Order at 24, 27. We discuss herein only those portions of the August 22 Order relevant to the issues on appeal, which relate solely to the summary judgment finding that the *'511 patent* was not [*1372] invalid on the grounds of anticipation and obviousness.

Claim 1, the only independent claim of the *'511 patent*, is set forth below, with the element numbers from Figure 1 inserted into the claim.

> 1. A composite solar/safety film **[24]** for use in a laminated window assembly **[10]** comprising:
>
> a flexible, transparent plastic substrate layer **[16]** having a carrier surface and an opposing back surface;
>
> a multilayer solar control coating **[18]** on said carrier surface, said coated substrate defining a solar control film **[20]**; and
>
> at least one flexible, transparent, energy absorbing plastic safety layer **[23 and/or 22]** bonded to a surface of said solar control film;
>
> wherein said ***solar control film contributes no more than about 2% visible reflectance***, based on total visible incident radiation, in a laminated window assembly containing [**6] said composite solar/safety film laminated to at least one rigid transparent member **[30 and/or 28]**.

'511 patent, col. 14, l. 57 to col. 15, l. 4 (emphasis added and emphasized numbers added to identify elements shown in Figure 1 above).

Crown argued that *U.S. Patent No. 4,017,661* to

Gillery (the "Gillery patent") anticipates the *'511 patent*. The district court held otherwise, because, while the Gillery patent discloses the first three limitations of claim 1 of the *'511 patent*, it does not disclose the two percent visible reflectance limitation. The court found that neither the Gillery patent claims nor its description expressly disclose a two percent limit on reflectance contribution from the solar control film layer. Crown argued that the two percent limitation was inherently present in the Gillery patent's teachings because the Gillery patent disclosed an assembly with PVB layers, substrate layer, and substrate metal-coating - arguably of the same composition and thickness of the films disclosed by the *'511 patent*. Thus, Crown argued, because the structure, thickness and materials of the assembly were the same or within the same range(s), the Gillery patent must [**7] inherently disclose a two percent limitation. The district court rejected this argument because it found that none of the embodiments disclosed by the Gillery patent meet the two percent visible light reflectance limit. [1]

1 The district court, applying a similar analysis, also found that UK Patent Application GB 2 057 355 (the "UK patent") did not anticipate the *'511 patent* because it did not have the two percent limitation.

In its August 22 Order, the district court also held that the *'511 patent* was not rendered invalid for obviousness by Gillery or the other prior art cited by Crown because no prior art discloses: (i) that reflectance below two percent will mask wrinkles; (ii) a solar control film layer with reflectance below two percent; or (iii) any suggestion, motivation or teaching to reduce solar control film visible light reflectivity below two percent. Although the prior art generally sought to reduce visible light reflectivity, it also taught disadvantages of a very thin metal-coating on the [**8] substrate, including sacrificing infrared reflectivity. Thus, it taught that the proper compromise to achieve the conflicting goals of infrared (non-visible light) reflectance, visible light transmission and conductivity [*1373] was a solar control film with a visible light reflectivity greater than two percent.

B. The *'258 Patent*

The *'258 patent* is directed at eliminating optical distortion, called "applesauce," in safety and solar control glass assemblies of the type discussed above for the *'511 patent*. The *'258 patent* discloses a method to control distortion otherwise caused by the safety and solar film layer by measuring and controlling the texture of the surface of the PVB layers. The method expresses texture using a "wave index" and a "roughness value." The wave index calculation is at issue in this appeal. Wave index indicates the relative waviness of the surface of the PVB. Determining wave index involves measuring the surface of the PVB and then aggregating the measurements into a single number, the wave index, through a calculation purportedly described in the *'258 patent*.

The *'258 patent* directs one to use an instrument to physically measure the waviness of the surface of the [**9] PVB and capture the measurement into an electronic "trace line" representing the contours of the PVB surface. *'258 patent*, col. 7, ll. 54-65. Since the "trace line" is stored electronically, a computer program is used to calculate wave index from the trace. Three figures from the *'258 patent*, given below, provide examples of PVB surface trace lines.

[SEE FIGURES 7, 8, AND 9 IN ORIGINAL]

The rules for calculating the wave index implement a "smoothing" function. The smoothing process seeks to eliminate minor inflection points (peaks or valleys) to simplify the calculation of wave index. *'258 patent*, col. 7, l. 66 to col. 8, l. 2.

In the Initial Complaint, Crown sought a declaration that the *'258 patent* was invalid for anticipation and obviousness. Then, on May 26, 2000, Crown amended the complaint (the "Amended Complaint") to additionally claim in Count VI that the *'258 patent* is invalid under *35 U.S.C. § 112*, first paragraph, because it lacked enablement and written description due to ambiguities in the disclosed wave index calculation. In its August 22 Order, the district court found the *'258 patent* not anticipated and not invalid for obviousness. [**10] August 22 Order at 28-29.

With respect to Count VI of Crown's amended complaint, Solutia moved for [*1374] summary judgment on Crown's enablement and written description claim. Crown opposed Solutia's summary judgment motion, arguing that the *'258 patent* did not meet the enablement and written description requirements. The district court found the *'258 patent* not invalid for lack of enablement, but did not discuss in its opinion the written description requirement. August 30 Order at 8-13. We discuss herein only those portions of the August 30 Order

relevant to the issues on appeal, which relate to summary judgment finding the *'258 patent* not invalid on the grounds of enablement and the procedural disposition of the written description issue.

Claim 1 of the *'258 patent* is set forth below. In the language of this claim, "laminate" refers to the complete glass, PVB and solar control film assembly, and "functional performance layer" refers to the solar control coating. *'258 patent*, col. 3, ll. 45-65.

> 1. A laminate which is substantially free of reflected distortion when used in a safety glazing comprising:
>
> a transparent, thermoplastic substrate layer, optionally surface treated [**11] or coated, bearing one or more functional performance layers; and
>
> at least one layer of plasticized polyvinyl butyral bonded on one side to a functional performance layer or the substrate layer and having a roughened de-airing surface on its other side characterized by a roughness value, Rz, of at least 10 micrometers;
>
> said at least one plasticized polyvinyl butyral [PVB] layer, before bonding to the substrate layer or functional performance layer, ***possessing low surface waviness on each side characterized by a wave index value, WI, of less than 15,000 square micrometers***.

'258 patent, col. 12, ll. 2-16 (emphasis added).

Crown argued that the rules disclosed by the *'258 patent* for calculating wave index are not sufficiently precise to enable a person of ordinary skill in the art to practice the *'258 patent* without undue experimentation. The wave index calculation as described by the *'258 patent* is set forth below.

> In this regard, considering the waviness profile as a series of peaks and valleys, the smoothing rules of the program consider an inflection point to be a true peak or valley if it is: i) at least 100 micrometers away from the immediately preceding [**12] prior peak or valley and ii) at least 0.5 micrometer above or below the immediately preceding prior peak or valley, a valley being at least 0.5 micrometer below the immediately preceding prior peak. Pitch (P) is the distance between one valley and the next valley or in other words across the base of a peak. Average amplitude (H avg) and average pitch (P avg) are determined by the program for the smoothed trace of ten 12.5 mm tracing lengths (the second five lengths being 90 degrees to the first five lengths). From the average of the averaged H's and P's, a WI value is computed from the equation: Wave Index (WI) = (H avg) x (P avg) where H avg and P avg are in microns.

'258 patent, col. 8, ll. 3-19.

Crown asserted that according to the disclosed wave index "calculation," one of ordinary skill in the pertinent art would not know whether to instruct the smoothing program to disregard a peak by comparing it to an immediately preceding peak, or to a valley. The district court held that common sense and the clarifying clause "a valley being at least 0.5 micrometer [*1375] below the immediately preceding prior peak" defeated Crown's argument. Thus, the district court held that the alleged [**13] grammatical ambiguities in the rules disclosed for calculating wave index did not invalidate the patent for lack of enablement.

Crown timely appealed the district court's two orders, raising the issues of anticipation and obviousness of the *'511 patent*, and lack of enablement and written description of the *'258 patent*. We have jurisdiction pursuant to *28 U.S.C. § 1295(a)(1)*.

II. STANDARD OF REVIEW

We review a district court's grant of summary judgment without deference. *Atmel Corp. v. Info. Storage Devices, Inc., 198 F.3d 1374, 1378, 53 USPQ2d 1225, 1227 (Fed. Cir. 1999)*. Summary judgment is appropriate when the moving party demonstrates that "there is no genuine issue as to any material fact and that the moving party is entitled to a judgment as a matter of law." *Fed. R. Civ. P. 56(c)*; *Celotex Corp. v. Catrett, 477 U.S. 317, 322-23, 91 L. Ed. 2d 265, 106 S. Ct. 2548*

(1986). On summary judgment, the evidence must be viewed in the light most favorable to the party opposing the motion, *Poller v. Columbia Broad. Sys., Inc., 368 U.S. 464, 473, 7 L. Ed. 2d 458, 82 S. Ct. 486 (1962)*, with doubts resolved in favor [**14] of the nonmovant, *Cantor v. Detroit Edison Co., 428 U.S. 579, 582, 49 L. Ed. 2d 1141, 96 S. Ct. 3110 (1976)*; *Transmatic, Inc. v. Gulton Indus., Inc., 53 F.3d 1270, 1274, 35 USPQ2d 1035, 1038 (Fed. Cir. 1995)*. Once the moving party has satisfied its initial burden, the opposing party must establish a genuine issue of material fact and cannot rest on mere allegations, but must present actual evidence. *Anderson v. Liberty Lobby, Inc., 477 U.S. 242, 248, 91 L. Ed. 2d 202, 106 S. Ct. 2505 (1986)*. Issues of fact are genuine only "if the evidence is such that a reasonable jury could return a verdict for the nonmoving party." Id. A disputed fact is material if it might affect the outcome of the suit such that a finding of that fact is necessary and relevant to the proceeding. Id.; *General Mills, Inc. v. Hunt-Wesson, Inc., 103 F.3d 978, 980, 41 USPQ2d 1440, 1442 (Fed. Cir. 1997)*.

A patent is invalid for anticipation when the same device or method, having all of the elements contained in the claim limitations, is described in a single prior art reference. *Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989)*; [**15] *Perkin-Elmer Corp. v. Computervision Corp., 732 F.2d 888, 894, 221 USPQ 669, 673 (Fed. Cir. 1984)*. An anticipating reference must describe the patented subject matter with sufficient clarity and detail to establish that the subject matter existed in the prior art and that such existence would be recognized by persons of ordinary skill in the field of the invention. See *In re Spada, 911 F.2d 705, 708, 15 U.S.P.Q.2D (BNA) 1655, 1657 (Fed. Cir. 1990)*; *Diversitech Corp. v. Century Steps, Inc., 850 F.2d 675, 678, 7 USPQ2d 1315, 1317 (Fed. Cir. 1988)*.

Obviousness is a legal conclusion based on underlying facts of four general types, all of which must be considered by the trier of fact: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) any objective indicia of nonobviousness. See *Graham v. John Deere Co., 383 U.S. 1, 17-18, 15 L. Ed. 2d 545, 86 S. Ct. 684 (1966)*; *Continental Can Co. USA, Inc. v.* [*1376] *Monsanto Co., 948 F.2d 1264, 1270, 20 USPQ2d 1746, 1750-51 (Fed. Cir. 1991)*; *Panduit Corp. v. Dennison Mfg. Co., 810 F.2d 1561, 1566-68, 1 USPQ2d 1593, 1594 (Fed. Cir. 1987)*. [**16]

"Determination of obviousness cannot be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention." *ATD Corp. v. Lydall, Inc., 159 F.3d 534, 546, 48 USPQ2d 1321, 1329 (Fed. Cir. 1998)*. There must be a teaching or suggestion within the prior art, within the nature of the problem to be solved, or within the general knowledge of a person of ordinary skill in the field of the invention, to look to particular sources, to select particular elements, and to combine them as combined by the inventor. See *Ruiz v. A.B. Chance Co., 234 F.3d 654, 665, 57 USPQ2d 1161, 1167 (Fed. Cir. 2000)*; *ATD Corp, 159 F.3d at 546, 48 USPQ2d at 1329*; *Heidelberger Druckmaschinen AG v. Hantscho Commercial Prods., Inc., 21 F.3d 1068, 1072, 30 USPQ2d 1377, 1379 (Fed. Cir. 1994)* ("When the patented invention is made by combining known components to achieve a new system, the prior art must provide a suggestion or motivation to make such a combination.").

The written description inquiry is a factual one and must be assessed on a case-by-case basis. See *Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1561, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991)* [**17] (quoting *In re Smith, 59 C.C.P.A. 1025, 458 F.2d 1389, 1395, 173 USPQ 679, 683 (CCPA 1972)* ("Precisely how close the original description must come to comply with the description requirement of *§ 112* must be determined on a case-by-case basis.")). In order to satisfy the written description requirement, the disclosure as originally filed does not have to provide in haec verba support for the claimed subject matter at issue. See *Fujikawa v. Wattanasin, 93 F.3d 1559, 1570, 39 USPQ2d 1895, 1904 (Fed. Cir. 1996)*. Nonetheless, the disclosure must convey with reasonable clarity to those skilled in the art that the inventor was in possession of the invention, *Vas-Cath Inc., 935 F.2d at 1563-64, 19 USPQ2d at 1116-17*, although we have also clarified that the possession test alone is not always sufficient to meet the written description requirement, *Enzo Biochem, Inc. v. Gen-Probe Inc., 285 F.3d 1013, 62 U.S.P.Q. 2d 1289, at *7 (Fed. Cir. Apr. 2, 2002)*. As such, "the written description requirement is satisfied by the patentee's disclosure of 'such descriptive means as words, structures, figures, diagrams, formulas, etc., that fully [**18] set forth the claimed invention.'" Enzo Biochem,

2002 WL at *7 (quoting *Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997)).* Put another way, one skilled in the art, reading the original disclosure, must reasonably discern the limitation at issue in the claims. *Waldemar Link GmbH & Co. v. Osteonics Corp., 32 F.3d 556, 558, 31 U.S.P.Q.2D (BNA) 1855, 1857 (Fed. Cir. 1994).*

Whether a claim is enabled under *35 U.S.C. § 112*, first paragraph is a question of law, although based upon underlying factual findings. See *PPG Indus., Inc. v. Guardian Indus. Corp., 75 F.3d 1558, 1564, 37 USPQ2d 1618, 1623 (Fed. Cir. 1996)*; *In re Goodman, 11 F.3d 1046, 1049-50, 29 USPQ2d 2010, 2013 (Fed. Cir. 1993).*

DISCUSSION

A. The *'511 Patent*

On appeal, Crown describes various purported errors in the district court's analysis [*1377] of the validity of the *'511 patent*. Despite Crown's contentions, we ascertain no error requiring reversal of the district court's determination of validity over Crown's claims of anticipation and obviousness.

Regarding alleged anticipation by the [**19] Gillery patent, on its face the Gillery patent does not disclose or discuss a two percent limitation for the reflectance contribution of the solar control film. Crown maintains that the *'511 patent* merely claims a preexisting property inherent in the structure disclosed in the prior art. Crown urges us to accept the proposition that if a prior art reference discloses the same structure as claimed by a patent, the resulting property, in this case, two percent solar control film reflectance, should be assumed. We decline to adopt this approach because this proposition is not in accordance with our cases on inherency. If the two percent reflectance limitation is inherently disclosed by the Gillery patent, [2] it must be necessarily present and a person of ordinary skill in the art would recognize its presence. *In re Robertson, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999)*; *Continental Can, 948 F.2d at 1268, 20 USPQ2d at 1749*. Inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *948 F.2d at 1269, 20 USPQ2d at 1749* [**20] (quoting I n re *Oelrich, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981)).*

2 In order to claim "equivalent structure" between the Gillery patent and the *'511 patent*, Crown's inherency argument rests on a precondition of its own making - that the Gillery patent discloses use of TiO[2], even though it specifies TiOx, where x is greater than 1.0 but less than 2.0. Although Crown vigorously argues this point, we do not reach this issue because even if Crown is correct that the structures are equivalent, Crown's inherency argument fails for the reasons set forth herein.

In arguing inherent disclosure of the two percent limitation in the Gillery patent, Crown bears an evidentiary burden to establish that the limitation was necessarily present. [3] The moving party in a summary judgment motion has the burden to show "that there is an absence of evidence to support the non-moving party's case;" the non-moving party must affirmatively demonstrate by specific factual allegations that a genuine issue [**21] of material fact exists for trial. *Celotex Corp. v. Catrett, 477 U.S. 317, 322-23, 91 L. Ed. 2d 265, 106 S. Ct. 2548 (1986).* A patent enjoys a presumption of validity, see *35 U.S.C. § 282*, which can be overcome only through clear and convincing evidence, see *United States Surgical Corp. v. Ethicon, Inc., 103 F.3d 1554, 1563, 41 USPQ2d 1225, 1232 (Fed. Cir. 1997).* Given the presumption of validity afforded the *'511 patent*, Crown has failed to meet its burden because it has not presented sufficient evidence to rebut the facial evidence offered by Solutia that the Gillery patent does not [*1378] disclose the two percent limitation. See *Eli Lilly & Co. v. Barr Lab. Inc., 251 F.3d 955, 962, 58 USPQ2d 1869, 1874 (Fed. Cir. 2001)* ("[A] moving party seeking to have a patent held not invalid at summary judgment must show that the nonmoving party, who bears the burden of proof at trial, failed to produce clear and convincing evidence on an essential element of a defense upon which a reasonable jury could invalidate the patent."); *In re Robertson, 169 F.3d at 745* (recognizing that extrinsic evidence may be [**22] required to establish inherency). Instead, Crown offers only an assumption and its own contentions. [4]

3 Crown's reliance on *Pall Corp. v. Micron Separations, Inc., 66 F.3d 1211, 36 USPQ2d 1225 (Fed. Cir. 1995)*, and *O.I. Corp. v. Tekmar Co., 115 F.3d 1576, 42 USPQ2d 1777 (Fed. Cir. 1997)*, to characterize the two percent limitation as a "performance limitation" similar to the claim terms at issue in those cases is unpersuasive and

overbroad. Respectively, Pall and Tekmar dealt with the claim terms "skinless" and "passage." Beyond the readily apparent difference between these potentially broad terms and the precise specification of a two percent limit in the *'511 patent*, characterizing a claim limitation as a "performance characteristic" is not helpful as to whether the "necessarily present" requirement of inherency is met.

4 As indicated by this Court's questions at oral argument concerning the seemingly direct route to prove that the Gillery patent contains the two percent limitation - implementing an embodiment of the Gillery patent and testing it - this Court finds puzzling Crown's reluctance regarding this approach to generate extrinsic proof that the Gillery patent inherently meets the two percent limitation.

[**23] Crown also argues that the district court erred by comparing reflectance values in the Gillery patent to non-corresponding values in the *'511 patent*. August 22 Order at 23-24. While perhaps the district court could have been more careful to explain the basis of its comparison, on a close reading of the district court's analysis we find that the alleged improper comparison only supported the district court's primary point - that no embodiment of the Gillery patent disclosed the two percent limitation, a conclusion that Crown has not shown to be in error.

Finally, Crown argues that various prior art references invalidate the *'511 patent* as obvious in view of such prior art. Crown's arguments lack merit because it has not shown that the prior art contains a teaching, suggestion or motivation to reduce the reflectance contribution of the solar control film to "no more than about two percent," and the district court properly concluded that there was no such teaching, suggestion or motivation in the prior art cited by Crown. See *Ruiz, 234 F.3d at 665*, 57 USQP2d at 1167; *In re Rouffet, 149 F.3d 1350, 1359, 47 USPQ2d 1453, 1459 (Fed. Cir. 1998)*.

B. [**24] The *'258 Patent*

On appeal, Crown argues that the district court erred in analyzing the impact of the ambiguities in the wave index calculation on the enablement requirement for the *'258 patent*. In addition to its enablement attack, Crown also argues that the *'258 patent* does not meet the written description requirement of *§ 112*, first paragraph.

The two requirements, while related and springing from the same factual predicates, [5] each carry a separate purpose. The purpose of the enablement requirement is to "ensure[] that the public [*1379] knowledge is enriched by the patent specification to a degree at least commensurate with the scope of the claims." *Nat'l Recovery Techs., Inc. v. Magnetic Separation Sys., 166 F.3d 1190, 1196, 49 USPQ2d 1671, 1675 (Fed. Cir. 1999)*. One of our predecessor courts has held the enablement and written description requirements to be separate and distinct, and has held that a "specification may contain a disclosure that is sufficient to enable one skilled in the art to make and use the invention and yet fail to comply with the description of the invention requirement." *In re Barker and Pehl, 559 F.2d 588, 591, 194 USPQ 470, 472 (CCPA 1977)*. [**25] Subsequently, this court has held that the purpose of the written description is distinct from merely explaining how to make and use the invention. See *Enzo Biochem, 285 F.3d 1013 *7-8*; *Vas-Cath, 935 F.2d at 1563-64, 19 USPQ2d at 1117*. In light of the odd procedural setting of the written description issue in this appeal, our disposition of this appeal based on enablement, and given that the two requirements are distinct and each are necessary, we do not reach the written description issue except to note that it appears to remain available for adjudication or disposition by the district court on remand. [6]

5 Also springing from these same underlying factual predicates is the *§ 112*, second paragraph, definiteness requirement. This requirement is distinct from the enablement and description requirements, which arise from *§ 112*, first paragraph.

> Definiteness and enablement are analytically distinct requirements, even though both concepts are contained in *35 U.S.C. § 112*. The definiteness requirement of *35 U.S.C. § 112*, P 2 is a legal requirement, based on the court's role as construer of patent claims . . . Definiteness requires the language of the claim to set forth clearly the domain over which the applicant seeks exclusive rights. . . . The test for whether a claim meets the definiteness requirement is "whether one skilled in the art

> would understand the bounds of the claim when read in light of the specification."
>
> *Process Control Corp., 190 F.3d 1350 at 1358 n.2, 52 USPQ2d 1029 at 1034 n.2* (internal citations omitted). See also 3 Donald S. Chisum, *Chisum on Patents, § 8.03* at 8-14 (2001) (noting the difference between the requirements of "definiteness, which claims must meet, from the requirements of enablement, which the disclosures of the specification must meet").

[**26]

> 6 Based on the record before us, the written description issue has the following procedural posture: (i) Crown's Count VI of its amended complaint raised the written description issue; (ii) Solutia's summary judgment motion argued that the *'258 patent* met the written description requirement; (iii) in opposition Crown argued that the written description requirement was not met; (iv) the district court did not dispose of the written description issue or discuss the issue in its opinion in a way that enables our review; and (v) Crown preserved the written description issue in its appeal to this court and thus has not waived its further adjudication on remand.

Turning to the enablement issue, we agree with Crown that the ambiguities and lack of specified boundary conditions, and Crown's proffered evidence concerning the same, raise a genuine issue of material fact as to whether a person of ordinary skill in the pertinent art could make or use the invention of the *'258 patent* [7] without undue experimentation. *White Consol. Indus. v. Vega Servo-Control, 713 F.2d 788, 791, 218 USPQ 961, 963-64 (Fed. Cir. 1983).* [**27] The district court found otherwise. However, it appears not to have considered the statements of Crown's expert concerning the effect of unspecified boundary conditions on the calculation of wave index.

> 7 All seventeen claims of the *'258 patent* refer to wave index, thus they all stand or fall together.

Following the reasoning of the district court, Solutia argues that a person of ordinary skill in the pertinent art could overcome any ambiguities in the wave index calculation without undue experimentation by testing a limited number of possibilities for computing the wave index. In response, Crown offers statements of its expert that the *'258 patent* does not define amplitude and that a person of ordinary skill in the art would not know whether to measure amplitude: (i) from a centerline running horizontally through the "middle" of the trace; (ii) from "peak-to-peak," i.e., from the bottom of a valley to the top of a peak; or (iii) from some other baseline or reference running horizontally somewhere through [**28] the trace. On its face, the *'258 patent* does not define amplitude. However, average amplitude directly impacts the wave index calculation because wave index [*1380] is the result of multiplying average amplitude by average pitch. Simply put, the wave index calculation would produce two separate numbers if calculated with a centerline versus a "peak-to-peak" amplitude. Worse yet, a range of various wave index values are possible for amplitude baselines running horizontally somewhere through the trace at various locations. To show that the wave index calculation is enabled, Solutia cites various details from the *'258 patent* concerning how to perform the test to generate a trace of the PVB surface to calculate wave index. However, Solutia does not present sufficient evidence to rebut Crown's demonstration of the amplitude ambiguity in the wave index calculation. This is so because: (i) the amplitude is a direct input to the critical claim limitation, a wave index of less than 15,000 square micrometers; and (ii) the novel aspects of the invention must be disclosed and not left to inference, that is, a patentee may not rely on the inference of a person of ordinary skill in the pertinent art to [**29] supply such novel aspects. See *Genentech Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1366, 42 USPQ2d 1001, 1005 (Fed. Cir. 1997)* (stating that the knowledge of a hypothetical person of ordinary skill in the art cannot be used to supply the patentable aspects of the invention).

Compounding the amplitude ambiguity, Crown also notes that the wave index is the result of two independently varying, unbounded terms: average pitch and average amplitude. On its face, this does not seem to be a problem. However, Crown's expert noted that because boundary conditions are not specified, the claim covers inoperative embodiments. For example, a wave index of 15,000 square micrometers results from an average height of 1000 micrometers multiplied by an average pitch of 15 micrometers. Yet, according to Crown's expert, an average height of 1000 micrometers would not be acceptable for the PVB. As with the amplitude ambiguity, the problem goes well beyond this single example because a full range of resulting

inoperative embodiments are possible for values of average height and average pitch that, when multiplied, produce a wave index value that meets the limitation of the claim. Such inoperative [**30] embodiments do not necessarily invalidate the claim. See *Atlas Powder Co. v. E.I. du Pont de Nemours & Co., 750 F.2d 1569, 1576-77, 224 USPQ 409, 414 (Fed. Cir. 1984)*; *In re Cook, 58 C.C.P.A. 1049, 439 F.2d 730, 735, 169 USPQ 298, 302 (CCPA 1971)* (noting that although claims may read on some inoperative embodiments, this does not necessarily invalidate the claim if the necessary information to limit the claims to operative embodiments is known to a person of ordinary skill in the art). [8] However, the inoperative embodiments support Crown's assertion that there is a genuine issue of material fact with respect to enablement. See *Atlas Powder, 750 F.2d at 1576-77*; see also *Process Control Corp. v. HydReclaim Corp., 190 F.3d 1350, 1358-59, 52 USPQ2d 1029, 1034-35 (Fed. Cir. 1999)* (holding that the district court failed in its [*1381] claim construction to consider the effect of inoperative embodiments on invalidity due to lack of enablement). [9]

8 The court in In re Cook further notes that a claim may be invalid if it reads on significant numbers of inoperative embodiments. *In re Cook, 439 F.2d at 734, 169 USPQ at 301-02* (citing *Graver Tank & Mfg. Co. v. Linde Air Products Co., 336 U.S. 271, 276-77, 80 USPQ 451, 453, 93 L. Ed. 672, 69 S. Ct. 535 (1949)*). See also *In re Moore, 58 C.C.P.A. 1042, 439 F.2d 1232, 1236 169 USPQ 236, 239 (CCPA 1971)* (noting that the question is whether the scope of enablement conveyed by the disclosure to a person of ordinary skill in the art is commensurate with the scope of protection taught by the claims); *Chisum, § 7.03[7][a]* at 7-108 & n.6.

[**31]

9 The inoperative embodiment inquiry informs the enablement inquiry; they are not the same inquiry. *Nat'l Recovery Techs., 166 F.3d at 1196, 49 USPQ2d at 1676.*

Further compounding the ambiguities with the wave index rules, the *'258 patent*'s rules for determining which inflection points are "true" inflection points additionally support Crown's argument that it has raised a genuine issue of material fact. Crown demonstrated in various ways through its experts and arguments the potential indeterminacy in the rules. Solutia's expert admitted that there was some ambiguity in the rules with respect to whether a preceding peak or valley was the reference point in selecting a "true" peak or valley.

Solutia argues that even if the disclosed wave index calculation has ambiguities and is indeterminate, a person of ordinary skill in the pertinent art would be able to make and use the invention with some experimentation, but less than "undue" experimentation. Solutia argues that such a skilled person would only have to try two possibilities for amplitude, centerline and "peak-to-peak," [**32] and that experimenting to discover which of two possibilities to use is well within the boundary of undue experimentation. Crown counters that the amplitude ambiguity and potential inoperative embodiments, combined with the ambiguities in the smoothing rules, seems to suggest a wide range of possibilities which one must try. [10] With this wide range of possibilities, we agree that Crown has raised a genuine issue of material fact as to the amount and type of experimentation required, facts that will determine whether such experimentation is undue. See *Enzo Biochem Inc., v. Calgene Inc., 188 F.3d 1362, 1371, 52 USPQ2d 1129, 1135-36 (Fed. Cir. 1999)* (holding that a reasonable amount of experimentation does not invalidate a patent, but undue experimentation does invalidate, and holding that the Wands factors, which determine whether a patent's disclosure is insufficient such that the experimentation required would be undue, apply to inter partes litigation). [11] While ultimately a trier of fact may reach the conclusion that any required experimentation is not undue, Crown has shown that sufficient potential for undue experimentation exists such that disposal on summary [**33] judgment is improper.

10 We note that the specification for the *'258 patent* states that in the disclosed embodiment the wave index is calculated using a software program running on a personal computer being fed the trace line. *'258 patent*, col. 7, ll. 64-68. Undoubtedly, Solutia took care to ensure that the program contained the necessary boundary conditions and other information to calculate wave index to practice the invention. It appears, however, that Solutia took substantially less care in transcribing the information from the program into the specification's rules for calculating wave index. This incongruity will be relevant to the question of enablement upon remand. See *Chisum, § 7.03[4][e]* at 7-86 & n.77 ("A

specification that claims an invention requiring implementation through computer software but fails to set forth the details of computer programming may present issues of whether the experimentation required to write the programming is reasonable or unreasonable.") (summarizing the teachings of various cases).

11 The Wands factors are:

> (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.
>
> *In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).*

[**34] [*1382] CONCLUSION

Because we hold that the *'511 patent* has not been shown to be invalid due to anticipation or obviousness and that a genuine issue of material fact exists with respect to facts underlying the determination of enablement for the *'258 patent*, we affirm-in-part and reverse-in-part the district court's decision and remand for additional proceedings consistent with this opinion.

AFFIRMED-IN-PART, REVERSED-IN-PART, AND REMANDED.

COSTS

Each party bears its own costs.

EXHIBIT G

Not Reported in F.Supp.2d, 2000 WL 33906466 (W.D.Wis.)
(Cite as: 2000 WL 33906466 (W.D.Wis.))

United States District Court, W.D. Wisconsin.
CROWN OPERATIONS INTERNATIONAL, LTD. and Marshall H. Krone, Plaintiffs,
v.
SOLUTIA INC., Defendant.

No. 99-C-0802-S.
Aug. 22, 2000.

MEMORANDUM AND ORDER

SHABAZ, J.

***1** Plaintiffs Crown Operations International, Ltd. (Crown) and Marshall H. Krone (Krone) commenced this action against defendant Solutia Inc. (Solutia) alleging breach of contract, invalidity of a contractual covenant not to compete and violation of the Wisconsin Fair Dealership Law (WFDL). Plaintiffs also seek declaratory relief that defendant's United States Patents Nos. 4,973,511 (the '511 patent) and 5,091,258 (the '258 patent) are invalid. The Court has jurisdiction pursuant to 28 U.S.C. §§ 1338(a) and 1367, as well as 28 U.S.C. § 1332. The matter is presently before the Court on cross motions for summary judgment.

BACKGROUND

This case arises from the contractual relationships between several companies manufacturing prelaminates to be incorporated in auto and window glass. Prelaminates are multilayer films that are later incorporated between layers of glass to produce laminated glass with certain enhanced properties. When plasticized polyvinyl butyral ("PVB") film alone is added it imparts glass with additional impact resistance. Solar control prelaminates which reflect or filter out certain wavelengths of sunlight are made by placing metal-coated polyethylene terephthalate (PET) film between layers of PVB. The metal coating on the solar control film also acts as a conductor for defrosting a windshield. The process by which PET is placed between layers of PVB is known as encapsulation.

Plaintiff Crown encapsulates solar control prelaminates. Plaintiff Krone is Crown's sole shareholder. Defendant Solutia manufactures PVB and is successor in interest to Monsanto Chemical Company and to the contracts relevant in this action. In 1987 and 1988 Monsanto met with plaintiff Krone to discuss a relationship to develop laminating machinery designs and methods for encapsulating solar control prelaminates for Monsanto customers. Plaintiff Krone incorporated plaintiff Crown to conduct this encapsulation business.

In October 1988 Crown and Monsanto entered into an agreement (the Crown Agreement) whereby Crown would perform encapsulation services for Monsanto. Monsanto would provide PET it purchased from Southwall Technologies, Inc. ("Southwall") and its own Saflex brand of PVB. At Monsanto's request Crown erected a facility to encapsulate Solarflex. Monsanto had access to the Crown facility and had a major role in its design. Monsanto at all times owned the PVB, PET and finished product handled by plaintiff. Crown would fabricate the prelaminate (which was ascribed the Monsanto trade name "Solarflex") and receive a fee in return. Paragraph 13 of the Crown Agreement included a secrecy provision that forbade plaintiff Crown to use or disclose certain information Monsanto disclosed during the course of the relationship ("Monsanto Information") or to manufacture a solar "Saflex type product" except pursuant to their agreement.

In 1990 the '511 Patent was issued and assigned to Monsanto. The '511 patent is directed toward resolving the problem that functionally coated PET tends to wrinkle during the encapsulation process. "These wrinkles, which are particularly noticeable at oblique viewing angles, render the resulting windshield unacceptable...." The object of the invention is to produce a window assemble which "exhibits good solar rejection characteristics and acceptable low visible distorted reflection images from wrinkles in the solar control film." See column 1 line 58 through column 2 line 30. The invention is summarized as follows at column 8, line 58 through column 9, line 6 of the specification:

***2** Thus, according to this invention the relationship between the substrate wrinkling and visible light

reflection contribution from the solar film is recognized. More specifically, the adverse optical effects of these wrinkles are masked by controlling to two percent or less the visible light reflection contribution of the solar film to the overall laminate. In this manner, the wrinkles are not eliminated but rendered less visible to the human eye since the reflection contribution of substrate layer 16 is controlled below a predetermined visibility threshold.

Claim 1, the only independent claim of the '511 patent, is as follows:

1. A composite solar/safety film for use in a laminated window assembly comprising:

a flexible, transparent plastic substrate layer having a carrier surface and an opposing back surface;

a multilayer solar control coating on said carrier surface, said controlled substrate defining a solar control film; and

at least one flexible, transparent, energy absorbing plastic safety layer bonded to the surface of said solar control film;

wherein said solar control film contributes no more than 2% visible reflectance, based on total visible incident radiation, in a laminated window assembly containing said composite solar/safety film laminated to at least one rigid transparent member.

In 1992 the '258 patent was issued and assigned to Monsanto. The '258 patent is also directed to eliminating optical distortion, known as "applesauce", in laminated glass. The patent describes a method to control distortion by measuring and controlling the texture of the surface of the PVB components of the laminate defined in terms of a "wave index" (WI) and a "roughness value" (Rz). Specification at column 2, lines 36-56. Claim 1 of the '258 patent is as follows:

1. a laminate which is substantially free of reflected distortion when used in a safety glazing comprising:

a transparent, thermoplastic substrate layer, optionally surface treated or coated, bearing one or more functional performance layers; and

at least one layer of [PVB] bonded on one side to a functional performance layer or the substrate layer and having a roughened deairing surface on the other side characterized by a roughness value, Rz, of at least 10 micrometers;

said at least one [PVB] layer, before bonding to the substrate layer of functional performance layer, possessing low surface waviness on each side characterized by a wave index value, WI, of less than 15,000 square micrometers.

In the early 1990's Monsanto decided to curtail its Solarflex operation. Consequently, the Crown Agreement underwent two amendments. In 1994 Monsanto agreed to partially waive the restrictions in Paragraph 13 of the Crown Agreement so that plaintiff could use the Monsanto Information and encapsulate prelaminates for Southwall if Monsanto PVB was used ("the 1994 Amendment"). In 1995 Monsanto agreed to further waive its Paragraph 13 restrictions so that plaintiff could encapsulate prelaminates for third parties other than Southwall so long as Monsanto PVB was used ("the 1995 Amendment"). The 1995 Amendment provided that the partial waiver of the restrictions was subject to revocation upon twelve months prior written notice.

***3** Additionally, Monsanto and Southwall entered into a new agreement in 1994 ("the Southwall Agreement") under which Monsanto agreed not to assert its '511 and '258 Patents and therefore to allow Southwall and certain third parties to produce, use and sell solar control prelaminates.

In July, 1999 defendant Solutia, as a successor to Monsanto's contracts, revoked its partial waiver of the Paragraph 13 restrictions pursuant to the Crown Amendments effective July 7, 2000. Plaintiffs filed this action in response.

MEMORANDUM

Both parties move for summary judgment under Federal Rule of Civil Procedure 56(c). A movant will prevail on its motion if "the pleadings, depositions, answers to interrogatories, and admissions on file show that there is no genuine issue as to any material fact and that the moving party is entitled to judgment as a matter of law ." Fed.R.Civ.P. 56(c). In other words, Rule 56(c) requires the entry of summary judgment against a party that fails to establish the

existence of an element essential to the party's case when that party bears the burden of proof at trial. *Celotex v. Catrett*, 477 U.S. 317, 322 (1986).

The crux of the summary judgment inquiry lies in the phrase "no genuine issue as to any material fact." Facts are "material" if they are outcome influencing under the substantive law governing the action. *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 248 (1986). A dispute over a material fact is "genuine" if from the evidence a reasonable jury could find for the non-moving party. *Id.* at 248. In making this determination ambiguities and reasonable inferences are resolved against the moving party. *See id.* at 255. Where there are no genuine issues of material fact the district court need only determine whether the moving party is entitled to judgment as a matter of law.

Breach of Contract

Plaintiffs' amended complaint alleges that defendant is liable for breaching the Southwall Agreement. Under the Southwall Agreement, plaintiffs' maintain that Crown has an unrestricted right to fabricate solar control prelaminates for Southwall. Plaintiffs maintain that defendant's withdrawal of its waiver under the amended Crown Agreement made it impossible for Crown to encapsulate prelaminates for Southwall-a violation of the Southwall Agreement.

It is undisputed that Crown is not a party to the Southwall Agreement. Nevertheless, plaintiffs allege that Crown is a third-party beneficiary with rights under it. The relevant language in the Agreement reads:

> 22. Monsanto agrees, on a worldwide basis, not to assert any patents, which it owns or controls, and that cover the composition, use or application of coated PET films or sheet (PVB, EVA, or other comparable product) adhered to or in combination with coated PET films ... which would impair the right of Southwall, or a customer or licensee of Southwall or their customers, to make, have made, use and/or sell laminates containing (a) sheet ... and (b) the Southwall product currently known as XIR coated PET film ...; provided, however, in the event such sheet is not purchased from Monsanto, Southwall will pay Monsanto a royalty in the amount of one cent ($.01) per square foot of laminate sold.

***4** Southwall Agreement ¶ 22. It is undisputed that plaintiff Crown is not a customer or licensee of Southwall. Plaintiff maintains that by exercising its right to revoke the waiver under the 1994 and 1995 Crown Amendments, thus effectively barring Crown from using Monsanto Information or encapsulating a solar "Saflex type product" for anyone but Monsanto, defendant impaired Southwall's right under the Southwall Agreement to "have [prelaminates] made" and Crown's asserted reciprocal third-party right to make those prelaminates for Southwall.

The parties agree that New York law governs the Southwall Agreement. New York recognizes third-party beneficiaries to contracts, but only "intended beneficiaries" may recover as third-party beneficiaries. *Fourth Ocean Putnam Corp. v. Interstate Wrecking Co., Inc.*, 485 N.E.2d 208, 211-12 (N.Y.1985) (citing with approval Restatement (Second) of Contracts § 302 (1977)). A third-party qualifies as an intended beneficiary where "the language of the contract clearly evidences an intent to permit enforcement by the third party...." *Fourth Ocean*, 485 N.E.2d at 212; *see also* Restatement (Second) of Contracts § 302(1)(b) ("intended beneficiary" where "the promisee intends to give the beneficiary the benefit of the promised performance"). Other courts examining New York law have added that the proposed third-party beneficiary need not be specifically mentioned by name in the contract. *See e.g., Newman v. Schwartz v. Asplundh Tree Expert Co.*, 102 F.3d 660, 663 (2nd Cir.1996) (citations omitted). Nevertheless, these courts still recognize that New York law "requires that the parties' intent to benefit a third-party must be shown on the face of the agreement." *Id.*

No language in Paragraph 22 of the Southwall Agreement shows an intent to confer a benefit upon Crown. The only language plaintiffs cite is that language recognizing the right of Southwall, its customers and licensees and its licensees' customers to "have [prelaminates] made". *See* Southwall Agreement ¶ 22. Plaintiffs believe this includes a reciprocal contractual right vested with plaintiff Crown to make those prelaminates for Southwall. However, no such right appears on the face of the Agreement which identifies only Southwall customers, licensees and licensee's customers as third party beneficiaries. Paragraph 22 is silent as to any impairment of rights of those fabricating prelaminates for Southwall.