IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patentee:	Yang et al.	Examiner:	Diamond, Alan D.
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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

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