PROLLENIUM US INC.
V. ALLERGAN INDUSTRIE, SAS

IPR2019-01505
IPR2019-01506
IPR2019-01508
IPR2019-01509
IPR2019-01617
IPR2019-01632
IPR2020-00084

PATENT OWNER'S DEMONSTRATIVES

Demonstrative Exhibit –
NOT EVIDENCE

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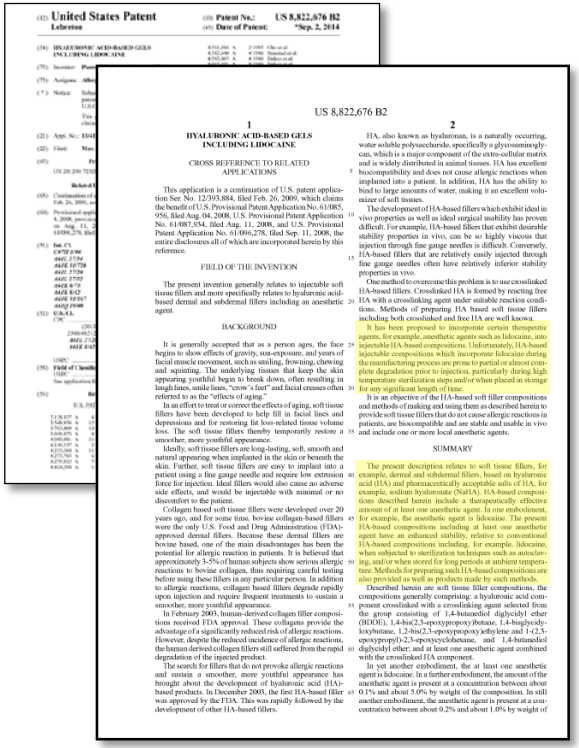
Unless otherwise noted, citations herein are to the papers and exhibits of record in the -01617 IPR

BACKGROUND AND STATE OF THE ART

ALLERGAN'S INVENTIONS



US 8,822,676 B2

1

HYALURONIC ACID-BASED GELS INCLUDING LIDOCAINE

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 12/393,884, filed Feb. 26, 2009, which claims the benefit of U.S. Provisional Patent Application No. 61/085,956, filed Aug. 04, 2008, U.S. Provisional Patent Application No. 61/087,934, filed Aug. 11, 2008, and U.S. Provisional Patent Application No. 61/096,278, filed Sep. 11, 2008, the entire disclosures all of which are incorporated herein by this reference.

FIELD OF THE INVENTION

The present invention generally relates to injectable soft tissue fillers and more specifically relates to hyaluronic acid-based dermal and subdermal fillers including an anesthetic agent.

BACKGROUND

It is generally accepted that as a person ages, the face begins to show effects of gravity, sun-exposure, and years of facial muscle movement, such as smiling, frowning, chewing and squinting. The underlying tissues that keep the skin appearing youthful begin to break down, often resulting in laugh lines, smile lines, "crow's feet" and facial creases often referred to as the "effects of aging."

In an effort to treat or correct the effects of aging, soft tissue fillers have been developed to help fill in facial lines and depressions and for restoring fat loss-related tissue volume loss. The soft tissue fillers thereby temporarily restore a smoother, more youthful appearance.

Ideally, soft tissue fillers are long-lasting, soft, smooth and natural appearing when implanted in the skin or beneath the skin. Further, soft tissue fillers are easy to implant into a patient using a fine gauge needle and require low extrusion force for injection. Ideal fillers would also cause no adverse side effects, and would be injectable with minimal or no discomfort to the patient.

Collagen based soft tissue fillers were developed over 20 years ago, and for some time, bovine collagen-based fillers were the only U.S. Food and Drug Administration (FDA)-approved dermal fillers. Because these dermal fillers are bovine based, one of the main disadvantages has been the potential for allergic reaction in patients. It is believed that approximately 3-5% of human subjects show serious allergic reactions to bovine collagen, thus requiring careful testing before using these fillers in any particular person. In addition to allergic reactions, collagen based fillers degrade rapidly upon injection and require frequent treatments to sustain a smoother, more youthful appearance.

In February 2003, human-derived collagen filler compositions received FDA approval. These collagens provide the advantage of a significantly reduced risk of allergic reactions. However, despite the reduced incidence of allergic reactions, the human derived collagen fillers still suffered from the rapid degradation of the injected product.

The search for fillers that do not provoke allergic reactions and sustain a smoother, more youthful appearance has brought about the development of hyaluronic acid (HA)-based products. In December 2003, the first HA-based filler was approved by the FDA. This was rapidly followed by the development of other HA-based fillers.

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HA, also known as hyaluronan, is a naturally occurring, water soluble polysaccharide, specifically a glycosaminoglycan, which is a major component of the extracellular matrix and is widely distributed in animal tissues. HA has excellent biocompatibility and does not cause allergic reactions when implanted into a patient. In addition, HA has the ability to bind to large amounts of water, making it an excellent volumizer of soft tissues.

The development of HA-based fillers which exhibit ideal in vivo properties as well as ideal surgical usability has proven difficult. For example, HA-based fillers that exhibit desirable stability properties in vivo, can be so highly viscous that injection through fine gauge needles is difficult. Conversely, HA-based fillers that are relatively easily injected through fine gauge needles often have relatively inferior stability properties in vivo.

One method to overcome this problem is to use crosslinked HA-based fillers. Crosslinked HA is formed by reacting free HA with a crosslinking agent under suitable reaction conditions. Methods of preparing HA based soft tissue fillers including both crosslinked and free HA are well known.

It has been proposed to incorporate certain therapeutic agents, for example, anesthetic agents such as lidocaine, into injectable HA-based compositions. Unfortunately, HA-based injectable compositions which incorporate lidocaine during the manufacturing process are prone to partial or almost complete degradation prior to injection, particularly during high temperature sterilization steps and/or when placed in storage for any significant length of time.

It is an objective of the HA-based soft filler compositions and methods of making and using them as described herein to provide soft tissue fillers that do not cause allergic reactions in patients, are biocompatible and are stable and usable in vivo and include one or more local anesthetic agents.

SUMMARY

The present description relates to soft tissue fillers, for example, dermal and subdermal fillers, based on hyaluronic acid (HA) and pharmaceutically acceptable salts of HA, for example, sodium hyaluronate (NaHA). HA-based compositions described herein include a therapeutically effective amount of at least one anesthetic agent. In one embodiment, for example, the anesthetic agent is lidocaine. The present HA-based compositions including at least one anesthetic agent have an enhanced stability, relative to conventional HA-based compositions including, for example, lidocaine, when subjected to sterilization techniques such as autoclaving, and/or when stored for long periods at ambient temperature. Methods for preparing such HA-based compositions are also provided as well as products made by such methods.

Described herein are soft tissue filler compositions, the compositions generally comprising: a hyaluronic acid component crosslinked with a crosslinking agent selected from the group consisting of 1,4-butanediol diglycidyl ether (BDDE), 1,4-bis(2,3-epoxypropoxy)butane, 1,4-bisglycidyloxybutane, 1,2-bis(2,3-epoxypropoxy)ethylene and 1-(2,3-epoxypropyl)-2,3-epoxycyclohexane, and 1,4-butanediol diglycidyl ether; and at least one anesthetic agent combined with the crosslinked HA component.

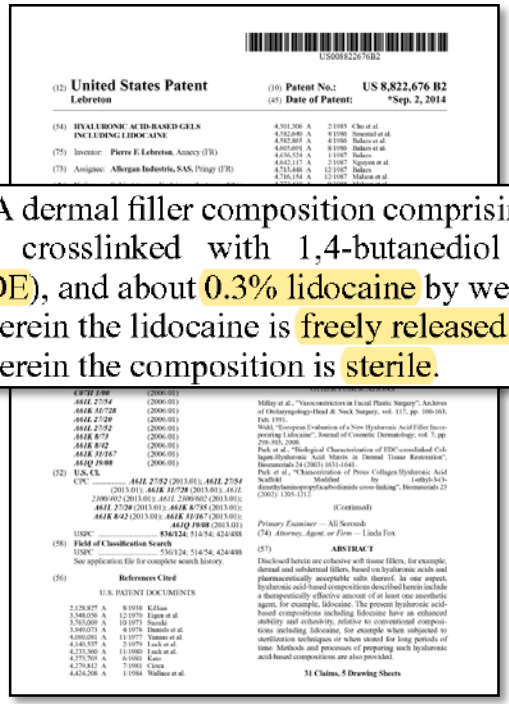
In yet another embodiment, the at least one anesthetic agent is lidocaine. In a further embodiment, the amount of the anesthetic agent is present at a concentration between about 0.1% and about 5.0% by weight of the composition. In still another embodiment, the anesthetic agent is present at a concentration between about 0.2% and about 1.0% by weight of

It has been proposed to incorporate certain therapeutic agents, for example, anesthetic agents such as lidocaine, into injectable HA-based compositions. Unfortunately, HA-based injectable compositions which incorporate lidocaine during the manufacturing process are prone to partial or almost complete degradation prior to injection, particularly during high temperature sterilization steps and/or when placed in storage for any significant length of time.

The present description relates to soft tissue fillers, for example, dermal and subdermal fillers, based on hyaluronic acid (HA) and pharmaceutically acceptable salts of HA, for example, sodium hyaluronate (NaHA). HA-based compositions described herein include a therapeutically effective amount of at least one anesthetic agent. In one embodiment, for example, the anesthetic agent is lidocaine. The present HA-based compositions including at least one anesthetic agent have an enhanced stability, relative to conventional HA-based compositions including, for example, lidocaine, when subjected to sterilization techniques such as autoclaving, and/or when stored for long periods at ambient temperature. Methods for preparing such HA-based compositions are also provided as well as products made by such methods.

Source: Ex. 1001 at 2:23-30, 2:39-52; POR at 15-16.

REPRESENTATIVE CLAIMS OF THE CHALLENGED PATENTS



US008822676B2

(12) **United States Patent**
Lebreton

(10) **Patent No.: US 8,822,676 B2**
(45) **Date of Patent: *Sep. 2, 2014**

(54) **HYALURONIC ACID-BASED GELS INCLUDING LIDOCAINE**

(75) Inventor: **Pierre F. Lebreton**, Annecy (FR)

(73) Assignee: **Allergan Industrie, SAS**, Pringy (FR)

1. A dermal filler composition comprising hyaluronic acid (HA) crosslinked with 1,4-butanediol diglycidyl ether (BDDE), and about 0.3% lidocaine by weight,
wherein the lidocaine is freely released in vivo; and
wherein the composition is sterile.

’676 Patent, claim 1

12. The composition of claim **1**, wherein the composition is sterilized by autoclave.

22. The composition of claim **1**, wherein the composition is sterilized by heat sterilization between about 120° C. and about 130° C.

23. The composition of claim **22**, having an extrusion force that is substantially constant during storage under ambient conditions for at least 3 months.

26. The composition of claim **22**, having a viscosity that is substantially constant during storage under ambient conditions for at least 3 months.

29. The composition of claim **22**, wherein the lidocaine does not substantially degrade the HA during storage under ambient conditions for at least 3 months.

’676 Patent, claims 12, 22-23, 26, 29

Source: POR at 15-16; Ex. 1001.

	’475 Patent -01505 IPR	’795 Patent -01506 and -01632 IPRs	’013 Patent -01508 IPR	’322 Patent -01509 IPR	’676 Patent -01617 IPR	’519 Patent -00084 IPR
Lidocaine Freely Released/ Unbound		1* (freely released in vivo); 22* (unbound lidocaine HCl); 37 (freely released in vivo); 38 (substantially unbound); 39 (substantially unbound)			1* (freely released in vivo)	2 (freely released in vivo); 4 (freely released in vivo); 8 (freely released in vivo)
Heat-Sterilized Filler	18* (filler heat sterilized); 31* (heat-sterilized, stable dermal filler); 34* (stable after heat sterilization at 120 °C and 130 °C)	28 (stable to autoclaving)	1* (heat sterile); 4* (heat sterilize 120 °C-130 °C for 1 min. to 15 mins.)	1* (sterile)	1* (sterile); 12 (sterilized by autoclave); 22 (sterilized by heat sterilization 120 °C and 130 °C)	
Maintain Various Filler Properties During Storage Over Time.		29* (stable at least 3 mos.); 30 (stable at least 6 mos.); 31 (stable at least 9 mos.); 32 (lido. conc. constant at least 3 mos.); 33 (HA conc. constant at least 3 mos.); 34 (EF constant at least 3 mos.); 35 (homogenous & transparent at least 3 mos.); 36 (no increase in 2,6-dimethyl-aniline at least 3 mos.); 41 (EF constant at least 6 mos.)	4* (stable at 25 deg. C for at least 6 mos. after heat sterilization)		13 (Extrusion force (“EF”) constant 3 mos.); 14 (EF constant 6 mos.); 15 (EF constant 9 mos.); 16 (Viscosity (“V”) constant 3 mos.) 17 (V constant 6 mos.); 18 (V constant 9 mos.); 19 (lido. not degrade 3 mos.); 20 (lido. not degrade 6 mos.); 21 (lido. not degrade 9 mos.); 23-31 (same limitations as claims 13-21, but post-sterilization)	5* (1st comp. as stable for 3 mos. as 2nd comp. w/o lido.); 6 (1st comp. as stable for 6 mos.); 7 (1st comp. as stable for 9 mos.)

Source: -1505, Ex. 1001; -1506/-1632, Ex. 1001; -1508, Ex. 1001; -1509, Ex. 1001; -1617, Ex. 1001; -0084, Ex. 1001. * = Independent Claims.

PERSON OF ORDINARY SKILL IN THE ART AND SCIENTIFIC BACKGROUND

PERSON OF ORDINARY SKILL IN THE ART

C. Person of Ordinary Skill in the Art

The POSITA at and before the priority date of the patent is a scientist involved in the development of dermal fillers, who would have an advanced degree, such as a Ph.D., M.S., or M.D., and several years of experience developing dermal fillers for cosmetic use, including HA-based dermal fillers. The POSITA would be aware of commercially sold dermal fillers, in the United States and abroad, as well as those products for which approvals were being publicly sought. EX1002 ¶ 69-72.

A POSITA would also be aware of the process by which FDA reviews dermal filler products, and how FDA communicates the results of such reviews to the public. In particular, the POSITA would have known that once FDA has approved a dermal filler, FDA would have hosted information about that filler on its webpage. EX1002 ¶ 73-75; EX1032, 227.

Petitioner's definition

In prior IPRs, the Board adopted a definition that captures the true nature of the POSA:

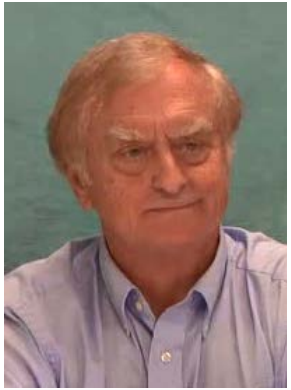
> [A] B.S. or M.S. in biochemistry, polymer chemistry, medicinal chemistry, pharmaceutical chemistry, or a related field with "several years" of practical experience. Alternatively, … the ordinary artisan would have had less practical experience but a Ph.D. in one of those fields, or an M.D. in dermatology, plastic surgery, or a specialty related to the clinical use of dermal fillers.

Teoxane S.A. v. Allergan, PLC, IPR2017-01906, Paper 15 at 8-9 (PTAB Mar. 9, 2018); *accord Teoxane S.A. v. Allergan, PLC*, IPR2017-02002, Paper 14 at 8 (PTAB Mar. 9, 2018). That definition should be adopted here.

Patent Owner's definition

Source: Pet. at 18; POR at 17.

PETITIONER'S EXPERTS



Dr. DeVore

- Misrepresented his Degrees
- Commercial Executive
- Agrees HA chemistry matters but does not know the chemistry
- Only testimony supporting Petitions

Dr. Prestwich

- Ph.D., Organic Chemistry
- Previously submitted declarations in Galderma and Teoxane IPRs
- Not aware of grounds
- Deleted unhelpful testimony

Source: POR at 26-31; Surreply at 5-8, 14, 16, 27; Ex. 1002; Ex. 1003; Ex. 1105, Ex. 1106; Ex. 2200, 429:18-432:13.

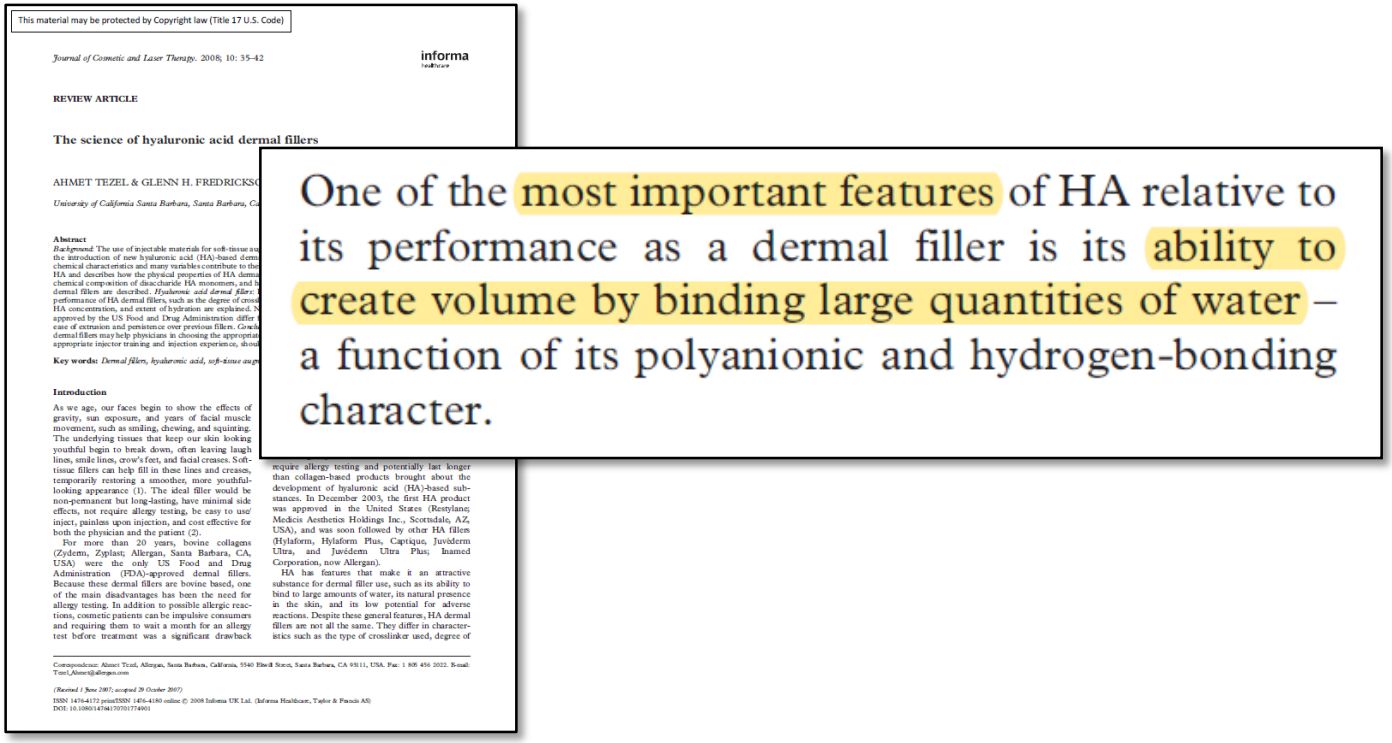
PATENT OWNER'S EXPERT

Dr. Berkland

- Ph.D., Chemical and Biomolecular Engineering
- Solon E. Summerfield Distinguished Professor in the Department of Pharmaceutical Chemistry at the University of Kansas
- Years of experience chemically modifying HA
- Authored ~25 papers on HA-based materials
- Explains complexity of designing HA fillers
- Supports testimony with contemporaneous art

Source: Ex. 2014; Ex. 2013 at ¶¶ 3-14; POR at 3.

DR. BERKLAND: HYDROPHILIC NATURE OF HA PROVIDES FILLER VOLUME AND LIFT



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Journal of Cosmetic and Laser Therapy, 2008; 10: 35–42

informa

REVIEW ARTICLE

The science of hyaluronic acid dermal fillers

AHMET TEZEL & GLENN H. FREDRICKS

University of California Santa Barbara, Santa Barbara, Ca

Abstract

Background: The use of injectable materials for soft-tissue au
the introduction of new hyaluronic acid (HA)-based derm
chemical characteristics and many variables contribute to the
HA and describes how the physical properties of HA derma
chemical composition of disaccharide HA monomers, and h
dermal fillers are described. *Hyaluronic acid dermal fillers:*
performance of HA dermal fillers, such as the degree of cross
HA concentration, and extent of hydration are explained. N
approved by the US Food and Drug Administration differ
ease of extrusion and persistence over previous fillers. Conclu
dermal fillers may help physicians in choosing the appropriat
appropriate injector training and injection experience, should

Key words: *Dermal fillers, hyaluronic acid, soft-tissue aug*

Introduction

As we age, our faces begin to show the effects of gravity, sun exposure, and years of facial muscle movement, such as smiling, chewing, and squinting. The underlying tissues that keep our skin looking youthful begin to break down, often leaving laugh lines, smile lines, crow's feet, and facial creases. Soft-tissue fillers can help fill in these lines and creases, temporarily restoring a smoother, more youthful-looking appearance (1). The ideal filler would be non-permanent but long-lasting, have minimal side effects, not require allergy testing, be easy to use/inject, painless upon injection, and cost effective for both the physician and the patient (2).

For more than 20 years, bovine collagens (Zyderm, Zyplast; Allergan, Santa Barbara, CA, USA) were the only US Food and Drug Administration (FDA)-approved dermal fillers. Because these dermal fillers are bovine based, one of the main disadvantages has been the need for allergy testing. In addition to possible allergic reactions, cosmetic patients can be impulsive consumers and requiring them to wait a month for an allergy test before treatment was a significant drawback require allergy testing and potentially last longer than collagen-based products brought about the development of hyaluronic acid (HA)-based substances. In December 2003, the first HA product was approved in the United States (Restylane; Medicis Aesthetics Holdings Inc., Scottsdale, AZ, USA), and was soon followed by other HA fillers (Hylaform, Hylaform Plus, Captique, Juvéderm Ultra, and Juvéderm Ultra Plus; Inamed Corporation, now Allergan).

HA has features that make it an attractive substance for dermal filler use, such as its ability to bind to large amounts of water, its natural presence in the skin, and its low potential for adverse reactions. Despite these general features, HA dermal fillers are not all the same. They differ in characteristics such as the type of crosslinker used, degree of

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One of the most important features of HA relative to its performance as a dermal filler is its ability to create volume by binding large quantities of water – a function of its polyanionic and hydrogen-bonding character.

Source: Ex. 1045 at 41; POR at 41; *see also* Ex. 2015 at 10; Ex. 2071 at 3336; Ex. 2013, ¶ 36, 42.

DR. BERKLAND: HA MUST BE MODIFIED TO INCREASE PRODUCT LONGEVITY

(1) As described above (¶ 37), unmodified HA is rapidly degraded inside the body. So one goal of HA modification is to increase product longevity *in vivo*, thereby lowering the frequency of repeat injections.

A normal-sized human of approximately 70 kg has 15 g of dry weight hyaluronic acid [8]. Almost one third of this hyaluronan is turned over daily; naturally occurring hyaluronic acid as a commercial product is too unstable to be injected into the skin or connective tissue (Figure 2) [9]. Most of the hyaluronic acid is cleared by the lymphatics and within 2 days is degraded to carbon dioxide and water by the liver [10].

To produce a hyaluronic acid soft-tissue filler with longer lasting effect, however, the naturally occurring hyaluronic acid molecules must be cross-linked to each other to develop a larger molecule that is resistant to the constant mechanical action and enzymatic degradation in the tissues. Various approaches have yielded different products, each with distinct chemical structures and sources of hyaluronic acid.

(D)

Figure 4. HA gel. Crosslinking HA polymer chains transform the HA solution (A) into a gel (C). Crosslinker molecules (B) bind individual HA polymer chains to create a network (C), which manifests macroscopically as a gel mass (D).

Source: Ex. 2013 at ¶ 52; Ex. 1045 at 37; Ex. 2049 at 65; POR at 4; *see also* Ex. 2015 at 12.

DR. BERKLAND: FILLERS MUST BE INJECTABLE, REMAIN IN PLACE AND MAINTAIN KEY PERFORMANCE PROPERTIES

(2) Another goal is to improve the ability of the HA composition to provide volume and lift; a runny, low viscosity liquid would not hold its shape. It is also desirable for the dermal filler to generally remain in place after injection.

(3) So a third goal of HA modification is to maintain the filler's physical performance properties following sterilization and during shelf-life storage. (Ex. 1011 at 370 ("We would like the ideal filler to be stored at room temperature, have a long shelf life . . . .").)

(4) Finally, it is important that a dermal filler have a viscosity and syringe extrusion force that permit a smooth injection with an acceptable size needle diameter.

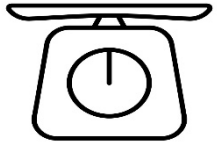
Further, the ideal filler would be painless on injection and nonallergenic (no skin tests required), noncarcinogenic, nonteratogenic, and we would expect it not to migrate once injected into the skin. We would like the ideal filler to be stored at room temperature, have a long shelf-life, and be free from all transmittable diseases. Further, we would want this ideal filler to have few, if any local adverse events, and be affordable to both the patient and the physician.

Viscosity, elasticity, and extrusion forces

We have discussed the concept of gel hardness G′, which is connected to the force required to make a small, rapid deformation of a gel. G′ thus provides information about the linear elastic properties of the gel. Of more clinical relevance is the extrusion force that the physician must apply to inject the HA filler through a needle and into soft tissue.

Source: Ex. 2013 at ¶¶ 53-55; Ex. 1011 at 370; Ex. 1045 at 40; POR at 5.

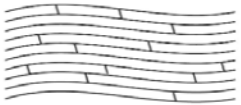
DR. BERKLAND: MANY COMPLEX FACTORS IMPACT DERMAL FILLERS



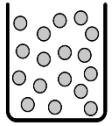
HA Molecular Weight

pH

Type of Crosslinker

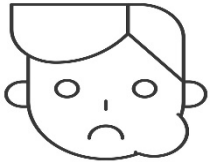


Density and Degree of Crosslinking



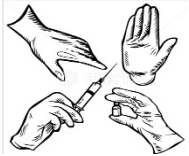
Particle Size Shape & Distribution

HA Concentration



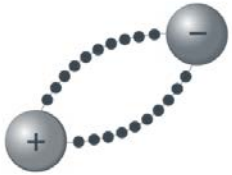
Degree of Swelling

Additives



Sterility

Post-Crosslinking Steps



Ionic Strength

HA Solubility

Crosslinking Conditions

Heating

Monophasic or Biphasic Gel

Source: POR at 4-15; Ex. 2013 at ¶ 62.

THE ART RECOGNIZED THE COMPLEXITY OF DERMAL FILLER COMPOSITIONS AND THEIR DIVERSITY

HA has features that make it an attractive substance for dermal filler use, such as its ability to bind to large amounts of water, its natural presence in the skin, and its low potential for adverse reactions. Despite these general features, HA dermal fillers are not all the same. They differ in characteristics such as the type of crosslinker used, degree of crosslinking, gel hardness, viscosity, extrusion force, gel consistency, total HA concentration (amount of HA per milliliter of finished product), and lifetime in the skin. Key to the performance of an HA dermal filler is how all of these characteristics act in concert to deliver a product that combines ease of injection with long life and efficacy as a filler.

Table I. Chemical and physical characteristics that influence hyaluronic acid dermal filler product performance.

Crosslinking of HA polymers	Crosslinking of HA polymers is an essential step in the production of HA dermal fillers. By chemically bonding the HA polymer chains together, enzymatic degradation of the HA gel is slowed down.
Degree of crosslinking	The degree of crosslinking contributes to the overall persistence of HA dermal fillers; however, an excessive degree of crosslinking may reduce the biocompatibility of the filler, resulting in adverse reactions in the body.
Gel hardness	G′ describes the hardness of a gel. HA dermal fillers with higher G′ values are more difficult to inject through a needle into the skin unless they incorporate large amounts of uncrosslinked HA into their formulation.
HA gel consistency	Manufacturing processes determine the final consistency of HA dermal fillers. Currently available products are gel particle formulations with well-defined particle size, and 'smooth consistency' formulations with a broad range of gel particle sizes. The newly FDA-approved smooth consistency formulations may offer improved ease of injection and potentially better persistence.
Viscosity and extrusion force	The viscosity and extrusion force characterize the ease with which an HA dermal filler can be injected through a syringe into the skin. These physical parameters depend on the degree of crosslinking, amounts of crosslinked HA and uncrosslinked HA, gel consistency, and proprietary manufacturing techniques, among other variables.
HA concentration and extent of hydration	The HA concentration and extent of hydration are important features that determine both the ability of an HA dermal filler to restore volume when in clinical use and the longevity of the implant. Formulations slightly below equilibrium hydration are preferred as dermal fillers, but their use requires appropriate training in order to avoid over- or undercorrection.

Source: Ex. 1045 at 35-36, 41; POR at 4-15; *see also, e.g.,* Ex. 2015 at 7-10, 14, 55-63, 68-69, 79-95; Ex. 2013 at ¶ 62.

DR. BERKLAND: THE TYPE OF CROSSLINKER IMPACTS REACTION CONDITIONS AND DRAMATICALLY AFFECT GEL CHARACTERISTICS

Dr. Berkland's declaration:

71. The type of cross linker chosen impacts the potential and actual reaction conditions to be considered or used. For example, HA crosslinking with divinyl sulfone (DVS) is preferentially performed at high pH values (0.2M NaOH, pH > 13) and forms sulfonyl bis-ethyl linkages between the hydroxyl groups of HA. (Ex. 2015 at 56; Ex. 2045; Ex. 2021 at 2674 ("The reaction is very fast.")). This crosslinking method has the advantage of occurring at room temperature.[9] (Ex. 2045 at 1:55-56 ("[D]ivinyl sulfone (DVS) reacts readily with HA in aqueous alkaline solutions at room temperature."); Ex. 2021 at 2674.)

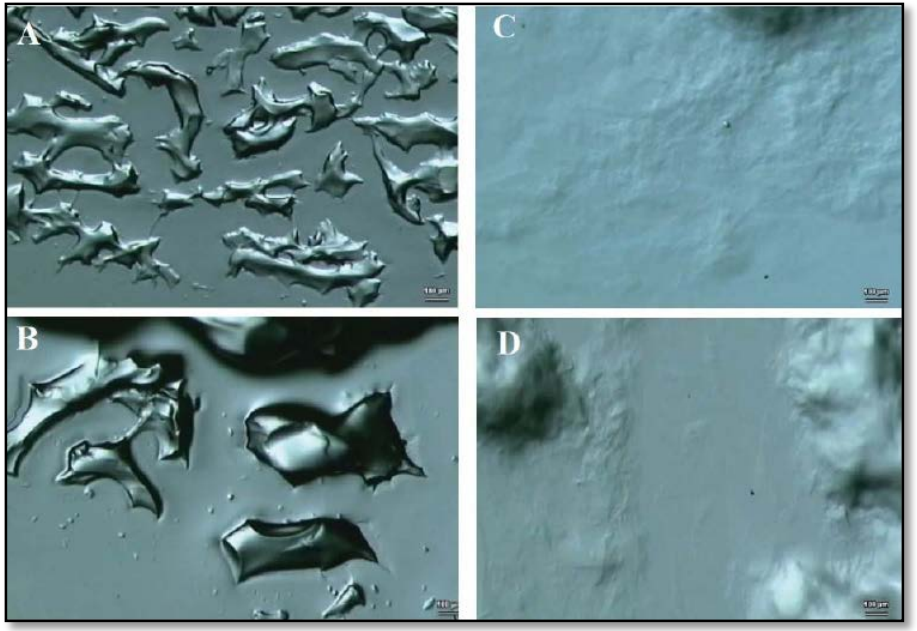
Cross-Linked HA Biomaterials

As already mentioned, HA presents many inherent advantages as a foundation for biomaterials. In addition to derivatization, cross-linking is another means of engineering HA's physicochemical properties. Depending on the cross-linking molecule and reaction chemistry, a wide variety of HA materials can be created, ranging from films with relatively low water content to highly swelling hydrogels. Most HA cross-linking methods fall into either of two general schemes: a one-step procedure consisting of the exposure of HA to a cross-linker, or a two-step procedure in which a highly reactive HA derivative is first synthesized and then cross-linked in a subsequent reaction. Following is a brief listing of common HA cross-linking techniques; see Refs. [2] and [13] for more detail.

Source: Ex. 2013 at ¶ 71; Ex. 2028 at 783; POR at 7-10.

DIFFERENT GELS ARISE FROM DIFFERENT PROCESSES

A new family of dermal fillers (the Juvéderm dermal fillers, Allergan, Santa Barbara, CA) was approved by the U.S. Food and Drug Administration (FDA) in June 2006. They are manufactured differently from other HA fillers previously approved by the FDA and, as a result, have a different consistency. A proprietary manufacturing process (known as Hylacross technology) avoids the need to press the filler through sieves to "size" the gel and produces a gel with a smooth consistency. The difference between this and the granular and uneven consistency of earlier HA fillers can be seen visually under a microscope.[3]



Source: Ex. 1015 at S128; Ex. 2061 at 977-78; POR at 10-11; Ex. 2013, ¶¶ 88-89, 113-114.

DR. BERKLAND: PROCESSING CONDITIONS CAUSE IRREVERSIBLE CHANGES IN GEL STRUCTURE THAT IMPACT GEL SWELLING

Dr. Berkland's declaration:

Mixing HA with such non-polar solvents can dehydrate it, which can lead to the formation of irreversible inter-chain connections between HA molecules. (Ex. 2072 at 298 ("acetone or propyl alcohol at high concentrations produces some irreversible changes in the gel structure"); Ex. 2062 at 126.) As I described above, the viscosity and other rheological properties of HA fillers depend on a large number of factors and the conditions under which crosslinking takes place further adds to the complexities.

The initial drying of the gel affects the ultimate swelling capacity as shown in Table II. The gel when dried without any prior swelling, swells only 2-3 times. The highly swollen gel upon drying does not reswell to the original swollen condition (only 50% of the original swelling). A similar observation was made by Laurent et al. (*24*). This drying was done at 35° C for 24 hours. It is possible that upon drying the pores are closed completely bringing about an irreversible change in the structure. Initial swelling might be preventing complete pore elimination. Hence these pores reopen when the gel is rewetted. Another possibility is the formation of new junctions between molecules. The junctions formed during drying will then act as crosslinks in the structure.

If the gel is allowed to swell first and then dried, it swells significantly yet is still affected by drying to some extent. This effect could be due to the introduction of some irreversible changes in the gel structure and in its water binding capacity by the drying process.

Source: Ex. 2013 at ¶ 73; Ex. 2062 at 125; Ex. 2072 at 296; POR at 12.

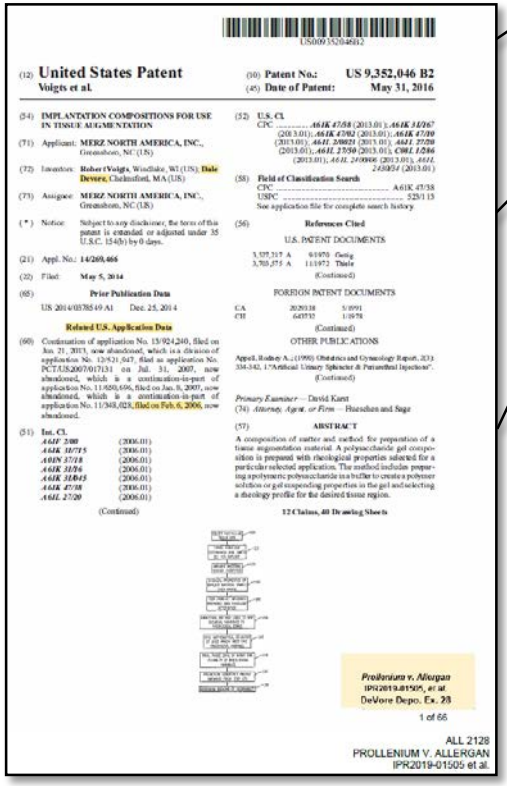
DR. BERKLAND: NON-COVALENT INTERACTIONS PLAY IMPORTANT ROLES IN THE PROPERTIES OF HA COMPOSITIONS

2. Non-covalent HA interactions affect the rheological properties of HA compositions

79. Chemical interactions such as hydrogen bonding, ionic interactions, and other non-covalent forces also play important roles in the rheological behavior, and ultimately clinical performance, of crosslinked HA filler compositions. (*See, e.g.*, Ex. 2015 at 7-9, 79-95; Ex. 2100 at 43:11-16 ("Q. And those bonds, whether they're covalent or non-covalent, they can have significant impact on how the molecules interact with each other; is that right? A. They can -- they can.").) These chemical interactions are affected by HA concentration, molecular weight, ionic strength, identity of the counterion, pH, and chemical modifications such as crosslinking, among several other factors. (*See, e.g.*, Ex. 2015 at 7-10, 55-63, 79-95; Ex. 2068 at 43.) In my opinion, Dr. DeVore downplayed the significance of such non-covalent interactions in his declaration.

Source: Ex. 2013 at ¶ 79; POR at 40; Surreply at 14.

DR. DEVORE: DESIGNING DERMAL FILLERS IS "FORMIDABLE"



US009352046B2

(12) **United States Patent**
Voigts et al.

(10) **Patent No.: US 9,352,046 B2**
(45) **Date of Patent: May 31, 2016**

(54) **IMPLANTATION COMPOSITIONS FOR USE IN TISSUE AUGMENTATION**

(71) Applicant: **MERZ NORTH AMERICA, INC.**, Greensboro, NC (US)

(72) Inventors: **Robert Voigts**, Windlake, WI (US); **Dale Devore**, Chelmsford, MA (US)

(73) Assignee: **MERZ NORTH AMERICA, INC.**, Greensboro, NC (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.

(21) Appl. No.: **14/269,466**

(22) Filed: **May 5, 2014**

(65) **Prior Publication Data**

US 2014/0378549 A1 Dec. 25, 2014

Related U.S. Application Data

(60) Continuation of application No. 13/924,240, filed on Jun. 21, 2013, now abandoned, which is a division of application No. 12/521,947, filed as application No. PCT/US2007/017131 on Jul. 31, 2007, now abandoned, which is a continuation-in-part of application No. 11/671,696, filed on Jan. 8, 2007, now abandoned, which is a continuation-in-part of application No. 11/368,028, filed on Feb. 6, 2006, now abandoned.

(51) **Int. Cl.**

A61K 2/00	(2006.01)
A61K 31/715	(2006.01)
A61N 37/18	(2006.01)
A61K 31/56	(2006.01)
A61K 31/043	(2006.01)
A61K 47/38	(2006.01)
A61L 27/20	(2006.01)

(Continued)

(52) **U.S. Cl.**
CPC ***A61K 47/38*** (2013.01); ***A61K 31/167*** (2013.01); ***A61K 47/02*** (2013.01); ***A61K 47/10*** (2013.01); ***A61L 26/023*** (2013.01); ***A61L 27/20*** (2013.01); ***A61L 27/50*** (2013.01); ***C08L 1/286*** (2013.01); ***A61L 2400/06*** (2013.01); ***A61L 2430/34*** (2013.01)

(58) **Field of Classification Search**
CPC A61K 47/38
USPC 525/13
See application file for complete search history.

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(Continued)

Primary Examiner — David Karst
(74) *Attorney, Agent, or Firm* — Riesenhen and Sage

(57) **ABSTRACT**

A composition of matter and method for preparation of a tissue augmentation material. A polysaccharide gel composition is prepared with rheological properties selected for a particular selected application. The method includes preparing a polymeric polysaccharide in a buffer to create a polymer solution or gel suspending properties in the gel and selecting a rheology profile for the desired tissue region.

12 Claims, 40 Drawing Sheets

Prollenium v. Allergan
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1 of 66

ALL 2128
PROLLENIUM V. ALLERGAN
IPR2019-01505 et al.

Inventors: **Robert Voigts**, Windlake, WI (US); **Dale Devore**, Chelmsford, MA (US)

Related U.S. Application Data

Continuation of application No. 13/924,240, filed on Jun. 21, 2013, now abandoned, which is a division of application No. 12/521,947, filed as application No. PCT/US2007/017131 on Jul. 31, 2007,

30 As can be concluded from consideration of the prior art, rheological and chemical properties of the implant involve many complex factors. As such, one can vary each of those components of the implant in order to design an implant with specific controlled in vivo properties. Such degrees of free-
35 dom are in fact so large and complex that designing the proper implant is a formidable task.

Source: Ex. 2128 at 6:30-36; Ex. 2100 at 200:8-203:21; POR at 5.

DR. DEVORE: MAKING DERMAL FILLERS IS UNPREDICTABLE

Q And you would agree that there is unpredictability involved in making an HA soft tissue filler, correct?

A There's generally unpredictability for any new product.

Q And that's true with HA soft tissue fillers, correct?

A Correct.

Q But you would agree, as written here, that differences in the various factors that go into designing a dermal filler make the analysis of the optimization of the filler composition and properties difficult to achieve?

A Yeah, I'll agree.

A That's why this is not something you simply take out of a recipe book and make. You have to do the testing and evaluation.

Source: Ex. 2100 at 103:20-104:4; 158:16-24; 367:18-21; POR at 27, 47.

DR. PRESTWICH: CREATING STABLE HA HYDROGELS IS CHALLENGING

"The creation of stable hydrogels from HA is challenging. Conditions can be selected that result in hydrogels with different physical properties and rates of gelation. The important parameters include pH, concentration and nature of metal ions present, ratios of HA to ECDI to linker, chemical nature of linker, nature and concentration of buffer, and molecular size range and concentration of HA."

Source: Surreply at 19; Ex. 2200 at 461:22-463:6.

DR. BERKLAND: POST-CROSSLINKING STEPS FURTHER AFFECT GEL PROPERTIES

3. Post-crosslinking processing affects the rheological properties of HA compositions

88. The way that crosslinked HA gel is treated after the crosslinking reaction, or is combined with other components to result in a dermal filler composition, may additionally impact the filler's rheological properties. (Ex. 2100 at 115:25-116:3.) A skilled artisan could, for example, isolate the HA gel by precipitation followed with rehydration, physically break up pieces of insoluble crosslinked HA, sieve the pieces, add soluble free HA of different molecular weights and concentrations, adjust ionic strength, change pH, add salts and other ions, add uncharged small molecules such as sucrose, and alter any number of other parameters that can affect the rheological characteristics of the HA composition. (*See, e.g.*, Ex. 1030 at ¶¶ [0085]-[0090].)

Source: Ex. 2013 at ¶ 88; POR at 11-12.

DR. BERKLAND: HEAT STERILIZATION DRAMATICALLY IMPACTS GEL PROPERTIES

94. Autoclave sterilization of HA fillers—*i.e.*, sufficient heating in an autoclave to destroy harmful microorganisms and spores[10]—can alter the filler's rheological properties because high heat accelerates chemical and physical degradation of HA polymers. (Ex. 2015 at 41; *accord* Ex. 2128 at 19:18-26 (high sterilization temperatures cause a "breakdown of polymeric chain" in CMC gels which has "an effect on the rheological parameters").) Unpredictable rheological changes caused by heat sterilization have to be considered in pre-sterilization processing steps, and dealt with in order to arrive at an dermal filler composition having clinically acceptable characteristics. (Ex. 1048 at 3:52-65 ("The effect of the heat treatment on specific polymers is *generally not predictable in advance*, and is based on such factors as the relative degree of cross-linking." (emphasis added)).)

Source: Ex. 2013 at ¶ 94; POR at 12-13.

PRIOR ART: HEAT STERILIZATION DRAMATICALLY IMPACTS GEL PROPERTIES

In one aspect of this embodiment, the properties of the gel are modified by subjecting the gel to heat treatment at a temperature in the range of from about 100° C. to about 150° C. Heat treatment has the effect of modifying the properties of the gel, such as its viscosity. The effect of the heat treatment on specific polymers is generally not predictable in advance, and is based on such factors as the relative degree of cross-linking. Heat treatment of a gel material can be employed to alter the final viscosity of the gel by either causing more polymer to dissolve in solution, which tends to increase the viscosity, or by reducing the molecular weight of the polymer, which tends to reduce the viscosity. Thus,

2.3.6 Heat Degradation

It is well known that HA, especially when in the form of an aqueous solution, cannot withstand elevated temperatures for any significant amount of time. Many have observed the dramatic decrease of viscosity of HA solutions when subjected to conditions of autoclaving (e.g., 121°C for 12 minutes). The degradation product shows a strong UV absorbance at 232 nm, strongly indicating the breaking of glycosidic bonds through elimination reaction and the formation of α, β unsaturated carboxylate.

Source: Ex. 1048, 3:52-62; Ex. 2015 at 41; POR at 12-13.

CUI: HEAT STERILIZATION DRAMATICALLY IMPACTS BDDE-CROSSLINKED HA GELS

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Exhibit A

The comparison of physicochemical properties of four Cross-linked sodium hyaluronate gels with different cross-linking agents

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[d]zylzhao@yahoo.com.cn, [e]17575528@qq.com,[f]82434853@qq.com

Keywords: cross-linked sodium hyaluronate gels, different cross-linking agents, dynamic viscosity, intrinsic viscosity, enzyme-resistant degradation properties *in vitro*

Abstract: Purpose The physicochemical properties of four cross-linked sodium hyaluronate gels (CHA) with different cross-linking agents were compared in order to research out the different stability and Enzyme-resistant degradation properties of these CHA gels. **Methods** The CHA hydrogels were prepared with different cross-linking agents, such as PEG20000, PDE, BDDE and ADH. The optimal reaction conditions were determined by single factor experiment. Dynamic viscosity was tested by Stabinger method. Intrinsic viscosity was determined by Uzziah's viscosity method. The enzyme-resistant degradation properties *in vitro* of CHA-gels were analysed by carbazole and spectrophotometry. **Results** The concentrations of NaOH/HCl, concentrations of HA and the ratio of cross-linking agent to HA are major factors of conditions which influenced the physicochemical properties of CHA gels. PDE-CHA and PEG20000-CHA gels possess better Dynamic viscosity, PDE-CHA gel has also better intrinsic viscosity, ADH-CHA and BDDE-CHA BDDE were compared in this paper.

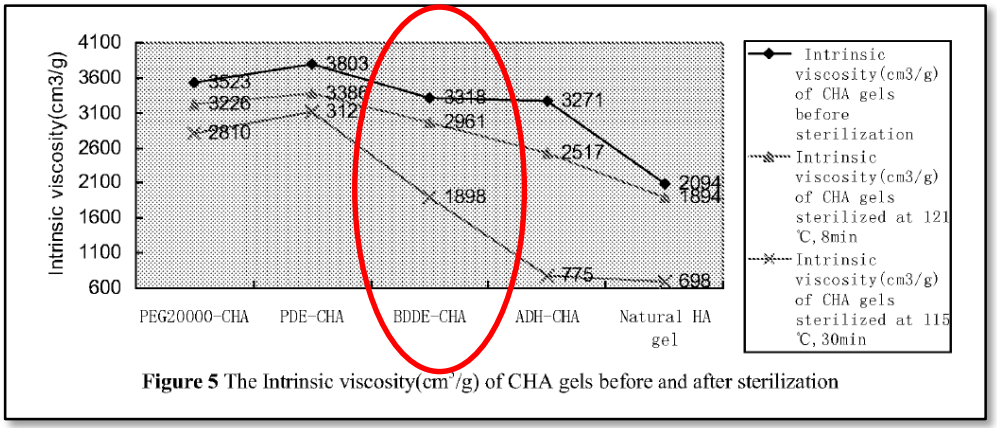


Figure 5 The Intrinsic viscosity(cm^3/g) of CHA gels before and after sterilization

Abstract: Purpose The physicochemical properties of four cross-linked sodium hyaluronate gels (CHA) with different cross-linking agents were compared in order to research out the different stability and Enzyme-resistant degradation properties of these CHA gels. **Methods** The CHA hydrogels were prepared with different cross-linking agents, such as PEG20000, PDE, BDDE and ADH. The optimal reaction conditions were determined by single factor experiment. Dynamic viscosity was tested by Stabinger method. Intrinsic viscosity was determined by Uzziah's viscosity method. The enzyme-resistant degradation properties *in vitro* of CHA-gels were analysed by carbazole and spectrophotometry. **Results** The concentrations of NaOH/HCl, concentrations of HA

Source: Ex. 1025 at 1506, 1510; Ex. 2013, ¶¶ 192-194; POR at 13, 32.

DR. BERKLAND: CHANGES IN pH CAN DESTABILIZE HA POLYMERS

Dr. Berkland's declaration:

99. The rate of HA hydrolysis accelerates under both basic and acidic conditions. (*See, e.g.*, Ex. 1056 at 543; Ex. 2015 at 34-37; Ex. 2100 at 73:16-18, 74:10-16.) "[E]ven short-term treatment of HA polymers at acidic or alkaline conditions can result in degradation . . . ." (Ex. 1056 at 543.) Although dramatic pH effects on hydrolysis of HA are observed mostly at below pH 4 and above pH 10, the impact of pH on hydrolysis rate can be significant even at more modest deviations around a neutral pH of 7, especially at higher temperatures.

The rate of the hydrolytic degradation of HA in aqueous solution is strongly dependent on pH. Table 1 shows the pH dependence of k_h at 40°C and 60°C. It is clear that HA is most stable at pH values around neutrality and more labile in acidic conditions than basic conditions. In addition, HA is less stable at higher temperature.

Moreover, even short-term treatment of HA polymers at acidic or alkaline conditions can result in degradation, including "peeling" from the reducing end and β-elimination, characteristic for the uronic acid-containing poly- and OSs (Kiss, 1974).

Source: Ex. 2038 at 270; Ex. 1056 at 543; Ex. 2013 at ¶¶ 99, 105-11; POR at 13-15; Surreply at 13.

DR. BERKLAND: THE COMBINATION OF LIDOCAINE AND HEAT CREATES ADDITIONAL COMPLEXITY AND INSTABILITY

178. The use of lidocaine HCl in HA-based dermal filler compositions acidifies the HA solution, promoting hydrolysis of the HA. (*See supra* ¶¶ 106-109.) Heating the composition with lidocaine and HA further acidifies the solution, accelerating the hydrolysis and compounding the degradation with thermal degradation as well. (*See supra* ¶ 100, 109.) A skilled artisan would therefore understand that a composition of lidocaine HCI and HA will experience multiple forms of chemical degradation at elevated autoclaving temperatures,

179. A skilled artisan also would be keenly aware that chemical degradation of HA by hydrolysis and thermal degradation can significantly impact an HA composition's rheological properties, including causing a decrease in viscosity, because of the associated decrease in molecular weight of the HA polymer chains. (*See supra* ¶¶ 103-104, 109.) This, in turn, affects its properties as a dermal filler. (*See* Ex. 2068 at 53 ("The importance of high molecular weight to the matrix forming properties of [HA], and, consequently, to its ability to form a smoothening viscoelastic matrix on the surface of skin is widely acknowledged.").)

Source: Ex. 2013 at ¶¶ 178-79; POR at 13-15.

DR. PRESTWICH: LIDOCAINE "MAY RESULT IN MORE HA DEGRADATION DURING AUTOCLAVING"

Dr. Prestwich's declaration contradicts his testimony on cross-examination:

Dr. Prestwich's declaration:

11. Lidocaine was known to stabilize HA compositions

172. I am not aware of any teaching from the scientific literature that lidocaine would destabilize crosslinked HA or uncrosslinked HA, either during autoclaving or when stored at room temperature. Indeed, the notion that lidocaine would destabilize HA products is counterintuitive to the POSITA familiar with HA products, including their preparation, sterilization, and storage.

Dr. Prestwich's deposition on adding lidocaine:

"This may result in more HA degradation during autoclaving, because it was known that low pH conditions and/or high temperature conditions cause degradation of HA."

That is what you wrote here, right?

A. Yes. That's correct -- that's what I wrote.

"This indicates that upon an increase in temperature, the pH of lidocaine-containing solution would be expected to decrease."

That's what you told the patent office in this paragraph, right?

A. Yes. That's what I understood to be the case at the time.

Source: Ex. 1105 at ¶ 172; Ex. 2200 at 191:7-16, 193:20-194:3; Surreply at 13-14.

DR. DEVORE: HEAT AND ACIDITY (FROM LIDOCAINE) DEGRADE HA

Q So at elevated temperatures, putting an equal amount of lidocaine hydrochloride salt into a solution as compared to room temperature, for example, is going to result in a solution that's even more acidic, correct?

A Yeah, I believe that's correct, more acidic.

The more acidic it is, the more degradation you're going to get?

A Correct.

Q And you would agree with me that temperature can affect the polysaccharide chains of HA when it's in solution, correct?

A Correct.

Q The colder the temperature, the more stable it is. The higher the temperature, the less stable it is?

A Correct.

Source: POR at 13-15, 31-33; Ex. 2100, 73:16-18; 76:10-17, 361:6-15.

DR. BERKLAND: LIDOCAINE HAS BEEN SHOWN TO INTERACT WITH HA, RESULTING IN A "STRONG DELAY EFFECT"

87. With respect to interactions between HA and lidocaine specifically, U.S. Patent Publication No. 2006/0122147 shows that when lidocaine is mixed with HA, lidocaine's ability to release from the solution is "reduced considerably." (Ex. 2046 at ¶ [0040].) Specifically, the reference reports that "the mechanism of the interaction between lidocaine and hya[luronic acid] is based on incorporation of lidocaine in the helix-like col of the hya. But also at pH values between 6.9 and 7.7, a strong reduction in lidocaine flux can be observed. This confirms that also ionic bonds and interaction between lidocaine and hya are involved." (*Id.*) And the reference concludes that "a strong delay effect with respect to the release of the lidocaine from the lidocaine-hya complex can be achieved. As a result, the effect of the lidocaine in biological systems (e.g., in the knee joint) can be considerably extended." (*Id.* at ¶ [0042]; *see also* Ex. 1030 at ¶ [0107] (describing a "synergistic effect" between lidocaine and pBCDI-crosslinked HA).)

[0040] With reference to the results which were obtained in the dialysis cell, it was shown that the flux of the lidocaine through this pore membrane was reduced considerably in the presence of the hya in the donor compartment. The most pronounced is the effect at pH=9.0, there lidocaine is present extensively undissociated. This confirms the results which were described in Example 3 that the mechanism of the interaction between lidocaine and hya is based on incorporation of the lidocaine in the helix-like coil of the hya. But also at pH values between 6.9 and 7.7, a strong reduction in the lidocaine flux can be observed. This confirms that also ionic bonds and the interaction between lidocaine and hya are involved.

Source: Ex. 2013, ¶ 87; Ex. 2046, ¶¶ 40, 42; POR at 50.

DR. BERKLAND: BUFFER IS NOT "SUFFICIENT TO PREVENT SIGNIFICANT VISCOSITY LOSS" AND INTRODUCES MORE COMPLEXITY

190. I disagree with Dr. DeVore that Sample 3 is not evidence of unexpected results, simply because a skilled artisan would be motivated to use a "physiological" pH. (IPR2019-01617, Ex. 1002 at ¶ 211.) First, data in Example 4 shows that pH adjustment is not always sufficient to prevent significant viscosity loss. (*Supra* Table 1 (Samples 1 and 2).) Second, a skilled artisan would appreciate that adjusting pH to neutralize the acidifying effect of lidocaine HCl in a complex HA composition would lead to a cascade of unpredictable, interrelated changes to various physical and rheological properties. (*See supra* ¶ 110.) For example, adding a base such as sodium hydroxide not only raises pH, but also increases ionic strength and osmolarity; both are factors that affect the rheological properties of HA compositions. (*Id.*) Moreover, the choice of base used to raise the pH affects rheology. (*Id.*; *see also* Ex. 2018 at 180.) And if the base selected is not fully dissociated at the relevant pH, its dissociation equilibrium would also affect the osmolarity and ionic strength of the composition. (*See supra* ¶ 110.) Third, a skilled artisan would recognize that increasing the pH of a lidocaine-containing composition increases the risk of precipitating lidocaine free base. (Ex. 2023 at 171.) An increase in pH could thus affect "free release" of the lidocaine or make the composition cloudy and unfit for use in patients. (Ex. 2043 at 936-37;

Source: Ex. 2013 at ¶ 190; POR at 34.

pH ADJUSTMENT IS NOT SUFFICIENT TO PREVENT SIGNIFICANT VISCOSITY LOSS

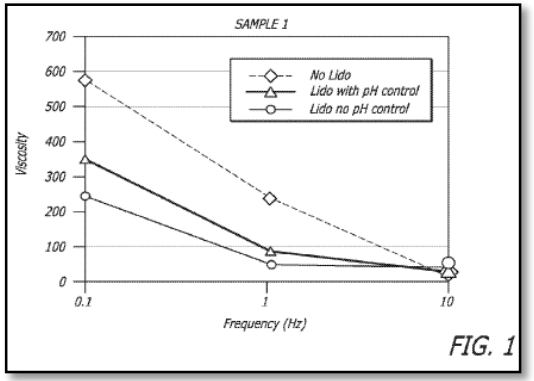


FIG. 1

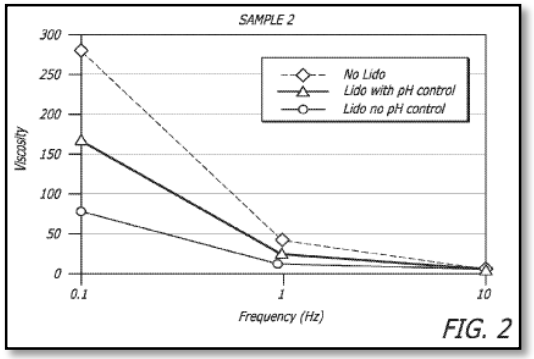


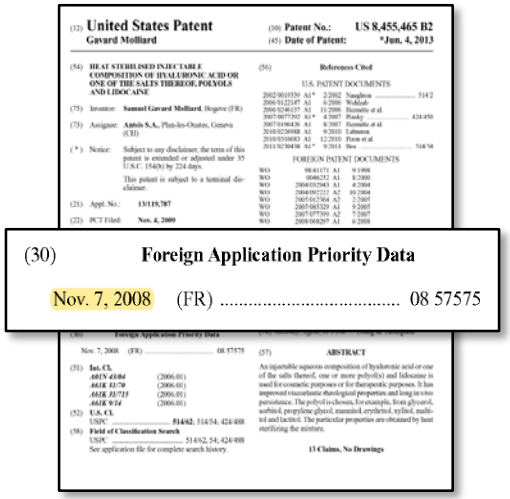
FIG. 2

Sample	Identity [Name] *Description*	Test 3 ("No lido")	Test 2 ("Lido with pH control")	Test 1 ("Lido no pH control")
		Viscosity		
1	free HA mixture 13.5 mg/g, with hydroxyl propyl methyl cellulose (HPMC) 5.5 mg/g [Rhexeal] *No description provided*	574	347 (-40%)	244 (-57/60%)
2	5.5-6.5 mg/mL of high molecular weight HA (about 4-6 MDa) [Hylaform] *Particulate*[20]	280	166 (-41%)	77 (-73/73%)
3	non-commercial gel made of distinct gel particles mixed with free HA (80/20, w/w) [SKGel; "similar to the gel having commercial name RESTYLANE"] *Distinct gel particles*	85	95 (+12%)	52 (-39/35%)
4	crosslinked HA formulation with an HA concentration of about 18 mg/mL, less than 6% crosslinking [Juvéderm Refine] *Cohesive*	14.6	13.4 (-8/4%)	10 (-32/30%)
5	crosslinked HA formulation with an HA concentration of about 24 mg/mL, about 6% crosslinking [Juvéderm Ultra Plus] *Cohesive*	100	112 (+12/9%)	99 (-1/0%)
6	crosslinked HA formulation with an HA concentration of about 20 mg/mL, about 5% crosslinking [Juvéderm Ultra Plus] *Cohesive*	417	402 (-4/2%)	363 (-13/13%)

Berkland Declaration, Table 1

Source: Ex. 1001, Figs. 1 and 2; Ex. 2013 at ¶185; POR at 34.

CONTEMPORANEOUS REFERENCES APPRECIATED THE INCLUSION OF LIDOCAINE AFFECTS GEL PROPERTIES



(12) **United States Patent**
Gavard Molliard

(10) **Patent No.: US 8,455,465 B2**
(45) **Date of Patent: *Jun. 4, 2013**

(54) **HEAT STERILISED INJECTABLE COMPOSITION OF HYALURONIC ACID OR ONE OF THE SALTS THEREOF, POLYOLS AND LIDOCAINE**

(75) Inventor: **Samuel Gavard Molliard**, Bogève (FR)

(73) Assignee: **Anteis S.A.**, Plan-les-Ouates, Geneva (CH)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 224 days.

This patent is subject to a terminated disclaimer.

(21) Appl. No.: **13/119,707**

(22) PCT Filed: **Nov. 4, 2009**

(56) **References Cited**

U.S. PATENT DOCUMENTS

FOREIGN PATENT DOCUMENTS

(30) **Foreign Application Priority Data**

Nov. 7, 2008 (FR) 08 57575

(51) **Int. Cl.**
A61K 47/04 (2006.01)
A61K 31/70 (2006.01)
A61K 31/725 (2006.01)
A61K 9/14 (2006.01)

(52) **U.S. Cl.**
USPC **514/62**; 514/54; 424/488

(58) **Field of Classification Search**
USPC 514/62, 54; 424/488
See application file for complete search history.

(57) **ABSTRACT**

An injectable aqueous composition of hyaluronic acid or one of the salts thereof, one or more polyol(s) and lidocaine is used for cosmetic purposes or for therapeutic purposes. It has improved viscoelastic rheological properties and long in vivo persistence. The polyol is chosen, for example, from glycerol, sorbitol, propylene glycol, mannitol, erythritol, xylitol, maltitol and lactitol. The particular properties are obtained by heat sterilizing the mixture.

13 Claims, No Drawings

SUMMARY OF THE INVENTION

It has now been discovered that the addition of a polyol and of lidocaine to a gel based on hyaluronic acid, regardless of whether it is noncrosslinked or crosslinked, grafted or non-grafted, or crosslinked and grafted, followed by heat-sterilization of this formulation, makes it possible to obtain (compared with a polyol-free and lidocaine-free gel):

- a very large improvement in the rheological properties of the gel,
- an improvement in the persistence of the gel by countering the three major types of degradation of a hyaluronic acid-based gel in vivo (enzymatic degradation by hyaluronidases, free-radical degradation, thermal degradation at 37° C.),
- an improvement in the rheological stability of the gel over time and therefore a product shelf-life that may be extended.

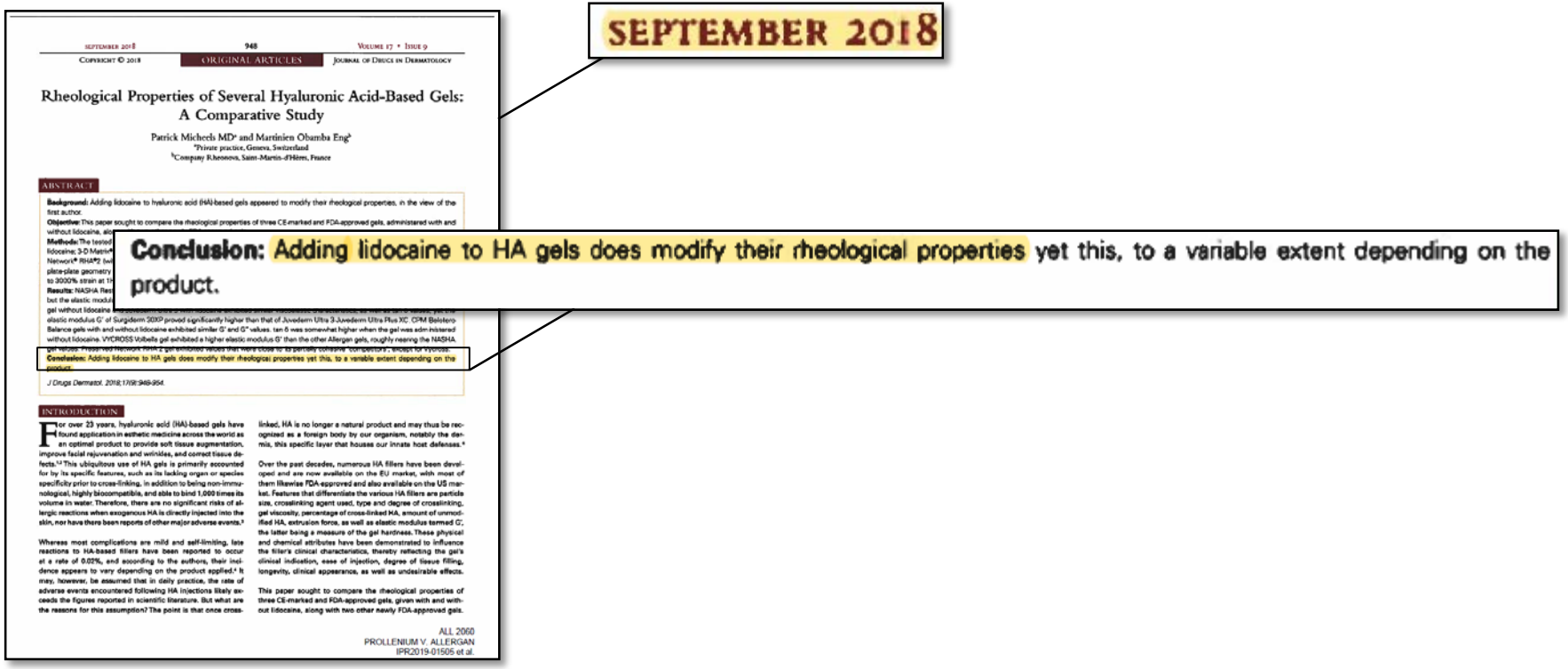
It has in fact been shown that, entirely surprisingly, the addition of one or more polyol(s) and of lidocaine to a hyaluronic acid-based gel:

- does not modify the rheological properties of the gel before heat sterilization,
- considerably modifies the rheological properties of the gel after heat sterilization (compared with a polyol-free and lidocaine-free gel).

Without wishing to be bound to a theoretical explanation of the effect of the polyol and of the lidocaine against the degradations of a hyaluronic acid-based gel, it is assumed that the lidocaine considerably increases the ability of a polyol to protect a hyaluronic acid-based gel.

Source: Ex. 2067, 2:30-53, 3:28-32; POR at 33.

THE ART STILL APPRECIATES THE INCLUSION OF LIDOCAINE AFFECTS GEL PROPERTIES



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Rheological Properties of Several Hyaluronic Acid-Based Gels: A Comparative Study

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[a]Private practice, Geneva, Switzerland
[b]Company Rheonova, Saint-Martin-d'Hères, France

ABSTRACT

Background: Adding lidocaine to hyaluronic acid (HA)-based gels appeared to modify their rheological properties, in the view of the first author.

Objective: This paper sought to compare the rheological properties of three CE-marked and FDA-approved gels, administered with and without lidocaine, also

Methods: The tested lidocaine; 3-D Matrix Network® RHA®2 (wi plate-plate geometry to 3000% strain at 1

Results: NASHA Res but the elastic modulu gel without lidocaine elastic modulus G' of Surgiderm 30XP proved significantly higher than that of Juvederm Ultra 3-Juvederm Ultra Plus XC. CPM Belotero Balance gels with and without lidocaine exhibited similar G' and G" values. tan δ was somewhat higher when the gel was administered without lidocaine. VYCROSS Vitbella gel exhibited a higher elastic modulus G' than the other Allergan gels, roughly nearing the NASHA gel values. Hyaluronic Acid's gel exhibited values that were close to, but generally lower than, those for Vycross.

Conclusion: Adding lidocaine to HA gels does modify their rheological properties yet this, to a variable extent depending on the product.

J Drugs Dermatol. 2018;17(9):948-954.

INTRODUCTION

For over 23 years, hyaluronic acid (HA)-based gels have found application in esthetic medicine across the world as an optimal product to provide soft tissue augmentation, improve facial rejuvenation and wrinkles, and correct tissue defects.[1,2] This ubiquitous use of HA gels is primarily accounted for by its specific features, such as its lacking organ or species specificity prior to cross-linking, in addition to being non-immunological, highly biocompatible, and able to bind 1,000 times its volume in water. Therefore, there are no significant risks of allergic reactions when exogenous HA is directly injected into the skin, nor have there been reports of other major adverse events.[3]

Whereas most complications are mild and self-limiting, late reactions to HA-based fillers have been reported to occur at a rate of 0.02%, and according to the authors, their incidence appears to vary depending on the product applied.[4] It may, however, be assumed that in daily practice, the rate of adverse events encountered following HA injections likely exceeds the figures reported in scientific literature. But what are the reasons for this assumption? The point is that once cross-linked, HA is no longer a natural product and may thus be recognized as a foreign body by our organism, notably the dermis, this specific layer that houses our innate host defenses.[4]

Over the past decades, numerous HA fillers have been developed and are now available on the EU market, with most of them likewise FDA-approved and also available on the US market. Features that differentiate the various HA fillers are particle size, crosslinking agent used, type and degree of crosslinking, gel viscosity, percentage of cross-linked HA, amount of unmodified HA, extrusion force, as well as elastic modulus termed G', the latter being a measure of the gel hardness. These physical and chemical attributes have been demonstrated to influence the filler's clinical characteristics, thereby reflecting the gel's clinical indication, ease of injection, degree of tissue filling, longevity, clinical appearance, as well as undesirable effects.

This paper sought to compare the rheological properties of three CE-marked and FDA-approved gels, given with and without lidocaine, along with two other newly FDA-approved gels.

Source: Ex. 2060 at Abstract; POR at 14.

THE BOARD SHOULD NOT RELY ON DR. DEVORE AS IT DID IN THE INSTITUTION DECISION

DR. DEVORE ADMITTED HE IMPROPERLY USED HINDSIGHT

Q So if we -- if we think about the claim like a puzzle with different pieces in it, you went and found each of the pieces of that puzzle in individual prior art references, correct?

A Again, I believe that's correct.

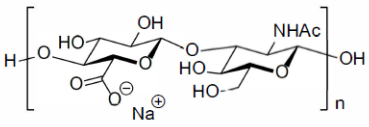
Source: Ex. 2100 at 371:24-372:5; POR at 28-29.

DR. DEVORE AGREES THAT KNOWLEDGE OF CHEMICAL STRUCTURES AND HOW THEY INTERACT IS IMPORTANT . . .

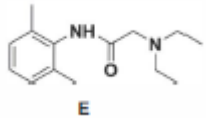
There are no functional groups in lidocaine that would be expected to react with a BDDE-crosslinked HA network or free HA, just like there are no functional groups in a DEO-, DVS-, or BDCI-crosslinked HA composition that react with lidocaine.

Q So in order to provide an opinion with respect to this non-reaction between HA and lidocaine, it's important for you to understand how those chemical structures interact or don't interact with each other, correct?

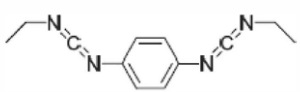
A That's correct.



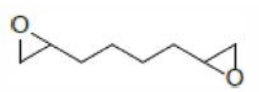
HA - Ex. 2158



Lidocaine - Ex. 2165



pBCDI - Ex. 2156



DEO - Ex. 2152

BDDE - Ex. 2153

Source: Ex. 1002 at ¶ 189; Ex. 2100 at 357:20-358:1; Ex. 2152; Ex. 2153; Ex. 2156, Ex. 2158, Ex. 2165; POR at 29-30.

BUT DR. DEVORE COULD NOT IDENTIFY THE RELEVANT STRUCTURES

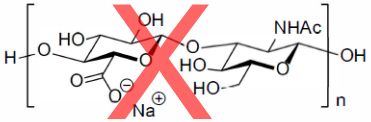
But Dr. DeVore was ***unable*** to identify, for example, the chemical structures for HA, lidocaine, or known crosslinkers, and thus, could not explain the reactions. EX2100, 58:9-59:3 (failed to property identify HA); 358:10-359:13 (failed to properly identify lidocaine); 346:23-349:10 (failed to properly identify BCDI); 354:6-11 (got "DEO and BDDE confused"); EX2155; EX2156; EX2152; EX2153; EX2155; EX2156; EX2158; EX2165; EX2013, ¶¶ 38 n.2, 68 n.8, 105 n.13.

Source: POR at 29-30.

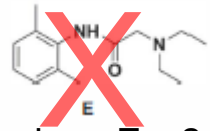
AND DR. DEVORE COULD NOT EXPLAIN THE CORE LIDOCAINE CHEMISTRY AT ISSUE IN THIS CASE

Q So given that you don't know which of these is lidocaine, you're not prepared to answer questions today relating to how the functional groups of these different -- how lidocaine interacts with HA, correct?

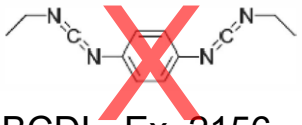
A Correct.



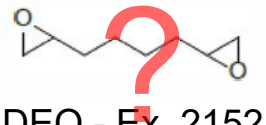
HA - Ex. 2158



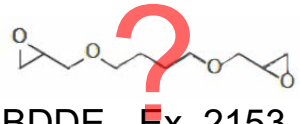
Lidocaine - Ex. 2165



pBCDI - Ex. 2156



DEO - Ex. 2152



BDDE - Ex. 2153

Source: Ex. 2100 at 359:6-13; Ex. 2013 at ¶ 68 n.8; POR at 29-30; Ex. 2152; Ex. 2153; Ex. 2156; Ex. 2158; Ex. 2165.

DR. DEVORE REPEATEDLY MISREPRESENTED HIMSELF AS HAVING DEGREES IN "BIOCHEMISTRY"

PTAB

BIOGRAPHICAL SKETCH

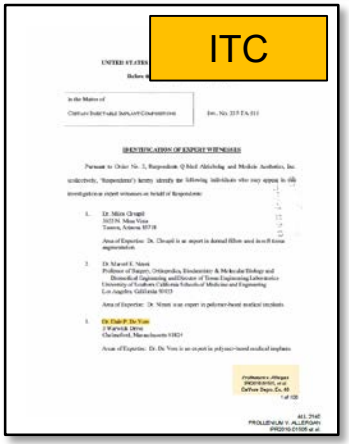
Name: **Dale P. DeVore, PhD**
Executive/Consultant to the Pharmaceuticals/Medical Device/Tissue Engineering Industry

Address: 3 Warwick Drive, Chelmsford, MA 01824

Education:

Rutgers University New Brunswick, NJ	B.S.	Biochemistry
Rutgers University	M.S.	Biochemistry
Rutgers University	Ph.D.	Biochemistry

ITC



D. Ct.

Q And then for your education, you've got your BS, MS, PhD in biochemistry from Rutgers, right?

A Right.

Q And is your CV, does it -- are you aware of any misrepresentations in your CV?

A No.

Q Any -- everything that is in here is truthful; is that right?

A Yes.

Q Sir, your degrees are not in biochemistry, are there?

A Food science and technology.

Source: Ex. 1003 at 3; Ex. 2100 at 48:14-17, 50:9-21; 312:2-4, Ex. 2129; Ex. 2140; POR at 30-31.

MISREPRESENTATION OF CREDENTIALS VIOLATES THE DUTY OF CANDOR

> While the argument may be made that Dr. Konchitsky's description of his Master's degree is merely harmless embellishment or an artful rewording having the same effective meaning, we find that Dr. Konchitsky, nevertheless, incorrectly described his Master's degree and misrepresented his credentials to the Board.

> Moreover, we agree with the sentiment that "[e]ven the slightest accommodation of deceit or a lack of candor in any material respect quickly erodes the validity of the process.

Source: POR at 31; *Blackberry Corp. v. Zipit Wireless, Inc.*, IPR2014–01506, Paper 50 at 10 (PTAB Mar. 29, 2016).

DR. PRESTWICH'S LATE DECLARATION IS PREJUDICIAL AND HE IS UNRELIABLE

DR. PRESTWICH DID NOT KNOW THE IPR GROUNDS

Q. Okay. Do you understand that there is a distinction between what is in the grounds and what other exhibits are being offered?

THE WITNESS: Perhaps, that's a -- that is a legal point that I am not clear on.

Q. Okay. So with respect to all of these exhibits, you are not -- you don't know whether they are just exhibits or whether they formed a part of the grounds that are asso- -- that are asserted by Prollenium. Is that fair?

A. It's my -- it's my understanding that the grounds are listed and that -- for example, in this grounds there are two -- two exhibits -- two exhibits of prior art that are the basis for the grounds.

In this case, we -- we're calling them Kinney and Zhao.

So the other ones are supporting exhibits.

Source: Ex. 2200, 429:10-432:13; Surreply at 6-7.

LARGE PORTIONS OF DR. PRESTWICH'S DECLARATION HAVE ALREADY BEEN CONSIDERED AND REJECTED

Q. Okay. Okay. So, ultimately, I think we discussed yesterday, in both of those cases the Board declined to institute the IPRs. Is that your understanding?

THE WITNESS: That's what I have come to learn subsequently.

Source: Ex. 2200 at 171:16-24; 477:4-12; Surreply at 7-8.

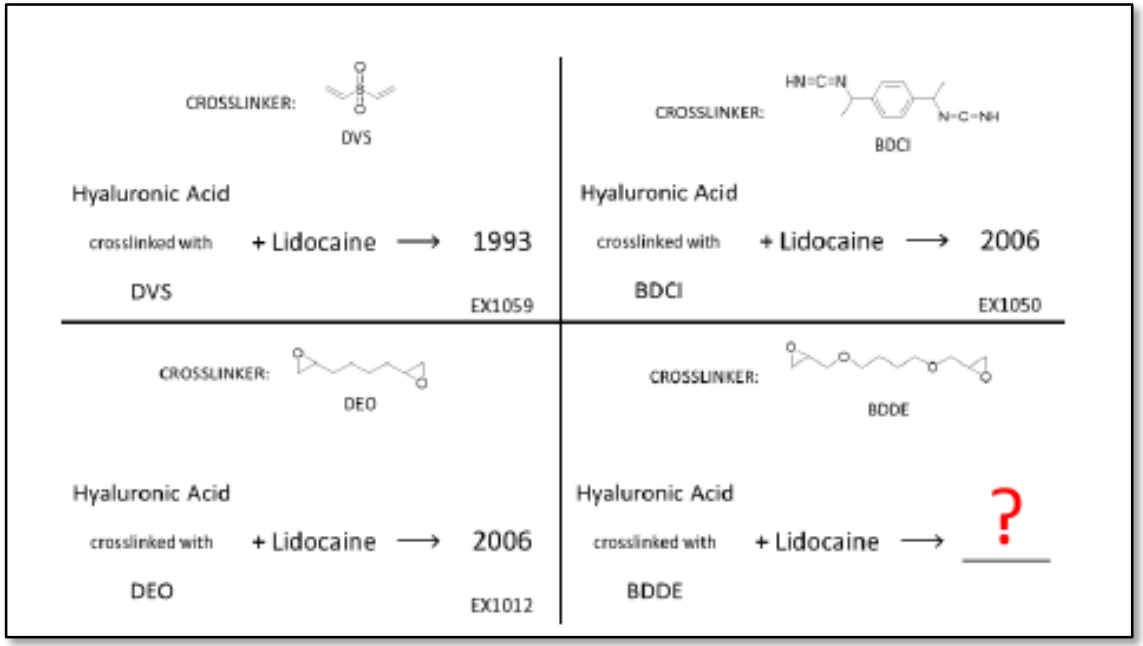
DR. PRESTWICH SELECTIVELY SUBMITTED EVIDENCE AND EXCLUDED RELEVANT PREVIOUS TESTIMONY

Galderma/Teoxane Declarations, ¶ 83	Redline to EX1105, ¶ 176
The pKa of lidocaine is known to be temperature dependent, with a pKa of about 7.9 at room temperature, and a pKa of about 6.6 at 100°C (*Powell*, Table 2). This indicates that upon an increase in temperature, the pH of a lidocaine-containing solution would be expected to decrease. For example, a solution of lidocaine HC1 will become even more acidic at an elevated temperature for autoclaving.	The pK_a of lidocaine is known to be temperature dependent, with a pK_a of about 7.9 at room temperature, ~~and a pKa of~~meaning a 50:50 ratio of lidocaine base (L) and protonated form (LH^+) at room temperature. Dr. Berkland at ¶ 105 (FN 12) and 109 agree with this statement. The pK_a increases to about 6.6 at 100°C (*Powell*, Exhibit 2042, Table 2). ~~This indicates that upon an increase in temperature, the pH of a lidocaine-containing solution would be expected to decrease. For example, a solution of lidocaine HCl will become even more acidic at an elevated temperature for autoclaving.~~

Source: *Compare* Ex. 2200G at ¶83 *with* Ex. 1105 at ¶176; Surreply at 14.

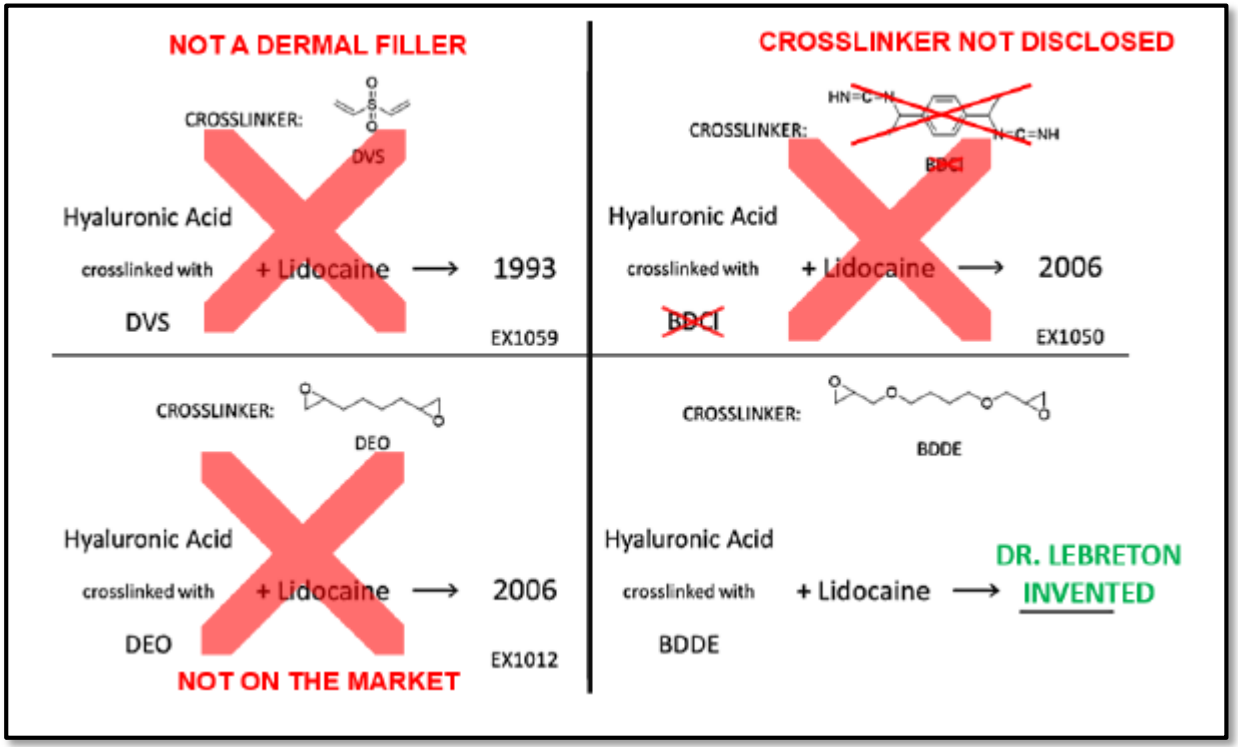
PETITIONER'S FOUR-CROSSLINKER UNIVERSE IS FICTION

PETITIONER'S FOUR-CROSSLINKER-UNIVERSE IS FICTION



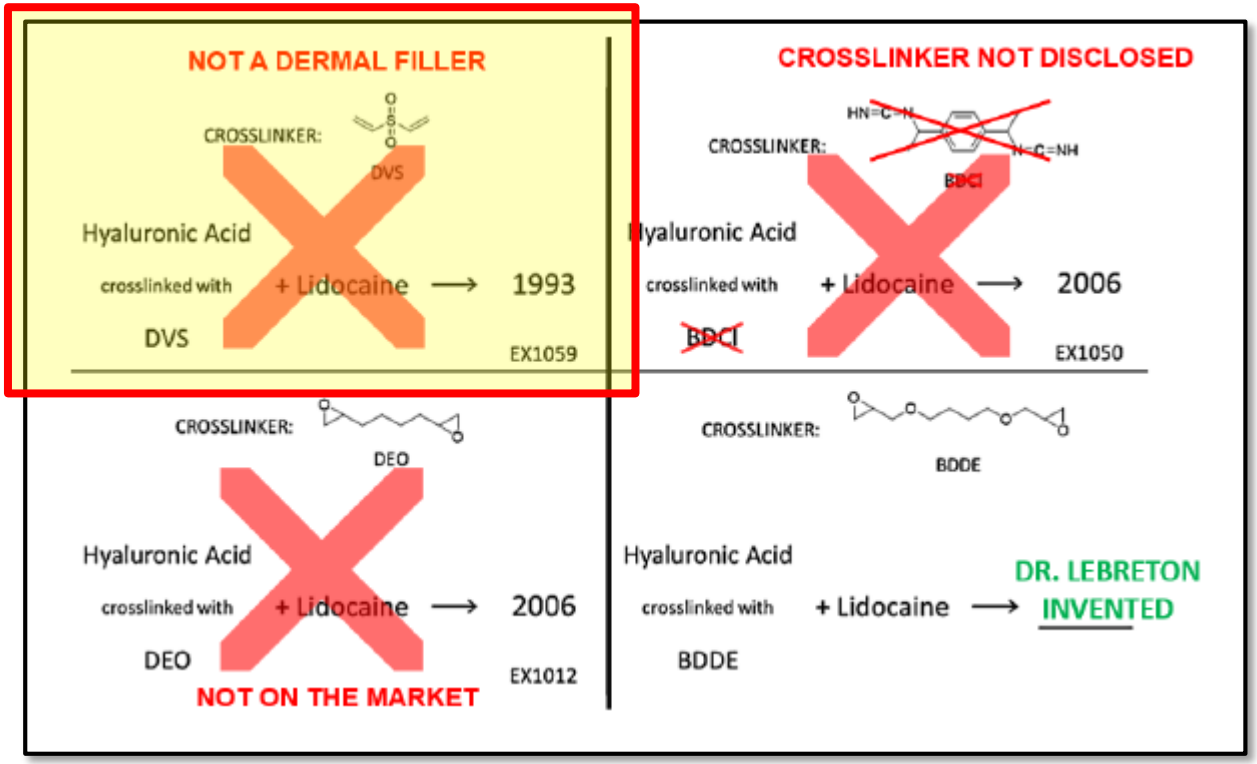
Source: Pet. at 12.

PETITIONER'S FOUR-CROSSLINKER-UNIVERSE IS FICTION



Source: POR at 41-42.

EX. 1059, REINMULLER, DOES NOT DISCLOSE A DVS-CROSSLINKED DERMAL FILLER



Source: POR at 41-42; Ex. 1059.

REINMULLER DOES NOT DISCLOSE A CROSSLINKED DERMAL FILLER WITH LIDOCAINE

EXAMPLE 1

Production of an injectable gel from the following components:

Component	Amount
cross-linked hyaluronic acid ("Hylagel" Biomatrix Co., NJ, USA)	0.004 g
lidocaine hydrochloride	0.02 g
water, purified (DAB 9)	to 1.0 g

Application example 1

The treatment of a ca. 3 cm×5 cm dark-red raised keloid is described which was present on the back of a 30 year old woman after a tangential cut by a broken pane of glass.

The patient complained about itching in the area of the keloid. The keloid was infiltrated with cross-linked hyaluronic acid (Hylon) by injection for a total of four times at intervals of 4 to 8 weeks. The itching had already disappeared a few hours after the first injection. The keloid became considerably paler within two weeks and a flattening was already recognizable after four weeks. After ca. 6 months there was a pale, only slightly raised scar.

Dr. DeVore's testimony:

Q But not as a -- as a dermal filler, correct?

A Correct, it's for treatment of keloids.

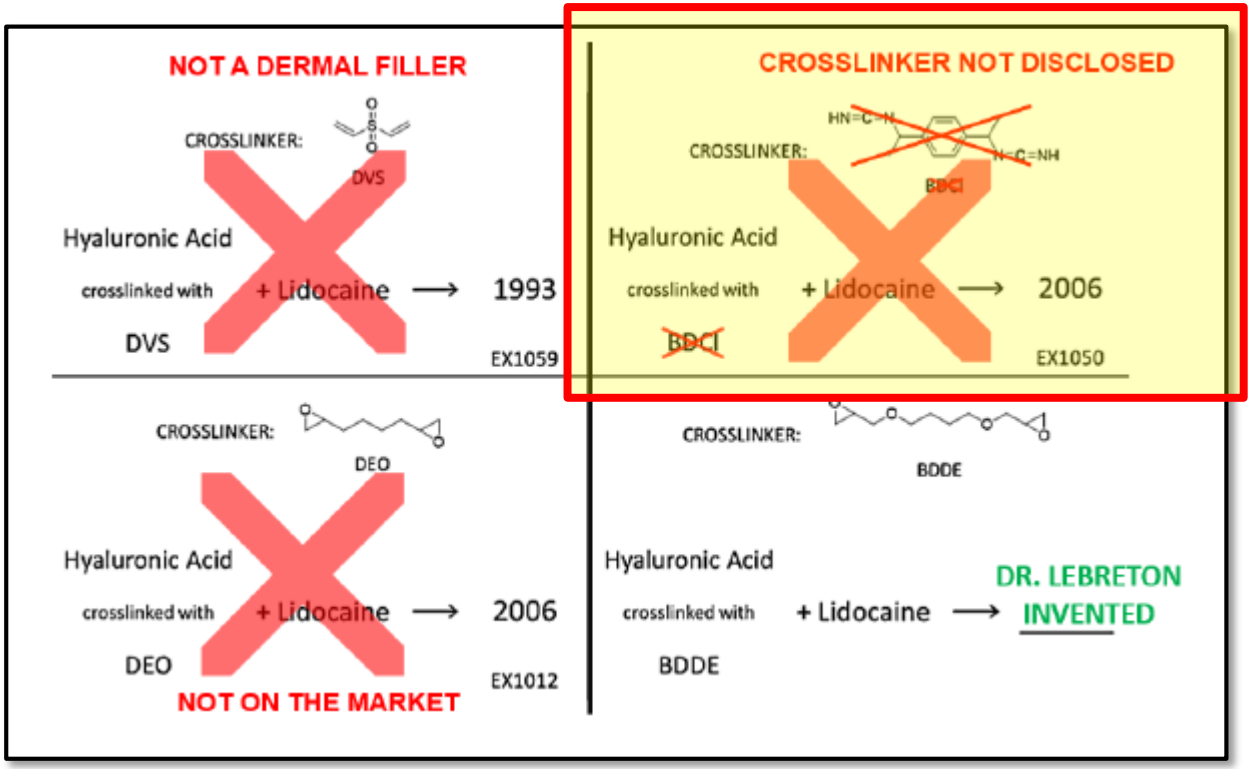
Source: Ex. 1059 at 7:1-29; Ex. 2100 at 438:20-25; POR at 41; -1508 POR at 27-28.

REINMULLER EXCLUDES CROSS-LINKED HA FROM COSMETIC APPLICATIONS

The present invention therefore also concerns the use of the cross-linked glycosaminoglycans described above with the exception of cross-linked hyaluronic acid or cross-linked N-carboxybutylchitosan for cosmetics or as skin care products. In particular the cross-linked glycosaminoglycans that were previously stated as being preferred and distinctively described are used for this.

Source: Ex. 1059 at 6:46-52; -1508 POR at 27.

EX. 1050, THE CTA SUMMARY, DOES NOT DISCLOSE A "BDCI" (pBCDI)-CROSSLINKED DERMAL FILLER



Source: POR at 41-42; Ex. 1050.

THE PETITION RELIES SOLELY ON DR. DEVORE'S PERSONAL KNOWLEDGE TO SHOW THAT ELEVESS WAS pBCDI-CROSSLINKED

-1617 Petition:

> For example, Anika Therapeutics developed a product called Cosmetic Tissue Augmentation Product (CTA), later renamed Elevess, which contained 28 mg/mL BDCI-crosslinked HA suspended in a buffer solution with 0.3% lidocaine. EX1050, 1; EX1002 ¶¶ 115-116.

> Two products had already received FDA approval by the earliest filing date of challenged patent. EX1020, 8 and EX1052 (Prevelle Silk); EX1019, 4 (Anika's Elevess, an implementation of Sadozai; EX1002 ¶ 116).

Dr. DeVore's declaration (¶ 115):

> From 2002-2004, I worked at Anika Therapeutics and was directly involved in the development of the Elevess product as a Technical Consultant and project leader. My responsibilities included coordinating all aspects of product development, manufacturing, preclinical requirements, and regulatory/clinical strategy. As such I have personal knowledge of the Elevess product.

Dr. DeVore's deposition:

> Q Now, you know from your work at Anika that CTA used the cross-linker that you identify as PBDCI; is that right?
>
> A That's right.

Source: Pet. at 11, 28; POR at 41-42; Ex. 1002 at ¶¶ 115-16; Ex. 2100 at 111:21-24.

DUE TO STABILITY PROBLEMS, ELEVESS WAS *NOT* ON THE MARKET AS OF 2008 PRIORITY DATE

As part of the agreement, the Company is working on implementing some product enhancements that address cosmetic issues and the shelf life of the product. These improvements are expected to increase the competitiveness of the product. These product and process modifications require supplements to our PMA and CE Mark approvals, which were filed late in the fourth quarter 2006. Since the modifications do not address safety or efficacy issues, we do not believe additional clinical trials will be required. Currently, Galderma is planning a worldwide launch of the enhanced version of the product in mid-2007. While we have received PMA approval and CE marking for our initial CTA product, it is the enhanced version of this product that Galderma intends to commercialize. We cannot assure you that: (1) we will successfully obtain regulatory approval for sales of ELEVESS in the U.S. or EU; or (2) if regulatory approvals are obtained, meaningful sales of ELEVESS will be achieved.

Do you understand the PMA was approved for a CTA in December of 2006; is that right?

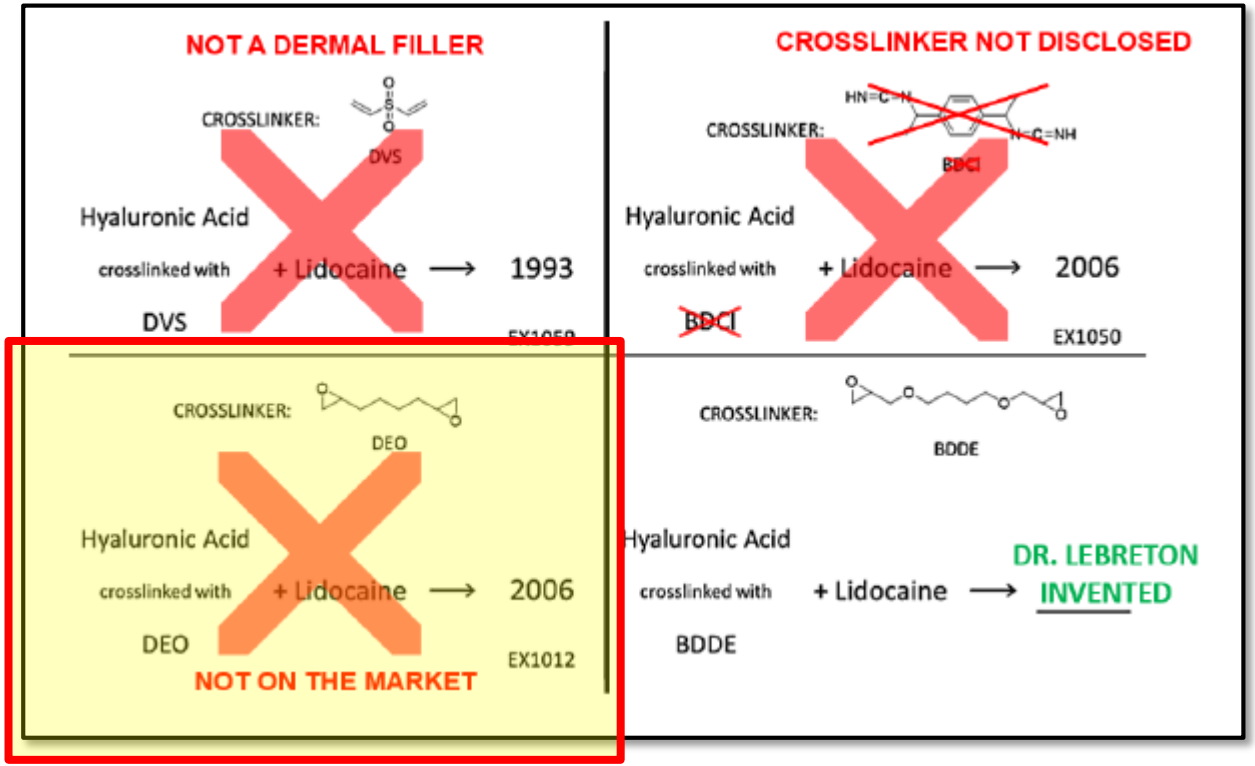
A Yes.

Q But no products under that -- under that PMA number were launched until August 5, 2008, correct?

A That's what I understand.

Source: POR at 42; Ex. 2100 at 236:19-237:3; Ex. 2105 at 5.

EX. 1012, KINNEY, DOES NOT DISCLOSE THE DETAILS OF A DEO-CROSSLINKED DERMAL FILLER



Source: POR at 41-42; Ex. 1012.

THE POSA WOULD HAVE BEEN AWARE OF UNRESOLVED "DIFFICULTIES" WITH PURAGEN PLUS

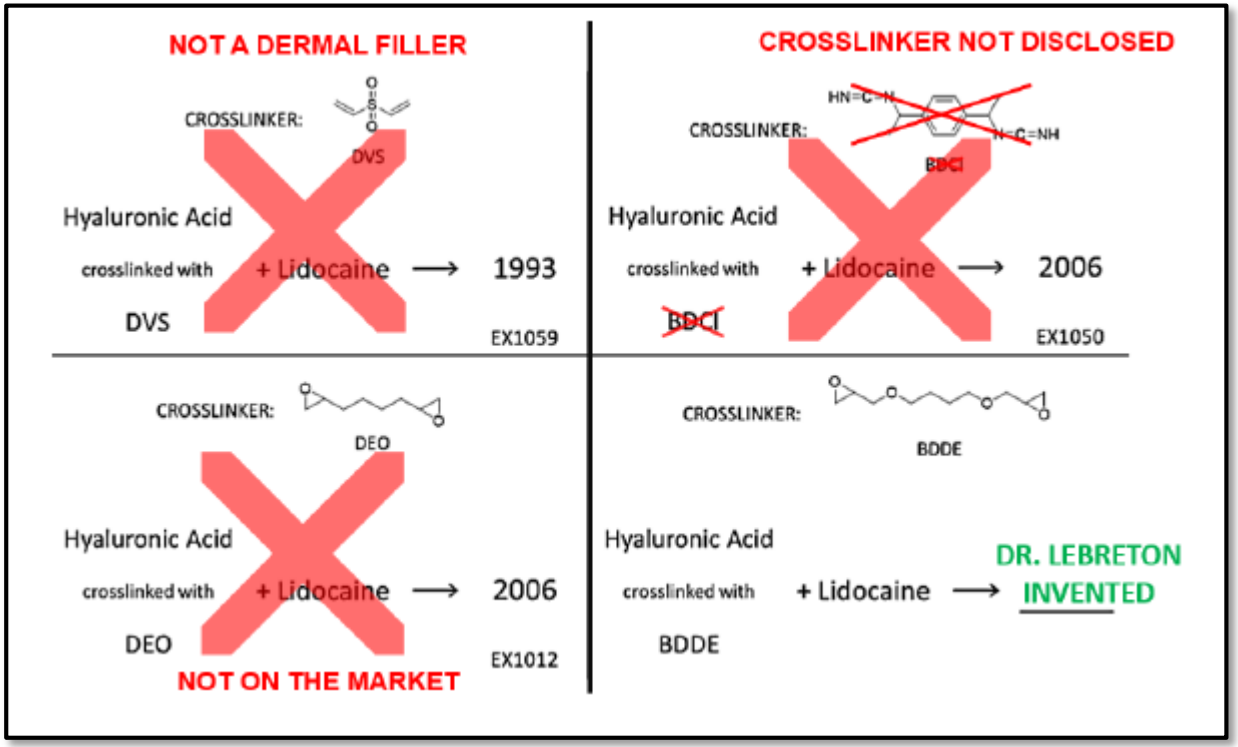
On February 6, 2006, we announced that, with respect to our Puragen Plus™ program in the U.S., we had identified potential issues that required further evaluation of our clinical study data and would result in a delay to our PMA submission timeline. We performed this evaluation, and we concurrently reviewed some of our critical production processes. Based on the results of this evaluation we have developed a plan to move forward with our Puragen Plus™ PMA process, and are targeting to submit the first module to FDA in late summer or early fall this year, and to complete the submission in the spring of 2007.

Q And this would indicate to a POSA as well that Mentor was continuing to have problems with Puragen Plus such that it needed to submit a second module to the FDA, correct?

A It would indicate they're having some difficulties.

Source: Ex. 2100 at 230:5-231:2; Ex. 2137 at 4; POR at 42.

PETITIONER'S FOUR-CROSSLINKER-UNIVERSE IS FICTION



Source: POR at 41-42.

CLAIM CONSTRUCTION

UNDISPUTED CLAIM CONSTRUCTIONS

Term	Relevant IPR	Agreed Construction
sterile	All except -1508	substantially free of detectable, viable microorganisms
stable	All except -1617	a composition that maintains at least one of the following aspects: transparent appearance, pH, extrusion force and/or rheological characteristics, hyaluronic acid (HA) concentration, sterility, osmolarity, and lidocaine concentration
uncrosslinked HA / free HA / soluble form HA	-1505, -1508, -1509, -1617	water soluble HA (i.e., uncrosslinked HA and/or lightly crosslinked HA)
particles	-1505, -1508	could be formed by a variety of methods—including sieving or mechanical homogenization—and can have a range of sizes

Source: Pet. at 19, 21; -1505 Pet. at 15-17; POR at 19; -1505 POR at 19-20.

THE SPECIFICATION DESCRIBES "FREELY RELEASED IN VIVO"

EXAMPLE 5

Kinetic Release

The following example illustrates the kinetic of release of lidocaine from cohesive HA gels according to the present description. The aim of the Example is to show that the lidocaine contained in cohesive HA gels according to the present description is freely released from the gels when placed in the skin.

Dialysis was performed for different periods of time (about 10 g of gel were placed in a small dialysis bag and then put in 30 g of water). After each dialysis was stopped at a given time, the gel was homogenized with a spatula and the amount of lidocaine was determined by UV method. The final concentration of the dialysis bath met the theoretical concentration of lidocaine which indicates the free release of lidocaine from the gel.

Table 3 illustrates lidocaine concentration in % (w/w), correction of the value and determination of the % of released lidocaine. Additionally, FIG. **9** graphically illustrates the results tabulated in Table 4 below. Within FIG. **9** is indicated the theoretical equilibrium concentration of lidocaine that would exist if the lidocaine were retained in the gel or if it were to be freely released. As is graphically illustrated therein, the data suggest that the lidocaine is freely released from the gel.

TABLE 4

	MMA3056	MMA4031-EC6	MMA4031-EC2	MMA4031-EC3	MMA4031-EC4	MMA4031-EC5	MMA4029-EC7
Dialysis time (h)	0 hr	1 hr 30 min	5 hr	7 hr	23 hr	48 hr	72 hr
[lidocaine] (%)	0.29	0.20	0.16	0.15	0.08	0.07	0.07

The concentration profile of lidocaine in Sample 5 from Example 4 (FIG. **9**) shows that over time it reaches an equilibrium that corresponds to free release of lidocaine. This in vitro study shows that lidocaine is freely released from the gel and not retained in the gel once implanted.

Source: Ex. 1001 at 17:4-45; POR at 19.

THE PROSECUTION HISTORY CONSISTENTLY EXPLAINS "FREELY RELEASED IN VIVO"

Wang teaches away from a composition wherein the lidocaine is freely released *in vivo*

As explained above, Wang suggests that HA degrades too rapidly *in vivo* to be useful "in biomedical purposes." A person of ordinary skill would have understood this to refer to a product that provides sustained delivery of the lidocaine because stability over a period of weeks or months is generally required for sustained drug delivery systems. If lidocaine is freely released *in vivo*, a composition cannot provide sustained delivery because it would be released within a few hours rather than over a period of weeks or months. Thus, Wang teaches away from the limitation of claim 23 that "the lidocaine is freely released *in vivo*."

Source: Ex. 1023 at 68; POR at 19.

DR. BERKLAND APPLIES THE PLAIN AND ORDINARY MEANING CONSISTENT WITH THE PATENT

208. In my opinion, the phrase "freely released" should have its ordinary meaning. A skilled artisan would have understood a compound like lidocaine to be "freely released" from an HA composition if it is released, unhindered, from the HA gel. A skilled artisan would have contrasted this understanding of "freely released" with the alternative of a sustained release due to physical, chemical, or other (*e.g.*, ionic, hydrophobic, hydrophilic, electrostatic, pi stacking) interactions between the lidocaine and crosslinked HA.

Source: Ex. 2013 at ¶ 208; Surreply at 22.

WHILE DR. PRESTWICH INTRODUCED AN ENTIRELY NEW CONSTRUCTION

Petition:

(iv) [1.3] *wherein the lidocaine is freely released in vivo; and*

The POSITA, understanding that lidocaine was loaded into the crosslinked gel by a diffusion process in Sadozai, would recognize that combining BDDE-crosslinked HA with a lidocaine-containing buffer would load lidocaine into that gel by diffusion as well. EX1002 ¶ 144. The POSITA would understand that no covalent bonds were formed during the loading process. EX1002 ¶ 147. Although Sadozai includes language suggesting that BDCI-crosslinked HA may be used for controlled release, the POSITA would not have considered this language relevant to the release of lidocaine.

The POSITA would consequently understand the lidocaine was not covalently bound to the DEO-double crosslinked HA described by Kinney. EX1002 ¶ 178 (explaining that a chemical modification to the lidocaine molecule itself would be needed to covalently attach lidocaine to the crosslinked HA, and such a modified compound would no longer be called "lidocaine hydrochloride.").

Dr. Prestwich's Reply Declaration:

From this, Dr. Berkland asserts without any evidence that the POSITA would have expected "controlled release" from the Sadozai gels, and not free release in a manner effective to relieve pain. I disagree with his reasoning and his unnecessarily restrictive use of the term "controlled release", which broadly implies control of release, not only *restricted* control of release. In other words, control of release allows for free release to occur by not restricting release. As I

Source: Petition at 31-32, 43-44; Ex. 1105 at ¶ 82; POR at 19; Surreply at 21-23.

DR. PRESTWICH'S TESTIMONY UNDERMINED BY SCIENTIFIC LITERATURE: "CONTROLLED RELEASE" IS NOT "FREELY RELEASED IN VIVO"

And so on that page, Page 381 at the top, it has a "Definitions" section. And below that there is an entry for [as read]:

"Controlled-release dosage forms."

Do you see that?

A. Yes. The types of controlled-release products and definitions.

Q. And the definition it provides there is [as read]:

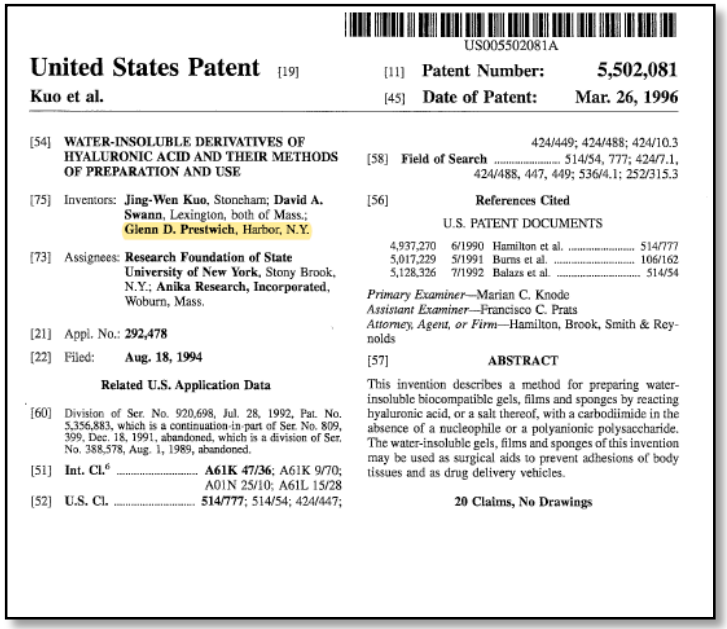
"A class of pharmaceuticals or other biologically active products from which a drug is release from the delivery system in a planned, predictable, and slower-than-normal manner."

Do you see that?

A. Yes. I see that -- the way in which they characterized it in this definition.

Source: Ex. 2200 at 385:8-24; Surreply at 22-23.

DR. PRESTWICH'S PUBLICATIONS CONTRADICT HIS DECLARATION



US005502081A

United States Patent [19]

Kuo et al.

[11] **Patent Number: 5,502,081**

[45] **Date of Patent: Mar. 26, 1996**

[54] **WATER-INSOLUBLE DERIVATIVES OF HYALURONIC ACID AND THEIR METHODS OF PREPARATION AND USE**

[75] Inventors: **Jing-Wen Kuo**, Stoneham; **David A. Swann**, Lexington, both of Mass.; **Glenn D. Prestwich**, Harbor, N.Y.

[73] Assignees: **Research Foundation of State University of New York**, Stony Brook, N.Y.; **Anika Research, Incorporated**, Woburn, Mass.

[21] Appl. No.: **292,478**

[22] Filed: **Aug. 18, 1994**

Related U.S. Application Data

[60] Division of Ser. No. 920,698, Jul. 28, 1992, Pat. No. 5,356,883, which is a continuation-in-part of Ser. No. 809,399, Dec. 18, 1991, abandoned, which is a division of Ser. No. 388,578, Aug. 1, 1989, abandoned.

[51] **Int. Cl.**[6] **A61K 47/36**; A61K 9/70; A01N 25/10; A61L 15/28

[52] **U.S. Cl.** **514/777**; 514/54; 424/447; 424/449; 424/488; 424/10.3

[58] **Field of Search** 514/54, 777; 424/7.1, 424/488, 447, 449; 536/4.1; 252/315.3

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,937,270	6/1990	Hamilton et al.	514/777
5,017,229	5/1991	Burns et al.	106/162
5,128,326	7/1992	Balazs et al.	514/54

Primary Examiner—Marian C. Knode
Assistant Examiner—Francisco C. Prats
Attorney, Agent, or Firm—Hamilton, Brook, Smith & Reynolds

[57] **ABSTRACT**

This invention describes a method for preparing water-insoluble biocompatible gels, films and sponges by reacting hyaluronic acid, or a salt thereof, with a carbodiimide in the absence of a nucleophile or a polyanionic polysaccharide. The water-insoluble gels, films and sponges of this invention may be used as surgical aids to prevent adhesions of body tissues and as drug delivery vehicles.

20 Claims, No Drawings

In yet another embodiment, this invention is directed to drug delivery systems having a pharmaceutically-active substance, such as a therapeutic drug, which covalently bonds to, or non-covalently interacts with, the modified HA polymer of the invention. The non-covalent interactions include ionic and hydrophobic interactions in which the drug is dispersed within the gel, film or sponge. In both cases, the modified HA functions as a vehicle which provides the controlled release of a drug from the system.

EXAMPLE 31

This example illustrates that the reaction of the biscarbodiimide p-phenylenebis-(ethyl)-carbodiimide and HA at a molar equivalent ratio of 12% yields a water-insoluble gel.

Source: U.S. Patent No. 5,502,081 at 4:7-15, 20:56-67; Surreply at 22-23.

DISPUTED TERMS: “UNBOUND,” “UNBOUND TO HA” (-1506, -1632)

C. Unbound lidocaine HCl

138. Claim 22 of the ’795 patent recites the filler composition comprises “unbound lidocaine HCl combined with the crosslinked HA component.”

139. The term “unbound” (and “unbound lidocaine HCl”) does not appear anywhere within the ’795 patent. However, based on the ordinary meaning of the phrase, in the context of the claim, it is my opinion that the POSITA would understand lidocaine to be “unbound” when it was not chemically bonded to another element of the composition, in particular not chemically bonded to the crosslinked HA component.

Source: -1506 Ex. 1002 at ¶¶ 138-139; -1632 POR at 21.

DISPUTED TERMS: "UNBOUND," "UNBOUND TO HA" (-1506, -1632)

215. The ordinary meaning of "unbound" is significantly more diverse. As just explained above (*supra* ¶¶ 86-87, 211), the dermal filler art makes plain that physical binding, ionic binding, and other non-covalent interactions can all take place between lidocaine and HA, not just covalent bonding. Accordingly, I disagree that the ordinary meaning of "unbound" is limited to "chemical[]" bonds.

Source: Ex. 2013 at ¶ 215; -1632 POR at 21.

DISPUTED TERM: "COHESIVE" (-1506)

Cohesive as used herein is the ability of a HA-based composition to retain its shape and resist deformation. Cohesiveness is affected by, among other factors, the molecular weight ratio of the initial free HA, the degree of crosslinking, the amount of residual free HA following crosslinking, and HA-based composition pH.

Source: -1506 Ex. 1001 at 5:62-67; -1506 POR at 20.

DISPUTED TERM: "HEAT STERILE" (-1508)

> The present products and compositions are considered to be sterile when exposed to temperatures of at least about 120° C. to about 130° C. and/or pressures of at least about 12 pounds per square inch (PSI) to about 20 PSI during autoclaving for a period of at least about 1 minute to about 15 minutes.

Source: - 1508 Ex. 1001 at 8:56-61; -1508 POR at 20-21.

DISPUTED TERM: "HEAT STERILE" (-1508)

201. Furthermore, a skilled artisan would have understood that heat sterilization is only one of a number of ways to obtain a sterile product, and that the selected method of sterilization will have an impact on the final structure and properties of the sterile dermal filler. (*See supra* ¶¶ 93-95.) The '013 patent discusses various means of sterilization but singles out autoclaving sterilization,

Source: Ex. 2013 at ¶ 201; -1508 POR at 20-21.

DISPUTED TERM: "STABLE TO AUTOCLAVING" (-1632)

> Autoclave stable or stable to autoclaving as used herein describes a product or composition that is resistant to degradation such that the product or composition maintains at least one, and preferably all, of the following aspects after effective autoclave sterilization: transparent appearance, pH, extrusion force and/or rheological characteristics, hyaluronic acid (HA) concentration, sterility, osmolarity, and lidocaine concentration.

Source: -1632 Ex. 1001 at 5:13-20; -1632 POR at 20-21.

PETITIONER MISAPPLIES THE LAW OF OBVIOUSNESS

PETITIONER BEARS THE BURDEN OF SHOWING BOTH MOTIVATION AND A REASONABLE EXPECTATION OF SUCCESS

In any *inter partes* review, "the ***petitioner shall have the burden*** of proving a proposition of unpatentability by a preponderance of the evidence."

35 U.S.C. § 316(e).

At every stage of the proceeding, the petitioner's burden "***never shifts*** to the patentee."

In re Magnum Oil Tools Int'l, Ltd., 829 F.3d 1364, 1378-79 (Fed. Cir. 2016).

It remains Petitioner's burden to demonstrate ***motivation*** to make the claimed composition in the first place, ***and a reasonable expectation of success*** of achieving it.

Sanofi-Synthelabo v. Apotex, Inc., 550 F.3d 1075, 1089 (Fed. Cir. 2008).

Source: Surreply at 4,15, 20.

RELIANCE ON THE PATENT TO PIECE TOGETHER CLAIM ELEMENTS IS IMPROPER HINDSIGHT

In any *inter partes* review, "the ***petitioner shall have the burden*** of proving a proposition of unpatentability by a preponderance of the evidence."

…

"[I]t is improper to combine references 'like ***separate pieces of a simple jigsaw puzzle***' without 'explaining what reason or motivation one of ordinary skill in the art at the time of the invention would have had to place these pieces together."

…

Where "the only way to arrive at the [claimed invention] is by using [the challenged patent] ***as a roadmap to piece together various elements*** of [the prior art]," "[t]hat represents an ***improper reliance on hindsight.***"

Merck Sharp & Dohme B.V. v. Warner Chilcott Co., LLC, 711 Fed. Appx. 633, 636-37 (Fed. Cir. 2017).

Source: POR at 29.

KNOWLEDGE OF EACH INDIVIDUAL PROCESSING STEP DOES NOT SHOW REASONABLE EXPECTATION OF SUCCESS

The Federal Circuit rejected an obviousness argument where, despite the "many scientific publications cited by both Dow and the PTO, **none suggests** that any process **could be used successfully** in this three-component system, to produce this product having the desired properties."

…

"There must be a reason or suggestion in the art for selecting the procedure used, other than the knowledge learned from the applicant's disclosure."

In re Dow Chem. Co., 837 F.2d 469, 473 (Fed. Cir. 1988).

Source: Surreply at 28.

PETITIONER'S OBVIOUSNESS ARGUMENTS FOCUS ON WHAT A POSA *COULD DO* NOT WHAT THEY *WOULD DO*

> There is simply no credible reason why the POSITA would have not expected that lidocaine could be successfully incorporated into a BDDE-crosslinked gel as well.

> The POSITA could have easily adapted the procedure disclosed in Lebreton to incorporate lidocaine into the BDDE-crosslinked gels. In particular, Lebreton teaches that after the crosslinking reaction, the resulting gel is dialyzed with a phosphate buffer. EX1029 ¶ [0070]. The POSITA could have easily incorporated lidocaine into the buffer solution at a concentration of 0.3% (such as taught by Sadozai), thereby obtaining a BDDE-crosslinked gel containing lidocaine. EX1002 ¶ 140.

Source: Pet. at 29, 30.

THERE IS A DIFFERENCE BETWEEN ABILITY AND MOTIVATION

Petitioner's Reply:

> Moreover, Berkland agreed it was within the POSITA's skill to make and add an appropriate lidocaine HCl solution to Lebreton's BDDE-crosslinked gel(s). EX1200, 199:24-200:8, 204:6-205:24, 243:10-21.

> Simply "add[] the necessary amount of lidocaine … to the [BDDE-crosslinked] gel and mix[] with the spatula." EX2067, 4:48-5:15.[10]

Dr. Berkland's testimony:

> Q. And I believe you testified yesterday one of ordinary skill in the art in 2008 would have been capable of adjusting pH in such a situation, correct, for example, by adding a base?
>
> A. In response to that question earlier, I recall saying they would have been capable to do so, but I don't think they would have been motivated to do so nor have reasonable expectation of success.

Source: Reply at 26-27; Ex. 1200 at 358:21-359:7; Surreply at 4.

THE QUESTION, AGAIN, IS WHAT THE POSA WOULD BE *MOTIVATED* TO DO

Dr. Prestwich agrees that, even when individual steps are within the level of skill of a POSA, the POSA still requires motivation:

> THE WITNESS: A POSA would need to be directed to do such action; and without a motivation to do the action, there's nothing there. There's nothing inventive unless you know that you are making something that is new.

Source: Ex. 2200 at 306:19-23; Surreply at 12.

THE OBVIOUSNESS INQUIRY REQUIRES ACTUAL MOTIVATION PROVIDED BY THE PRIOR ART, NOT CONCLUSORY EXPERT TESTIMONY

"Conclusory expert testimony does not qualify as substantial evidence."

TQ Delta, LLC v. Cisco Sys., 942 F.3d 1352, 1358 (Fed. Cir. 2019).

"The obviousness inquiry does not merely ask whether a skilled artisan ***could*** combine the references, but instead asks whether 'they ***would*** have been motivated to do so.'"

Adidas AG v. Nike, Inc., 963 F.3d 1355, 1359 (Fed. Cir. 2020).

Source: Surreply at 4, 13.

GROUP A: LEBRETON + SADOZAI
(& CTA SUMMARY IN -01632 IPR)

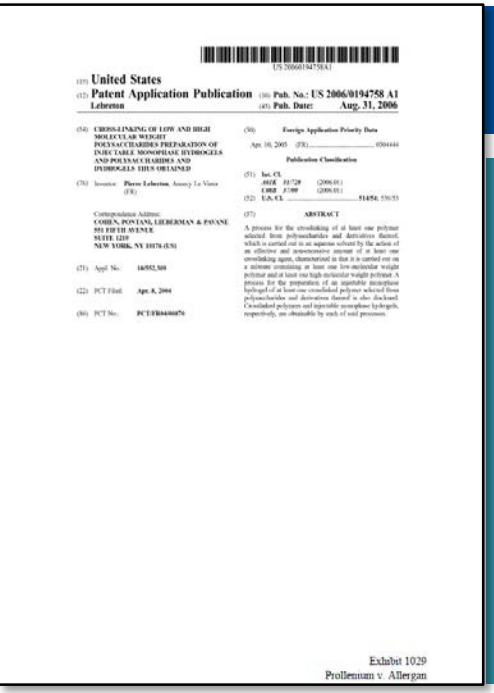
LEBRETON + SADOZAI COMBINATIONS

01505	01506	01508	01509	01617	01632	00084
	Lebreton + Sadozai			Lebreton + Sadozai + CTA Summary	Lebreton + Sadozai	Lebreton + Sadozai
Lebreton + Sadozai + Monheit		Lebreton + Sadozai + Monheit	Lebreton + Sadozai + Monheit	Lebreton + Sadozai + CTA Summary + Monheit		
Lebreton + Sadozai + Clark			Lebreton + Sadozai + Clark			
Lebreton + Sadozai + Smith						
					CTA Summary	

LEBRETON + SADOZAI COMBINATIONS

01505	01506	01508	01509	01617	01632	00084
	Lebreton + Sadozai			Lebreton + Sadozai + CTA Summary	Lebreton + Sadozai	Lebreton + Sadozai
Lebreton + Sadozai + Monheit		Lebreton + Sadozai + Monheit	Lebreton + Sadozai + Monheit	Lebreton + Sadozai + CTA Summary + Monheit		
Lebreton + Sadozai + Clark			Lebreton + Sadozai + Clark			
Lebreton + Sadozai + Smith						
					CTA Summary	

LEBRETON—EXHIBIT 1029



US 20060194758A1

(19) United States

(12) Patent Application Publication

Lebreton

(10) Pub. No.: US 2006/0194758 A1

(43) Pub. Date: Aug. 31, 2006

(54) CROSS-LINKING OF LOW AND HIGH MOLECULAR WEIGHT POLYSACCHARIDES PREPARATION OF INJECTABLE MONOPHASIC HYDROGELS AND POLYSACCHARIDES AND DERIVATIVES THUS OBTAINED

(75) Inventor: Pierre Lebreton, Annecy Le Vieux (FR)

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(21) Appl. No.: 10/552,308

(22) PCT Filed: Apr. 8, 2004

(86) PCT No.: PCT/FR04/00876

(30) Foreign Application Priority Data

Apr. 10, 2003 (FR) 0304444

Publication Classification

(51) Int. Cl.
A61K 31/728 (2006.01)
C08B 37/00 (2006.01)

(52) U.S. Cl. 514/54; 536/55

(57) ABSTRACT

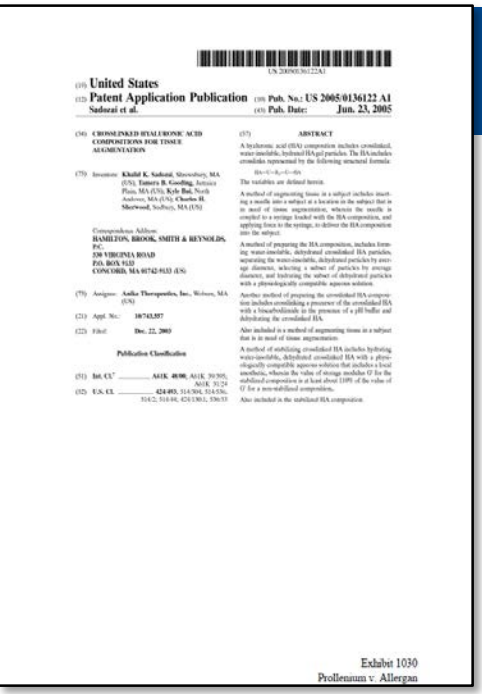
A process for the crosslinking of at least one polymer selected from polysaccharides and derivatives thereof, which is carried out in an aqueous solvent by the action of an effective and non-excessive amount of at least one crosslinking agent, characterized in that it is carried out on a mixture containing at least one low-molecular weight polymer and at least one high-molecular weight polymer. A process for the preparation of an injectable monophase hydrogel of at least one crosslinked polymer selected from polysaccharides and derivatives thereof is also disclosed. Crosslinked polymers and injectable monophase hydrogels, respectively, are obtainable by each of said processes.

Exhibit 1029
Prollenium v. Allergan

- Patent publication describing crosslinking with a mixture of high and low molecular weight HA for dermal filler application
- Lebreton describes “monophasic” gels with a “soft and free-flowing appearance”
- Lebreton’s BDDE-tailored processes use aqueous (not organic) solvents
- No discussion or suggestion of lidocaine

Source: POR at 19-20; Ex. 1029 at Abstract, ¶¶ 64-65, 74-76, 81, 85-91.

SADOZAI—EXHIBIT 1030



US 20050136122A1

(19) United States
(12) Patent Application Publication (10) Pub. No.: US 2005/0136122 A1
Sadozai et al. (43) Pub. Date: Jun. 23, 2005

(54) CROSSLINKED HYALURONIC ACID COMPOSITIONS FOR TISSUE AUGMENTATION

(57) ABSTRACT

A hyaluronic acid (HA) composition includes crosslinked, water-insoluble, hydrated HA gel particles. The HA includes crosslinks represented by the following structural formula:

The variables are defined herein.

A method of augmenting tissue in a subject includes inserting a needle into a subject at a location in the subject that is in need of tissue augmentation, wherein the needle is coupled to a syringe loaded with the HA composition, and applying force to the syringe, to deliver the HA composition into the subject.

A method of preparing the HA composition, includes forming water-insoluble, dehydrated crosslinked HA particles, separating the water-insoluble, dehydrated particles by average diameter, selecting a subset of particles by average diameter, and hydrating the subset of dehydrated particles with a physiologically compatible aqueous solution.

Another method of preparing the crosslinked HA composition includes crosslinking a precursor of the crosslinked HA with a bisepoxide in the presence of a pH buffer and dehydrating the crosslinked HA.

Also included is a method of augmenting tissue in a subject that is in need of tissue augmentation.

A method of stabilizing crosslinked HA includes hydrating water-insoluble, dehydrated crosslinked HA with a physiologically compatible aqueous solution that includes a local anesthetic, wherein the value of storage modulus G' for the stabilized composition is at least about 110% of the value of G' for a non-stabilized composition.

Also included is the stabilized HA composition

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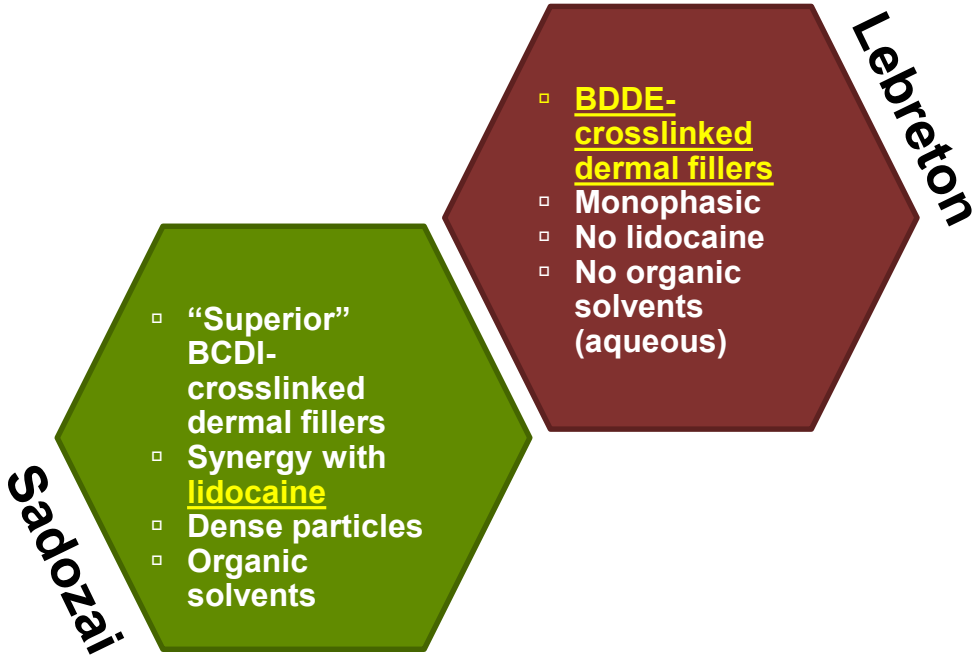
Publication Classification

Exhibit 1030
Prollenium v. Allergan

- Patent publication describes superiority of BCDI crosslinking of HA with lidocaine
- Describes “controlled or sustained release” of lidocaine from BCDI-crosslinked HA
- Describes BCDI-crosslinking processes resulting in “water-insoluble, hydrated HA gel particles”
- BCDI-crosslinked particles are isolated by precipitation with organic solvent prior to rehydration to prepare a dermal

Source: POR at 20-22; Ex. 1030 at Abstract, ¶¶ 8, 45-46, 54, 59, 105, 107.

THERE IS NO MOTIVATION TO COMBINE LEBRETON + SADOZAI

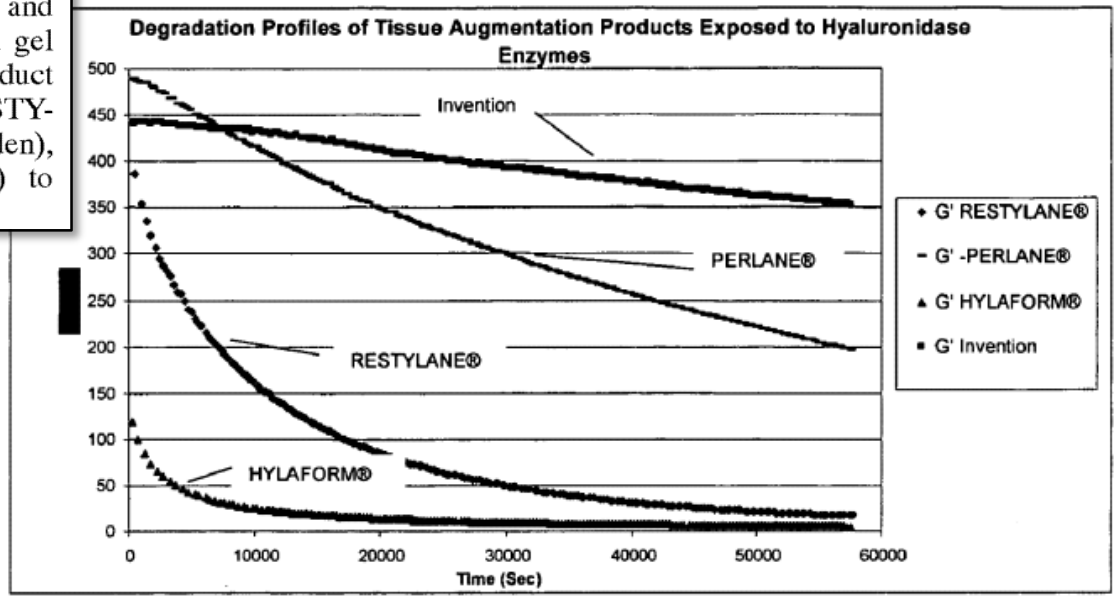


Source: POR at 19-22, 38-46.

SADOZAI MOTIVATED A POSA TO USE pBCDI CROSSLINKER WITH LIDOCAINE OVER OTHER KNOWN CROSSLINKERS

ΔG'/Δt for Invention is Superior to Competitive Products

[0105] Crosslinked HA obtained according Example 5 and processed according to Example 12 was made into a gel having a initial G' of 450 Pa. The resistance of this product and three competitive tissue augmentation products RESTYLANE®, PERLANE® (both Q-Med, Uppsala, Sweden), and HYLAFORM® (Genzyme, Cambridge, Mass.) to digestion with the hyaluronidase was evaluated.



Source: Ex. 1030 at Fig. 5, ¶ 105; POR at 20-21, 40.

SADOZAI MOTIVATED A POSA TO USE pBCDI CROSSLINKER WHEN INCORPORATING LIDOCAINE

[0107] Lidocaine can have a synergistic effect and increase the initial storage modulus G' of the gel compared to otherwise identical compositions prepared in a buffer without lidocaine. Crosslinked HA of Example-5 was processed as in Example-12 using three separate phosphate buffers 1 (no lidocaine), 2 (0.2% lidocaine), and 3(0.3% lidocaine). Gels were made to 32-mg/mL concentrations and the storage modulus G' and degradation profile $\Delta G'/\Delta t$ of each was measured according to the method described in Example-12. **FIG. 7** shows that the compositions with lidocaine have a significantly higher modulus G' over the time of the test. Thus, crosslinked HA with lidocaine can have good biostability, and can in some cases have a synergistic effect, increasing G'.

Source: Ex. 1030 at ¶¶ 90, 107, Fig. 7; POR at 21.

SADOZAI DESCRIBES SUSTAINED RELEASE

[0059] The crosslinked HA can function as a vehicle which provides the controlled or sustained release of the bioactive agent. In one embodiment, the controlled-release HA is placed in contact with a pre-selected tissue, and allowed to remain in place until a desired clinical result is achieved. The controlled-release HA according to an embodiment may be injected or implanted at the locus where delivery is desired, or may be administered orally or by a route that is a combination of two or more of these administration routes.

Source: Ex. 1030 at ¶ 59; POR at 48-49.

DR. DEVORE: NO MOTIVATION TO MODIFY EXISTING DERMAL FILLERS TO INCLUDE LIDOCAINE

Q You don't offer an opinion on your declarations that Restylane could have been modified to add lidocaine, correct?

A I still don't quite understand the rationale. Why would you want to modify Restylane?

Q That -- that was what I was asking you, so...

A There would be no need to -- as far as I know, there would be no need to modify Restylane in order to add lidocaine.

Source: Ex. 2100 at 426:17- 427:2; -1508 POR at 63.

DR. BERKLAND: SIGNIFICANT DIFFERENCES IN CHEMISTRY BETWEEN pBCDI AND BDDE

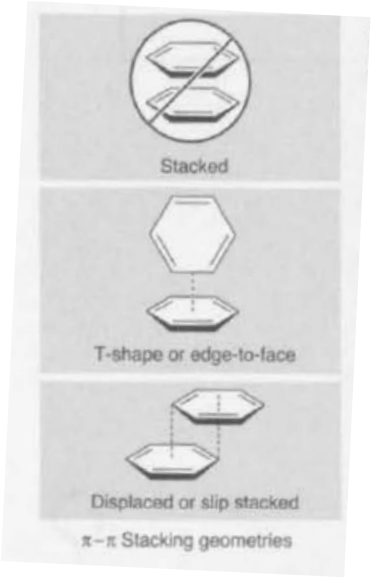
As I

BCDI crosslinkers react with the carboxylate groups of HA to form acylureas, which are amide-type bonds, while BDDE reacts at the pH described by Lebreton with the primary hydroxyl groups of HA to form ether bonds. (*Id.*) This difference in HA reaction site has a larger effect on the overall anionic character of the HA—crosslinking through the carboxylate group reduces that overall carboxylate content, which otherwise contributes negative charge to the HA, whereas the hydroxyl group is generally not ionized. Moreover, pBCDI is a shorter bridging group than BDDE, resulting in a less flexible linkage; it is more hydrophobic; and it contains an aromatic ring that can interact with another aromatic ring such as is found in, for example, lidocaine; BDDE, on the other hand, is more hydrophilic and flexible. (*See supra* ¶¶ 68-69, 72, 125.)

Source: Ex. 2013 at ¶ 221; POR at 39.

PETITIONER AND DR. DEVORE IGNORE THE DIFFERENCES BETWEEN pBCDI'S AND BDDE'S INTERACTIONS WITH LIDOCAINE

The distributed pi orbitals found in aromatic ring structures like in pBCDI and lidocaine can interact:



Petitioner failed to account for these interactions:

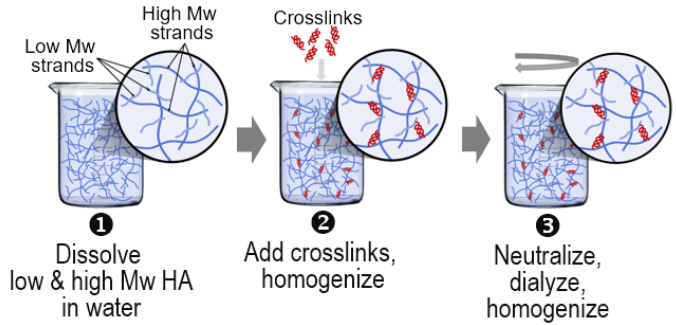
> The POSITA would have recognized that there were no functional groups in BDDE-crosslinked HA that would have interacted with lidocaine differently that those present in BDCI-crosslinked HA. EX1002 ¶ 153. As such, the POSITA would have reasonably

As did Petitioner's expert, Dr. DeVore:

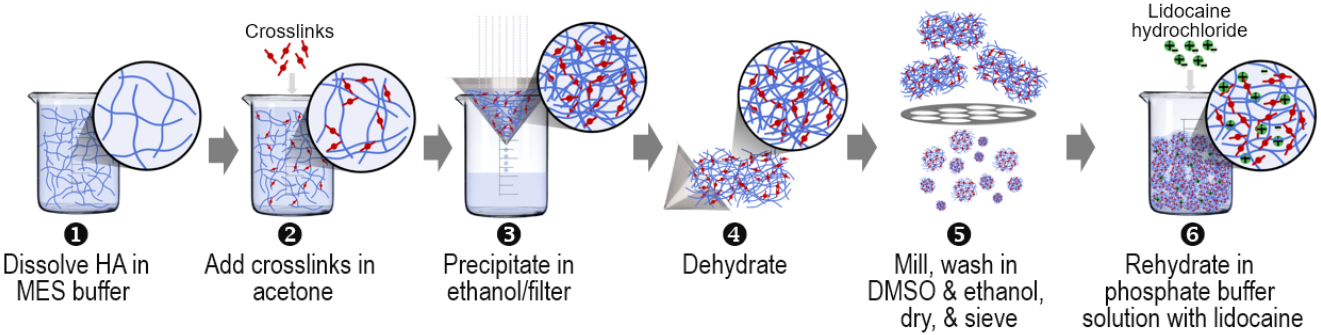
> Q And you don't discuss interactions between lidocaine and BCDI with respect to pi stacking interactions, correct?
>
> A Correct.

Source: Pet. at 33; POR at 40; Ex. 2100 at 364:24-365:2; Ex. 2013 at ¶ 125.

A POSA WOULD RECOGNIZE THAT THE PROCESSES OF LEBRETON AND SADOZAI WERE INCOMPATIBLE



Lebreton: Making a monophasic cohesive gel



Sadozai: Making a biphasic particulate gel with lidocaine

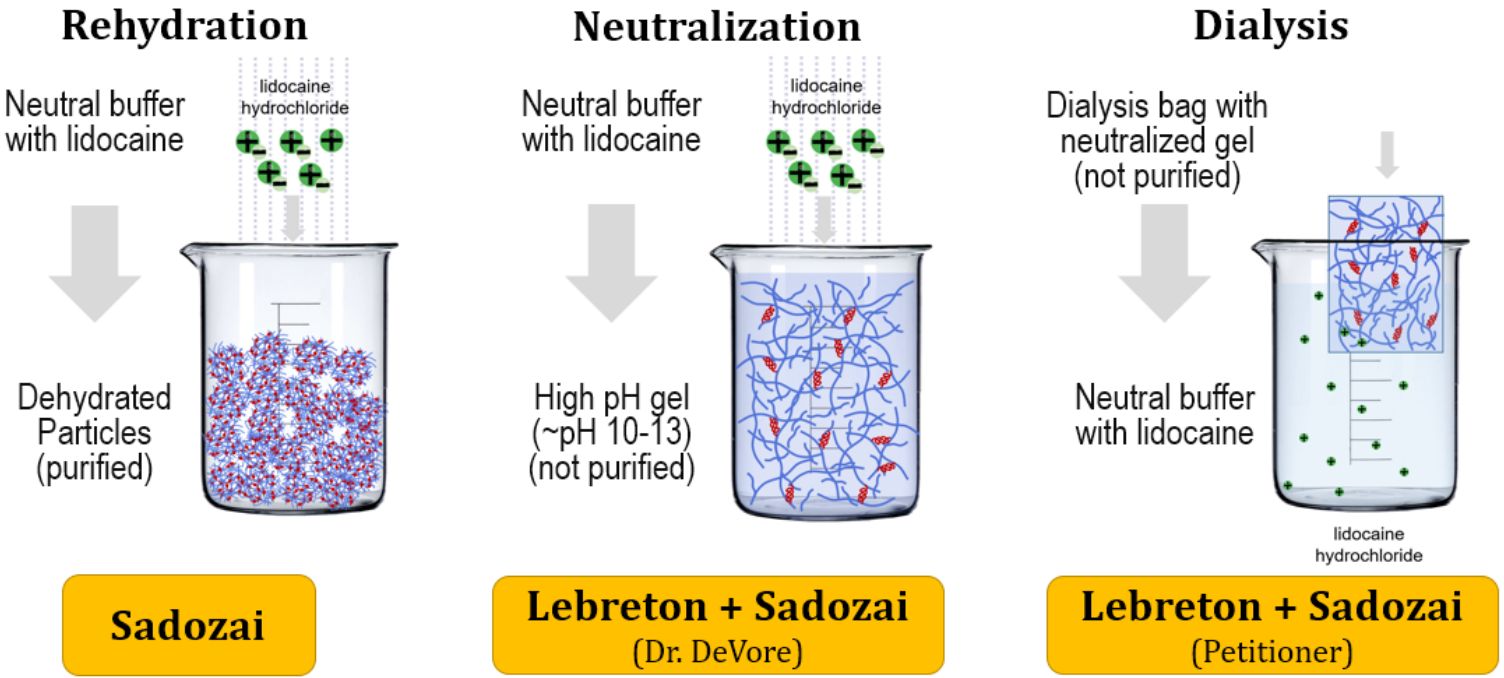
Source: POR at 44; Ex. 2013 at ¶¶ 220, 223, 231.

DR. BERKLAND EXPLAINED THE INCOMPATIBILITY THAT EXISTS BETWEEN LEBRETON AND SADOZAI

- Sadozai uses organic solvents, dehydration, and washing with solvents:
  - This would dehydrate HA, increasing H+ bonding and ionic interactions, cause chain entanglement and irreversible changes to the gel (reduced swelling capacity).
  - Results in densely packed particles suspended in a physiological buffer solution—*i.e.*, a biphasic composition.
- Lebreton does not teach organic solvents, dehydration, or solvent washing:
  - Aqueous NaOH solutions which avoid irreversible changes—only possible because BDDE is a water-soluble crosslinker.
  - Results in soft, free-flowing, monophasic composition—not biphasic with dense particles like in Sadozai

Source: Ex. 2013 at ¶¶ 223, 225, 231; POR at 44-45.

DR. BERKLAND: PROCESS STEPS AND THEIR ORDER AFFECT THE FINAL PROPERTIES



Source: POR at 45; *Compare* Pet. at 30 *with* Ex. 1002 at ¶ 140; *see* Ex. 2013 at ¶¶ 232-35.

DR. BERKLAND: THE POSA WOULD NOT ADD LIDOCAINE DURING NEUTRALIZATION STEP OR DIALYSIS STEP

- Problems with adding lidocaine during a neutralization step :
  - Solution pH is ~13.5—high enough to precipitate lidocaine
  - Lidocaine will affect buffer pH, osmolarity, and ionic strength
  - Composition is not yet purified—unreacted chemicals can have detrimental interactions with lidocaine
- Problems with adding lidocaine during a dialysis step:
  - Would require numerous lidocaine dialysate solutions—tremendous waste of lidocaine
  - Must continuously monitor to quantify equilibrated lidocaine
  - Would not use a process intended to *remove* impurities to *add* a highly pure active ingredient

Source: Ex. 2013 at ¶¶ 234, 235; POR at 45-46.

EVEN IF COMBINED, LEBRETON + SADOZAI DOES NOT DISCLOSE FREELY RELEASED OR UNBOUND LIDOCAINE

"Freely released in vivo"/ "unbound"

Petitioner relies on Sadozai's disclosures to supply this limitation

Dr. DeVore's declaration:

> 152. The POSITA would have expected that lidocaine, when incorporated in a BDDE-crosslinked gel, would diffuse from the gel similarly to how the lidocaine diffused from the gels in Sadozai.

Source: -1506 Pet. at 28-29; -1506 Ex. 1002 at ¶ 152; POR at 48-49; -1506 POR at 45-47; -1632 POR at 63-66.

LEBRETON + SADOZAI IS SILENT REGARDING SPECIFIC EXTRUSION FORCE AND VISCOSITY LIMITATIONS

Extrusion force and viscosity limitations

Petitioner relies solely on the alleged properties of certain products and unsubstantiated expert testimony, but does not point to any evidence establishing the claimed properties in the asserted references

Dr. DeVore's testimony:

Q And would your answer be the same with respect to the stability of extrusion force for any gels made according to the Sadozai 1030 processes?
A Again, without going through the entire document word by word, I haven't seen any reference to extrusion force.
Q And in Sadozai 1030, it also does not describe the viscosity remaining stable over a period of time?
Q And I'm talking about for the -- for the HA compositions made according to the Sadozai 1030 disclosure.
A I have not seen it thus far.

Source: -1506 Pet. at 32-37; -1506 POR at 52-57; Ex. 2100 at 396:11-397:19.

LEBRETON + SADOZAI DOES NOT DISCLOSE OR SUGGEST MANY OF THE CLAIMED LIMITATIONS

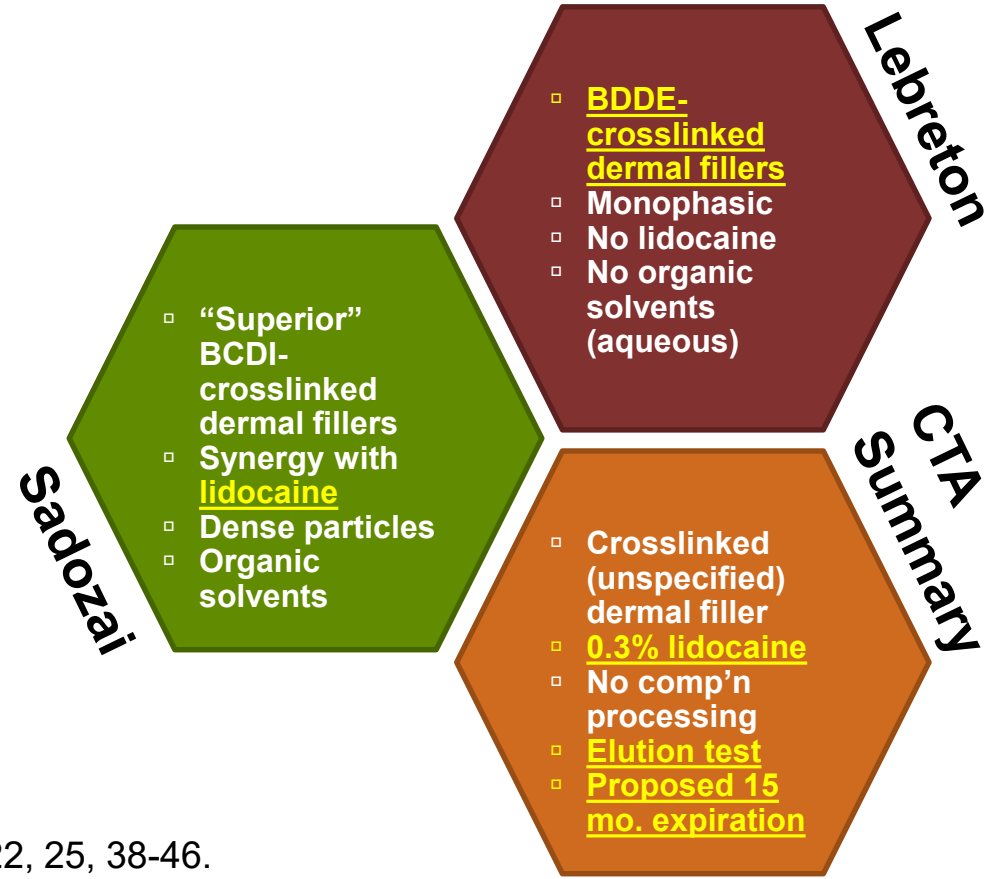
- Petitioner has failed to establish the following limitations in the asserted references:
  - Amount of free HA
  - Degree of crosslinking
  - Viscosity and extrusion force requirements
  - Lidocaine concentration, HA concentration, extrusion force, and appearance remain "substantially constant" during storage under ambient conditions for at least 3 months
  - pH
  - HA concentration
  - Cohesive composition
  - Dialysis equilibrium

Source: Pet. at 35-40; POR at 53-58; -1506 Pet. at 32-37; -1632 Pet. at 43; -1505 POR at 50-51, 53-56; -1506 POR at 47-48; -1632 POR at 48-49, 66.

LEBRETON + SADOZAI COMBINATIONS

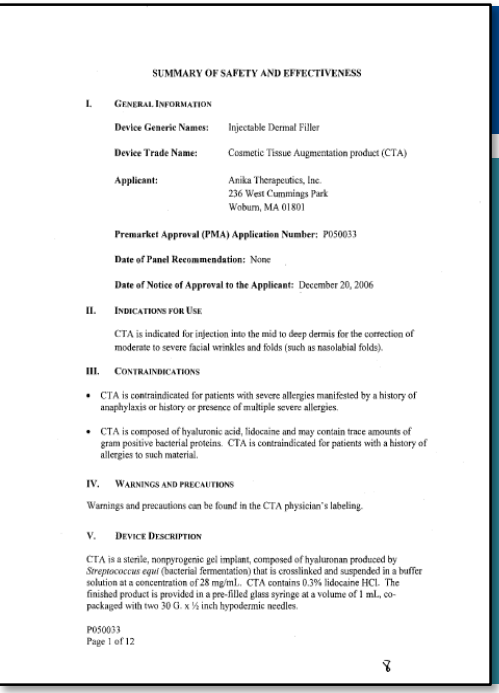
01505	01506	01508	01509	01617	01632	00084
	Lebreton + Sadozai			Lebreton + Sadozai + CTA Summary	Lebreton + Sadozai	Lebreton + Sadozai
Lebreton + Sadozai + Monheit		Lebreton + Sadozai + Monheit	Lebreton + Sadozai + Monheit	Lebreton + Sadozai + CTA Summary + Monheit		
Lebreton + Sadozai + Clark			Lebreton + Sadozai + Clark			
Lebreton + Sadozai + Smith						
					CTA Summary	

THERE IS NO MOTIVATION TO COMBINE LEBRETON + SADOZAI + CTA SUMMARY



Source: POR at 19-22, 25, 38-46.

CTA SUMMARY—EXHIBIT 1050



SUMMARY OF SAFETY AND EFFECTIVENESS

I. GENERAL INFORMATION

Device Generic Names: Injectable Dermal Filler

Device Trade Name: Cosmetic Tissue Augmentation product (CTA)

Applicant: Anika Therapeutics, Inc.
236 West Cummings Park
Woburn, MA 01801

Premarket Approval (PMA) Application Number: P050033

Date of Panel Recommendation: None

Date of Notice of Approval to the Applicant: December 20, 2006

II. INDICATIONS FOR USE

CTA is indicated for injection into the mid to deep dermis for the correction of moderate to severe facial wrinkles and folds (such as nasolabial folds).

III. CONTRAINDICATIONS

- CTA is contraindicated for patients with severe allergies manifested by a history of anaphylaxis or history or presence of multiple severe allergies.
- CTA is composed of hyaluronic acid, lidocaine and may contain trace amounts of gram positive bacterial proteins. CTA is contraindicated for patients with a history of allergies to such material.

IV. WARNINGS AND PRECAUTIONS

Warnings and precautions can be found in the CTA physician's labeling.

V. DEVICE DESCRIPTION

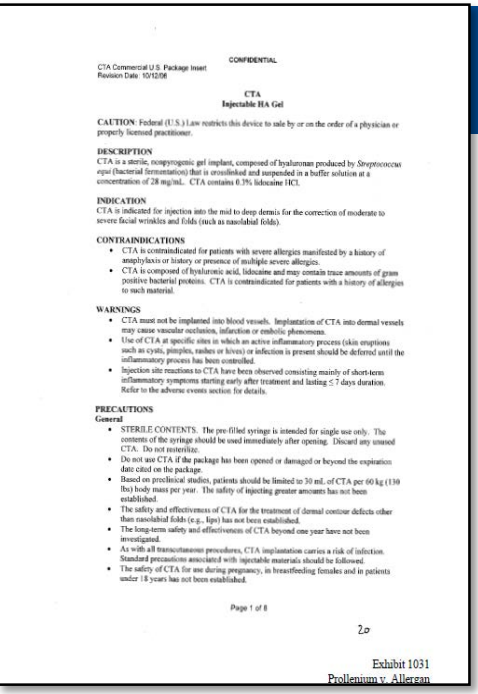
CTA is a sterile, nonpyrogenic gel implant, composed of hyaluronan produced by *Streptococcus equi* (bacterial fermentation) that is crosslinked and suspended in a buffer solution at a concentration of 28 mg/mL. CTA contains 0.3% lidocaine HCl. The finished product is provided in a pre-filled glass syringe at a volume of 1 mL, co-packaged with two 30 G. x ½ inch hypodermic needles.

P050033
Page 1 of 12

- Petitioner fails to demonstrate CTA Summary was publicly available as of August 2008
- Document provides only a partial description of CTA and its properties
- Does not identify the crosslinking agent, amount of crosslinking, or any details regarding processing, manufacturing, sterilization or stability

Source: Ex. 1050 at 6; POR at 25, 35-37.

DRAFT CTA LABEL—EXHIBIT 1031



CONFIDENTIAL

CTA Commercial U.S. Package Insert
Revision Date: 10/12/06

CTA
Injectable HA Gel

CAUTION: Federal (U.S.) Law restricts this device to sale by or on the order of a physician or properly licensed practitioner.

DESCRIPTION
CTA is a sterile, nonpyrogenic gel implant, composed of hyaluronan produced by *Streptococcus equi* (bacterial fermentation) that is crosslinked and suspended in a buffer solution at a concentration of 28 mg/mL. CTA contains 0.3% lidocaine HCl.

INDICATION
CTA is indicated for injection into the mid to deep dermis for the correction of moderate to severe facial wrinkles and folds (such as nasolabial folds).

CONTRAINDICATIONS
- CTA is contraindicated for patients with severe allergies manifested by a history of anaphylaxis or history or presence of multiple severe allergies.
- CTA is composed of hyaluronic acid, lidocaine and may contain trace amounts of gram positive bacterial proteins. CTA is contraindicated for patients with a history of allergies to such material.

WARNINGS
- CTA must not be implanted into blood vessels. Implantation of CTA into dermal vessels may cause vascular occlusion, infarction or embolic phenomena.
- Use of CTA at specific sites in which an active inflammatory process (skin eruptions such as cysts, pimples, rashes or hives) or infection is present should be deferred until the inflammatory process has been controlled.
- Injection site reactions to CTA have been observed consisting mainly of short-term inflammatory symptoms starting early after treatment and lasting ≤ 7 days duration. Refer to the adverse events section for details.

PRECAUTIONS
General
- STERILE CONTENTS. The pre-filled syringe is intended for single use only. The contents of the syringe should be used immediately after opening. Discard any unused CTA. Do not resterilize.
- Do not use CTA if the package has been opened or damaged or beyond the expiration date cited on the package.
- Based on preclinical studies, patients should be limited to 30 mL of CTA per 60 kg (130 lbs) body mass per year. The safety of injecting greater amounts has not been established.
- The safety and effectiveness of CTA for the treatment of dermal contour defects other than nasolabial folds (e.g., lips) has not been established.
- The long-term safety and effectiveness of CTA beyond one year have not been investigated.
- As with all transcutaneous procedures, CTA implantation carries a risk of infection. Standard precautions associated with injectable materials should be followed.
- The safety of CTA for use during pregnancy, in breastfeeding females and in patients under 18 years has not been established.

Page 1 of 8

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Exhibit 1031
Prollenium v. Allergan

- No evidence that Ex. 1030 is prior art or available to the POSA
- Ex. 1031 has no relevant date, is marked “CONFIDENTIAL,” and has markings of being a draft document
- Not in the grounds
- Document provides only a partial description of CTA
- Does not identify crosslinker, details regarding processing or manufacturing

Source: POR at 25; Ex. 1031 at 1.

CTA SUMMARY LIKEWISE DOES NOT SUPPLY THE "FREELY RELEASED" LIMITATION

"Freely released in vivo"

Dr. DeVore's testimony:

Q Exhibit 1050 does not disclose the cross-linker used for CTA, does it?

A It does not.

Q If we look at page 6 of Exhibit 1050, it mentions in vitro studies that were done, but it doesn't mention how the testing was conducted, correct?

A Correct.

A That information is generally not into -- in the summaries.

Q It would be in the PMA submission itself?

A Yes.

Q And that's the part that we talked about earlier that would be confidential at the FDA?

A Yes.

Source: Ex. 2100 at 237:20-22, 238:20-24, 239:13-21; POR at 50-51.

LEBRETON + SADOZAI + CTA DOES NOT SUGGEST THE CLAIMED DEGREE OF CROSSLINKING

Degree of crosslinking

- Petitioner fails to show how Lebreton's crosslinking ranges would inform the degree of crosslinking necessary for a BDDE-crosslinked dermal filler *with lidocaine*
- Petitioner cannot rely on a product, Restylane, to fill gaps in the prior art

Q And is that -- is that always predictable in that add more cross-linking, get more viscous, or does it depend on the formulation that's used?

A It depends on the total formulation.

Q And you would want to test that? You can't just assume it?

A Correct.

Additionally, the POSITA would have been aware that Restylane, another BDDE-crosslinked filler, had a degree of crosslinking of about 1%.

Source: Ex. 2100 at 113:18-114:2; Pet. at 35; POR at 53-54.

LEBRETON + SADOZAI + CTA DOES NOT SUGGEST EXTRUSION FORCE, VISCOSITY, AND DEGRADATION LIMITATIONS

Extrusion force, viscosity, and degradation limits

- Petitioner inappropriately relies on products like CTA, Puragen Plus, and Prevelle Silk to establish properties not in prior art
- Petitioner misapprehends that stability is not required for FDA approval—approval says nothing of extrusion force or viscosity

> And so a company could pick up a one-month shelf life, for example, for a dermal filler, and support it with testing for chemical and physical properties, correct?
>
> A A company could.

Source: Ex. 2100 at 107:23-108:3; Pet. at 37-40; POR at 55-58.

PETITIONER'S RELIANCE ON CTA IS MISPLACED—CTA CONTINUED TO HAVE STABILITY PROBLEMS

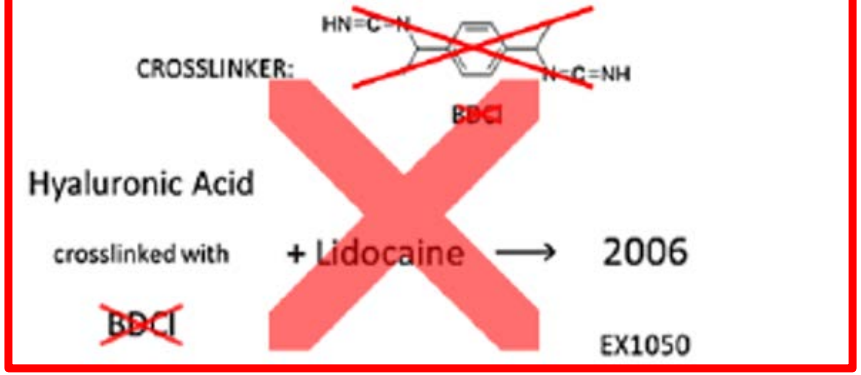
Do you understand the PMA was approved for a CTA in December of 2006; is that right?

A Yes.

Q But no products under that -- under that PMA number were launched until August 5, 2008, correct?

A That's what I understand.

CROSSLINKER NOT DISCLOSED



Approval Order Statement

APPROVAL FOR: 1) AN INCREASE N THE BUFFER CONCENTRATION OF THE FINAL PRODUCT FROM 12 MM TO 50 MM SODIUM PHOSPHATE; 2) THE INTRODUCTION OF AN ANTIOXIDANT, I.E., 0.1% SODIUM METABISULFITE, INTO THE FINAL PRODUCT; AND 3) THE INTRODUCTION OF AN 0.5 ML CONFIGURATION OF COSMETIC TISSUE AUGMENTATION PRODUCT (CTA).

Source: Ex. 2100 at 236:19-237:3; Ex. 2122 at 1; POR at 55-56; *see also* Ex. 2105 at 5.

LEBRETON + SADOZAI + CTA DOES NOT DISCLOSE OR SUGGEST MANY OF THE CLAIMED LIMITATIONS

- Petitioner has failed to establish the following limitations in the asserted references:
  - Average particle size
  - Degree of crosslinking
  - pH
  - Extrusion force and viscosity remain “substantially constant” and “lidocaine does not substantially degrade the HA” during storage under ambient conditions for at least 3, 6, or 9 months

Source: Pet. at 34-40; POR at 52-58; -1506 POR at 54-57.

LEBRETON + SADOZAI COMBINATIONS

01505	01506	01508	01509	01617	01632	00084
	Lebreton + Sadozai			Lebreton + Sadozai + CTA Summary	Lebreton + Sadozai	Lebreton + Sadozai
Lebreton + Sadozai + Monheit		Lebreton + Sadozai + Monheit	Lebreton + Sadozai + Monheit	Lebreton + Sadozai + CTA Summary + Monheit		
Lebreton + Sadozai + Clark			Lebreton + Sadozai + Clark			
Lebreton + Sadozai + Smith						
					CTA Summary	

MONHEIT DOES NOT DISCUSS ADDING FREE HA TO MONOPHASIC COMPOSITIONS

Q Monheit does not discuss monophasic HA compositions, correct?

A I believe that's correct.

Q And Monheit does not suggest adding free HA as a lubricant to a monophasic HA gel, correct?

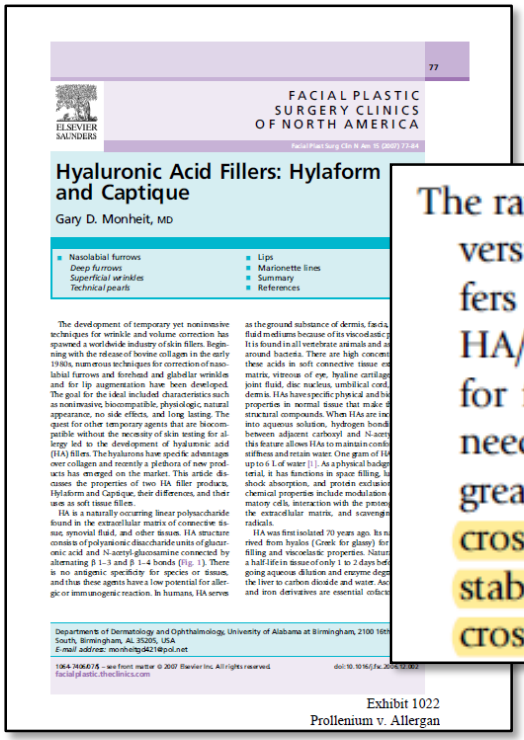
A Based on my quick examination, he does suggest free HA for some of the particulate products.

Q But not with respect to monophasic products?

A Not that I can find --

Source: Ex. 2100 at 453:23-454:2; 454:3-13; POR at 58-59.

MONHEIT RECOGNIZES DISADVANTAGES TO FREE HA



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FACIAL PLASTIC SURGERY CLINICS OF NORTH AMERICA

Hyaluronic Acid Fillers: Hylaform and Captique

Gary D. Monheit, MD

- Nasolabial furrows
  - *Deep furrows*
  - *Superficial wrinkles*
  - *Technical pearls*
- Lips
- Marionette lines
- Summary
- References

The development of temporary yet noninvasive techniques for wrinkle and volume correction has spawned a worldwide industry of skin fillers. Beginning with the release of bovine collagen in the early 1980s, numerous techniques for correction of nasolabial furrows and forehead and glabellar wrinkles and for lip augmentation have been developed. The goal for the ideal included characteristics such as nonimmunogenic, biocompatible, physiologic, natural appearance, no side effects, and long lasting. The quest for other temporary agents that are biocompatible without the necessity of skin testing for allergy led to the development of hyaluronic acid (HA) fillers. The hyaluronans have specific advantages over collagen and recently a plethora of new products has emerged on the market. This article discusses the properties of two HA filler products, Hylaform and Captique, their differences, and their uses as soft tissue fillers.

HA is a naturally occurring linear polysaccharide found in the extracellular matrix of connective tissue, synovial fluid, and other tissues. HA structure consists of polyanionic disaccharide units of glucuronic acid and N-acetyl-glucosamine connected by alternating β 1–3 and β 1–4 bonds (Fig. 1). There is no antigenic specificity for species or tissues, and thus these agents have a low potential for allergic or immunogenic reaction. In humans, HA serves as the ground substance of dermis, fascia, fluid mediums because of its viscoelastic
It is found in all vertebrate animals and
around bacteria. There are high concent
these acids in soft connective tissue
matrix, vitreous of eye, hyaline cartilage
joint fluid, disc nucleus, umbilical cord,
dermis. HAs have specific physical and bi
properties in normal tissue that make
structural compounds. When HAs are in
into aqueous solution, hydrogen bond
between adjacent carboxyl and N-acet
this feature allows HAs to maintain conf
stiffness and retain water. One gram of H
up to 6 L of water [1]. As a physical barrie
terial, it has functions in space filling, l
shock absorption, and protein exclusio
chemical properties include modulation
matory cells, interaction with the protei
the extracellular matrix, and scavengin
radicals.

HA was first isolated 70 years ago. Its n
ried from hyalos (Greek for glassy) for
filling and viscoelastic properties. Natur
a half-life in tissue of only 1 to 2 days bef
going aqueous dilution and enzyme degr
the liver to carbon dioxide and water. Ac
and iron derivatives are essential cofact

Departments of Dermatology and Ophthalmology, University of Alabama at Birmingham, 2100 16th
South, Birmingham, AL 35205, USA
E-mail address: monheitgd421@pol.net

1064-7406/07/$ – see front matter © 2007 Elsevier Inc. All rights reserved. doi:10.1016/j.fsc.2006.12.002
facialplastic.theclinics.com

Exhibit 1022
Prollenium v. Allergan

The ratio of soluble to insoluble HA: particulate versus fluid components (see Fig. 2). This refers to the amount of cross-linked HA to free HA/mL. The free HA is needed as a lubricant for flow characteristics, thus more free HA is needed as the G-1 or hardness of the HA is greater. The disadvantage is that free or non–cross-linked HA only lasts a few days and the stability of the implant is related to the cross-linked component.

Source: Ex. 1022 at 78; POR at 58-59.

DR. DEVORE: MONHEIT PROVIDES NO SPECIFIC DETAILS ON HOW A POSA WOULD INCORPORATE FREE HA

Q And Monheit doesn't specify, for example, the pH of the cross-linking reaction, how long the reaction is done, the HA concentration, the cross-linker concentration in any reaction, correct?

A That's not the objective of the paper, correct.

Q And so it's not disclosed in it, correct?

A Not that I can find.

Source: Ex. 2100 at 454:21-455:6; POR at 58-59.

LEBRETON + SADOZAI + MONHEIT DOES NOT DISCLOSE OR SUGGEST MANY OF THE CLAIMED LIMITATIONS

- Petitioner has failed to establish the following limitations in the asserted references:
  - pH
  - Extrusion force
  - Viscosity
  - Degree of crosslinking

Source: -1508 Pet. at 28-33; -1509 Pet. at 34; -1508 POR at 51-54; -1509 POR at 52-54.

LEBRETON + SADOZAI COMBINATIONS

01505	01506	01508	01509	01617	01632	00084
	Lebreton + Sadozai			Lebreton + Sadozai + CTA Summary	Lebreton + Sadozai	Lebreton + Sadozai
Lebreton + Sadozai + Monheit		Lebreton + Sadozai + Monheit	Lebreton + Sadozai + Monheit	Lebreton + Sadozai + CTA Summary + Monheit		
Lebreton + Sadozai + Clark			Lebreton + Sadozai + Clark			
Lebreton + Sadozai + Smith						
					CTA Summary	

DR. DEVORE: NEITHER SMITH NOR CLARK DISCUSS FREE HA IN MONOPHASIC HA GELS OR HA GELS WITH LIDOCAINE

Smith

Q And here, Smith is comparing the cohesive homogenous gel filler, such as Juvéderm, with granular hyaluronic acid suspensions.

Do you see that?

A Yes.

Q Now, Smith does not discuss lidocaine being added to any HA gels, correct?

A Correct.

Clark

Q So it doesn't compare factors that apply to biphasic products with monophasic formulations, correct?

A Correct.

Q And Clark does not discuss lidocaine as being something that should be added to any of these products, correct?

A Correct.

Source: Ex. 2100 at 446:18-23, 447:9-12, 449:7-10, 452:2-5; -1505 POR at 48-49.

LEBRETON + SADOZAI COMBINATIONS

01505	01506	01508	01509	01617	01632	00084
	Lebreton + Sadozai			Lebreton + Sadozai + CTA Summary	Lebreton + Sadozai	Lebreton + Sadozai
Lebreton + Sadozai + Monheit		Lebreton + Sadozai + Monheit	Lebreton + Sadozai + Monheit	Lebreton + Sadozai + CTA Summary + Monheit		
Lebreton + Sadozai + Clark			Lebreton + Sadozai + Clark			
Lebreton + Sadozai + Smith						
					CTA Summary	

THE CTA SUMMARY DOES NOT ENABLE THE CLAIMED INVENTIONS

- Dr. DeVore admits that CTA Summary does not describe what crosslinker was used, what crosslinking reaction conditions were followed, what, if any, post-crosslinking steps were performed, or how the product was sterilized.

Q Exhibit 1050 does not disclose the cross-linker used for CTA, does it?

A It does not.

Q And CTA summary does not disclose how CTA is processed, correct?

A Correct.

Q CTA summary also doesn't discuss how or disclose how CTA is manufactured, correct?

A That's correct.

Q And the CTA summary does not disclose how CTA is sterilized, correct?

A Correct.

In order to render a claimed apparatus or method obvious, the **prior art must enable** one skilled in the art to **make and use** the apparatus or method.

Beckman Instruments, Inc. v. LKB Produkter AB, 892 F.2d 1547, 1551 (Fed. Cir. 1989) (emphasis added).

Source: Ex. 2100 at 237:20-22, 238:8-19; -1632 POR at 37-39.

CTA SUMMARY DOES NOT DISCLOSE OR SUGGEST THE CLAIMED pH RANGES

pH range

- CTA Summary pH range is 6.2 to 7.6—does not suggest a pH above 7.5.
  See Atofina v. Great Lakes Chem. Corp., 441 F.3d 991, 1000 (Fed. Cir. 2006) (holding that "slightly overlapping range"—150 to 350 in reference as compared to 330 to 450 in patent—was insufficient to establish that limitation).

-1632 Ex. 1001 ('795 patent)

26. A composition comprising a crosslinked hyaluronic acid (HA) at a concentration of about 20 mg/mL to about 30 mg/mL and lidocaine at a concentration of about 0.1% to about 5% by weight, wherein the composition has a pH above about 7.5.

27. The composition of claim **26**, wherein the pH is about 7.5 to about 8.

28. The composition of claim **26**, wherein the composition is stable to autoclaving.

Ex. 1050 at 6

pH	All lots of avian and bacterial CTA met the specification of 6.2 – 7.6

Source: -1632 Ex. 1001 at claims 26-28; Ex. 1050 at 6; -1632 Pet. at 23-24; -1632 POR at 39-40.

CTA SUMMARY DOES NOT DISCLOSE OR SUGGEST AUTOCLAVE STERILIZATION

Autoclave sterilization

- Petitioner admits that CTA Summary does not disclose that it is autoclaved
- Cites to only the Lebreton patent for its claim that autoclaving was predominant method in 2008, but Dr. DeVore admitted other methods were used
- Petitioner cannot rely on Sadozai to gap-fill—POSA would recognize no connection between the two

-1632 Pet. at 25

EX1050, 1. While CTA Summary does not expressly disclose that the syringes are *autoclave* sterilized,

Ex. 2100 at 82:15-21

Q So you agree with me an HA solution could be sterilized by E-beam, correct?

A Yes.

Q And a hyaluronic acid solution could be sterilized by vapor hydrogen peroxide, correct?

A This formulation can be.

Source: -1632 Pet. at 25; -1632 POR at 41-43; Ex. 2100 at 82:15-21.

CTA SUMMARY DOES NOT DISCLOSE OR SUGGEST MANY OF THE CLAIMED LIMITATIONS

- Petitioner has failed to establish the following limitations in the asserted references:
  - HA concentration about 22 mg/mL
  - Stability, concentration, appearance, and extrusion force maintained from 3 to 9 months
  - “Freely released” or “substantially unbound” lidocaine
  - Dialysis to lidocaine equilibrium within 1 hour

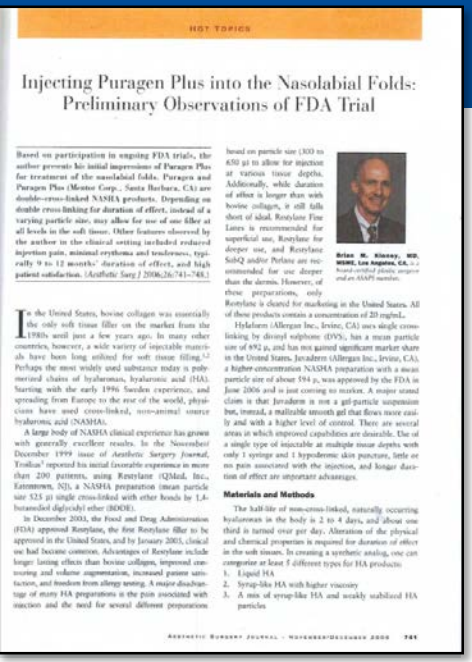
Source: -1632 Pet. at 24-30; -1632 POR at 43-49.

GROUP B: KINNEY + ZHAO + NARINS

KINNEY + ZHAO + NARINS COMBINATIONS

01505	01506	01508	01509	01617
	Kinney + Zhao + Narins	Kinney + Zhao + Narins		Kinney + Zhao + Narins
Kinney + Zhao + Narins + Monheit			Kinney + Zhao + Narins + Monheit	
Kinney + Zhao + Narins + Clark				
Kinney + Zhao + Narins + Smith			Kinney + Zhao + Narins + Smith	

KINNEY—EXHIBIT 1012



HOT TOPICS

Injecting Puragen Plus into the Nasolabial Folds: Preliminary Observations of FDA Trial

Based on participation in ongoing FDA trials, the author presents his initial impressions of Puragen Plus for treatment of the nasolabial folds. Puragen and Puragen Plus (Mentor Corp., Santa Barbara, CA) are double-cross-linked NASHA products. Depending on double cross-linking for duration of effect, instead of a varying particle size, may allow for use of one filler at all levels in the soft tissue. Other features observed by the author in the clinical setting included reduced injection pain, minimal erythema and tenderness, typically 9 to 12 months' duration of effect, and high patient satisfaction. (Aesthetic Surg J 2006;26:741–748.)

In the United States, bovine collagen was essentially the only soft tissue filler on the market from the 1980s until just a few years ago. In many other countries, however, a wide variety of injectable materials have been long utilized for soft tissue filling.[1,2] Perhaps the most widely used substance today is polymerized chains of hyaluronan, hyaluronic acid (HA). Starting with the early 1996 Sweden experience, and spreading from Europe to the rest of the world, physicians have used cross-linked, non-animal source hyaluronic acid (NASHAs).

A large body of NASHA clinical experience has grown with generally excellent results. In the November/December 1999 issue of *Aesthetic Surgery Journal*, Trollian[3] reported his initial favorable experience in more than 200 patients, using Restylane (Q-Med, Inc., Uppsala, Sweden), a NASHA preparation (mean particle size 525 μ) single cross-linked with ether bonds by 1,4-butanediol diglycidyl ether (BDDE).

In December 2003, the Food and Drug Administration (FDA) approved Restylane, the first Restylane filler to be approved in the United States, and by January 2005, clinical use had become common. Advantages of Restylane include longer lasting effects than bovine collagen, improved contouring and volume augmentation, increased patient satisfaction, and freedom from allergy testing. A major disadvantage of many HA preparations is the pain associated with injection and the need for several different preparations based on particle size (300 to 650 μ) to allow for injection at various tissue depths. Additionally, while duration of effect is longer than with bovine collagen, it still falls short of ideal. Restylane Fine Lines is recommended for superficial use, Restylane for deeper use, and Restylane SubQ and/or Perlane are recommended for use deeper than the dermis. However, of these preparations, only Restylane is cleared for marketing in the United States. All of these products contain a concentration of 20 mg/mL.

Brian M. Kinney, MD, MSME, Los Angeles, CA, is a board-certified plastic surgeon and an ASAPS member.

Hylaform (Allergan Inc., Irvine, CA) uses single cross-linking by divinyl sulphone (DVS), has a mean particle size of 892 μ, and has not gained significant market share in the United States. Juvaderm (Allergan Inc., Irvine, CA), a higher-concentration NASHA preparation with a mean particle size of about 594 μ, was approved by the FDA in June 2006 and is just coming to market. A major stated claim is that Juvaderm is not a gel-particle suspension but, instead, a malleable smooth gel that flows more easily and with a higher level of control. There are several areas in which improved capabilities are desirable. Use of a single type of injectable at multiple tissue depths with only 1 syringe and 1 hypodermic skin puncture, little or no pain associated with the injection, and longer duration of effect are important advantages.

Materials and Methods

The half-life of non-cross-linked, naturally occurring hyaluronan in the body is 2 to 4 days, and about one third is turned over per day. Alteration of the physical and chemical properties is required for duration of effect in the soft tissues. In creating a synthetic analog, one can categorize at least 3 different types for HA products:

1. Liquid HA
2. Syrup-like HA with higher viscosity
3. A mix of syrup-like HA and weakly stabilized HA particles

- Author's preliminary observations of "Puragen Plus" clinical trial performance at 1 trial site
- Describes Puragen as an HA-based dermal filler that is "double-crosslinked" with DEO and contains 0.3% lidocaine
- Kinney provides no discussion of:
  - How Puragen Plus dermal filler is prepared;
  - How lidocaine is incorporated; or
  - How the product is processed or sterilized

Source: Ex. 1012; POR at 23, 63.

ZHAO—EXHIBIT 1058

US 20050250939A1

(19) United States
(12) Patent Application Publication
Zhao

(10) Pub. No.: US 2005/0250939 A1
(43) Pub. Date: Nov. 10, 2005

(54) PROCESS FOR THE PRODUCTION OF MULTIPLE CROSS-LINKED HYALURONIC ACID DERIVATIVES

(75) Inventor: Xiaobin Zhao, Edinburgh (GB)

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MINNEAPOLIS, MN 55440-1022 (US)

(73) Assignee: Mentor Biopolymers Limited

(21) Appl. No.: 11/185,573

(22) Filed: Jul. 19, 2005

Related U.S. Application Data

(63) Continuation of application No. 09/926,266, filed on Aug. 7, 2001, which is a continuation of application No. PCT/GB00/00321, filed on Feb. 3, 2000.

(30) Foreign Application Priority Data

Feb. 3, 1999 (GB) 9902412.7

Publication Classification

(51) Int. Cl.[7] C08B 37/08
(52) U.S. Cl. 536/53

(57) ABSTRACT

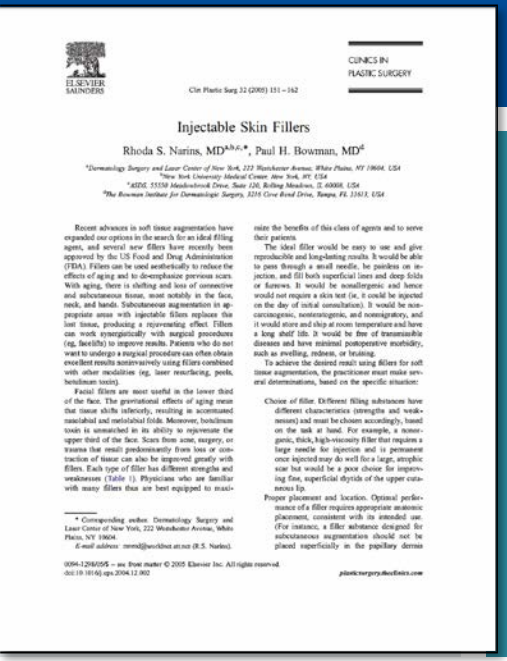
The present invention relates to a process for the production of cross-linked hyaluronic acid (HA) derivatives, in particular multiple, e.g. double cross-linked hyaluronic acid derivatives. The invention also provides novel cross-linked HA derivatives, products containing them and their uses in medical and pharmaceutical and cosmetic applications.

Exhibit 1058
Prollenium v. Allergan

- Patent publication describing Zhao's methods for double-crosslinking HA and HA derivatives
- Provides examples describing crosslinking of HA with DEO, glutaraldehyde, epichlorhydrin, and combinations thereof
- Zhao provides no discussion of:
  - How to prepare a dermal filler from double-crosslinked HA;
  - Sterilizing HA products; or
  - Incorporating lidocaine

Source: Ex. 1058; POR at 23-24, 63-64.

NARINS—EXHIBIT 1007



ELSEVIER SAUNDERS

CLINICS IN PLASTIC SURGERY

Clin Plastic Surg 32 (2005) 151–162

Injectable Skin Fillers

Rhoda S. Narins, MD[a,b,c,*], Paul H. Bowman, MD[d]

[a]Dermatology Surgery and Laser Center of New York, 122 Westchester Avenue, White Plains, NY 10604, USA
[b]New York University Medical Center, New York, NY, USA
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[d]The Bowman Institute for Dermatologic Surgery, 3255 Cove Bend Drive, Tampa, FL 33613, USA

Recent advances in soft tissue augmentation have expanded our options in the search for an ideal filling agent, and several new fillers have recently been approved by the US Food and Drug Administration (FDA). Fillers can be used aesthetically to reduce the effects of aging and to diminish/minimize previous scars. With aging, there is shifting and loss of connective and subcutaneous tissue, most notably in the face, neck, and hands. Subcutaneous augmentation in appropriate areas with injectable fillers replaces this lost tissue, producing a rejuvenating effect. Fillers can work synergistically with surgical procedures (eg, facelifts) to improve results. Patients who do not want to undergo a surgical procedure can often obtain excellent results noninvasively using fillers combined with other modalities (eg, laser resurfacing, peels, botulinum toxin).

Facial fillers are most useful in the lower third of the face. The gravitational effects of aging mean that tissue shifts inferiorly, resulting in accentuated nasolabial and melolabial folds. Moreover, botulinum toxin is unmatched in its ability to rejuvenate the upper third of the face. Scars from acne, surgery, or trauma that result predominantly from loss or contraction of tissue can also be improved greatly with fillers. Each type of filler has different strengths and weaknesses (Table 1). Physicians who are familiar with many fillers thus are best equipped to maximize the benefits of this class of agents and to serve their patients.

The ideal filler would be easy to use and give reproducible and long-lasting results. It would be able to pass through a small needle, be painless on injection, and fill both superficial lines and deep folds or furrows. It would be nonallergenic and hence would not require a skin test (ie, it could be injected on the day of initial consultation). It would be noncarcinogenic, nonteratogenic, and nonimmunogenic, and it would store and ship at room temperature and have a long shelf life. It would be free of transmissible diseases and have minimal postoperative morbidity, such as swelling, redness, or bruising.

To achieve the desired result using fillers for soft tissue augmentation, the practitioner must make several determinations, based on the specific situation:

Choice of filler. Different filling substances have different characteristics (strengths and weaknesses) and must be chosen accordingly, based on the task at hand. For example, a nonorganic, thick, high-viscosity filler that requires a large needle for injection and is permanent once injected may do well for a large, atrophic scar but would be a poor choice for improving fine, superficial rhytids of the upper cutaneous lip.

Proper placement and location. Optimal performance of a filler requires appropriate anatomic placement, consistent with its intended use. (For instance, a filler substance designed for subcutaneous augmentation should not be placed superficially in the papillary dermis

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E-mail address: rnmd@worldnet.att.net (R.S. Narins).

doi:10.1016/j.cps.2004.12.002

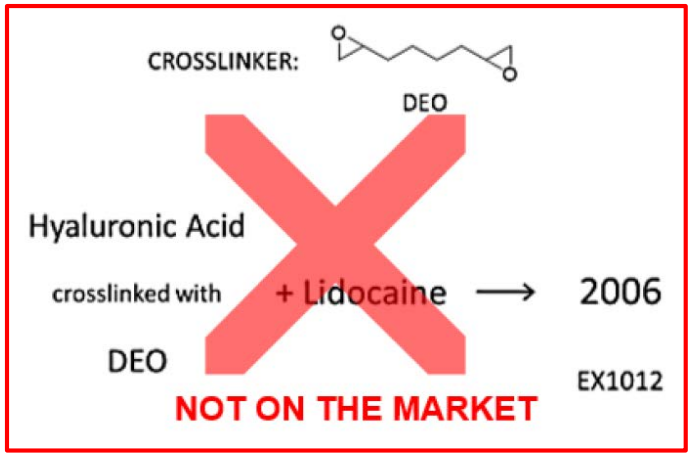
- A review of basic properties of a variety of FDA-approved dermal fillers (Petitioner points to disclosures regarding Restylane)
- No Puragen/Puragen Plus
- Narins provides no discussion of:
  - How Restylane is prepared;
  - Incorporating lidocaine into any HA dermal filler

Source: Ex. 1007; POR at 24-25.

THERE IS NO MOTIVATION TO COMBINE KINNEY + ZHAO + NARINS

Source: POR at 60-62.

IT WAS KNOWN THAT PURAGEN PLUS HAD UNRESOLVED PROBLEMS



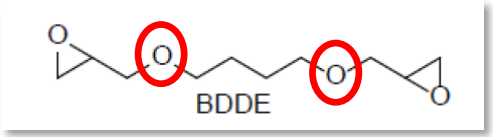
Q And this would indicate to a POSA as well that Mentor was continuing to have problems with Puragen Plus such that it needed to submit a second module to the FDA, correct?

A It would indicate they're having some difficulties.

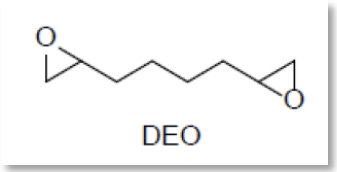
We continue to pursue FDA approval for Puragen Plus in the U.S. and for Prevelle Silk in certain territories outside of the U.S. In addition, as part of our commercialization agreement with Genzyme, we are pursuing FDA approval of dermal gel extra, a "next-generation" hyaluronic acid-based dermal filler product.

Source: POR at 42, 56-57; Ex. 2100, 223:22-224:8, 230:5-231:2; Ex. 2139 at 5.

UNDISPUTED STRUCTURAL DIFFERENCES TRANSLATE TO DIFFERENCES IN PROPERTIES



- Longer
- Hydrophilic
- More reactive



- Shorter
- Hydrophobic
- Lower reactivity

Dr. Prestwich's prior declarations contradict his current declaration:

The first crosslinking step of HA with DEO follows a similar chemical pathway as that described above for BDDE, modifying primarily the 6- hydroxyl groups of GlcNAc residues in the HA chain. ~~In contrast to~~While BDDE~~, which~~ is 12 atoms in length and ~~is hydrophilic due to the presence of~~has two oxygen atoms in the chain, DEO is eight atoms in length, and ~~is more hydrophobic, lacking~~lacks any oxygen atoms in the chain. ~~In addition~~Nonetheless, the terminal epoxide groups of DEO ~~are of somewhat lower reactivity than~~react by the same reaction mechanism as for the epoxide groups of the glycidyl ethers of BDDE.

Source: POR at 60-61; Reply at 39; Surreply at 27-28; Ex. 2013 at ¶¶ 72, 280.

TOGETHER, KINNEY AND ZHAO REINFORCE THEIR MUTUAL TEACHINGS TO USE DEO, NOT BDDE

Kinney

Puragen and Puragen Plus (Mentor Corp., Santa Barbara, CA) are double-cross-linked NASHA products. The ester bonds confer increased stability in vitro by resisting the enzymatic degradation by hyaluronidase and by protecting the ether bonds during sterilization. The ether bonds are hydrophobic and resist enzymatic degradation. The first chemical reaction is performed at high pH with 1, 2, 7, 8–diepoxyoctane (DEO), a hydrophobic epoxide that builds an HA network through ether bonds between hydroxyl groups. The second chemical low-pH reaction, using the same agent (DEO), further cross-links carboxyl groups to form ester bonds. The increased chemical stability allows for the addition of lidocaine 0.3% for a relatively pain-free injection.

Zhao

[0020] To form an ether linkage the cross-linking agent is preferably selected from formaldehyde, gluteraldehyde, divinyl sulfone and, in alkaline conditions, bis and poly epoxides. Preferably the crosslinker contains a hydrophobic hydrocarbon segment, e.g. 1,2,3,4,-diepoxybutane, or most preferably 1,2,7,8-diepoxyoctane.

[0021] To form an ester linkage the cross-linking agent is preferably selected from polyhydric alcohols, carbodi-imides, polyanhydrides, carboxylic acid chlorides and, in acid conditions, bis and poly epoxides. Preferably the crosslinker contains a hydrophobic hydrocarbon segment, e.g. 1,2,3,4,-diepoxybutane, or most preferably 1,2,7,8-diepoxyoctane.

Source: Ex. 1012 at 742; Ex. 1058 at ¶¶ 20-21; POR at 23-24, 60-61; Surreply at 26-27.

PETITIONER'S ALLEGED MOTIVATION TO USE BDDE IN PLACE OF DEO RE-WRITES THIS EVIDENCE

> Further, a POSITA would have been motivated to replace DEO in Kinney's double-DEO crosslinked HA with BDDE because: (1) Zhao *prefers* and *claims* bisepoxides (such as BDDE) to form ether and ester linkages in double-crosslinked HA (EX1058 ¶¶ [0020-0021], claims 26-28); and (2) Kinney teaches a combination of "ether and ester bonds" from bisepoxide crosslinkers provides "increased chemical stability" and "allows [] addition of lidocaine." EX1012, 742.

Source: Reply at 39.

KINNEY + ZHAO + NARINS IS SILENT ON HOW TO PREPARE A DERMAL FILLER, LET ALONE WITH LIDOCAINE

Petitioner's Reply:

But methods of crosslinking and methods for the pre- or post-crosslinking processing of HA to form fillers were well known and routine in 2008. EX1013, 18:21-23; EX1105 ¶¶ 41, 118; *see* Section I.C.2 above. And Zhao elsewhere described autoclaving, homogenizing, and testing rheology from double DEO-crosslinked HA gels. EX1113, 423; EX1105 ¶ 118.

Narins:

Restylane

Restylane (Q-Med AB, Uppsala, Sweden) is a stabilized, partially cross-linked HA gel. The HA is produced from cultures of *Streptococcus equi* by fermentation in the presence of sugar, which is alcohol-precipitated, filtered, and dried. The HA chains are then chemically stabilized through permanent cross-linking with epoxides. The material is heat-sterilized in its final container and has a shelf life of 1.5 years from the date of manufacture. Because its production does not require an animal source, it has been termed a non-animal, stabilized hyaluronic acid.

Source: POR at 63-64; Reply at 41; Surreply at 28; Ex. 1007 at 156.

KINNEY + ZHAO + NARINS DOES NOT DISCUSS HOW LIDOCAINE IS RELEASED

“Freely released in vivo”

Petitioner relies solely on Puragen Plus providing a “relatively pain-free injection” (from Kinney)

Dr. DeVore’s testimony:

Q Now, Kinney 1012 also does not discuss how lidocaine is released from Puragen Plus, correct?

A In reviewing, I don't remember seeing it included in this article.

Q And there's no kinetic study in Kinney on evaluating lidocaine release rate from Puragen Plus, correct?

A Not in this article.

Source: Pet. at 43; POR at 64; Ex. 2100 at 410:5-15.

KINNEY + ZHAO + NARINS DOES NOT SHOW HOW TO INCORPORATE FREE HA OR PROVIDE A MOTIVATION TO DO SO

"Free HA"

Petitioner relies solely on Kinney's disclosure that *Restylane* has "minimally modified HA":

Kinney teaches that Restylane, a BDDE-crosslinked filler, contains "minimally modified HA." EX1012, 742. The term *free HA* includes "very lightly crosslinked HA." See Claim Construction Section V.C; EX1001, 5:54-62. Thus, the POSITA would have been motivated to include free HA in the BDDE-double crosslinked filler as well. EX1002 ¶ 181. Moreover, the POSITA could have added free HA to optimize the flow characteristics of the gel. EX1002 ¶ 181.

Kinney's disclosure:

Using a gel with a smaller average particle size (220 μ) may create a *smoother* injection (more continuous application of pressure). A gel with higher viscosity may require more pressure to inject. Depending on double cross-linking for duration of effect, instead of a varying particle size, may allow for use of 1 filler at all levels in the soft tissue.

Source: Pet. at 45; POR at 65; Ex. 1012 at 742.

KINNEY + ZHAO + NARINS DOES NOT DISCLOSE OR SUGGEST THE CLAIMED DEGREES OF CROSSLINKING

Degree of crosslinking

Petitioner points solely to Zhao's disclosure of a crosslinking range of 10-50%, and Zhao's silence on lower degrees of crosslinking:

Zhao does *not* teach or suggest that lower degrees of crosslinking are incompatible with the double crosslinking process. EX1002 ¶ 185. Rather, given the commercial and clinical success of Restylane, the POSITA would have been motivated to also select a similar degree of crosslinking, i.e., about 1% or about 2%. EX1002 ¶ 185.

Zhao's disclosure:

[0056] Double-crosslinked HA according to the present invention may have a degree of cross-linking in the range 10 to 50%, eg 15 to 30, preferably 20 to 25% (where 100% is represented by cross-linking of all OH groups at the C6 position and all COOH groups at the C5 position). The degree of cross-linking may be measured by elemental analysis or solid state NMR analyis.

Source: Pet. at 46-47; POR at 66-67; Ex. 1058 at ¶ 56; -1505 POR at 53-56; -1506 POR at 63-64; -1509 POR at 60-62.

KINNEY + ZHAO + NARINS IS SILENT REGARDING SPECIFIC EXTRUSION FORCE, VISCOSITY, AND DEGRADATION LIMITATIONS

Extrusion force, viscosity, and degradation limits post-heat sterilization

Petitioner relies solely on the supposed "shelf lives" of certain products, but does not point to any evidence establishing the claimed properties

Dr. Berkland's testimony:

> Dr. DeVore equates "shelf life" with the specific properties required by these claims, but a skilled artisan would not understand them to have the same meaning. As FDA guidance on the shelf life of dermal fillers makes clear, a product can experience observable degradation during its shelf life, so long as it is *within specified limits* (*i.e.*, product specifications). (Ex. 2078 at 1.) These shelf-life specifications are not generally made public for a particular product. Moreover, no particular shelf life is required to obtain FDA approval. (*Supra* ¶ 195.) In addition, a skilled artisan would have been aware that the compositions, manufacturing processes, and resulting properties underlying these particular product trade names can change over time and in ways that are not publicly announced.

Source: Pet. at 49-50; POR at 68-69; Ex. 2013 at ¶ 300.

KINNEY + ZHAO + NARINS DOES NOT DISCLOSE OR SUGGEST MANY OF THE CLAIMED LIMITATIONS

- Petitioner has also failed to establish the following limitations in the asserted references:
  - Average particle size
  - pH
  - Viscosity and extrusion force
- **Petitioner did not address any of these shortcomings in its Reply**

> **C. Other specific limitations**
>
> The arguments in Section II.C above generally apply to this Ground as well.

Source: Pet. at 46, 48; POR at 65-68; Reply at 42; Surreply at 29; -1506 POR at 64; -1508 POR at 60; -1505 POR at 55-56.

KINNEY + ZHAO + NARINS COMBINATIONS

01505	01506	01508	01509	01617
	Kinney + Zhao + Narins	Kinney + Zhao + Narins		Kinney + Zhao + Narins
Kinney + Zhao + Narins + Monheit			Kinney + Zhao + Narins + Monheit	
Kinney + Zhao + Narins + Clark				
Kinney + Zhao + Narins + Smith			Kinney + Zhao + Narins + Smith	

NONE OF MONHEIT, SMITH, OR CLARK SHOW HOW TO ADD FREE HA, AND EMPHASIZE PROBLEMS WITH FREE HA FORMULATIONS

Specific amounts of free HA

Dr. Berkland's declaration:

> Specifically, a skilled artisan would not turn to them because Monheit, Clark, and Smith do not teach when or how to add free HA to any HA gel. A skilled artisan would have understood that in adding to free HA to the hypothetical lidocaine-containing BDDE-double crosslinked HA composition, the manner and process by which free HA is added, and the downstream processing of such composition, *i.e.* autoclaving, would impact the rheological properties of the resulting composition, would lead to unpredictable results, and could compromise the stability and usability of the resulting system. (*See supra* Section IV.E.)

Monheit:

> The disadvantage is that free or non–cross-linked HA only lasts a few days and the stability of the implant is related to the cross-linked component.

Smith:

> In addition, there appears to be less nocturnal swelling after the use of Juvéderm, particularly after lip enhancement. This observation may be explained by the presence of a smaller amount of free hyaluronic acid and a slower rate at which tissue in the treated area is exposed to free hyaluronic acid.

Source: Ex. 2013 at ¶¶ 59, 260, 304; Ex. 1022 at 78; Ex. 1009 at 73S; -1505 POR at 50-52, 61-62; *see also* Ex. 2100 at 445:13- 455:6.

GROUP C: REINMULLER + LEBRETON (-01506, -01508, AND -01509 IPRS)

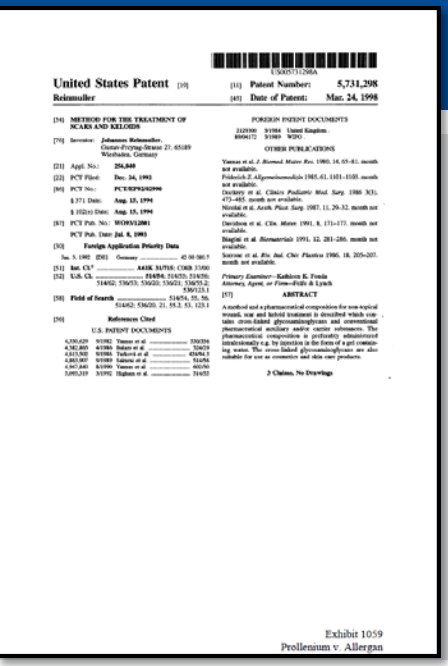
REINMULLER + LEBRETON COMBINATIONS

01506	01508	01509
Reinmuller + Lebreton + Monheit	Reinmuller + Lebreton + Monheit	Reinmuller + Lebreton + Monheit
		Reinmuller + Lebreton + Smith

REINMULLER + LEBRETON COMBINATIONS

01506	01508	01509
Reinmuller + Lebreton + Monheit	Reinmuller + Lebreton + Monheit	Reinmuller + Lebreton + Monheit
		Reinmuller + Lebreton + Smith

REINMULLER—EXHIBIT 1059



US005731298A

United States Patent [19]
Reinmuller

[11] Patent Number: 5,731,298
[45] Date of Patent: Mar. 24, 1998

[54] METHOD FOR THE TREATMENT OF SCARS AND KELOIDS

[75] Inventor: Johannes Reinmuller, Gustav-Freytag-Strasse 27, 65189 Wiesbaden, Germany

[21] Appl. No.: 256,040
[22] PCT Filed: Dec. 24, 1992
[86] PCT No.: PCT/EP92/02990
§ 371 Date: Aug. 15, 1994
§ 102(e) Date: Aug. 15, 1994
[87] PCT Pub. No.: WO93/12801
PCT Pub. Date: Jul. 8, 1993

[30] Foreign Application Priority Data

Jan. 3, 1992 [DE] Germany 42 00 080.5

[51] Int. Cl.[6] A61K 31/715; C08B 37/00
[52] U.S. Cl. 514/54; 514/55; 514/56; 514/62; 536/53; 536/20; 536/21; 536/55.2; 536/123.1
[58] Field of Search 514/54, 55, 56, 514/62; 536/20, 21, 55.2, 53, 123.1

[56] References Cited
U.S. PATENT DOCUMENTS

FOREIGN PATENT DOCUMENTS

OTHER PUBLICATIONS

[57] ABSTRACT

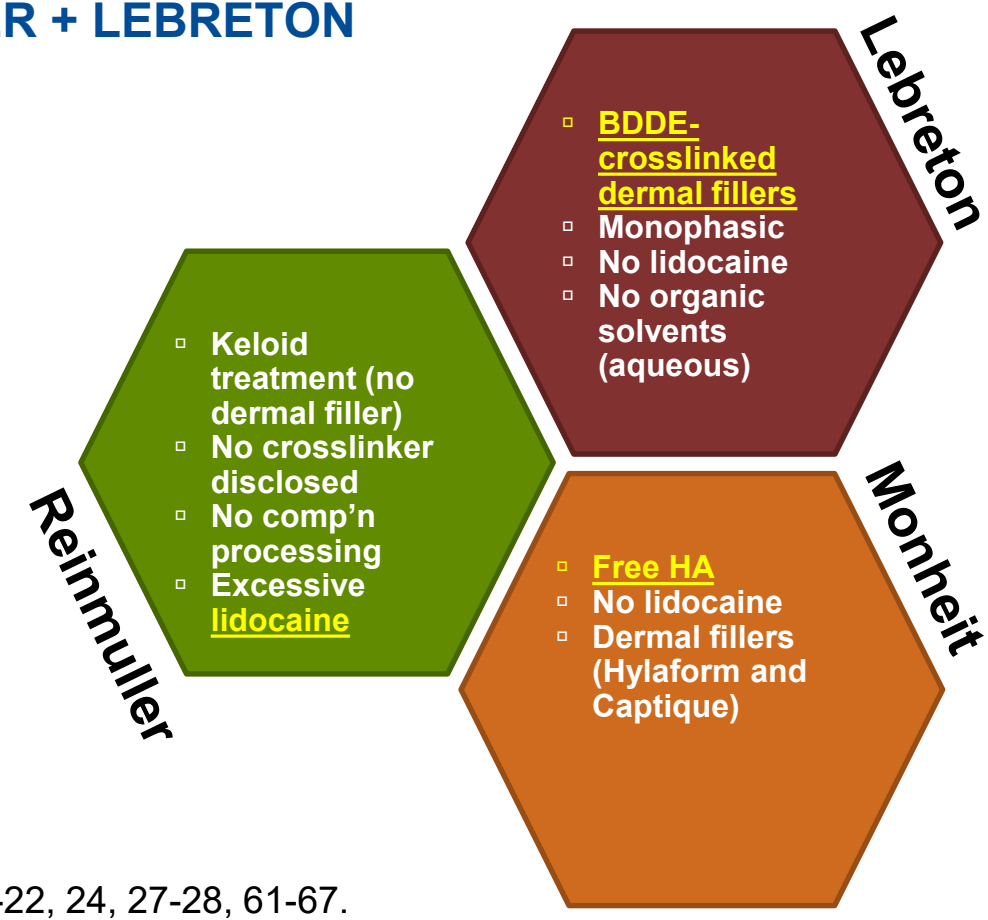
2 Claims, No Drawings

Exhibit 1059
Prollenium v. Allergan

- Reinmuller describes “active substances (cross-linked glycosaminoglycans)” in pharmaceutical compositions “for the treatment of wounds, scars and primarily keloids”
- Does not discuss dermal fillers, or how to make or use them
- No HA crosslinker disclosed
- Specifically excludes crosslinked HA for “cosmetics or as skin care products”

Source: Ex. 1059 at 4:37-40, 6:3-9, 6:47-53; Ex. 2013 at ¶¶ 319-322; -1508 POR at 27-28, 64-65.

THERE IS NO MOTIVATION TO COMBINE REINMULLER + LEBRETON



Source: -1508 POR at 21-22, 24, 27-28, 61-67.

REINMULLER DOES NOT DISCLOSE DERMAL FILLERS

EXAMPLE 1

Production of an injectable gel from the following components:

Component	Amount
cross-linked hyaluronic acid ("Hylagel" Biomatrix Co., NJ, USA)	0.004 g
lidocaine hydrochloride	0.02 g
water, purified (DAB 9)	to 1.0 g

Application example 1

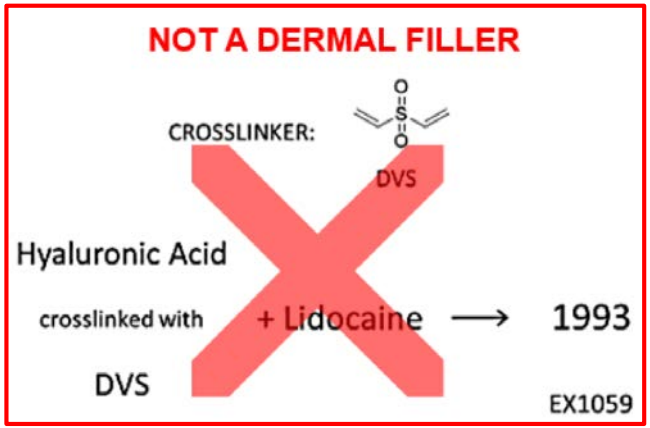
The treatment of a ca. 3 cm×5 cm dark-red raised keloid is described which was present on the back of a 30 year old woman after a tangential cut by a broken pane of glass.

The patient complained about itching in the area of the keloid. The keloid was infiltrated with cross-linked hyaluronic acid (Hylon) by injection for a total of four times at intervals of 4 to 8 weeks. The itching had already disappeared a few hours after the first injection. The keloid became considerably paler within two weeks and a flattening was already recognizable after four weeks. After ca. 6 months there was a pale, only slightly raised scar.

Dr. DeVore's testimony:

Q But not as a -- as a dermal filler, correct?

A Correct, it's for treatment of keloids.



Source: Ex. 1059 at 7:1-29; Ex. 2100 at 438:20-25; POR at 41-42; -1508 POR at 27-28, 61, 63.

REINMULLER DOES NOT DISCLOSE DERMAL FILLERS

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Dr. Berkland's declaration:

> The resulting composition contains 4 mg/mL HA and 20 mg/mL (or 2%) lidocaine, and has a pH of 7.0. (*See id.*) This is approximately 7.5 to 33 times the ratio of lidocaine to HA in a typical dermal filler product with 0.3% lidocaine added.[16]

> In particular, Example 1 of Reinmuller discloses using a low amount of Hylagel, a "cross-linked hyaluronic acid," 0.004 g, while using five times that amount of lidocaine HCl, 0.02 g. (*Id.* at 7:1-12.) A skilled artisan would not have reasonably expected such a composition would work as a dermal filler, where administering a greater amount of HA into the skin was understood to be beneficial to provide the desired filler benefits. (*See supra* Sections IV.D.)

Source: Ex. 1059 at 7:1-29; -1506 POR at 25-26, 65-69; Ex. 2013 at ¶¶ 53, 145, 317-18, 320-22.

REINMULLER'S CROSSLINKER IS NOT DISCLOSED

EXAMPLE 1

Production of an injectable gel from the following components:

Component	Amount
cross-linked hyaluronic acid ("Hylagel" Biomatrix Co., NJ, USA)	0.004 g
lidocaine hydrochloride	0.02 g
water, purified (DAB 9)	to 1.0 g

Such glycosaminoglycans are partly commercially available already in a cross-linked state and can be used directly according to the invention (e.g. "Hylon" and "Hylagel", a cross-linked hyaluronic acid from the Biomatrix Company NJ, USA; for the production c.f. also U.S. Pat. Nos. 4,713,448, 4,605,691).

The '448 patent is generally about the modification of HA in animal tissues (specifically, rooster combs) before it is extracted from the tissue. (Ex. 1063 at 2:47-57.) It describes "Hylan"[14] as a "new polymer, obtained as a result of an in situ chemical reaction between HA and a crosslinking-agent," formaldehyde.

The '691 patent relates to crosslinked HA gels and describes various ways to make them, using DVS as the crosslinking agent, including numerous preparation examples evaluating the effects of HA molecular weight, alkali concentration, HA concentration, HA/DVS ratio, sodium chloride, and mixture with other polymers on the swelling properties of the gel. (Ex. 1062 at 1:56-2:24, Examples 1-16.) Neither patent referenced "Hylagel" or associated it with a particular HA preparation.

Source: Ex. 1059 at 3:49-54, 7:1-12; Ex. 2013 at ¶ 144; -1508 POR at 62.

REINMULLER SPECIFICALLY EXCLUDES CROSSLINKED HA FOR "COSMETICS OR AS SKIN CARE PRODUCTS"

The present invention therefore also concerns the use of the cross-linked glycosaminoglycans described above with the exception of cross-linked hyaluronic acid or cross-linked N-carboxybutylchitosan for cosmetics or as skin care products. In particular the cross-linked glycosaminoglycans that were previously stated as being preferred and distinctively described are used for this.

Source: Ex. 1059 at 6:47-53; -1508 POR at 27.

REINMULLER DISCLOSES "CONTROLLED" AND "PROLONGED" RELEASE

These substances can be present bound firmly to the glycosaminoglycans such as e.g. antibiotics with a heteropolar charge of opposite polarity i.e. as a component of the cross-linked glycosaminoglycans and are then released during the degradation of the cross-linked glycosaminoglycans or they can be released by a controlled release type of system.

In the preferred application according to the invention in the form of an injection, the preparations can for example contain local anaesthetics to avoid pain when the injection cannula is inserted. The preparations preferably contain an anionically or cationically charged molecule such as gentamycin as an antibiotic which is bound as a counter-ion to the cross-linked glycosaminoglycans and thus remains immobilized in loco which prolongs the action accordingly.

Source: Ex. 1059 at 4:38-5:2; -1508 POR at 27.

REINMULLER + LEBRETON + MONHEIT DOES NOT DISCLOSE OR SUGGEST MANY OF THE CLAIMED LIMITATIONS

- Petitioner has also failed to establish the following limitations in the asserted references:
  - pH of about 7
  - Specific amounts of free HA
  - Extrusion force and viscosity
  - Degree of crosslinking
- **Petitioner abandoned its Reinmuller arguments on Reply**

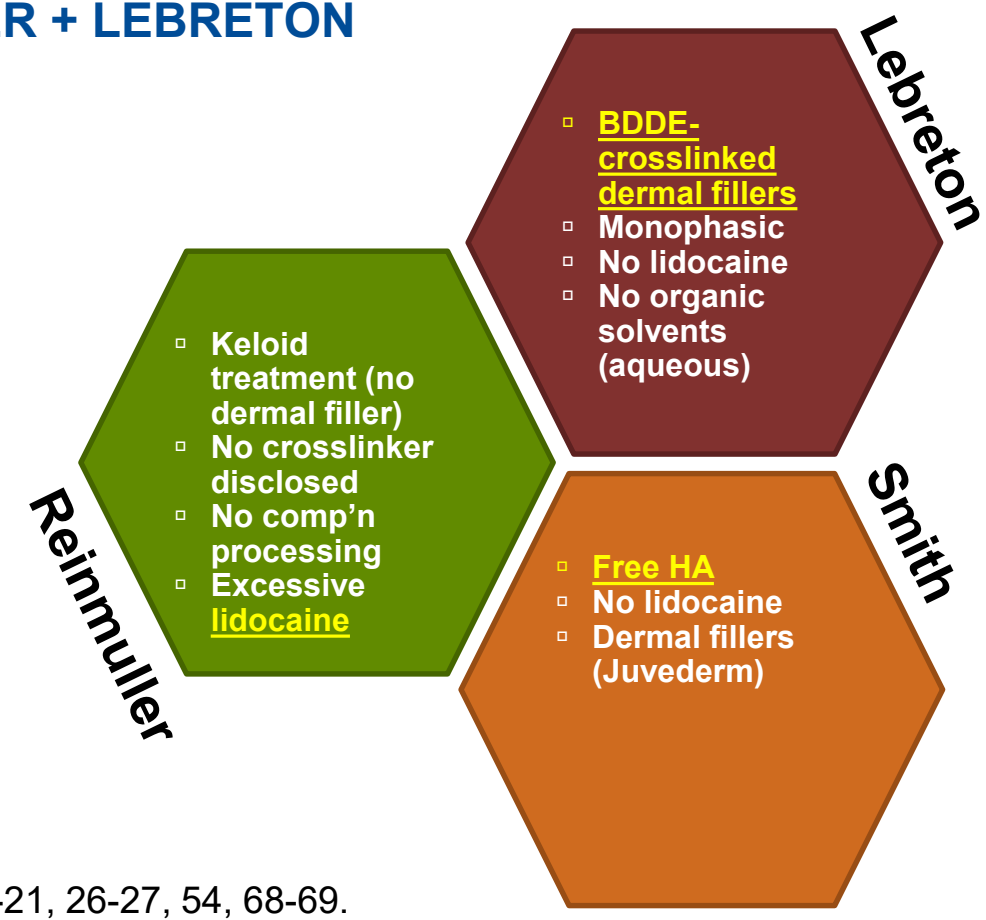
> [13] Reinmuller too suggests success, even if it was not a "dermal" filler. EX1059, 7:1-18.

Source: -1506 Pet. at 42-44; -1508 Pet. at 41-42; -1506 POR at 70; -1508 POR at 67; Reply at 42; -1506 Reply at 32 n.13; -1508 Reply at 32 n.13.

REINMULLER + LEBRETON COMBINATIONS

01506	01508	01509
Reinmuller + Lebreton + Monheit	Reinmuller + Lebreton + Monheit	Reinmuller + Lebreton + Monheit
		Reinmuller + Lebreton + Smith

THERE IS NO MOTIVATION TO COMBINE REINMULLER + LEBRETON



Source: -1509 POR at 20-21, 26-27, 54, 68-69.

GROUP D: -00084 IPR GROUNDS

IPR2020-00084 GROUNDS

00084
PMA P050047/S005
Weinkle
U.S. 2010/0028438
P050047 + Kinney

IPR2020-00084 GROUNDS

00084
PMA P050047/S005
Weinkle
U.S. 2010/0028438
P050047 + Kinney

CLAIMS 1-4 OF THE '519 PATENT ARE ADEQUATELY DESCRIBED BY THE PROVISIONAL APPLICATIONS

It is believed by the inventor of the present invention that such degradation may primarily occur because many, perhaps most crosslinked HA based gels are conventionally manufactured in a manner that produces gels which are "biphasic" in nature, and are not sufficiently cohesive to prevent such degradation when lidocaine HCl is added. It has now been discovered that the addition of lidocaine HCl to sufficiently cohesive crosslinked HA-based compositions does not cause any substantial or significant degradation of the compositions, and the compositions maintain their integrity, in terms of rheology, viscosity, appearance and other characteristics even when stored for a lengthy period of time and even when subjected to heat and pressure sterilization, for example, autoclaving.

Source: Ex. 1013 at 14; -0084 POR at 35-36.

FIGURES 6-8 ALSO DESCRIBE CLAIMS 1-4

Fig. 6 (SAMPLE 5)

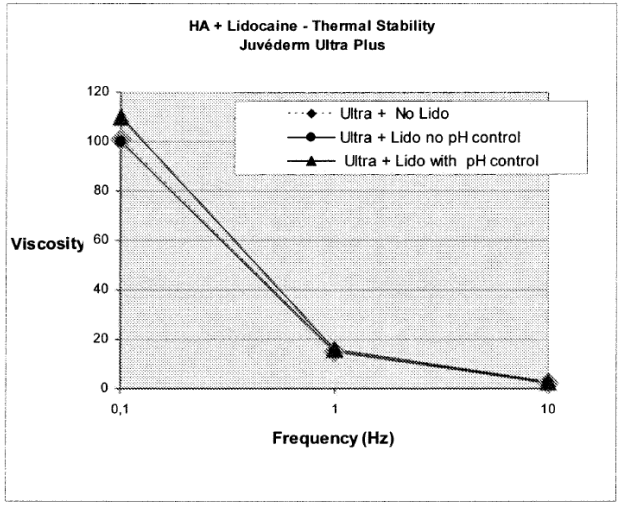


Fig. 7 (SAMPLE 5)

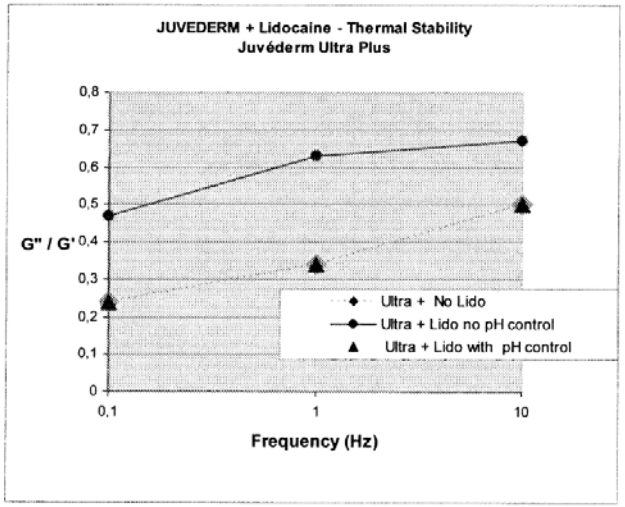
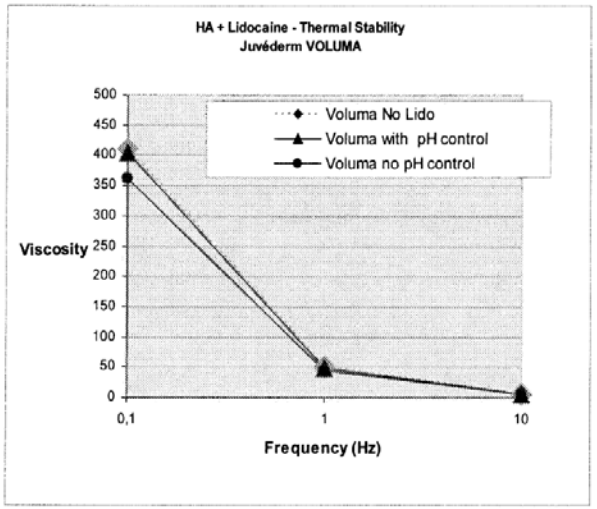


Fig. 8 (SAMPLE 6)



Source: Ex. 1013 at 41-43; -0084 POR at 35-37.

EXAMPLE 2 DESCRIBES CLAIMS 1-4

The Table below provides a summary of stability testing results on the composition manufactured in accordance with the invention.

Test	HA/lidocaine Composition		
	3 month results	6 month results	9 month results
Aspect Transparent and homogeneous	Conforms	Conforms	Conforms
pH	7.2	7.2	7.2
Extrusion Force (N)	11.9	11.1	11.9
NaHA Concentration (mg/g)	23.8	23.1	24.2
Sterility	Conforms	Conforms	Conforms
Osmolarity (mOsm/kg)	349	329	342
Lidocaine Content (%)	0.29	0.29	0.29
2,6-dimethylaniline content	Conforms	Conforms	Conforms

It is discovered that at 9 months time (from manufacture date), the composition continues to meet the product specifications.

Source: Ex. 1013 at 25; -0084 POR at 36-37.

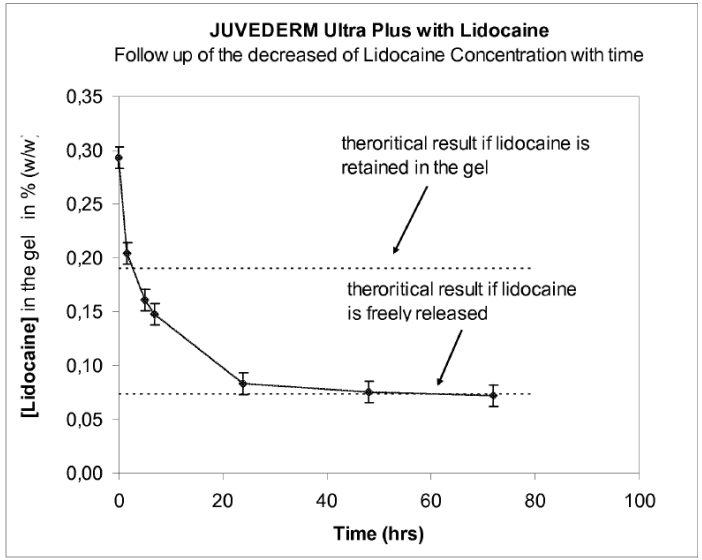
THE PROVISIONAL APPLICATIONS ALSO DISCLOSE SUFFICIENT SPECIES AND MORE

The step of crosslinking may be carried out using means known to those of skill in the art. Those skilled in the art appreciate how to optimize the conditions of crosslinking according to the nature of the HA, and how to carry out the crosslinking to an optimized degree. The degree of crosslinking is preferably sufficient for the final hydrogel composition obtained from the present methods to remain implanted at the injection site without excessive diffusion away from this injection site. In some embodiments of the present invention, the degree of crosslinking is at least about 2% to about 20%, and more preferably is about 4% to about 12%, wherein the degree of crosslinking is defined as the percent weight ratio of the crosslinking agent to HA-monomeric units in the composition.

Source: Ex. 1013 at 18; -0084 POR at 37-38.

THE PROVISIONAL APPLICATIONS ALSO DISCLOSE SUFFICIENT SPECIES AND MORE

Curve 2:



The profile of the concentration of lidocaine in the gel Juvéderm Ultra Plus with time shows that it reaches the equilibrium that corresponds to free release of Lidocaine

This in vitro study shows that the lidocaine is not retained in the Juvéderm Gel with Lidocaine and is freely released.

Source: Ex. 1013 at 29; -0084 POR at 37-38.

THE ’884 APPLICATION / ’795 PATENT DISCLOSES THE SAME STABILITY TESTS AS THE PRIORITY APPLICATIONS

The Specification of US 8,357,795 B2 (the “’795 patent,” which issued from the ’884 application) discloses the same stability tests as the priority applications. *See* Ex. 1082 cols. 15–17, ll. 21–2).

Source: -0084 ID at 23; *see also* Ex. 1082 at cols. 15-17.

THE ’884 APPLICATION / ’795 PATENT PROVIDES EVEN MORE DISCLOSURE THAN THE PROVISIONAL APPLICATIONS

The step of crosslinking may be carried out using any means known to those of ordinary skill in the art. Those skilled in the art appreciate how to optimize conditions of crosslinking according to the nature of the HA, and how to carry out crosslinking to an optimized degree.

Degree of crosslinking for purposes of the present disclosure is defined as the percent weight ratio of the crosslinking agent to HA-monomeric units within the crosslinked portion of the HA based composition. It is measured by the weight ratio of HA monomers to crosslinker (HA monomers: crosslinker).

The degree of crosslinking in the HA component of the present compositions is at least about 2% and is up to about 20%.

In other embodiments, the degree of crosslinking is greater than 5%, for example, is about 6% to about 8%.

In some embodiments, the degree of crosslinking is between about 4% to about 12%. In some embodiments, the degree of crosslinking is less than about 6%, for example, is less than about 5%.

In some embodiments, the HA component is capable of absorbing at least about one time its weight in water. When neutralized and swollen, the crosslinked HA component and water absorbed by the crosslinked HA component is in a weight ratio of about 1:1. The resulting hydrated HA-based gels have a characteristic of being highly cohesive.

The HA-based gels in accordance with some embodiments of the invention may have sufficient cohesivity such that the gels will not undergo substantial phase separation after centrifugation of the gel at 2000 rd/min for 5 minutes. In another embodiment, the gels have the characteristic of being capable of absorbing at least one time their weight of water and have sufficient cohesivity such that when swollen with water at a gel/water weight ratio of about 1:1, the gels maintain their integrity, for example, when subjected to centrifugation.

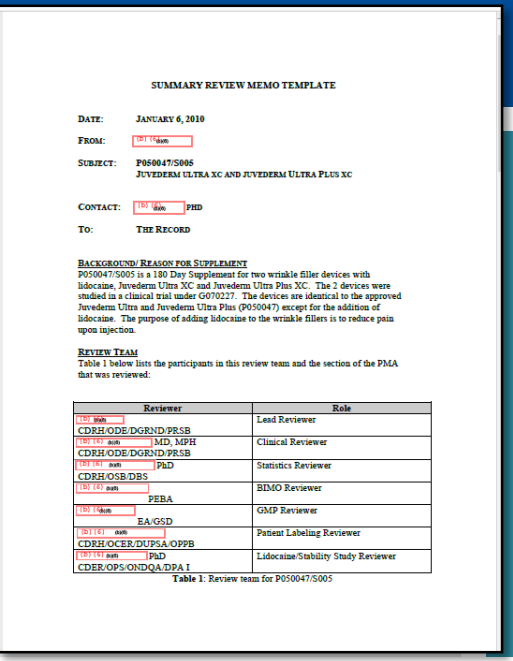
Source: Ex. 1082 at 10:11-45; -0084 POR at 38.

CLAIMS 1-4 OF THE ’519 PATENT ARE NOT ANTICIPATED BY P050047/S005, WEINKLE, OR US 2010/0028438

> Because the filing date of the ’884 application antedates the dates of the art references cited by Petitioner, we determine that P050047/S005, Weinkle, and the ’438 application do not qualify as prior art to the ’519 patent, we find that the evidence presented does not demonstrate a reasonable likelihood that Petitioner would prevail on Grounds 1–3.

Source: -0084 ID at 24.

P050047/S005—EXHIBIT 1060



SUMMARY REVIEW MEMO TEMPLATE

DATE: JANUARY 6, 2010

FROM: [b) (6) duvm]

SUBJECT: P050047/S005
JUVEDERM ULTRA XC AND JUVEDERM ULTRA PLUS XC

CONTACT: [(b) (6) duvm] PHD

TO: THE RECORD

BACKGROUND/ REASON FOR SUPPLEMENT
P050047/S005 is a 180 Day Supplement for two wrinkle filler devices with lidocaine, Juvederm Ultra XC and Juvederm Ultra Plus XC. The 2 devices were studied in a clinical trial under G070227. The devices are identical to the approved Juvederm Ultra and Juvederm Ultra Plus (P050047) except for the addition of lidocaine. The purpose of adding lidocaine to the wrinkle fillers is to reduce pain upon injection.

REVIEW TEAM
Table 1 below lists the participants in this review team and the section of the PMA that was reviewed:

Reviewer	Role
[(b) duvm] CDRH/ODE/DGRND/PRSB	Lead Reviewer
[(b) (6) duvm] MD, MPH CDRH/ODE/DGRND/PRSB	Clinical Reviewer
[(b) (6) duvm] PhD CDRH/OSB/DBS	Statistics Reviewer
[(b) (6) duvm] PEBA	BIMO Reviewer
[(b) (6) duvm] EA/GSD	GMP Reviewer
[(b) (6) duvm] CDRH/OCER/DUPSA/OPPB	Patient Labeling Reviewer
[(b) (6) duvm] PhD CDER/OPS/ONDQA/DPA I	Lidocaine/Stability Study Reviewer

Table 1: Review team for P050047/S005

- Not qualified as prior art
- Purports to be the fifth supplement to P050047 relating to Juvederm Ultra XC and Ultra Plus XC
- Discloses HA filler with lidocaine but does not provide information regarding crosslinker used

Source: Ex. 1060 at 1, 2, 6; -0084 POR at 20, 59-60.

WEINKLE—EXHIBIT 1070

Original Contribution

A multi-center, double-blind, randomized controlled study of the safety and effectiveness of Juvéderm® injectable gel with and without lidocaine

Susan H Weinkle, MD,[1] David E Bank, MD,[2] Charles M Boyd, MD,[3] Michael H Gold, MD,[4] Jane A Thomas, AAS, CCRA,[5] & Diane K Murphy, MBA[5]

[1]Bradenton, Florida, USA
[2]The Center for Dermatology, Cosmetic & Laser Surgery, Mt. Kisco, New York, USA
[3]The Boyd Dillard Institute of Aesthetic and Dermatologic Surgery, Ypsilanti, Michigan, USA
[4]Tennessee Clinical Research Center, Nashville, Tennessee, USA
[5]Allergan, Santa Barbara, California, USA

Summary

Introduction Pain is a common patient complaint during dermal filler injections. The primary objective of this study was to compare a new formulation of Juvéderm® injectable gel with lidocaine (denoted as JUV + L) to commercially-available Juvéderm® injectable gel without lidocaine (denoted as JUV) with respect to procedural pain scores in subjects desiring nasolabial fold (NLF) correction.

Methods Subjects received randomized treatment with the lidocaine filler in one NLF and the filler without lidocaine in the other NLF. Investigators determined the appropriate formulation (Ultra or Ultra Plus) and volume of material to inject but were blinded as to which syringe contained lidocaine. Subjects rated procedural pain (pain during injection) using an 11-point scale within 30 min after receiving treatment in both NLFs and compared procedural pain between right and left NLFs using a 5-point scale. NLF severity was rated by both subjects and investigators before and 2 weeks after treatment.

Results The mean difference on the procedural pain scale was 3.4 ($P < 0.0001$), and 93% of subjects found JUV + L to be less or slightly less painful than JUV. Improvement in NLF severity was comparable for both products. Common treatment site reactions (CTRs) of pain and tenderness were considerably less frequent for JUV + L than JUV while all other CTRs showed no statistically significant differences.

Conclusion The dermal filler formulated with lidocaine is effective in reducing procedural pain during correction of facial wrinkles and folds while maintaining a similar safety and effectiveness profile to the filler without lidocaine.

Keywords: dermal filler, hyaluronic acid, patient satisfaction, wrinkles, randomized controlled trial

Introduction

Pain is a common patient complaint during dermal filler injections, and anesthetics are frequently used to make the procedure more comfortable. However, administration of injectable anesthesia takes time and may distort the area to be treated, and the effects of topical anesthetic are limited and not immediate.

Collagen-based fillers have typically included an anesthetic (lidocaine) in their formulations to reduce procedural pain such that injectable anesthesia may not be required. Hyaluronic acid (HA)-based dermal fillers

Correspondence: Diane Murphy, 71 South Los Carneros, Goleta, CA 93117.
E-mail: murphy_diane@allergan.com

Accepted for publication April 24, 2009

- Describes clinical trial to compare pain scores of patients receiving different versions of Juvederm (with and without lidocaine)
- Does not describe chemical or physical properties of Juvederm products
- Addition of lidocaine (mixed into final product by physician) prompts questions of sterility, consistency, and could change flow characteristics

Source: Ex. 1070 at 205, 208; -0084 POR at 21.

P050047/S005 DOES NOT DISCLOSE A STERILE BDDE-CROSSLINKED HA DERMAL FILLER

Q Now, Exhibit 1060 does not discuss how to make either of the Juvéderm products discussed in Exhibit 1060, correct?

A I do not see that information included.

Q And Exhibit 1060 does not identify the cross-linker that's used in these products, correct?

A It is not included in this document.

Q Exhibit 1060 does not disclose the pH, the HA concentration, the cross-linker concentration or the time required for the reaction to make the HA composition, does it?

A That information is not included in this document.

Q And Exhibit 1060 does not disclose how to sterilize the product in Exhibit 1060, correct?

A Not included in this document.

Source: Ex. 2100 at 466:15-467:23; -0084 POR at 40.

WEINKLE DOES NOT DISCLOSE THE CROSSLINKER OR STERILIZATION USED IN THE PRODUCT IT DESCRIBES

Q Weinkle 1070 does not mention the cross-linker used in Juvéderm, correct?

A Correct.

Q And Weinkle 1070 does not describe how to sterilize the HA product described in 1070, correct?

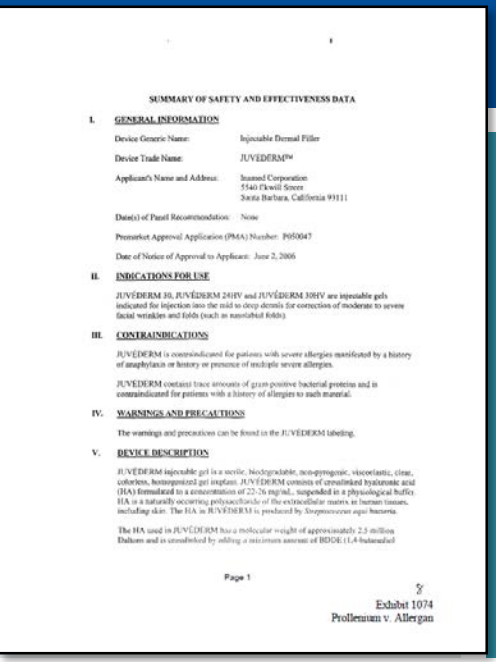
A Just checking. She does not provide that information.

Source: Ex. 2100 at 464:13-15; 465:12-17; -0084 POR at 41.

IPR2020-00084 GROUNDS

00084
PMA P050047/S005
Weinkle
U.S. 2010/0028438
P050047 + Kinney

P050047—EXHIBIT 1074



SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name: Injectable Dermal Filler

Device Trade Name: JUVÉDERM™

Applicant's Name and Address: Inamed Corporation
5540 Ekwill Street
Santa Barbara, California 93111

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P050047

Date of Notice of Approval to Applicant: June 2, 2006

II. INDICATIONS FOR USE

JUVÉDERM 30, JUVÉDERM 24HV and JUVÉDERM 30HV are injectable gels indicated for injection into the mid to deep dermis for correction of moderate to severe facial wrinkles and folds (such as nasolabial folds).

III. CONTRAINDICATIONS

JUVÉDERM is contraindicated for patients with severe allergies manifested by a history of anaphylaxis or history or presence of multiple severe allergies.

JUVÉDERM contains trace amounts of gram-positive bacterial proteins and is contraindicated for patients with a history of allergies to such material.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the JUVÉDERM labeling.

V. DEVICE DESCRIPTION

JUVÉDERM injectable gel is a sterile, biodegradable, non-pyrogenic, viscoelastic, clear, colorless, homogenized gel implant. JUVÉDERM consists of crosslinked hyaluronic acid (HA) formulated to a concentration of 22-26 mg/mL, suspended in a physiological buffer. HA is a naturally occurring polysaccharide of the extracellular matrix in human tissues, including skin. The HA in JUVÉDERM is produced by *Streptococcus equi* bacteria.

The HA used in JUVÉDERM has a molecular weight of approximately 2.5 million Daltons and is crosslinked by adding a minimum amount of BDDE (1,4-butanediol

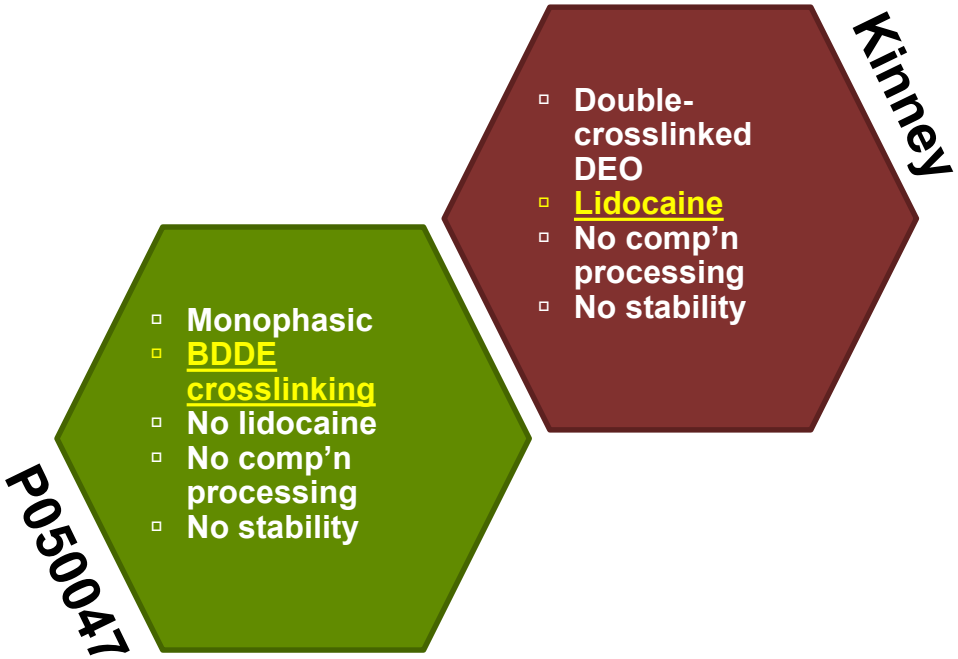
Page 1

Exhibit 1074
Prollenium v. Allergan

- Not demonstrated publicly accessible as of August 2008
- Provides only a partial description of Juvederm and its properties; no information on how to make Juvederm
- Does not disclose or suggest lidocaine

Source: Ex. 1074 at 1; -0084 POR at 24, 59-60.

THERE IS NO MOTIVATION TO COMBINE P050047 AND KINNEY



Source: -0084 POR at 60-61.

P050047 + KINNEY DOES NOT DISCLOSE OR SUGGEST MANY OF THE CLAIMED LIMITATIONS

- Petitioner has also failed to establish the following limitations in the asserted references:
  - Dermal filler with lidocaine would have performed substantially the same as an otherwise identical composition without lidocaine
  - Lidocaine freely released in vivo
  - Claimed composition substantially as stable as comparative, non-lidocaine-containing composition for at least 3, 6, and 9 months

Source: -0084 Pet. at 47-52; -0084 POR at 65-69.

IPR2019-01505	IPR2019-01506	IPR2019-01508	IPR2019-01509	IPR2019-01617	IPR2019-1632	IPR2020-0084
'475	'795	'013	'322	'676	'795	'519
Grounds	Grounds	Grounds	Grounds	Grounds	Grounds	Grounds
Group A **Ground 1:** Lebreton in view of Sadozai and Monheit **Ground 2:** Lebreton in view of Sadozai and Clark **Ground 3:** Lebreton in view of Sadozai and Smith	**Group A** **Ground 1:** Lebreton in view of Sadozai	**Group A** **Ground 1:** Lebreton in view of Sadozai and Monheit	**Group A** **Ground 1:** Lebreton in view of Sadozai and Monheit **Ground 2:** Lebreton in view of Sadozai and Smith	**Group A** **Ground 1:** Lebreton in view of Sadozai and CTA Summary **Ground 2:** Lebreton in view of Sadozai , CTA Summary, and Monheit	**Group A** **Ground 1:** CTA Summary **Ground 2:** Lebreton in view of Sadozai	**Group A** **Ground 4:** Lebreton in view of Sadozai
Group B **Ground 4:** Kinney in view of Zhao, Narins, and Monheit **Ground 5:** Kinney in view of Zhao, Narins, and Clark **Ground 6:** Kinney in view of Zhao, Narins, and Smith	**Group B** **Ground 2:** Kinney in view of Zhao and Narins	**Group B** **Ground 2:** Kinney in view of Zhao and Narins	**Group B** **Ground 3:** Kinney in view of Zhao, Narins, and Monheit **Ground 4:** Kinney in view of Zhao, Narins, and Smith	**Group B** **Ground 3:** Kinney in view of Zhao and Narins		
	Group C **Ground 3:** Reinmuller in view of Lebreton and Monheit	**Group C** **Ground 3:** Reinmuller in view of Lebreton and Monheit	**Group C** **Ground 5:** Reinmuller in view of Lebreton and Monheit **Ground 6:** Reinmuller and Lebreton in view of Smith			
						Group D **Ground 1:** PMA P050047/S005 **Ground 2:** Weinkle **Ground 3:** U.S. 2010/0028438 **Ground 5:** PMA P050047 in view of Kinney

ALLERGAN'S MOTION TO EXCLUDE

DR. DEVORE'S TESTIMONY SHOULD BE EXCLUDED UNDER FED. R. EVID. 702

EXPERT TESTIMONY MUST MEET THE STANDARDS OF FED. R. EVID. 702 AND 703

- Board must act in "a gatekeeping role" to ensure the "scientific validity—and thus the evidentiary relevance and reliability" of expert testimony. *Daubert v. Merrell Dow. Pharm., Inc.*, 509 U.S. 579, 594-95, 597 (1993).
- Must be based on "facts or data" and use "reliable principles and methods." Fed. R. Evid. 702.
- Should "flow from existing research." *Daubert v. Merrell Dow Pharm., Inc.*, 43 F.3d 1311, 1317 (9th Cir. 1995).
- Petitioner bears the burden of establishing the relevance and reliability of its experts' testimony by a preponderance of the evidence. *United States v. Williams*, 506 F.3d 151, 160 (2d. Cir. 2007).

Source: Patent Owner's MTE at 3.

DR. DEVORE'S DECLARATION IS UNRELIABLE

- Used the wrong legal standard—hunting for claim limitations like "**pieces of [a] puzzle** in individual prior art references."
- **Could not answer questions** about the chemical structures of lidocaine, HA, or the crosslinkers—which all experts agreed a POSA would know.
- Misrepresented his credentials and **does not have a Biochemistry degree.**
- "**[L]itigation-driven testimony**" that is inconsistent with the expert's earlier, non-litigation writings, should be given little, if any, weight. *Velander v. Gardner*, 348 F.3d 1359, 1371 (Fed. Cir. 2003).

Source: Ex. 2100 at 45:17-47:8, 58:9-59:3, 311:11-314:10, 346:23-359:13, 371:24-372:5; Ex. 2200 at 154:6-24; Ex. 2013 at ¶¶ 38-39, IV.E.2; Ex. 1002 at ¶ 5; Patent Owner's MTE at 4-5.

DR. DEVORE ADMITTED HE IMPROPERLY USED HINDSIGHT

So your first step was identifying the patent that was to be challenged, correct?

MR. THOMAS: Objection, scope. Objection, form.

A I believe that's correct.

And then you looked at the claims to be challenged, correct?

MR. THOMAS: Objection, form, misstates testimony.

A I believe that's correct.

Q So if we -- if we think about the claim like a puzzle with different pieces in it, you went and found each of the pieces of that puzzle in individual prior art references, correct?

A Again, I believe that's correct.

"[I]t is improper to combine references 'like separate pieces of a simple jigsaw puzzle' without 'explain[ing] [a] reason or motivation . . . to place these pieces together.'"

Merck Sharp & Dohme B.V. v. Warner Chilcott Co., LLC, 711 F. App'x 633, 636 (Fed. Cir. 2017) (quoting *InTouch Techs., Inc. v. VGO Commc'ns, Inc.*, 751 F.3d 1327, 1349 (Fed. Cir. 2014)).

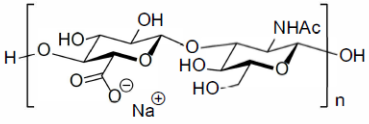
Source: Ex. 2100 at 370:12-23, 371:24-372:6; POR at 28-29.

DR. DEVORE AGREES THAT KNOWLEDGE OF CHEMICAL STRUCTURES AND HOW THEY INTERACT IS IMPORTANT . . .

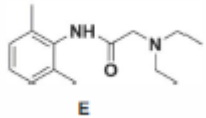
There are no functional groups in lidocaine that would be expected to react with a BDDE-crosslinked HA network or free HA, just like there are no functional groups in a DEO-, DVS-, or BDCI-crosslinked HA composition that react with lidocaine.

Q So in order to provide an opinion with respect to this non-reaction between HA and lidocaine, it's important for you to understand how those chemical structures interact or don't interact with each other, correct?

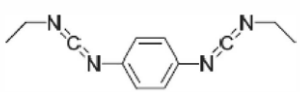
A That's correct.



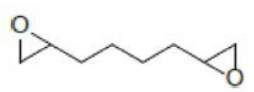
HA - Ex. 2158



Lidocaine - Ex. 2165



pBCDI - Ex. 2156



DEO - Ex. 2152

BDDE - Ex. 2153

Source: Ex. 1002 at ¶ 189; Ex. 2100 at 357:20-358:1; Ex. 2013 at ¶ 38; POR at 29-30.

DR. DEVORE COULD NOT IDENTIFY THE CHEMICAL SUBSTITUENTS OF HA

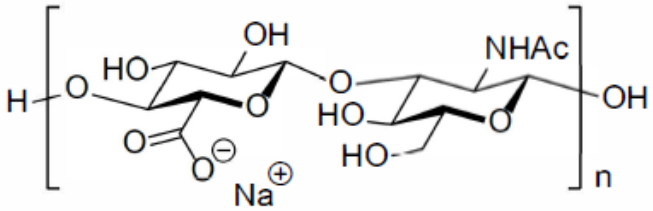
Q And which one is which? Do you know whether -- is the glucuronic acid on the left or on the right?

A Glucuronic acid is on -- I get these confused -- the right.

Q Okay.

And so the N-acetyl glucosamine, then, would be on the left; is that right?

A Yes.



Ex. 2158

D-Glucoronic acid N-Acetyl-D-Glucosamine

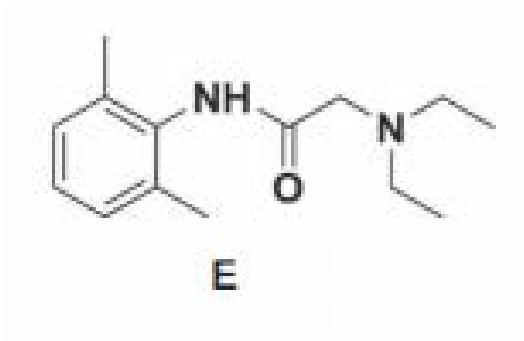
Ex. 2013 at ¶ 38

Source: Ex. 2100 at 58:19-59:3; Ex. 2013 at ¶ 38 n.2; Patent Owner's MTE at 14-15.

DR. DEVORE COULD NOT IDENTIFY LIDOCAINE

your declarations are there in front of you -- are you able to identify which of these structures is lidocaine that's depicted here on Exhibit 65?

A No.



E

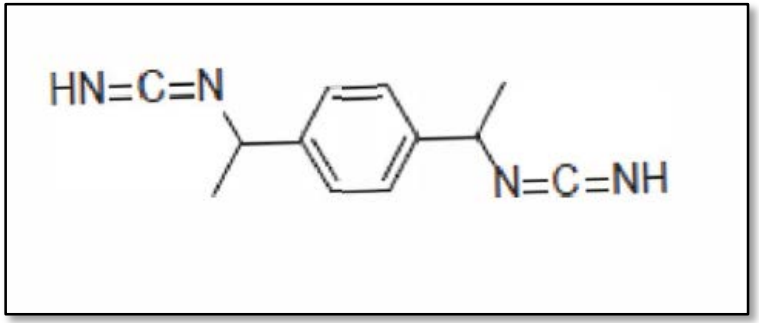
Lidocaine - Ex. 2165 (“E”)

Source: Ex. 2100 at 359:1-5; Ex. 2165; Ex. 2013 at ¶ 105; Patent Owner's MTE at 14-15.

DEVORE USED THE WRONG STRUCTURE OF PBCDI

Q In your reports, when you were discussing either BDCI or BCDI in the reports that are at issue in this case, the molecule that you're talking about there is what's shown on Exhibit 55, correct?

A Right.



Ex. 2155 ("Exhibit 55," wrongly cited by Dr. DeVore as pBCDI)

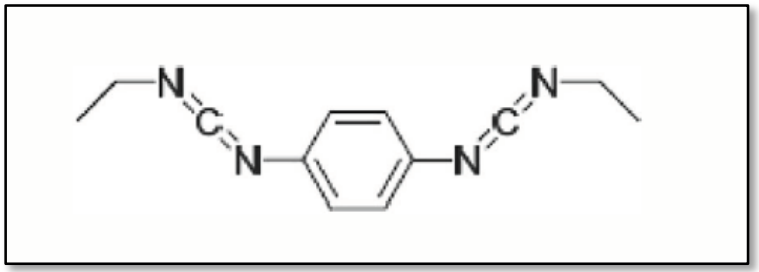


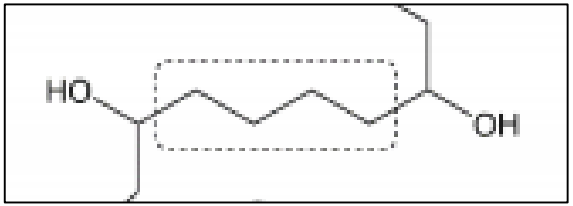
Exhibit 2156 ("Exhibit 56," correct pBCDI)

Source: Ex. 2100 at 348:20-25; Ex. 2013 at ¶ 68 n.8; POR at 39 n.3.

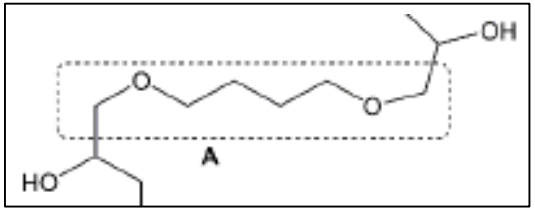
DR. DEVORE CONFUSED DEO AND BDDE

Q Now, taking a look at the compounds shown on Exhibit C, the structure there, what cross-linking agent is used there?

A Sometimes I get DEO and BDDE confused, but it's -- I think it was -- I think this one is BDDE.



DEO - Ex. 2174 (“C”)



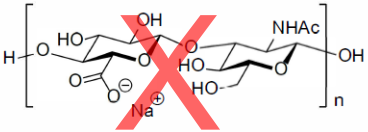
BDDE - Ex. 2174 (“A”)

Source: Ex. 2100 at 354:6-11; Patent Owner's MTE at 14.

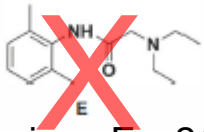
AND DR. DEVORE COULD NOT EXPLAIN THE CORE LIDOCAINE CHEMISTRY AT ISSUE IN THIS CASE

Q So given that you don't know which of these is lidocaine, you're not prepared to answer questions today relating to how the functional groups of these different -- how lidocaine interacts with HA, correct?

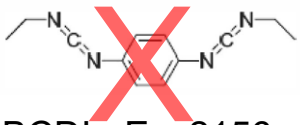
A Correct.



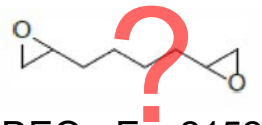
HA - Ex. 2158



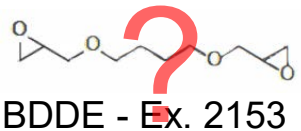
Lidocaine - Ex. 2165



pBCDI - Ex. 2156



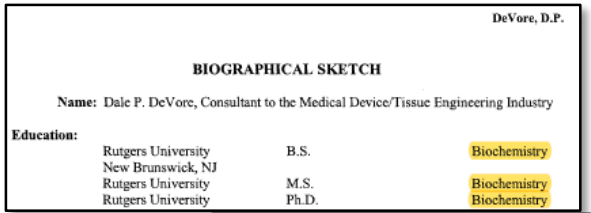
DEO - Ex. 2152



BDDE - Ex. 2153

Source: Ex. 2100 at 359:6-13; Ex. 2165; Ex. 2013 at ¶ 68 n.8; POR at 29-30.

DR. DEVORE REPEATEDLY MISREPRESENTED HIMSELF AS HAVING DEGREES IN "BIOCHEMISTRY"



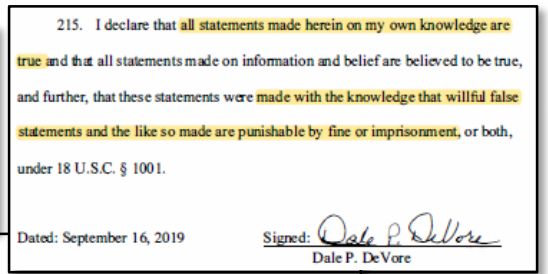
DeVore, D.P.

BIOGRAPHICAL SKETCH

Name: Dale P. DeVore, Consultant to the Medical Device/Tissue Engineering Industry

Education:

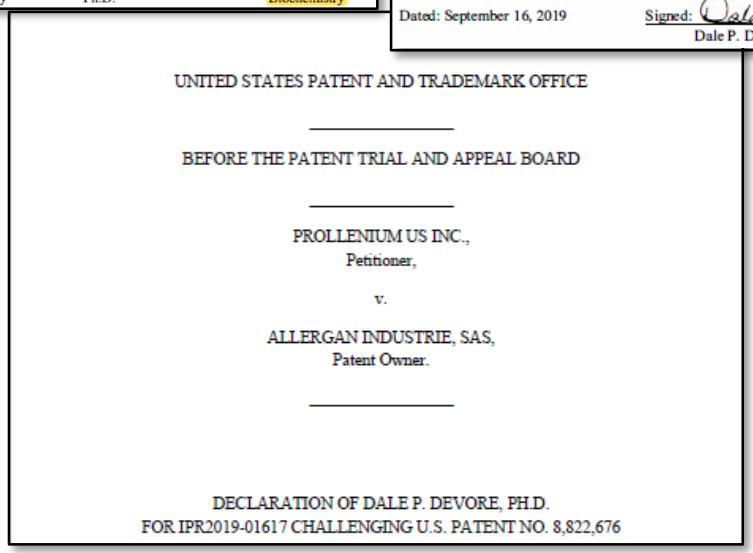
Rutgers University New Brunswick, NJ	B.S.	Biochemistry
Rutgers University	M.S.	Biochemistry
Rutgers University	Ph.D.	Biochemistry



215. I declare that all statements made herein on 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 18 U.S.C. § 1001.

Dated: September 16, 2019

Signed: Dale P. DeVore
Dale P. DeVore



UNITED STATES PATENT AND TRADEMARK OFFICE

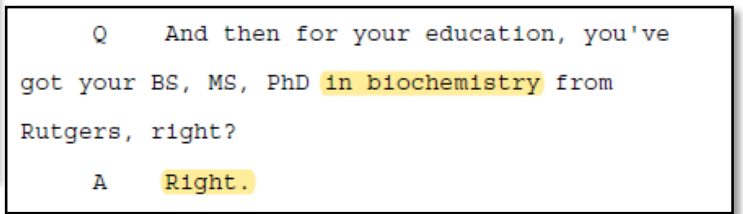
BEFORE THE PATENT TRIAL AND APPEAL BOARD

PROLLENIUM US INC.,
Petitioner,

v.

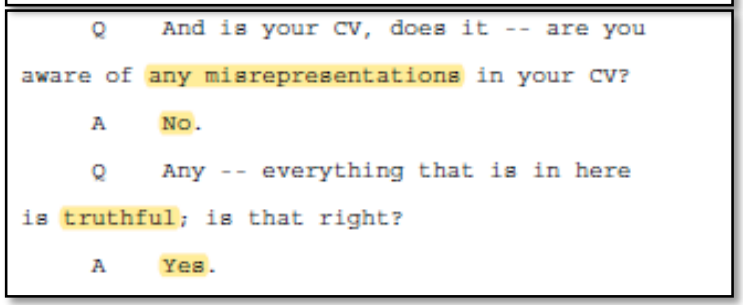
ALLERGAN INDUSTRIE, SAS,
Patent Owner.

DECLARATION OF DALE P. DEVORE, PH.D.
FOR IPR2019-01617 CHALLENGING U.S. PATENT NO. 8,822,676



Q And then for your education, you've got your BS, MS, PhD in biochemistry from Rutgers, right?

A Right.



Q And is your CV, does it -- are you aware of any misrepresentations in your CV?

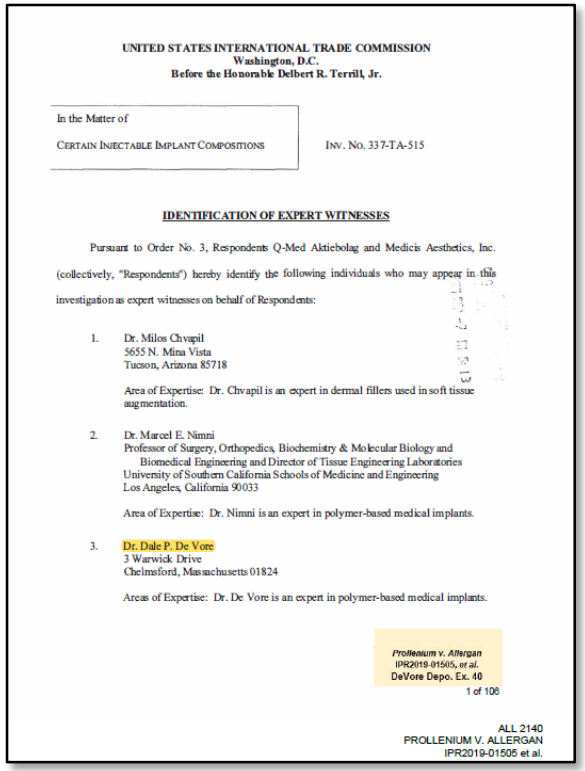
A No.

Q Any -- everything that is in here is truthful; is that right?

A Yes.

Source: Ex. 1002 at 1, ¶ 215; Ex. 2100 at 50:9-21; POR at 30-31; *see also* Patent Owner's MTE at 5; Patent Owner's MTE Reply at 1.

DR. DEVORE MISREPRESENTED HIS CREDENTIALS TO THE INTERNATIONAL TRADE COMMISSION IN 2004



UNITED STATES INTERNATIONAL TRADE COMMISSION
Washington, D.C.
Before the Honorable Delbert R. Terrill, Jr.

In the Matter of
CERTAIN INJECTABLE IMPLANT COMPOSITIONS — INV. NO. 337-TA-515

IDENTIFICATION OF EXPERT WITNESSES

Pursuant to Order No. 3, Respondents Q-Med Aktiebolag and Medicis Aesthetics, Inc. (collectively, "Respondents") hereby identify the following individuals who may appear in this investigation as expert witnesses on behalf of Respondents:

1. Dr. Milos Chvapil
5655 N. Mina Vista
Tucson, Arizona 85718

Area of Expertise: Dr. Chvapil is an expert in dermal fillers used in soft tissue augmentation.

2. Dr. Marcel E. Nimni
Professor of Surgery, Orthopedics, Biochemistry & Molecular Biology and Biomedical Engineering and Director of Tissue Engineering Laboratories
University of Southern California Schools of Medicine and Engineering
Los Angeles, California 90033

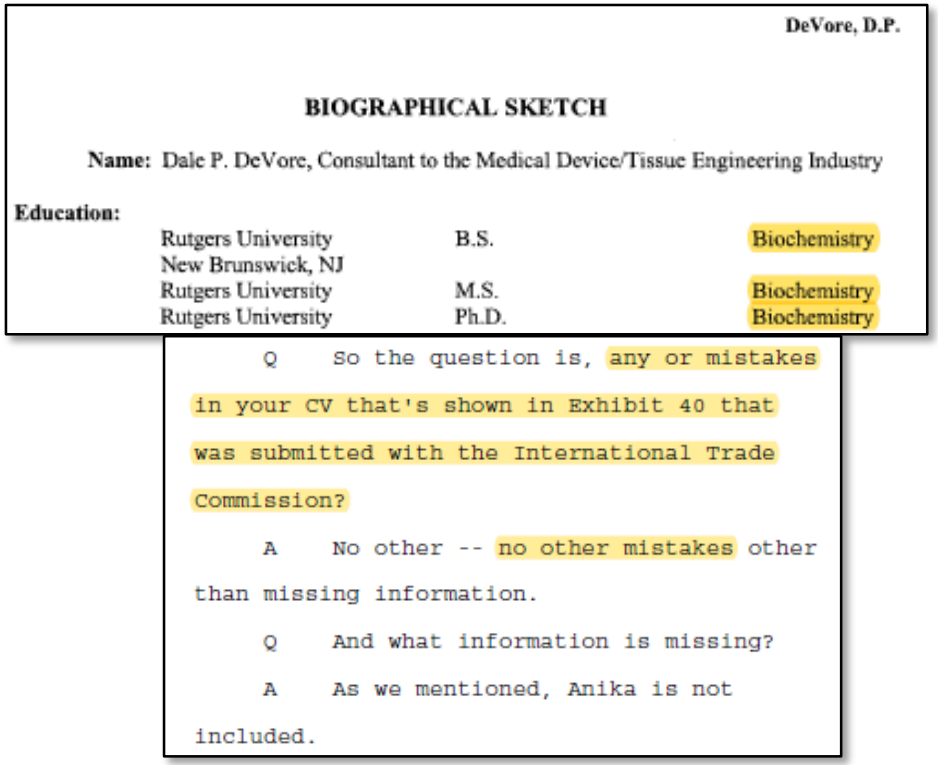
Area of Expertise: Dr. Nimni is an expert in polymer-based medical implants.

3. Dr. Dale P. De Vore
3 Warwick Drive
Chelmsford, Massachusetts 01824

Areas of Expertise: Dr. De Vore is an expert in polymer-based medical implants.

Prollenium v. Allergan
IPR2019-01505, *et al.*
DeVore Depo. Ex. 40
1 of 106

ALL 2140
PROLLENIUM V. ALLERGAN
IPR2019-01505 et al.



DeVore, D.P.

BIOGRAPHICAL SKETCH

Name: Dale P. DeVore, Consultant to the Medical Device/Tissue Engineering Industry

Education:

Rutgers University New Brunswick, NJ	B.S.	Biochemistry
Rutgers University	M.S.	Biochemistry
Rutgers University	Ph.D.	Biochemistry

Q So the question is, any or mistakes in your CV that's shown in Exhibit 40 that was submitted with the International Trade Commission?

A No other -- no other mistakes other than missing information.

Q And what information is missing?

A As we mentioned, Anika is not included.

Source: Ex. 2140 at 1, 78; Ex. 2100 at 310:8-16; POR at 30-31; *see also* Patent Owner's MTE at 5; Patent Owner's MTE Reply at 1.

DR. DEVORE MISREPRESENTED HIS CREDENTIALS TO THE UNITED STATES DISTRICT COURT FOR THE W.D. MISSOURI IN 2011

3. I received my PhD in 1973 from Rutgers University in Biochemistry.

IN THE UNITED STATES DISTRICT COURT
FOR THE WESTERN DISTRICT OF MISSOURI
FOR THE SOUTHERN DIVISION

Exhibit B

ESM TECHNOLOGIES, INC.
Plaintiff,
v.
BIOVA, LLC,
AND MATTHEW STEGENGA
Defendants.

Civil Action No. 6:10cv03009-RED

DECLARATION OF DALE PAUL DEVORE, PhD

I, Dale P. DeVore state as follows:

1. I am over the age of twenty-one (21) and have personal knowledge of the facts stated herein. I submit this Declaration in support of Plaintiff ESM Technologies, Inc.'s proposed claim constructions in the above-entitled matter.

2. I am a co-inventor of U.S. Patent No. 6,946,551 entitled: "PREPARATION OF HYALURONIC ACID FROM EGGSHELL MEMBRANE," (hereinafter "the '551 patent"). I am also employed by the assignee of the patent, ESM Technologies, Inc., as a technical consultant.

3. I received my PhD in 1973 from Rutgers University in Biochemistry. Since that time, for the past 38 years, I have worked in the medical device and tissue engineering industry in various capacities for a number of major manufacturing and design companies, such as 3M, Medchem Products, and BioForm Medical. My work has focused on the development of biochemical products for various applications, with an emphasis on research and development. I am currently working as Chief Scientist for Euclid Systems Corporation, an ophthalmic company, and as a consultant to a number of medical device and tissue engineering companies. My CV is attached as Exhibit 1 and contains a detailed listing of my work history, my

1

Prollenium v. Allergan
IPR2019-01505, et al.
DeVore Depo. Ex. 29
1 of 39

ALL 2129
PROLLENIUM V. ALLERGAN
IPR2019-01505 et al.

I declare under penalty of perjury that the foregoing is true and accurate.

Executed this 13th day of July, 2011.

Dale P. DeVore, PhD

1	Q Your declaration was truthful when
2	you signed it, correct?
3	A Correct.
4	Q And the statements made in it are
5	accurate?
6	A If I cite it, I believe they were
7	accurate.
8	Q They were truthful?
9	A Yes.
10	Q And there weren't
11	misrepresentations?
12	A No.

Source: Ex. 2129 at 1, 10; Ex. 2100 at 276:1-12; POR at 30-31; *see also* Patent Owner's MTE at 5; Patent Owner's MTE Reply at 1.

DR. DEVORE MISREPRESENTED HIS CREDENTIALS TO THE UNITED STATES DISTRICT COURT FOR THE C.D. CALIFORNIA IN 2013

Case 8:12-cv-00516-JVS-RNB Document 116-1 Filed 03/19/13 Page 2 of 22 Page ID #:2088

DALE P. DE VORE, PH.D.

BIOGRAPHICAL SKETCH

Name: **Dale P. DeVore, PhD**
Executive/Consultant to the Pharmaceuticals/Medical Device/Tissue Engineering Industry

Address: 3 Warwick Drive, Chelmsford, MA 01824

Education:

Rutgers University New Brunswick, NJ	B.S.	Biochemistry
Rutgers University	M.S.	Biochemistry
Rutgers University	Ph.D.	Biochemistry

Q So were there -- were there any other mistakes in your CV that were submitted to either the Western District of Michigan in the ESM case or the declaration -- or the CV that was submitted to the Central District of California in the BioCell case?

A Hmm, that's weird. Hmm. I don't think so. I never noticed it.

Source: Ex. 2130 at 1, 4; Ex. 2100 at 308:3-8, 19-20; POR at 30-31; *see also* Patent Owner's MTE at 5; Patent Owner's MTE Reply at 1.

DR. DEVORE MISREPRESENTED HIS CREDENTIALS

Q Sir, your degrees are not in biochemistry, are there?

A Food science and technology.

Q Your degrees -- you have a BS, an MS and a PhD in food science?

A That's what I just said.

Q Correct. Okay.

You did not tell the Patent Trial and Appeal Board that you had a degree in food science, did you, sir?

A Not specifically, no.

Source: Ex. 2100 at 312:2-8, 313:10-13; POR at 30-31; *see also* Patent Owner's MTE at 5; Patent Owner's MTE Reply at 1.

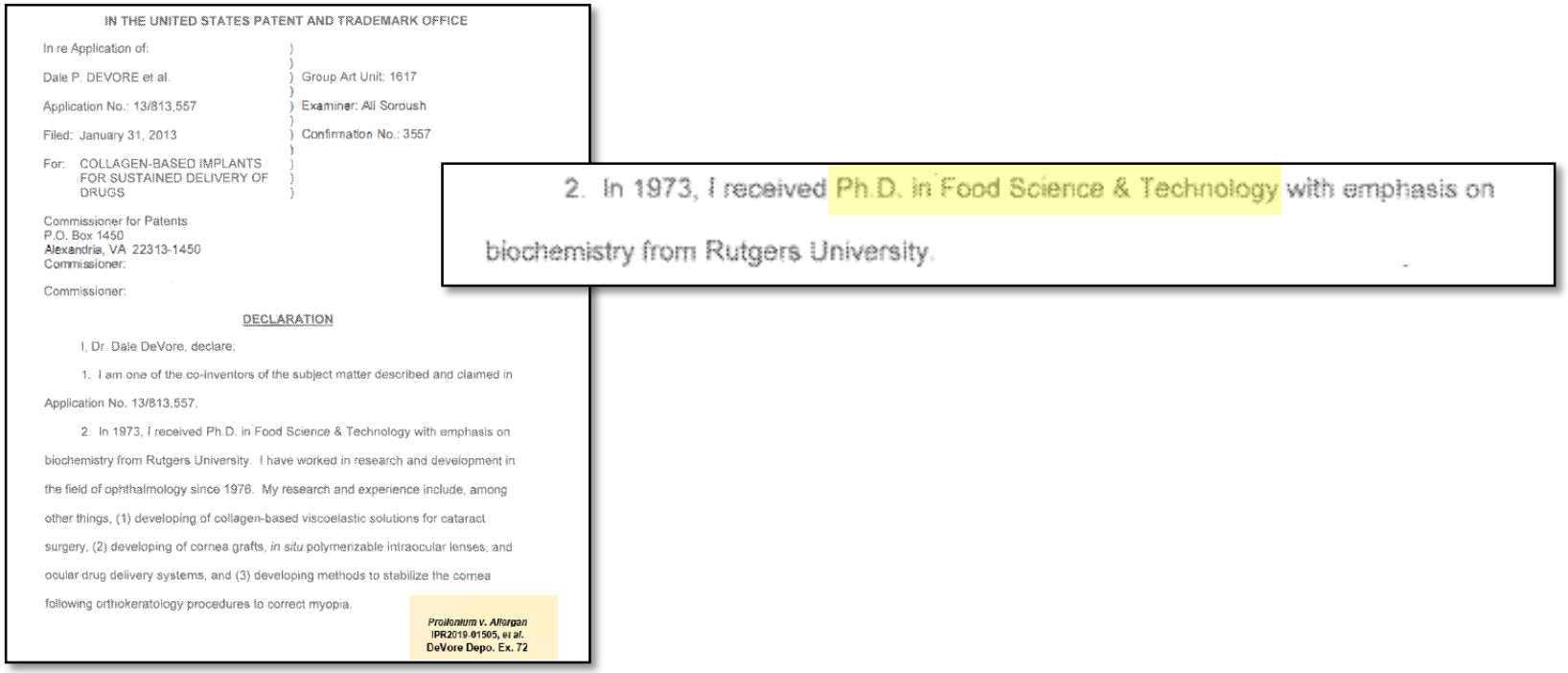
MISREPRESENTATION OF CREDENTIALS VIOLATES THE DUTY OF CANDOR

> While the argument may be made that Dr. Konchitsky's description of his Master's degree is merely harmless embellishment or an artful rewording having the same effective meaning, we find that Dr. Konchitsky, nevertheless, incorrectly described his Master's degree and misrepresented his credentials to the Board.

> Moreover, we agree with the sentiment that "[e]ven the slightest accommodation of deceit or a lack of candor in any material respect quickly erodes the validity of the process.

Source: POR at 31; *Blackberry Corp. v. Zipit Wireless, Inc.*, IPR2014–01506, Paper 50 at 10 (PTAB Mar. 29, 2016).

DR. DEVORE WAS TRUTHFUL WHEN HIS CREDENTIALS WERE NOT RELEVANT



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Dale P. DEVORE et al.
Application No.: 13/813,557
Filed: January 31, 2013
For: COLLAGEN-BASED IMPLANTS FOR SUSTAINED DELIVERY OF DRUGS

Group Art Unit: 1617
Examiner: Ali Soroush
Confirmation No.: 3557

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450
Commissioner:

Commissioner:

DECLARATION

I, Dr. Dale DeVore, declare:

1. I am one of the co-inventors of the subject matter described and claimed in Application No. 13/813,557.

2. In 1973, I received Ph.D. in Food Science & Technology with emphasis on biochemistry from Rutgers University. I have worked in research and development in the field of ophthalmology since 1976. My research and experience include, among other things, (1) developing of collagen-based viscoelastic solutions for cataract surgery, (2) developing of cornea grafts, *in situ* polymerizable intraocular lenses, and ocular drug delivery systems, and (3) developing methods to stabilize the cornea following orthokeratology procedures to correct myopia.

Prollenium v. Allergan
IPR2019-01505, *et al.*
DeVore Depo. Ex. 72

2. In 1973, I received Ph.D. in Food Science & Technology with emphasis on biochemistry from Rutgers University.

Source: Ex. 2172 at 1; *see also* Ex. 2173 at 1; POR at 31.

DR. PRESTWICH'S TESTIMONY SHOULD BE EXCLUDED UNDER FED. R. EVID. 702 AND 703

EXPERT TESTIMONY MUST MEET THE STANDARDS OF FED. R. EVID. 702 AND 703

- Board must act in "a gatekeeping role" to ensure the "scientific validity—and thus the evidentiary relevance and reliability" of expert testimony. *Daubert v. Merrell Dow. Pharm., Inc.*, 509 U.S. 579, 594-95, 597 (1993).
- Must be based on "facts or data" and use "reliable principles and methods." Fed. R. Evid. 702.
- Should "flow from existing research." *Daubert v. Merrell Dow Pharm., Inc.*, 43 F.3d 1311, 1317 (9th Cir. 1995).
- Petitioner bears the burden of establishing the relevance and reliability of its experts' testimony by a preponderance of the evidence. *United States v. Williams*, 506 F.3d 151, 160 (2d. Cir. 2007).

Source: Patent Owner's MTE at 3.

DR. PRESTWICH'S DECLARATION IS UNRELIABLE

- **Selectively submitted testimony** from previously rejected declarations, omitting important concessions.

- **Advances a claim construction** that contradicts his own published writings, the rest of the literature, and common sense.

- **Relies on cherry-picked data** in his current declaration.

Source: Patent Owner's MTE at 5-8.

DR. PRESTWICH SELECTIVELY SUBMITTED EVIDENCE AND EXCLUDED RELEVANT PREVIOUS TESTIMONY

Q. Did you -- did you copy and paste it?

A. In some cases. But in each case, I re-edited each of the phrases

Galderma/Teoxane Declarations, ¶ 83	Redline to EX1105, ¶ 176
The pK_a of lidocaine is known to be temperature dependent, with a pK_a of about 7.9 at room temperature, and a pKa of about 6.6 at 100°C (*Powell*, Table 2). This indicates that upon an increase in temperature, the pH of a lidocaine containing solution would be expected to decrease. For example, a solution of lidocaine HCl will become even more acidic at an elevated temperature for autoclaving.	The pK_a of lidocaine is known to be temperature dependent, with a pK_a of about 7.9 at room temperature, ~~and a pKa of~~meaning a 50:50 ratio of lidocaine base (L) and protonated form (LH^+) at room temperature. Dr. Berkland at ¶ 105 (FN 12) and 109 agree with this statement. The pK_a increases to about 6.6 at 100°C (*Powell*, Exhibit 2042, Table 2). ~~This indicates that upon an increase in temperature, the pH of a lidocaine-containing solution would be expected to decrease. For example, a solution of lidocaine HCl will become even more acidic at an elevated temperature for autoclaving.~~

Source: Surreply at 14 (comparing Ex. 2200G and Ex. 2200I with Ex. 1105); Patent Owner's MTE at 7, 15 (citing Ex. 2200, 20:23-21:5).

DR. PRESTWICH SELECTIVELY SUBMITTED EVIDENCE AND EXCLUDED RELEVANT PREVIOUS TESTIMONY

Galderma/Teoxane Declarations, ¶ 47	Redline to EX1105, ¶ 148
The first crosslinking step of HA with DEO follows a similar chemical pathway as that described above for BDDE, modifying primarily the 6-hydroxyl groups of GlcNAc residues in the HA chain. In contrast to BDDE, which is 12 atoms in length and is hydrophilic due to the presence of two oxygen atoms in the chain, DEO is eight atoms in length, and is more hydrophobic, lacking any oxygen atoms in the chain. In addition, the epoxide groups of DEO are of somewhat lower reactivity than the glycidyl ethers of BDDE.	The first crosslinking step of HA with DEO follows a similar chemical pathway as that described above for BDDE, modifying primarily the 6- hydroxyl groups of GlcNAc residues in the HA chain. ~~In contrast to~~While BDDE~~, which~~ is 12 atoms in length and ~~is hydrophilic due to the presence of~~has two oxygen atoms in the chain, DEO is eight atoms in length, and ~~is more hydrophobic, lacking~~lacks any oxygen atoms in the chain. ~~In addition~~Nonetheless, the terminal epoxide groups of DEO ~~are of somewhat lower reactivity than~~react by the same reaction mechanism as for the epoxide groups of the glycidyl ethers of BDDE.

Source: Surreply at 27 (comparing Ex. 2200G and Ex. 2200I with EX1105); Patent Owner's MTE at 8.

DR. PRESTWICH SELECTIVELY SUBMITTED EVIDENCE AND EXCLUDED RELEVANT PREVIOUS TESTIMONY

Galderma/Teoxane Declarations, ¶ 82 (excerpt)	Redline to EX1105, ¶ 173 (excerpt)
The non-ionized free base form of lidocaine is nearly insoluble in water, whereas the protonated ammonium form is highly soluble in water. The pK_a of lidocaine is about 7.9 at room temperature (*Powell*, Table 2). The pKa expresses the relationship between the two forms of lidocaine: at a pH equal to the pKa, the base and protonated forms of lidocaine are present at equilibrium in equal amounts. At a pH higher than the pKa, the protonated form becomes de-protonated, resulting in a greater proportion of the free base form (a); and at a pH lower than the pKa, the base form becomes protonated (b), resulting in a greater proportion of the protonated form. It was reported that at 25 °C, the pH of maximum stability for lidocaine is 3-6 (*Powell*, p44). Thus, for better solubility and stability, lidocaine is usually provided as the protonated form in an acidic solution, most commonly as a lidocaine HCl solution. Lidocaine HCl powder is commercially available. Dissolving lidocaine HCl powder in water results in an acidic solution. For example, a 0.5% (w/w) solution of lidocaine HCl has a pH of 4-5.5 (See *Ph. Eur. monograph 0227*).	~~The non-ionized free base form of lidocaine is nearly insoluble in water, whereas the protonated ammonium form is highly soluble in water. The pKa of lidocaine is about 7.9 at room temperature (Powell, Table 2). The pKa expresses the relationship between the two forms of lidocaine: at a pH equal to the pKa, the ba e and protonated forms of lidocaine are present at equilibrium in equal amounts. At a pH higher than the pKa, the protonated form becomes de-protonated, resulting in a greater proportion of the free base form (a); and at a pH lower than the pKa, the base form becomes protonated (b), resulting in a greater proportion of the protonated form. It was reported that at~~ At 25 °C, the pH range of maximum stability for lidocaine is 3-6 (*Powell*, Exhibit 2042, p44). Thus, for better solubility and stability, lidocaine is usually provided as the protonated form in an acidic solution, most commonly as a lidocaine HCl solution. Lidocaine HCl powder is commercially available. Dissolving lidocaine HCl powder in water results in an acidic solution. For example, a 0.5% (w/w) solution of lidocaine HCl has a pH of 4-5.5 ~~(See *Ph. Eur. monograph 0227*).~~ EX2043 936-37.

Source: Surreply at 16 (comparing Ex. 2200G and Ex. 2200I with EX1105); *see also* Patent Owner's MTE at 7.

WHILE DR. PRESTWICH INTRODUCED AN ENTIRELY NEW CONSTRUCTION

Petition:

(iv) [1.3] *wherein the lidocaine is freely released in vivo; and*

The POSITA, understanding that lidocaine was loaded into the crosslinked gel by a diffusion process in Sadozai, would recognize that combining BDDE-crosslinked HA with a lidocaine-containing buffer would load lidocaine into that gel by diffusion as well. EX1002 ¶ 144. The POSITA would understand that no covalent bonds were formed during the loading process. EX1002 ¶ 147. Although Sadozai includes language suggesting that BDCI-crosslinked HA may be used for controlled release, the POSITA would not have considered this language relevant to the release of lidocaine.

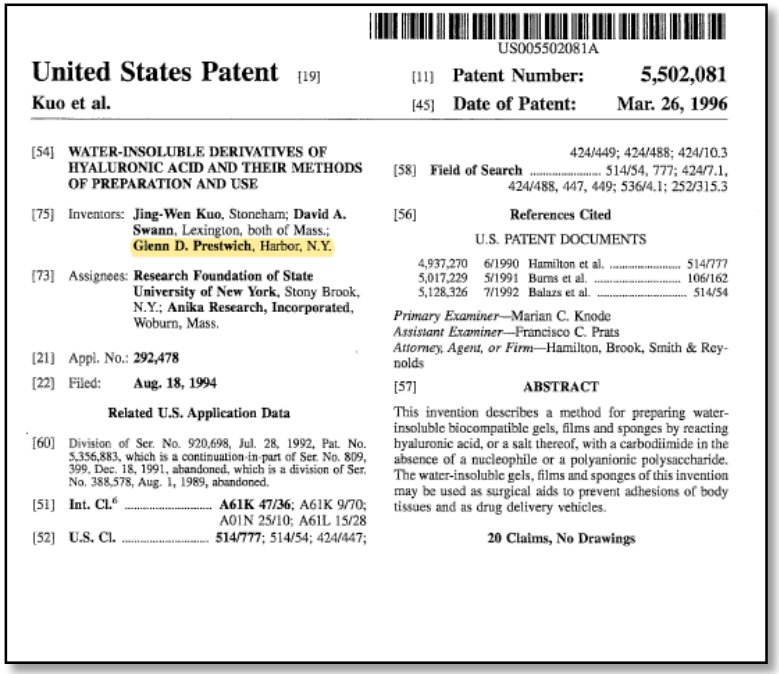
The POSITA would consequently understand the lidocaine was not covalently bound to the DEO-double crosslinked HA described by Kinney. EX1002 ¶ 178 (explaining that a chemical modification to the lidocaine molecule itself would be needed to covalently attach lidocaine to the crosslinked HA, and such a modified compound would no longer be called "lidocaine hydrochloride.").

Dr. Prestwich's Reply Declaration:

From this, Dr. Berkland asserts without any evidence that the POSITA would have expected "controlled release" from the Sadozai gels, and not free release in a manner effective to relieve pain. I disagree with his reasoning and his unnecessarily restrictive use of the term "controlled release", which broadly implies control of release, not only *restricted* control of release. In other words, control of release allows for free release to occur by not restricting release.

Source: Petition at 31-32, 44; Ex. 1105 at ¶ 82; POR at 19; Surreply at 21-23; Patent Owner's MTE at 5-6.

DR. PRESTWICH'S CONSTRUCTION OF "FREELY RELEASED" CONTRADICTS HIS OWN PATENT



US005502081A

United States Patent [19]

Kuo et al.

[11] **Patent Number: 5,502,081**

[45] **Date of Patent: Mar. 26, 1996**

[54] **WATER-INSOLUBLE DERIVATIVES OF HYALURONIC ACID AND THEIR METHODS OF PREPARATION AND USE**

[75] Inventors: **Jing-Wen Kuo**, Stoneham; **David A. Swann**, Lexington, both of Mass.; **Glenn D. Prestwich**, Harbor, N.Y.

[73] Assignees: **Research Foundation of State University of New York**, Stony Brook, N.Y.; **Anika Research, Incorporated**, Woburn, Mass.

[21] Appl. No.: **292,478**

[22] Filed: **Aug. 18, 1994**

Related U.S. Application Data

[60] Division of Ser. No. 920,698, Jul. 28, 1992, Pat. No. 5,356,883, which is a continuation-in-part of Ser. No. 809,399, Dec. 18, 1991, abandoned, which is a division of Ser. No. 388,578, Aug. 1, 1989, abandoned.

[51] **Int. Cl.**[6] **A61K 47/36**; A61K 9/70; A01N 25/10; A61L 15/28

[52] **U.S. Cl.** **514/777**; 514/54; 424/447; 424/449; 424/488; 424/10.3

[58] **Field of Search** 514/54, 777; 424/7.1, 424/488, 447, 449; 536/4.1; 252/315.3

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,937,270	6/1990	Hamilton et al.	514/777
5,017,229	5/1991	Burns et al.	106/162
5,128,326	7/1992	Balazs et al.	514/54

Primary Examiner—Marian C. Knode
Assistant Examiner—Francisco C. Prats
Attorney, Agent, or Firm—Hamilton, Brook, Smith & Reynolds

[57] **ABSTRACT**

This invention describes a method for preparing water-insoluble biocompatible gels, films and sponges by reacting hyaluronic acid, or a salt thereof, with a carbodiimide in the absence of a nucleophile or a polyanionic polysaccharide. The water-insoluble gels, films and sponges of this invention may be used as surgical aids to prevent adhesions of body tissues and as drug delivery vehicles.

20 Claims, No Drawings

In yet another embodiment, this invention is directed to drug delivery systems having a pharmaceutically-active substance, such as a therapeutic drug, which covalently bonds to, or non-covalently interacts with, the modified HA polymer of the invention. The non-covalent interactions include ionic and hydrophobic interactions in which the drug is dispersed within the gel, film or sponge. In both cases, the modified HA functions as a vehicle which provides the controlled release of a drug from the system.

EXAMPLE 31

This example illustrates that the reaction of the biscarbodiimide p-phenylenebis-(ethyl)-carbodiimide and HA at a molar equivalent ratio of 12% yields a water-insoluble gel.

Source: Patent Owner's MTE at 6 (citing Ex. 2200CC, U.S. Patent 5,502,081, col. 4 ll. 7-15, col. 20 ll. 52-56).

DR. PRESTWICH'S TESTIMONY UNDERMINED BY SCIENTIFIC LITERATURE: "CONTROLLED RELEASE" IS NOT "FREELY RELEASED IN VIVO"

And so on that page, Page 381 at the top, it has a "Definitions" section. And below that there is an entry for [as read]:

"Controlled-release dosage forms."

Do you see that?

A. Yes. The types of controlled-release products and definitions.

Q. And the definition it provides there is [as read]:

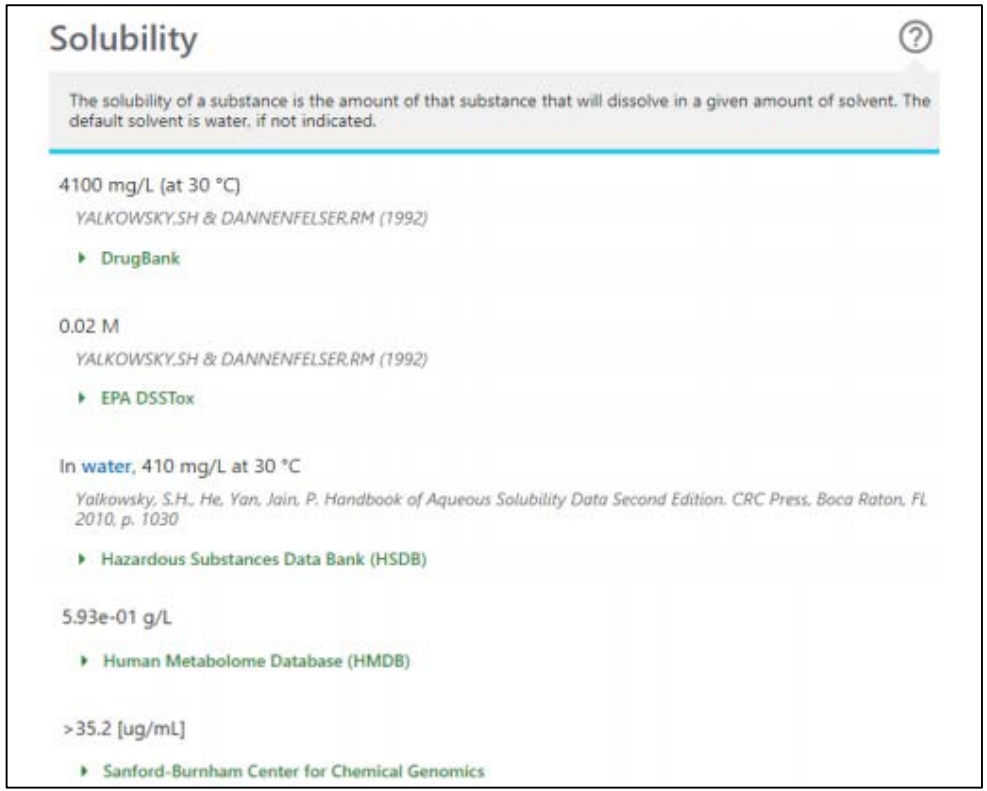
"A class of pharmaceuticals or other biologically active products from which a drug is release from the delivery system in a planned, predictable, and slower-than-normal manner."

Do you see that?

A. Yes. I see that -- the way in which they characterized it in this definition.

Source: Ex. 2200 at 385:8-24; Ex. 2200ZZ; Surreply at 22-23; Patent Owner's MTE at 5-6.

DR. PRESTWICH CHERRY-PICKED EVIDENCE FROM THE ART



Solubility

The solubility of a substance is the amount of that substance that will dissolve in a given amount of solvent. The default solvent is water, if not indicated.

4100 mg/L (at 30 °C)

YALKOWSKY,SH & DANNENFELSER,RM (1992)

▸ DrugBank

0.02 M

YALKOWSKY,SH & DANNENFELSER,RM (1992)

▸ EPA DSSTox

In water, 410 mg/L at 30 °C

Yalkowsky, S.H., He, Yan, Jain, P. Handbook of Aqueous Solubility Data Second Edition. CRC Press, Boca Raton, FL 2010, p. 1030

▸ Hazardous Substances Data Bank (HSDB)

5.93e-01 g/L

▸ Human Metabolome Database (HMDB)

>35.2 [ug/mL]

▸ Sanford-Burnham Center for Chemical Genomics

Source: Patent Owner's MTE at 7 (citing Ex. 2200FFF); Surreply at 15-16.

DR. PRESTWICH DID NOT EVEN KNOW THE IPR GROUNDS

Q. Okay. Do you understand that there is a distinction between what is in the grounds and what other exhibits are being offered?

THE WITNESS: Perhaps, that's a -- that is a legal point that I am not clear on.

BY MS. GEERS:

Q. Okay. So with respect to all of these exhibits, you are not -- you don't know whether they are just exhibits or whether they formed a part of the grounds that are asso- -- that are asserted by Prollenium. Is that fair?

A. It's my -- it's my understanding that the grounds are listed and that -- for example, in this grounds there are two -- two exhibits -- two exhibits of prior art that are the basis for the grounds.

In this case, we -- we're calling them Kinney and Zhao.

So the other ones are supporting exhibits.

Source: Ex. 2200 at 431:4-24; Surreply at 7.

DR. PRESTWICH'S TESTIMONY IS UNFAIRLY PREJUDICIAL AND SHOULD BE EXCLUDED UNDER FED. R. EVID. 403

DR. PRESTWICH'S TESTIMONY IS UNFAIRLY PREJUDICIAL AND OUTSIDE THE SCOPE OF REPLY

- **Alters the instituted ground (as does the Reply)** from Lebreton in view of Sadozai to just Lebreton, and cites new evidence to show motivation to add lidocaine (Ex. 1216).

> The differences between Lebreton and Sadozai are irrelevant to motivation. First, the alleged "incompatibility" is a red herring because Prollenium's Ground is that a POSITA would simply add lidocaine *to Lebreton's gels*.

> 163. In addition, multiple patent references (including ones published before and with filing dates before or around the priority date of the Challenged Patents) taught or suggested crosslinked HA dermal fillers containing lidocaine.

Source: Reply at 27; Ex. 1105 at ¶ 163; Patent Owner's MTE at 10-11; Patent Owner's ID Paper at 1.

DR. PRESTWICH'S TESTIMONY IS UNFAIRLY PREJUDICIAL AND OUTSIDE THE SCOPE OF REPLY

Cites new evidence to try to show a reasonable expectation of success of adding 0.3% lidocaine (Ex. 1103, Ex. 1216); and to allegedly show autoclaving was used to sterilize virtually all HA compositions (Ex. 1107).

63. There are other reasons why a POSITA would not be concerned with precipitation. The POSITA knew that 0.3% (w/w) lidocaine had been used in all of the regulatory approved, lidocaine-containing dermal fillers, including three of which that contained crosslinked HA, before the priority date of the Challenged Patents. EX1012, 742; EX1216, 155; Exhibit 1103, 25.

166. Autoclaving was used to sterilize virtually all types of HA compositions prior to 2008. For example, an aqueous formulation containing uncrosslinked sodium HA was sterilized in an autoclave at a temperature of 121°C for 30 minutes. Drizen, Exhibit 1107, 7:19-25.

Source: Ex. 1105 at ¶¶ 63, 166; Patent Owner's MTE at 10-11, 13.

DR. PRESTWICH'S TESTIMONY IMPROPERLY TRIES TO FILL THE GAPS IN DR. DEVORE'S TESTIMONY

For the free HA limitation, Dr. DeVore asserted without evidence that Monheit would give the POSA motivation to add free HA (to meet that claim limitation). But then Prestwich cited new Ex. 1210 for that same proposition:

Dr. DeVore

155. Claim 2 depends from claim 1 and specifies that the composition also includes free HA. In my opinion, the POSITA would have been motivated, in particular by Monheit, to incorporate uncrosslinked (free) HA into the lidocaine-containing BDDE-crosslinked HA composition. The POSITA would have been

Dr. Prestwich

44. As discussed at ¶¶ [153-156], it was conventional to include free HA in a dermal filler to optimize injectability; and adding free HA to dermal fillers was a simple task within the level of skill in the art in August 2008. For example, Piron 2008, Exhibit 1210 (published in June 2008 from applications filed in 2006 and

Source: Ex. 1002 at ¶ 155; Ex. 1105 at ¶ 44; Patent Owner's MTE at 14.

DR. PRESTWICH'S TESTIMONY IMPROPERLY TRIES TO FILL THE GAPS IN DR. DEVORE'S TESTIMONY

DeVore asserted without evidence that the four **crosslinkers** were similar, and then Prestwich cited new portions of Zhao for the same (wrong) assertion:

Dr. DeVore

153. The BDCI-crosslinked gels share far more similarities with BDDE-crosslinked gels than differences. Both are crosslinked networks of hyaluronic

189. The prior art explicitly taught that both DVS- and BDCI-crosslinked HA compositions were successfully autoclave-sterilized in the presence of lidocaine, and the POSITA would have inferred that the double DEO-crosslinked HA composition (i.e., Puragen Plus) was heat sterilized as well because that was the standard sterilization method for dermal fillers at the time (as still is today). In my opinion, the similarities between the differently crosslinked HA gels far outweigh any differences that might exist between them.

Dr. Prestwich

118. Methods of performing these crosslinking reactions as well as methods for the pre- and post-crosslinking processing of HA to form fillers were well known in the art by 2008. Further, Zhao includes examples which demonstrate the double crosslinking of HA with structurally diverse crosslinkers including DEO, glutaraldehyde, and epichlorohydrin. EX1058, Tables 1-3.

Source: Ex. 1002 at ¶¶ 153, 189; Ex.1105 at ¶ 118; Patent Owner's MTE at 14.

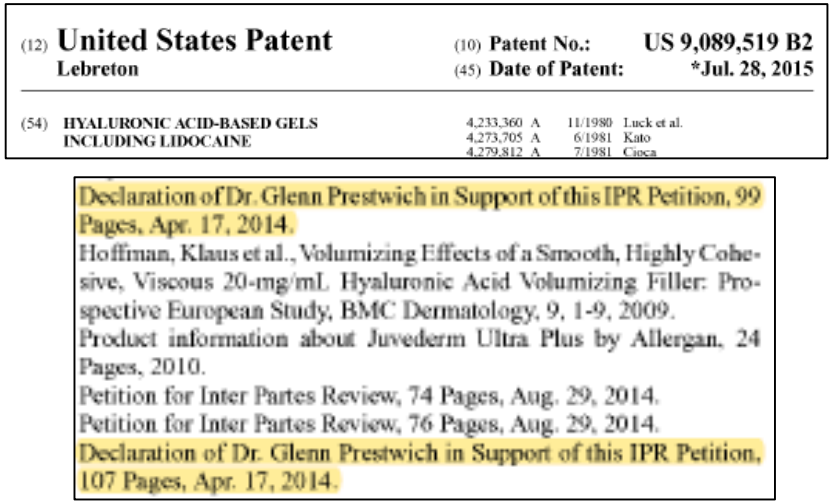
LARGE PORTIONS OF DR. PRESTWICH'S DECLARATION HAVE ALREADY BEEN CONSIDERED AND REJECTED IN PRIOR IPRS

Q. Okay. Okay. So, ultimately, I think we discussed yesterday, in both of those cases the Board declined to institute the IPRs. Is that your understanding?

THE WITNESS: That's what I have come to learn subsequently.

Source: Ex. 2200 at 477:4-12; *see also id.* at 171:16-24; Surreply at 7-8; *see also* Patent Owner's MTE at 15-16.

LARGE PORTIONS OF DR. PRESTWICH'S DECLARATION WERE CONSIDERED AND REJECTED DURING PROSECUTION



(12) **United States Patent**
Lebreton

(10) **Patent No.: US 9,089,519 B2**
(45) **Date of Patent: *Jul. 28, 2015**

(54) **HYALURONIC ACID-BASED GELS INCLUDING LIDOCAINE**

4,233,360	A	11/1980	Luck et al.
4,273,705	A	6/1981	Kato
4,279,812	A	7/1981	Cioca

Declaration of Dr. Glenn Prestwich in Support of this IPR Petition, 99 Pages, Apr. 17, 2014.

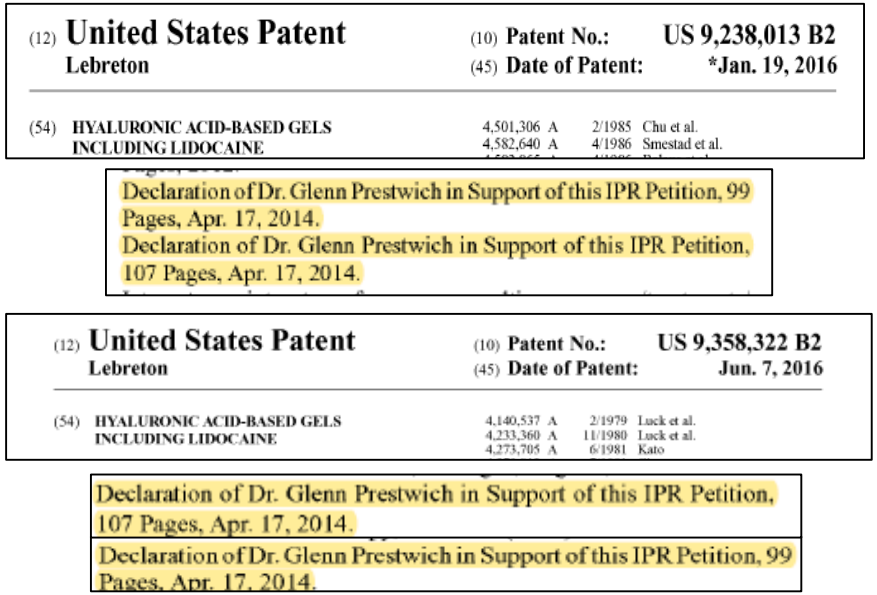
Hoffman, Klaus et al., Volumizing Effects of a Smooth, Highly Cohesive, Viscous 20-mg/mL Hyaluronic Acid Volumizing Filler: Prospective European Study, BMC Dermatology, 9, 1-9, 2009.

Product information about Juvederm Ultra Plus by Allergan, 24 Pages, 2010.

Petition for Inter Partes Review, 74 Pages, Aug. 29, 2014.

Petition for Inter Partes Review, 76 Pages, Aug. 29, 2014.

Declaration of Dr. Glenn Prestwich in Support of this IPR Petition, 107 Pages, Apr. 17, 2014.



(12) **United States Patent**
Lebreton

(10) **Patent No.: US 9,238,013 B2**
(45) **Date of Patent: *Jan. 19, 2016**

(54) **HYALURONIC ACID-BASED GELS INCLUDING LIDOCAINE**

4,501,306	A	2/1985	Chu et al.
4,582,640	A	4/1986	Smestad et al.

Declaration of Dr. Glenn Prestwich in Support of this IPR Petition, 99 Pages, Apr. 17, 2014.

Declaration of Dr. Glenn Prestwich in Support of this IPR Petition, 107 Pages, Apr. 17, 2014.

(12) **United States Patent**
Lebreton

(10) **Patent No.: US 9,358,322 B2**
(45) **Date of Patent: Jun. 7, 2016**

(54) **HYALURONIC ACID-BASED GELS INCLUDING LIDOCAINE**

4,140,537	A	2/1979	Luck et al.
4,233,360	A	11/1980	Luck et al.
4,273,705	A	6/1981	Kato

Declaration of Dr. Glenn Prestwich in Support of this IPR Petition, 107 Pages, Apr. 17, 2014.

Declaration of Dr. Glenn Prestwich in Support of this IPR Petition, 99 Pages, Apr. 17, 2014.

Source: -1508 IPR, Ex. 1001 at 4; -1509 IPR, Ex. 1001 at 6; -0084 IPR, Ex. 1001 at 3; Surreply at 7-8.

PROLLENIUM'S NEW ARGUMENTS AND EVIDENCE VIOLATE BOARD RULES AND THE APA

Petitioner cannot offer new theory of motivation to combine. *Intelligent BioSys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1369 (Fed. Cir. 2016).

> The differences between Lebreton and Sadozai are irrelevant to motivation. First, the alleged "incompatibility" is a red herring because Prollenium's Ground is that a POSITA would simply add lidocaine *to Lebreton's gels*.

> 63. There are other reasons why a POSITA would not be concerned with precipitation. The POSITA knew that 0.3% (w/w) lidocaine had been used in all of the regulatory approved, lidocaine-containing dermal fillers, including three of which that contained crosslinked HA, before the priority date of the Challenged Patents. EX1012, 742; EX1216, 155; Exhibit 1103, 25.

Source: Reply at 27; EX1105 at ¶ 63; Patent Owner's MTE at 10-11.

PROLLENIUM'S NEW ARGUMENTS AND EVIDENCE VIOLATE BOARD RULES AND THE APA

Petitioner cannot cite new sections of reference to "make a meaningfully distinct contention." *Ariosa Diagnostics v. Verinata Health, Inc.*, 805 F.3d 1359, 1367 (Fed. Cir. 2015).

44. As discussed at ¶¶ [153-156], it was conventional to include free HA in a dermal filler to optimize injectability; and adding free HA to dermal fillers was a simple task within the level of skill in the art in August 2008. For example, Piron 2008, Exhibit 1210 (published in June 2008 from applications filed in 2006 and 2007), discloses a BDDE-crosslinked, monophasic hydrogel that can include free HA in varying amounts: "5% to 50%, preferably 10% to 30%, and even more preferably 15% by weight of the [HA] is in free form." Exhibit 1210, 6.

118. Methods of performing these crosslinking reactions as well as methods for the pre- and post-crosslinking processing of HA to form fillers were well known in the art by 2008. Further, Zhao includes examples which demonstrate the double crosslinking of HA with structurally diverse crosslinkers including DEO, glutaraldehyde, and epichlorohydrin. EX1058, Tables 1-3.

Source: EX1105 at ¶¶ 44, 118; Patent Owner's MTE at 11, 14.

PROLLENIUM'S NEW ARGUMENTS AND EVIDENCE VIOLATE BOARD RULES AND THE APA

Petitioner cannot proceed in a new direction with a new approach on Reply under 37 C.F.R. § 42.23(b). Consolidated Trial Practice Guide (Nov. 2019) at 73-75.

> 75. To the contrary, a POSITA would have expected the increased storage modulus taught by Sadozai to be applicable to a wide range of crosslinked HA fillers, including BDDE-crosslinked HA fillers. It was known that viscosity loss during autoclave sterilization of biopolymers, including HA, was reduced by including a radical scavenging species in the biopolymer composition, including hyaluronic acid. EX1115 ("Ji") ¶¶ [0004, 0051]. Although Ji does not expressly include lidocaine as a suitable radical scavenging moiety, the POSITA would have known that it would be.

Prollenium submitted a declaration from a new expert, including new arguments and over 60 paragraphs of previously-rejected testimony.

Source: EX1105 at ¶¶ 75,120-80; Patent Owner's MTE at 12, 15.