

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ARGENTUM PHARMACEUTICALS LLC
Petitioner

v.

CIPLA LTD.
Patent Owner

Patent No. 8,168,620
Issue Date: May 1, 2012
Title: COMBINATION OF AZELASTINE AND STEROIDS

Inter Partes Review No.: IPR2017-00803

DECLARATION OF DR. MAUREEN D. DONOVAN, Ph.D.

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I, Maureen Donovan, do declare as follows:

I. Introduction

1. I am over the age of eighteen (18) and otherwise competent to make this declaration.
2. I have been retained as an expert witness on behalf of Argentum Pharmaceuticals LLC for a *inter partes* review (IPR) for U.S. Patent No. 8,168,620 (Ex. 1001). I am being compensated for my time in connection with this IPR at my standard consulting rate, which is \$400 per hour for any consulting and \$600 per hour for any deposition appearances. I understand that my declaration accompanies a petition for *inter partes* review involving the above-mentioned U.S. Patent.

I. My Background And Qualifications

3. My area of expertise is in the field of pharmaceuticals and nasal formulations. At University of Iowa's College of Pharmacy, I am presently a Professor in the Department of Pharmaceutical Sciences and Experimental Therapeutics within the Division of Pharmaceutics and Translational Therapeutics. I am also the Associate Dean for Undergraduate Education.

4. My research areas include the development and evaluation of novel drug delivery systems for mucosal drug delivery especially via the nasal,

gastrointestinal and vaginal epithelia. I also study the mechanisms of drug absorption and disposition.

5. I obtained a Bachelor of Science in Pharmacy from University of Minnesota in 1983 and a Ph.D. in Pharmaceutics from the University of Michigan in 1989.

6. My *curriculum vitae* is attached as Ex. 1052 to this document.

7. In view of my experiences and expertise outlined above and provided in my *curriculum vitae*, I am an expert in the field of pharmaceuticals and nasal formulations.

II. The Basis For My Opinion

8. In formulating my opinion, I considered the following documents:

Ex. #	Exhibit Name
1001	U.S. Patent No. 8,168,620 (“’620 patent”)
1002	Prosecution History of U.S. Patent No. 8,168,620
1006	UK Patent Application GB 0213739.6
1007	U.S. Patent No. 5,164,194 (“Hettche”)
1008	Astelin® Label (rev. 2000)
1009	U.S. Patent No. 4,335,121 (“Phillipps”)
1010	Flonase® Label (rev. 1998)
1011	European Patent Application No. 0780127 (“Cramer”)
1012	PCT Publication No. WO 98/48839 to Segal (“Segal”)
1013	British Pharmaceutical Codex (1973)

1014	U.S. Patent Publication No. 20040136918 (“Garrett”)
1027	Ansel, et al., <i>Pharmaceutical Dosage Forms and Drug Delivery Systems</i> , ch. 7 (6th ed. 1995)
1033	Wade & Weller, <i>HANDBOOK OF PHARMACEUTICAL EXCIPIENTS</i> (1994)
1046	IMITREX Prescribing Information (2013)
1048	Rabago, David, et al., “Efficacy of daily hypertonic saline nasal irrigation among patients with sinusitis: A randomized controlled trial,” <i>The Journal of Family Practice</i> , Vol. 51, No. 12, 1049-1055 (2002)
1049	Budavari, S., et al. (Ed), “Edetate Disodium,” <i>The Merck Index</i> , Eleventh Edition, 550 (1989)
1054	“Avicel® RC-591 Microcrystalline Cellulose and Carboxymethylcellulose Sodium, NF, BP,” FMC Corporation (1994)

9. I understand that an obviousness analysis involves comparing a claim to the prior art to determine whether the claimed invention would have been obvious to a person of ordinary skill in the art (POSA) in view of the prior art, and in light of the general knowledge in the art. I also understand that when a POSA would have reached the claimed invention through routine experimentation, the invention may be deemed obvious. I understand that a finding of obviousness for a specific range or ratio in a patent can be overcome if the claimed range or ratio is proven to be critical to the performance or use of the claimed invention.

10. I also understand that obviousness can be established by combining or modifying the teachings of the prior art to achieve the claimed invention. It is also

my understanding that where there is a reason to modify or combine the prior art to achieve the claimed invention, there must also be a reasonable expectation of success in so doing. I understand that the reason to combine prior art references can come from a variety of sources, not just the prior art itself or the specific problem the patentee was trying to solve. And I understand that the references themselves need not provide a specific hint or suggestion of the alteration needed to arrive at the claimed invention; the analysis may include recourse to logic, judgment, and common sense available to a person of ordinary skill that does not necessarily require explication in any reference.

11. I understand that when considering the obviousness of an invention, one should also consider whether there are any secondary considerations that support the nonobviousness of the invention. However, I offer no opinion on secondary considerations as I understand from counsel that another expert has been retained to opine on such matters.

III. Summary of Opinions

12. Based on my investigation and analysis and for the reasons set forth below, it is my opinion that claims 1, 4-6, 24-26, and 29 of the '620 patent would have been obvious to one of ordinary skill in the art at the time of the alleged invention in view of the combined teachings of U.S. Patent No. 5,164,194 ("Hettche"), U.S. Patent No. 4,335,121 ("Phillipps"), and PCT Publication No. WO

98/48839 (“Segal”).

13. In addition, it is my opinion that claims 42-44 would have been obvious to one of ordinary skill in the art at the time of the alleged invention in view of Hettche, Phillipps, the Flonase® Label, and Segal.

IV. Person Of Ordinary Skill In The Art

14. I understand that as of June 14, 2002, a hypothetical POSA would “be aware of all the pertinent prior art” at the time of the alleged invention. For the purposes of this analysis, a hypothetical POSA would be part of a multidisciplinary team including a clinician/scientist and a formulator.

15. The formulator of ordinary skill in the art would have: (i) at least a bachelor’s degree in chemistry, biology, chemical engineering, or pharmaceuticals, or in a related field in the biological or chemical sciences, and have at least three to five years of experience in developing nasal dosage forms and the ability to operate independently on formulation activities. A POSA would also have familiarity with pharmaceutical excipients and their uses. Such a person may also have (ii) a Master’s degree in chemistry, biology, chemical engineering, or pharmaceuticals, or in a related field in the biological or chemical sciences, and have at least one to three years of experience in formulation development of nasal agents as well as the ability to operate independently on formulation activities. Such a person may also have (iii) a Ph.D. in chemistry, chemical engineering, or pharmaceutical sciences with at least

one year of experience in formulation development of sterile dosage forms. These persons would also have familiarity with pharmaceutical excipients and their uses. These descriptions are approximate, and a higher level of education or specific skill might make up for less experience, and vice-versa.

V. The '620 Patent

16. I understand that U.S. Patent No. 8,168,620 (“the ’620 patent”) (Ex. 1001) issued from U.S. Patent Application No. 10/518,016 (“the ’016 application”), as the 35 U.S.C. § 371 national stage application of International Application No. PCT/GB03/02557 (“PCT/GB03/02557”) filed on June 13, 2003. PCT/GB03/02557 purports on its face to claim priority to UK Patent Application No. 0213739.6 (“GB 0213739.6”, Ex. 1006), titled “Pharmaceutical Compositions,” filed on June 14, 2002 (the earliest possible effective date).

17. I understand that the priority date to which the ’620 patent is entitled may be in dispute. I have been instructed to base my opinion from the perspective of a POSA as of June 14, 2002. However, if I were to use June 13, 2003 as the relevant date, my opinion would be the same.

18. Independent claim 1 of the ’620 patent recites:

“A pharmaceutical formulation comprising: azelastine, or a pharmaceutically acceptable salt thereof, and a pharmaceutically

acceptable ester of fluticasone, wherein said pharmaceutical formulation is in a dosage form suitable for nasal administration.”

19. The specification of the '620 patent states:

It is known to use antihistamines in nasal sprays and eye drops to treat allergy-related conditions. Thus, for example, it is known to use the antihistamine azelastine (usually as the hydrochloride salt) as a nasal spray against seasonal or perennial allergic rhinitis, or as eye drops against seasonal and perennial allergic conjunctivitis.

It is also known to treat these conditions using a corticosteroid, which will suppress nasal and ocular inflammatory conditions. Among the corticosteroids known for nasal use are, for example, beclomethasone, mometasone, fluticasone, budesonide and cyclofenide [sic].

Ex. 1001, 1:20-30.

VI. Technical Background

20. Nasal sprays are a common form of topical drug delivery of therapeutically active agents to the mucous membranes of the nose. They have long been used to deliver agents such as antihistamines and corticosteroids for the treatment of allergy symptoms such as runny nose, itching, sneezing, etc. Nasal sprays contain a solution and/or suspension of the active ingredient(s) in a vehicle which may include a mixture of excipients such as preservatives, buffers,

emulsifiers, solvents and solubilizing agents, viscosity modifiers, humectants and others. A nasal spray must be formulated so that 1) the spray pump can reliably deliver the same amount of active ingredient(s) with each actuation, 2) the solution or mixture is shelf-stable and avoids bacterial contamination, and 3) is as comfortable as possible for the patient without compromising the therapeutic efficacy and safety of the nasal spray. Formulators routinely balance these objectives by employing well-known excipients having well-known functions to control solubility, settling (for suspensions), pH, viscosity, osmolality, preservation, and user comfort.

VII. Prior Art

A. Astelin® Label

21. The Astelin® Label discloses a nasal spray formulation containing the active ingredient, azelastine hydrochloride. This label shows all of the excipients in the Astelin® formulation, all of which are also described in Hettche, which discloses a formulation with the same excipients and concentration of azelastine hydrochloride as the Astelin® formulation. Most of the excipients are also identical to those claimed and described in the '620 patent.

22. The Astelin® Label discloses an aqueous solution of 0.1% azelastine

hydrochloride. Ex. 1008, 3147. This can be approximated to 0.1% w/w.¹ In addition, the label discloses that after priming, each metered spray delivers 0.137 mL mean volume containing 137 mcg of azelastine hydrochloride. *Id.*

23. In Astelin®, the vehicle for the formulation is purified water, and the excipients include benzalkonium chloride and edetate disodium, hydroxypropylmethyl cellulose, citric acid and dibasic sodium phosphate, and sodium chloride. *Id.* Because the formulation is an aqueous solution rather than a suspension, no particle size is disclosed because the formulations does not contain particles. *Id.*

B. Hettche

24. Issued in 1992, U.S. Patent No. 5,164,194 (“Hettche”) claims a method of intranasal treatment with azelastine and discloses an intranasal spray formulation that contains the same excipients and concentration of azelastine hydrochloride as the Astelin® formulation. Hettche describes nearly every excipient claimed in the formulations of the ’620 patent.

25. Claim 1 of Hettche is as follows: A method for the treatment of irritation or disorders of the nose and eye which comprises applying directly to nasal tissues or to the conjunctival sac of the eyes a medicament which contains a member

¹ Because the mass of 1 mL of water is about 1 g at 25 °C, I have assumed the density of the Astelin aqueous formulation is about 1 g/mL. Hence, w/w% is essentially equivalent to w/v% in this instance.

selected from the group consisting of azelastine and its physiologically acceptable salts.” Other claims define the amounts of azelastine (claims 2-4), the type and amounts of excipients (claims 5-8) used in the method of claim 1. Claim 9 of Hettche calls for the medicament to be applied “by spraying.”

26. Hettche also discusses the amounts and concentration of azelastine to be used in the nasal formulation. Ex. 1007, 2:20-23. Hettche discloses that the formulations of the invention contain “0.0005 to 2, preferably 0.001 to 1, in particular 0.003 to 0.5% (weight/weight) of azelastine (related to the free azelastine base). *Id.*, 3:26-32. Where the azelastine is “present as a salt, the amounts should be recalculated as necessary to give the amounts of azelastine itself mentioned above.” *Id.*, 3:31-34. The formulations of azelastine may be solutions or suspensions. *Id.*, 3:26-27.

27. Hettche discloses that preservatives should be used in a nasal formulation containing azelastine hydrochloride. *Id.*, 2:46-47 (“solutions or formulations preferably contain preservatives and stabilizers”) (“Ethylene diamine tetra-acetic acid (edetate) and their alkali salts (for example dialkali salts such as disodium salt, calcium salt, calcium-sodium salt)” are highlighted as suitable preservatives. *Id.*, 2:47-50. It is understood that edetic acid, edetate, and EDTA refer to the same compound. Ex. 1049, 550 (entry 3481). Hettche also notes that

“preferred preservatives among the quaternary ammonium compounds are, however, alkylbenzyl dimethyl ammonium chloride and mixtures thereof, for example the compounds generally known as “benzalkonium chloride.”” *Id.*, 2:68-3:4. Further, “the preservative used is preferably a combination of edetic acid (for example as the disodium salt) and benzalkonium chloride.” *Id.*, 4:4-6.

28. Hettche discloses the use of 2-phenylethanol, which is commonly understood as phenylethyl alcohol, and that it may be used in combination with the preservative benzalkonium chloride. *Id.*, 3:19-25.

29. Isotonization agents are also disclosed. As a POSA would appreciate, isotonization agents “adjust the osmotic pressure of the formulations to the same osmotic pressure as nasal secretion.” *Id.*, 4:36-38. Hettche discloses that “in the case of dosage forms containing water, it is optionally possible to use additional isotonization agents. Isotonization agents which may, for example, be used are: ... glycerine....” *Id.*, 4:33-35. Glycerine is also a preferred solvent for an azelastine nasal spray formulation. *Id.*, 2:39.

30. Thickening agents are used by Hettche to “prevent the solution from flowing out of the nose too quickly and to give the solution a viscosity of about 1.5 to 3, preferably 2 Mpa.s.” *Id.*, 4:51-54. Hettche discloses that “such thickening agents may, for example, be: cellulose derivatives” and lists carboxymethyl cellulose

and hydroxypropylmethylcellulose as suitable thickeners. *Id.*, 4:55-60.

31. Finally, Hettche provides a working example of how to prepare an aqueous solution of azelastine hydrochloride for use as a nasal spray, nasal drops or eye drops. *Id.*, 6:7-35. 0.1% Azelastine hydrochloride (10 g in 10.05 kg of water and excipients) is present in this formulation (*Id.*, 6:8-20), just as in Astelin® (Ex. 1008, 3147). The excipients in the formulation are identical to those in Astelin® and include edetic acid disodium salt dihydrate, sodium chloride, benzalkonium chloride, citric acid, sodium monohydrogen phosphate hydrate and hydroxypropylmethyl cellulose. Ex. 1007, 6:11-18.

C. Flonase® Label

32. The Flonase® Label, published in June 2002, discloses a nasal spray formulation containing the active ingredient, fluticasone propionate. It lists the Phillips patent, US Patent No. 4,335,121, on its face, indicating that the Flonase® formulation is protected by Phillips. Ex. 1010, 8. This label also discloses that the formulation contains many of the same excipients found in the claimed formulations of the '620 patent.

33. The Label describes Flonase® Nasal Spray as an “aqueous suspension of microfine fluticasone propionate for topical administration to the nasal mucosa by means of a metering, atomizing spray pump.” *Id.*, 1. With each actuation, a dose of “50 mcg of fluticasone propionate in 100 mg of formulation” is delivered through

the nasal adapter. *Id.* Fifty micrograms is equivalent to 0.05 milligrams per 100 mg spray. In other words, the weight/weight concentration of fluticasone propionate in Flonase® is 0.05%.²

34. The Flonase® Label also discloses the following excipients in the formulation: “microcrystalline cellulose and carboxymethylcellulose sodium,” “0.02% w/w benzalkonium chloride, polysorbate 80, and 0.25% w/w phenylethyl alcohol.” *Id.*

35. The combination of microcrystalline cellulose and carboxymethylcellulose sodium disclosed by the Label are often used to “thicken” a formulation and delay the settling of the particles in a suspension. Ex. 1033, 84. This combination is widely available commercially by the brand-name , Avicel®

D. Phillipps Patent

36. U.S. Patent No. 4,335,121 (“Phillipps”) was issued in 1982 and is listed on the Flonase® Label to indicate that the product is patented. Ex. 1010, 8. Phillips discloses androstane carbothioates, including fluticasone propionate, the active ingredient of Flonase.

37. Claim 13 of Phillipps states: “A compound as claimed in claim 1 which

² Percent fluticasone propionate is calculated as follows: (0.05 milligrams of fluticasone propionate)(100%)/(100 milligrams) = 0.05% fluticasone propionate.

is S-fluoromethyl 6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -propionyloxyandrost-1,4-diene-17 β -carbothioate.” The Flonase® Label shows that this is the chemical name of fluticasone propionate. Ex. 1010, 1.

38. Phillipps discloses suitable concentrations for most types of formulations of its disclosed steroids, including preferred ranges “from 0.01 to 0.25%,” and, with powders for inhalation or insufflation, “the proportion used will be within the range of from 0.1%-2%.” Ex. 1009, 33:27-33. Phillipps also discloses an aerosol spray containing 0.059% w/w of active ingredient, *e.g.*, fluticasone propionate. Ex. 1009, Example (C), 34:55-62.

39. Phillipps also states that its fluticasone propionate formulation must be “micronised,” to have a particle size as defined in BPC 1973 pg. 911 for ultrafine powder. *Id.*, 34:47-49. “BPC 1973” refers to British Pharmaceutical Codex in 1973, which explains that an ultrafine powder is a “powder of which the maximum diameter of 90 per cent of the particles is not greater than 5 μ m and of which the diameter of none of the particles is greater than 50 μ m.” Ex. 1013, 911.

VIII. The co-formulation of fluticasone propionate and azelastine would have been obvious to a skilled formulator in the art

40. For my analysis, I have been asked by counsel to assume it was obvious to combine azelastine hydrochloride and fluticasone propionate into a single nasal spray based on the cited prior art references, including International PCT Publication

WO98/048839 (“Segal”) and the knowledge in the art. I have therefore considered only whether it would have been obvious to co-formulate azelastine hydrochloride and fluticasone propionate as a nasal spray with the excipients claimed in the ’620 patent.

41. It is my expert opinion that in view of FDA-approved nasal formulations for both drugs and the disclosures of the corresponding patents, Hettche and Phillipps, there were a limited number of excipients that a formulator would have turned to in order to co-formulate a combination fluticasone propionate and azelastine as a nasal spray. A formulator would have understood that all of the excipients claimed in the ’620 patent were used in Flonase® and/or Astelin® and were described on their labels and/or in their corresponding patents. These excipients were well known in the art as shown, *e.g.*, by the *Handbook of Pharmaceutical Excipients* (an excerpt of which is Ex. 1033). In view of the widespread knowledge of each of the excipients used in the labels and patents as well as the knowledge and skill in the art and the fact that the Patent Owner relied on routine testing to make the patented invention, a skilled formulator would have had a reasonable expectation of success in co-formulating a combined fluticasone propionate/azelastine hydrochloride nasal spray.

A. Nasal formulation comprising azelastine or a pharmaceutically acceptable salt and a pharmaceutically acceptable ester of fluticasone

42. Claims 1, 24, and 25 cover a pharmaceutical formulation suitable for nasal administration or nasal sprays. All require azelastine or a “pharmaceutically acceptable salt thereof” (cl. 1, 25) or the “hydrochloride,” (cl. 24) and a “pharmaceutically acceptable ester of fluticasone” (cl. 1, 25) or “fluticasone propionate (cl. 24), and not much more. Ex. 1001, cls. 1, 24, 25. Claims 1 and 25 have few or no non-compositional limitations, while claim 24 requires a pharmaceutically acceptable carrier or excipient therefor.

B. Microfine particle size

43. Claim 4 of the '620 patent requires that the formulation of claim 1 has a particle size of less than 10 μm . It is my opinion that both the Flonase Label and Phillips disclose such formulations, and that a formulator would have been motivated to prepare formulations with a particle size of less than 10 μm .

44. A POSA would have understood “microfine” in the Flonase® Label to mean 10 microns or less in diameter for several reasons. As noted above, the Flonase Label® discloses that the nasal formulation is “an aqueous suspension of *microfine* fluticasone propionate.” Ex. 1010, 1. A formulator would have understood that “microfine” is commonly used to describe drug particles that are of a low-micron size range. For example, Ansel discloses that the size of “micronized”

particles is under 10 microns (μm). Ex. 1027, 255. A person of ordinary skill in the art would have been motivated to use the definitions that are disclosed in Ansel's *Pharmaceutical Dosage Forms and Drug Delivery Systems* to ensure that the particle size complied with industry-wide standards.

45. Moreover, the Phillipps patent, which is referenced by the Flonase Label, states that in preparing formulations of the disclosed steroids such as fluticasone propionate, the drugs should be micronized to a particle size defined by the *British Pharmaceutical Codex* ("BPC"). Ex. 1009, 34:63-64. The BPC specifies a micronized "powder of which the maximum diameter of 90 per cent of the particles is not greater than 5 μm and of which the diameter of none of the particles is greater than 50 μm ." Ex. 1013, 911. From the BPC, a formulator would have understood the expected range of particle sizes in a powder for pharmaceutical use. It is therefore my opinion that a person of ordinary skill would have had a reason to keep drug particles of "fluticasone propionate" "preferably in the range 1 to 10 microns." Ex. 1014, [0001], [0023], [0030].

C. Concentrations of azelastine and fluticasone propionate

46. The concentrations of azelastine and fluticasone propionate in the '620 patent would have been obvious to a formulator of ordinary skill. As stated above, in the field of pharmaceuticals one would have first considered the specific concentrations disclosed in the Flonase® and Astelin® labels as well as their

corresponding patents to formulate a combination drug product.

47. Claims 5, 6, and 26 of the '620 patent disclose a range of "0.0357 to 1.5% (weight/weight)" of fluticasone ester/fluticasone propionate. Ex. 1001, cls. 5, 6, 26. A formulator would have understood that the concentrations disclosed in Phillipps of 0.01 to 0.25%, 0.1% to 2% and 0.059% (Ex. 1009, 33:27-33; 34:55-62) and the concentration on the Flonase® Label of 0.05% w/w (Ex. 1010, 1) would have overlapped or been directly within the range mentioned in claims 5, 6, and 26. It would have been obvious to a person of ordinary skill in the art at the time of the invention to use an amount of fluticasone propionate disclosed in Phillips or on the Flonase® Label. Any further modification to the amount of fluticasone propionate within the claimed range would have been routine optimization to meet the potency required by the application at hand and within the skill of the formulator.

48. Similarly, Claim 5 of the '620 patent discloses a range of azelastine between "0.0005% (weight/weight) to 2% (weight/weight)." Ex. 1001, cl. 5. Claim 6 discloses a range of "0.001% (weight/weight) to 1% (weight/weight) of said azelastine," while claim 26 describes a formulation containing only "0.1% (weight/weight) of azelastine hydrochloride." Ex. 1001, cls. 6, 26.

49. As stated above, Hettche discloses that the formulations of the invention contain "0.0005 to 2, preferably 0.001 to 1, in particular 0.003 to 0.5%

(weight/weight) of azelastine (related to the free azelastine base)” as well as a formulation example with 0.1% azelastine hydrochloride. Ex. 1007, 3:26-32, 6:8-9. The ranges and amounts of azelastine concentrations disclosed in Hettche are either identical or fall within the ranges disclosed in Claims 5 and 6 of the ’620 patent. Hettche discloses the range of “0.0005% (weight/weight) to 2% (weight/weight).” *Id.* Indeed, the range of 0.001 to 1% w/w in Claim 6 is a preferred concentration range disclosed in Hettche. *Id.* Moreover, like Example 1 in Hettche, the Astelin® Label teaches an amount of 0.1% w/w of azelastine hydrochloride, which is exactly the same concentration described in Claim 26 of the ’620 patent. Ex. 1008, 3147. A person of ordinary skill in the art therefore would have been motivated to use the concentration ranges for azelastine and fluticasone propionate as claimed in the ’620 patent.

D. Nasal spray

50. Claims 24, 25, and 29 require that the formulation be a nasal spray. It would have been obvious for a person of ordinary skill in the art to formulate the combination of fluticasone propionate and azelastine as a nasal spray. Both Flonase® and Astelin® are nasal sprays, and their corresponding patents likewise describe nasal spray formulations. Ex. 1007, 2:12-17; Ex. 1009, 33:12-13. A skilled formulator would have been motivated to rely both on the individual drug labels and Hettche and Phillipps when formulating a combination drug product because they

demonstrate that nasal sprays are a common and successful method of delivery for these drugs. *Id.* As such, it would have been obvious to a person of ordinary skill in the art to retain the same type of dosage form for the combination fluticasone propionate and azelastine product, *i.e.*, a nasal spray.

51. Furthermore, other references disclosing a combined azelastine and fluticasone propionate product were formulated as a nasal spray. PCT Publication No. WO 98/48839 (“Segal”), described a co-formulated nasal spray containing both azelastine and fluticasone propionate.³ Notably, Segal states that “preferred nasal formulations are nose drops or nasal sprays.” Ex. 1012, 4:4-5. Similarly, European Patent Application No. 0780127 (“Cramer”) published in 1997 also disclosed a “nasal spray” containing a glucocorticoid and an antihistamine. Ex. 1011, 1:54-57. Cramer specifically names both fluticasone and azelastine for use in the combination product. *Id.*, 3:15-18, 27-28. A skilled formulator would have been further motivated to formulate the combination fluticasone propionate and azelastine drug product as a nasal spray in view of Segal or Cramer.

³ Segal refers to fluticasone propionate as “fluticasone proprionate” several times. *E.g.*, Ex. 1012 at 2:25-26, cls. 2, 11. A person of ordinary skill would have immediately understood that Segal was referring to fluticasone propionate.

E. Edetate disodium, benzalkonium chloride, and phenylethyl alcohol

52. It is well known that multi-use formulations such as nasal sprays must be preserved against microbial contamination. It would have been obvious to a person of ordinary skill in the art to select commonly used antimicrobial preservatives such as edetate disodium, benzalkonium chloride, and phenylethyl alcohol which had already been used in one or both of the preexisting nasal formulations of azelastine and fluticasone propionate.

53. Hettche discloses the use of edetic acid, *e.g.*, as the disodium salt and benzalkonium chloride alone (Ex. 1007, 2:47-50, 2:68-3:4) or together (*Id.*, 4:4-6) as a preferred preservative combination for an azelastine drug formulation. The Astelin® Label lists both benzalkonium chloride and edetate disodium as preservatives in the formulation. Ex. 1008, 3147. Hettche further discloses that 2-phenylethanol (an alternative chemical name for phenylethyl alcohol) may be used in combination with benzalkonium chloride. Ex. 1007, 3:19-26. Similarly, the Flonase® Label discloses the use of “0.02% w/w benzalkonium chloride,” and “0.25% w/w phenylethyl alcohol.” Ex. 1010, 1. These excipients are not only commonly used, but have also already been successfully employed in either or both azelastine and fluticasone propionate nasal formulations. As such, Hettche and Phillips alone and/or in view of the Astelin® and Flonase® Labels would have motivated a formulator to include edetic acid disodium, benzalkonium chloride and

phenylethyl alcohol as preservatives in a nasal spray formulation of fluticasone propionate and azelastine hydrochloride.

54. Just as with the labels, a skilled formulator would have considered the *Handbook of Pharmaceutical Excipients* (“*Handbook*”). A person of ordinary skill in the art would have recognized that the *Handbook* contains data on the physical properties of excipients, their safety and potential toxicities. The *Handbook* is also widely recognized by drug formulators, drug manufacturers, regulatory associations and legal bodies as a go-to reference for information about excipients for pharmaceutical use. The *Handbook* shows that all three preservatives disclosed in the ’620 patent are well-known. The *Handbook* also discloses that “when used with other antimicrobial preservatives edetic acid [EDTA] demonstrates a marked synergistic effect in its antimicrobial activity.” Ex. 1033, 16. Furthermore, the *Handbook* also found that edetic acids and edetates are “frequently used in combination with...benzalkonium chloride.” *Id.* Synergistic effects are also reported when phenylethyl alcohol is combined with benzalkonium chloride. *Id.*, 27. This common knowledge in the art would have further motivated a formulator to use benzalkonium chloride, edetate disodium, and phenylethyl alcohol as preservatives in a combined fluticasone propionate and azelastine nasal formulation.

55. Even though edetate disodium is not specifically disclosed in the

Flonase® formulation, it is a common antimicrobial preservative used in pharmaceutical formulations. The same reasoning can be applied to the absence of phenylethyl alcohol in the Astelin® formulation. In view of the *Handbook*, a formulator also would have been motivated to use all three preservatives to obtain the known synergistic effects of edetic acid on antimicrobial activity. Also, I am unaware of any prior art reference that specifically criticizes, discredits, or discourages the use of phenylethyl alcohol in an azelastine formulation or the use of edetate disodium in a fluticasone propionate formulation.

F. Glycerine

56. Glycerine would have been an obvious tonicity adjuster to use in a combination fluticasone propionate and azelastine nasal spray. Hettche disclosed that glycerin is a preferable solvent and isotonization agent. Ex. 1007, 2:39, 4:34. Tonicity adjusters are commonly used to modify the tonicity of formulations depending on the intended use, and typically have very little impact on the formulation as a whole. Glycerine also has solvent and humectant properties, adding to the attractiveness of its use. Ex. 1007, 2:35-39; Ex. 1012, 4:8-10; Ex. 1008, 3147. Even though there are a number of tonicity adjusters to choose from, a skilled formulator would have considered glycerin because Hettche discloses its suitability for use with azelastine formulations.

G. Microcrystalline cellulose and sodium carboxymethyl cellulose

57. A person of ordinary skill in the art would have been motivated to use the thickening agents microcrystalline cellulose (MCC) and sodium carboxymethyl cellulose (CMC) in a combination fluticasone propionate and azelastine nasal formulation.

58. Because fluticasone propionate is insoluble in water, it is formulated as a suspension in Flonase®. Ex. 1010, 1. A formulator would have recognized that a coformulation including fluticasone propionate would also be readily prepared as a suspension. A formulator would have further recognized that Flonase® contains specific excipients designed to stabilize the suspension as well as ensure that the suspension could remain in contact with the mucosa for a sufficient length of time. These excipients are microcrystalline cellulose and sodium carboxymethyl cellulose. *Id.*

59. The *Handbook* teaches that CMC is used as a “suspending agent,” which aids in the continued dispersion of the particles in the suspension. Ex. 1033, 12. In addition, the *Handbook* discloses that CMC sodium is used as a “viscosity-increasing agent,” which assists in the formulation’s retention on the nasal mucosa. *Id.*, 84. It also teaches that “mixtures of microcrystalline cellulose and carboxymethylcellulose sodium” are “suitable as suspending vehicles in pharmaceutical formulations.” *Id.* at 86. In such a mixture, the colloidal MCC

provides a structured dispersion vehicle, while the CMC facilitates dispersion and serves as a protective colloid. Ex. 1054, 3. Furthermore, Hettche discloses that an appropriate thickening agent for use in an azelastine formulation includes carboxymethyl cellulose and other cellulose derivatives. Ex. 1007 at 4:51-60. Hence, a person of ordinary skill in the art would have been motivated by Hettche and the Flonase Label alone (or even the *Handbook* alone) to include both microcrystalline cellulose and carboxymethylcellulose sodium as thickening and suspending agents in a co-formulated nasal formulation including fluticasone propionate and azelastine. The dual functions of the combination of microcrystalline cellulose and carboxymethylcellulose sodium to serve as both a suspending and thickening agent for fluticasone propionate makes these excipients particularly attractive to a skilled formulator.

60. I am also unaware of any prior art literature that discourages the use of CMC/MCC mixtures in a formulation containing azelastine hydrochloride. Its absence from both the Astelin® Label and Hettche would not have discouraged a formulator to use both microcrystalline cellulose and carboxymethyl cellulose sodium in a combined fluticasone propionate and azelastine nasal spray.

H. Polysorbate 80

61. It would have been obvious to include polysorbate 80 in any nasal spray formulation that contains as an active ingredient, fluticasone propionate. Fluticasone

propionate exists in a suspension in the nasal formulation and surfactants, such as polysorbate 80, help disperse the compound in the vehicle. Ex. 1010, 1. In addition, the *Handbook* describes polysorbate 80 as a “nonionic surfactant,” the use of which is commonly understood among expert formulators. Ex. 1033, 29-30.

62. Although polysorbate 80 is not used in the Astelin® formulation, Hettche nevertheless indicates that polyethoxylated sorbitan fatty acid esters (of which polysorbate 80 is one (*Id.*)) are suitable for use in azelastine formulations. Ex. 1007, 4:14-19. Also, I am unaware of any prior art reference that specifically criticizes, discredits, or discourages the use of such an excipient in a formulation containing azelastine. Hence, the use of polysorbate 80 would have been obvious to a skilled formulator combining fluticasone propionate and azelastine hydrochloride into a nasal spray.

I. Purified water

63. It would have been obvious to a person of ordinary skill in the art to use purified water in a nasal spray. Water is used in both Astelin® and Flonase®, and is disclosed for use in the nasal formulations of Hettche and Phillipps. Ex. 1008, 3147; Ex. 1010, 1; Ex. 1007, 6:19-21; Ex. 1009, 33:12-13, 32:66-34:1, 34:30-40 (Example (B)).

64. In addition, a person of ordinary skill in the art would have considered how other prior art references disclosing combination therapies were formulated.

Segal described a co-formulated nasal spray containing both azelastine and fluticasone propionate and also taught that “preferred nasal formulations are nose drops or nasal sprays containing a *water* buffered aqueous solution as a carrier.” Ex. 1012, 4:4-5. Cramer also disclosed that “preferred nasal dosage forms are solutions, suspensions and gels, which normally contain sodium chloride in a major amount of *water* (preferably *purified water*) in addition to the antihistamine and glucocorticoid.” Ex. 1011, 3:45-47. A skilled formulator would have strongly preferred to select water over any other potential fluid vehicle.

J. Reasonable expectation of success

65. A skilled formulator would have had a reasonable expectation of success in formulating a combined fluticasone propionate and azelastine nasal spray. As stated above, a formulator would have turned to a limited number of excipients in view of the prior art references. Given that both Astelin® and Flonase® were already successfully formulated, a person of ordinary skill in the art would have looked to these two drug products to formulate a combined nasal spray. All of the excipients disclosed in the Astelin® and Flonase® Labels and the Hettche and Phillipps patents are included in the '620 patent. Moreover, the excipients are all disclosed in the *Handbook*, which is a go-to reference for formulators. This suggests that the excipients and active ingredients claimed in the '620 patent were obvious to use in combination formulations.

66. In addition, no special methods or techniques were required in formulating the combination fluticasone propionate and azelastine nasal spray claimed in the '620 patent. The '620 patent even admits that the “formulations according to the present invention ... are prepared by *techniques well known in the art.*” Ex. 1001, 7:67-8:2. None of the Examples containing both azelastine hydrochloride and fluticasone propionate describe any synthesis, processing, or mixing techniques whatsoever. *Id.*, Examples 3, 5, 9, 10. A skilled formulator would have had the skills and experience in June 2002 to readily formulate the combination product claimed in the '620 patent. Because of the guidance offered in the art and the previous success of routine techniques to prepare the individual formulations, it is my expert opinion that a skilled formulator would have had a reasonable expectation of success in formulating a fluticasone propionate and azelastine nasal spray.

67. A skilled formulator would also have had a reasonable expectation of success even though azelastine hydrochloride was “sparingly soluble” in water and fluticasone propionate remained in “suspension.” Ex. 1008, 3147, Ex. 1010, 1. These two ingredients, when present together in water, would have been expected to retain their respective behaviors (as they do in Dymista®). A person of ordinary skill in the art would have had only a finite number of ways of mixing together

ingredients, some of which are in solution and some of which are in suspension.

Furthermore, I am unaware of any prior art references that indicate that combining one active ingredient in solution and one in suspension would have been difficult. In any case, the '620 patent does not disclose any novel way of overcoming such a problem even if it did exist. As stated above, the '620 patent does not teach any new techniques and admits that its “formulations are prepared by techniques well known in the art.” Ex. 1001, 7:67-8:2. Additionally, neither Segal nor Cramer disclose any special mixing techniques or observed any problems when combining azelastine and fluticasone propionate. As such, a skilled formulator would have been able to combine two such active ingredients together despite their differences in solubility.

IX. Cramer Example III is not inoperable

68. I understand that during the prosecution of the '620 patent, the Patent Owner submitted a declaration by inventor Ms. Geena Malhotra, alleging that Example III of Cramer was “inoperable” and “unacceptable” (Ex. 1002, 284-287 (¶¶ 6, 9)) and that no appropriate comparison could be made to the '620 claims (*id.*, 287 (¶ 10)). I understand from counsel that the '620 patent was issued on the basis of secondary considerations that did not involve the testing performed by Ms. Malhotra. *See id.*, 143-146.

69. In any event, Ms. Malhotra's analysis is flawed because her conclusion does not represent what a formulator would have understood from Cramer's

Example III. As a matter of routine practice, a skilled formulator would have performed multiple tests, different mixing procedures, and adjusted excipients to modify the particular formulation to prepare an acceptable nasal spray. Unlike Ms. Malhotra, a formulator would not simply run a single test and deem a composition inoperable or unacceptable. In addition, hypertonic nasal solutions (such as Cramer's Example III) were understood as viable for both intranasal administration of drugs as well as daily use in relieving inflamed sinuses.

70. As a matter of routine practice, a person of ordinary skill in the art would have performed multiple tests and adjusted excipients to modify the particular formulation to provide a preferred nasal spray, and further a POSA would have examined different well-known mixing techniques to achieve a successful product.

71. Cramer itself illustrates that a POSA would expect to engage in such modification and understand how to modify Cramer's Example III to provide a preferred nasal spray and would not be restricted to the meager analysis provided in Ms. Malhotra's declaration. Ms. Malhotra focused her analysis on her opinion of desirable nasal sprays. Ex. 1002, 286-287 (¶9). Yet Cramer does not describe Example III as a nasal spray but as an intranasal administration composition (Ex. 1011, 6:27-28, 43-44), where such compositions may be in a variety of nasal dosage forms that are not nasal sprays, such as drops, suspensions, ointments, and gels (*id.*,

3:43-45). *See also* Ex. 1007, 6:37-56 (describing a nasal ointment with azelastine hydrochloride). Cramer states that Example III may include a fluticasone corticosteroid instead of triamcinolone acetonide, and that those skilled in the art can modify Example III into any suitable dosage form. Ex. 1011, 6:44-52. Cramer provides further guidance on appropriate concentration ranges for components. *See, e.g., id.*, 3:37-38; 4:11-12; 5:6-7, 15, 20-22. The reason Cramer provides this guidance is clear – such modifications were expected of a formulator as a matter of routine practice. *See, e.g., id.*, 3:39-50. Cramer further recognizes a formulator would readily modify a composition to provide the desired tonicity. *Id.* Ms. Malhotra does not opine on any of the possible dosage forms in deeming Cramer’s Example III “inoperable,” nor does she comment on any other discussion by Cramer, and is completely silent on a formulator’s skill in providing appropriate nasal dosage forms. *See* Ex. 1002, 285-287. Of course, a POSA’s understanding goes far beyond Cramer.

72. For example, the *Handbook* (Ex. 1033) provides concentration ranges for each excipient, such the concentration range for glycerin (aka glycerol) when used as a humectant versus when it is used as a antimicrobial preservative. Ex. 1033, 20. The *Handbook* also shows the effects of glycerol on the viscosity of an aqueous solution and how adjusting the amount of glycerol increases or decrease

viscosity. *Id.*, 21. The entry for hydroxypropyl methylcellulose similarly provides viscosity effects, suspension/solubilization effects, and exemplary concentrations for each recited effect. *Id.*, 23. The family of polysorbates, including polysorbate 80, is also provided with exemplary concentrations and effects in solution. *Id.*, 30. This specific guidance would be in addition to the knowledge and understanding of a POSA in formulating a nasal spray.

73. Hettche also discloses acceptable excipients particularly for nasal sprays including azelastine hydrochloride. For the excipients, Hettche generally provides ranges and includes preferred ranges. *See, e.g.*, Ex. 1007, 2:13-5:16. Hettche provides excipients for obtaining iso-osmotic nasal solutions, including substitutes for sodium chloride in order to obtain an isotonic solution. *Id.*, 4:31-46. In particular, Hettche provides a working example of a nasal sprays with azelastine hydrochloride that recites the amounts of components used. *Id.*, 6:7-35.

74. Thus, Cramer itself as well as the *Handbook* and Hettche show a POSA understood how Cramer's Example III may be modified to provide a nasal spray including both azelastine and a fluticasone corticosteroid, and that such modification was a routine matter in formulating nasal sprays. Ms. Malhotra's declaration fails to address these facts. While Ms. Malhotra describes "unacceptable" traits such as osmolality as well as those that appear to involve viscosity such as the jet discharge (Ex. 1002,

286-287 (¶¶ 8-9)), viscosity and osmolality are two parameters readily modified by a POSA. Ex. 1011, 3:39-50; Ex. 1033, 21; Ex. 1007, 4:31-46. Further, even if viscosity was not modified (which, if truly unacceptable in multiple tests, it would be), a POSA would have understood that a desired spray mist can be achieved by adjusting the coordination between the composition and the spray container. A POSA would only need to select from a limited number of commercially available spray devices container to optimize the spray mist emitted by a particular formulation— another routine modification upon which Ms. Malhotra is silent. In regards to the settling and difficulty in re-suspending described by Ms. Malhotra (Ex. 1002, 286 (¶¶ 8-9)), a POSA would have anticipated settling of a suspension upon storage. In fact, Ms. Malhotra does not explain why it was difficult to re-suspend. Even so, a POSA would know how to address this, such as by optimizing the suspending agents as discussed in Cramer, the *Handbook*, and Hettche.

75. Lastly, an osmolality of 554 mOsm/kg would not have prevented acceptance as a nasal spray because hypertonic intranasal drug solutions were FDA-approved and in use prior to 2002 in addition to the fact that daily use of hypertonic solutions as nasal washes applied directly to the nasal mucosa was well-known to manage symptoms of inflamed sinuses. Ms. Malhotra asserts that because Cramer's Example III is hypertonic this renders the composition unsuitable for intranasal

administration, in part because hypertonic solutions would be expected to irritate the nasal mucosa. Ex. 1002, 287 (¶ 9). However, Ms. Malhotra ignores governmental approval and public use of hypertonic nasal sprays –for example, Imitrex® Nasal Spray (first marketed in 1997) containing 20 mg sumatriptan in a hypertonic intranasal spray with an osmolality of 742 mOsmol. Ex. 1046, 9, 26-27. In addition, daily use of hypertonic saline solutions have long been practiced to relieve inflamed sinuses where a POSA would know scientific studies show such daily use provides an overall improvement of sinus-related quality of life and decrease in symptoms. Ex. 1048, 1049. Further, a POSA would have continued to optimize the excipients to resolve any osmolality or viscosity issues, where such optimization is discussed in Cramer itself as well as in the *Handbook*. See *supra* ¶¶65-66.

X. Conclusion

76. In signing this declaration, I recognize that the declaration will be filed as evidence in a contested case before the Patent Trial and Appeal Board of the United States Patent and Trademark Office. I also recognize that I may be subject to cross-examination in the case and that cross-examination will take place within the United States. If cross-examination is required of me, I will appear for cross-examination within the United States during the time allotted for cross-examination.

77. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Dated: 2/2/17



Maureen D. Donovan, Ph.D.