# IN THE UNITED STATES DISTRICT COURT FOR THE DISTRICT OF DELAWARE

MEDA PHARMACEUTICALS, INC. and CIPLA LTD.	) ) )
Plaintiffs,	)
V.	)
APOTEX, INC. and APOTEX CORP.	)

Civil Action No. 14-1453 (LPS)

Defendants.

# EXPERT REPORT OF MAUREEN D. DONOVAN, PH.D.

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1. I, Maureen Donovan, have been retained by Defendants Apotex, Inc., and Apotex Corp. as an expert to analyze certain aspects of U.S. Patent Nos. 8,163,723 ("the '723 patent"); 8,168,620 ("the '620 patent"); and 9,259,428 ("the '428 patent"), in connection with this lawsuit.

I have formulated certain opinions about those patents and their asserted claims.
My opinions are set forth in this report, and I expect to testify about them at trial if asked to do so.

3. The basis for my opinions includes the documents and other materials cited in this report, my education, and my years of experience, teaching, and researching in the relevant field.

4. I reserve the right to amend or supplement my opinions in light of evidence presented by or on behalf of Meda Pharmaceuticals and Cipla Ltd., or in connection with additional information that may be made available to me in the future.

5. In addition to the information, materials and opinions discussed in this report, I may use demonstrative exhibits at trial to the extent useful for explaining and understanding the opinions I set forth in this report.

6. I may testify at trial about background scientific concepts related to my opinions to the extent that is useful for understanding my opinions.

7. I am being compensated for my time on this matter at a rate of \$250/hour for general document and background review, \$400/hour for preparing reports, and \$600/hour for testifying at trial or depositions. Those are my standard consulting rates. My compensation is in no way dependent on the outcome of this case.

8. In the past five years, I have been deposed only once, in *Sanofi Aventis v. Sandoz et al.*, but I was not a testifying expert at trial.

# I. PERSONAL BACKGROUND

9. I am a Professor in the Division of Pharmaceutics at the University of Iowa

College of Pharmacy. I have more than 25 years of experience working and consulting in the field of pharmaceutics. My *curriculum vitae* is attached to this report as Exhibit A.

10. I am an expert in pharmaceutics. I received my Bachelor of Science in Pharmacy from the University of Minnesota College of Pharmacy in 1983 and my Ph.D. in Pharmaceutics from the University of Michigan in 1989.

11. My professional experience includes working as a Staff Pharmacist for Clark Professional Pharmacy from 1986 until 1989 and as a Visiting Scholar for SmithKline Beecham Pharmaceuticals in 1991. From 1989 through the present, I have held various positions at the University of Iowa College of Pharmacy. Specifically, in the Division of Pharmaceutics, I was an Assistant Professor from 1989 until 1996, and an Associate Professor from 1996 until 2008. I was promoted to the position of a Professor in 2008 in the College of Pharmacy, and I currently hold this position. From 2008 until 2013, I was the Division Head for the Division of Pharmaceutics. In 2013, I became the Associate Dean for Undergraduate Programs at the College of Pharmacy, and I currently hold this position.

12. I have over 25 years of experience in pharmaceutical research and development including actively teaching drug delivery, pharmaceutical preformulation, and compounding to pharmacy students and graduate students, and directing research programs focused on drug absorption, nasal drug delivery, and alternative routes of drug delivery and delivery systems.

13. I have published numerous articles, book chapters, and abstracts in the area of pharmaceutics, drug absorption, drug delivery, and materials characterization. I also belong to several professional societies for pharmaceutical science and technology, including the American Association of Pharmaceutical Scientists and the Controlled Release Society.

14. In addition to my knowledge, education, and experience in the field of

pharmaceutical formulation, I have reviewed materials in forming the opinions I express in this report. A full list of those materials is attached as Exhibit B.

### II. LEGAL STANDARDS

15. Counsel for Apotex has asked me to offer my opinions on whether or not I think the asserted claims of the patents-in-suit and particular aspects of them are inventive or obvious.

16. In order to form my opinions on these questions in the context of this litigation, counsel has explained to me certain legal standards. I include below my understanding of these relevant legal standards, as these make up the framework in which I did my analysis.

#### A. Obviousness

17. I have been informed a patent claim is invalid as obvious if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time that the invention was made to a person of ordinary skill in the art (a "POSA"). For my analysis of obviousness, I have considered and applied the following factors: (a) the scope and content of the prior art; (b) the differences between the prior art and the asserted claims; and (c) the level of ordinary skill in the field of the invention. I also understand that courts may review certain other objective indicators tending to show that patent claims are non-obvious or obvious. I have identified some of my opinions on such indicators in this report. I reserve the right to supplement those opinions based on evidence, arguments or opinions presented by or on behalf of Meda or Cipla.

18. I also have been informed and understand that a claimed invention may be obvious if at the time of the alleged invention there was a reason that would have prompted a POSA in the field of the invention to combine the known elements in a way the claimed invention does, taking into account such factors as: (1) whether the claimed invention was merely the predictable result of using prior art elements according to their known functions; (2) whether the claimed invention provides an obvious solution to a known problem in the relevant field; (3) whether the prior art teaches or suggests the desirability of combining elements claimed in the invention; (4) whether the prior art teaches away from combining elements in the claimed invention; (5) whether it would have been obvious to try the combinations of elements, such as when there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions; and (6) whether the change resulted more from design incentives or other market forces.

19. I also have been informed that a claimed invention may be obvious to try where at the time of the invention, there was a known problem or need in the art, there was a finite number of identified, predictable potential solutions to that need or problem, and a POSA could have pursued those solutions with a reasonable expectation of success. If this leads to the claimed invention, it is not because of innovation but rather because of ordinary skill and common sense.

20. I further understand that the prior art must provide to the POSA a reasonable expectation of successfully making and using the alleged invention.

21. I further understand that in determining whether the claimed invention was obvious, one must not use hindsight, and must instead consider only what was known at the time of the invention.

#### **B.** Person of Ordinary Skill in the Art.

22. As mentioned, I evaluated the issues of obviousness from the perspective of a POSA. I was informed that to determine the level of ordinary skill in the subject matter of the asserted patents, I should consider (1) the levels of education and experience of the inventors and other persons actively working in the field; (2) the types of problems encountered in the field; (3)

prior art solutions to those problems; (4) rapidity with which innovations are made; and (5) the sophistication of the technology. The subject matter of the asserted patents is generally directed to pharmaceutical compositions and methods of using them for the administration of intranasal steroids and intranasal antihistamines for the treatment of allergic rhinitis and other conditions. The asserted claims are generally directed to particular formulations of the compositions, and their use.

23. I understand that for the obviousness analysis I was to conduct my analysis from the perspective of a POSA as of the date of the alleged invention of the asserted claims. I have been asked to assume that the date of invention is June 2002.

# C. Level of Person of Ordinary Skill in the Art.

24. In my opinion, the relevant "art" to which the patents are directed is pharmaceutical formulations of topical agents, specifically nasal suspensions and/or solutions. A person of ordinary skill in this field has at least a bachelor's degree in chemistry, biology, chemical engineering or pharmaceutical sciences with significant experience, 3-5 years in formulation development of nasal dosage forms, and the ability to operate independently on formulation activities. A person of skill in the art would also have familiarity with pharmaceutical excipients and their uses.

25. A person of ordinary skill in the art may also have a Master's degree in chemistry, biology, chemical engineering, or pharmaceutical sciences with 1-3 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 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.

26. I have reviewed the report of Robert P. Schleimer, who defines a person of ordinary skill in the art as someone having an M.D., Ph.D. or Pharm.D. in the field of allergy/immunology and/or pharmacology (or the equivalent), and at least three additional years of experience in the treatment, or research for treatments, of allergic rhinitis, including with nasally administered steroids and antihistamines. I agree with Dr. Schleimer's opinion regarding a person of ordinary skill in the field of allergic rhinitis research and treatment. My opinion is that a person of ordinary skill in formulation would coordinate with a person of ordinary skill in the field of allergic rhinitis research and treatment.

### III. SUMMARY OF OPINIONS

27. I have analyzed the patents-in-suit, their file histories, and the asserted claims, which I understand are Claims 8, 11, 14, 25 and 28 of the '723 patent; Claims 4, 29, and 42-44 of the '620 patent; and Claims 10, 11, 13, 15, 16, 18-20, 22-24, 26, and 28-30 of the '428 patent. In addition to these items and the other materials I discuss in this report, all of which I have reviewed and am prepared to discuss at trial if asked to do so, I have reviewed the expert report of Dr. Robert Schleimer. He offers certain opinions that it would have been obvious to a POSA at the time of the alleged invention to make and administer a combination nasal spray product having both azelastine hydrochloride (HCl) and fluticasone propionate as active ingredients. I agree with his opinion, especially in light of the actual prescribing practices at the time, that it would have been at least obvious for a POSA to try combining these two active ingredients.

28. It is my opinion that each of the asserted claims would have been obvious to a POSA as of the earliest purported priority date of the asserted patents, which I understand is June 2002.

29. It is my opinion that all of the asserted claims of '620, '723, and '428 patents

would have been obvious to a POSA in view of the prior art I discuss in more detail in this report.

30. In brief, each of the asserted claims covers the use of a pharmaceutical nasal spray composition containing azelastine HCl and fluticasone propionate in amounts that are effective for the treatment of allergic rhinitis in humans. Dr. Schleimer opines that the concept of this composition would have been obvious to a POSA considering how to treat allergic rhinitis in 2002. As explained above, I agree with his opinion. It is my further opinion that it would have been obvious to a POSA at that time how to make such a product. Making this product would have resulted in a formulation with characteristics within the scope of the asserted claims.

31. Asserted claims 29 of the '620 patent, and 10, 11, 13, 15, 16, 18-20, 22-24, 26 and 28-30 of the '428 patent also require certain amounts or ranges of amounts of the active ingredients. It is my opinion that making a formulation meeting those requirements would have been obvious to a POSA at the time of the alleged invention. These claims cover the amounts of the active ingredients that were present in two monotherapies from the prior art—Astelin<sup>®</sup> and Flonase<sup>®</sup>. Using the same amounts of active ingredients as two commercially marketed products would have been obvious because, for example, those amounts would already have been known to be safe and effective.

32. Asserted claims 25 and 28 of the '723 patent, claims 42-44 of the '620 patent, and all of the asserted claims of the '428 patent contain various limitations that identify specific inactive ingredients, and/or types of inactive ingredients, and/or amounts of inactive ingredients. It is my opinion that a POSA would have found formulations meeting each of those requirements to have been obvious as of 2002. Each of these ingredients was well known to a POSA as a pharmaceutically acceptable excipient. All but one had been used in either or both of the

Astelin<sup>®</sup> or Flonase<sup>®</sup> products, and each was at least otherwise disclosed as acceptable for use in nasal sprays. Each of those ingredients also has been used in the prior art to perform one or more of the same functions later required by the asserted claims.

33. Asserted claims 11 of the '723 patent and 4 of the '620 patent require that the claimed composition or formulation have a particle size of less than 10  $\mu$ m. It is my opinion that making a formulation in which azelastine HCl and fluticasone propionate (and other ingredients that have measurable particle size) were less than 10  $\mu$ m would have been obvious to a POSA.

34. Asserted claims 15 and 28 of the '428 patent also requires the formulation to be within the pH range of 4.5 to about 6.5. It is my opinion that formulating an azelastine HCl/fluticasone propionate combination product with a pH in that range would have been obvious to a POSA.

# IV. ANALYSIS OF THE PRIOR ART

35. I began my analysis by considering the following: If a POSA were asked immediately prior to the date of the alleged invention to make a combination nasal spray product using azelastine HCl and fluticasone propionate as active ingredients (consistent with Dr. Schleimer's report and the actual prescribing practices at the time), what would be the obvious way to proceed? To answer that question, I considered the relevant knowledge of a POSA at that time.

# A. State of the art of nasal drug delivery systems.

36. By 2002, it was well known to a POSA that various drugs could be administered by the nasal route, for example through sprays or drops. One example was Afrin, which contains the active ingredient oxymetazoline, a drug that can cause vasoconstriction and thus reduce nasal congestion and related symptoms. It has been available for decades.

37. Nasal sprays typically comprise a bottle or other container that contains the active

ingredient in its formulation. A device capable of forming a spray or mist of droplets is attached to an appropriate container (bottle), and by 2002, the most common nasal spray devices used a hand-activated, compression-driven pump system to produce the spray droplets as the formulation exits the spray orifice, typically located at the tip of the actuator. In 2002, nasal spray device systems were readily available from commercial vendors.

38. The nasal sprays that were commercially available prior to 2002 and are most relevant to a POSA trying to develop an azelastine/fluticasone combination product were products containing azelastine HCl or fluticasone propionate as the active ingredients.

# **B.** Azelastine HCl and Astelin<sup>®</sup>

39. One such product was called Astelin<sup>®</sup>, which contained azelastine HCl as the active ingredient. I have reviewed the FDA-approved labeling for Astelin<sup>®</sup> available in 2000. This label was available at this time to any prescriber, consumer, or researcher purchasing Astelin<sup>®</sup> and was generally available as the FDA-approved label for the drug product. The label indicates that the product was "indicated for the treatment of the symptoms of seasonal allergic rhinitis...." Astelin<sup>®</sup> Label, at 3-4.

40. One portion of the label states as follows:

#### ASTELIN<sup>•</sup>

(azelastine hydrochloride) Nasal Spray, 137 mcg IN-023S3-

#### DESCRIPTION

Astelin® (azelastine hydrochloride) Nasal Spray, 137 micrograms (mcg), is an antihistamine formulated as a metered-spray solution for intranasal administration. Azelastine hydrochloride occurs as a white, almost odorless, crystalline powder with a bitter taste. It has a molecular weight of 418.37. It is sparingly soluble in water, methanol, and propylene glycol and slightly soluble in ethanol, octanol, and glycerine. It has a melting point of about 225°C and the pH of a saturated solution is between 5.0 and 5.4. Its chemical name is (±)-1-(2H)-phthalazinone,4-[(4chlorophenyl) methyl]-2-(hexahydro-1-methyl-1Hazepin-4-yl)-, monohydrochloride. Its molecular formula is C22H24CIN3O+HCI with the following chemical structure:



Astelin<sup>•</sup> Nasal Spray contains 0.1% azelastine hydrochloride in an aqueous solution at pH  $6.8 \pm$ 0.3. It also contains benzalkonium chloride (125 mcg/mL), edetate disodium, hydroxypropyl methyl cellulose, citric acid, dibasic sodium phosphate, sodium chloride, and purified water.

After priming, each metered spray delivers a 0.137 mL mean volume containing 137 mcg of azelastine hydrochloride (equivalent to 125 mcg of azelastine base). Each bottle can deliver 100 metered sprays.

Astelin<sup>®</sup> Label, at 1.

41. As can be seen, the label provides much information about the active ingredient itself, including its chemical structure, that it is an antihistamine, that it is sparingly soluble in water and slightly soluble in glycerine, and that the product contains 0.1% azelastine hydrochloride in an aqueous solution at pH 6.8 +/-0.3. Each spray of the drug contains a mean

volume of 0.137 mL, and delivers 137  $\mu$ g of azelastine hydrochloride. That is equivalent to 125  $\mu$ g of azelastine base. Each bottle can deliver 100 metered sprays. *Id*.

42. The fact that azelastine is administered as a "metered-spray solution" means that it is dissolved in a solvent. The product is described as an "aqueous solution," i.e., water is included in the solvent system. The azelastine hydrochloride is described as "sparingly soluble" in water, which means to a POSA that it requires somewhere between 30-100 parts of water to dissolve one part of azelastine HCl. See, for example, Remington's (2000) at 209, from which the following chart is reproduced:

Descriptive terms	Parts of solvent needed for 1 part solute
Very soluble	< 1
Freely soluble	1-10
Soluble	10-30
Sparingly soluble	30-100
Slightly soluble	100-1000
Very slightly soluble	1000-10,000
Practically insoluble or insoluble	> 10,000

43. The "pH" of an aqueous solution is used as a description of how acidic or basic it is on a scale of 0 to 14, with 0 being the most acidic and 14 being the most basic. A pH of 7 is defined as neutral.

44. The label also provides information about the other ingredients in each spray in

addition to azelastine HCl. It contains  $125 \,\mu$ g/mL of benzalkonium chloride. This concentration of benzalkonium chloride in Astelin<sup>®</sup> is 0.0125% weight/volume (w/v), which is also approximately its weight/weight (w/w) concentration.<sup>1</sup> The product also contains edetate disodium (sometimes abbreviated "disodium EDTA"); hydroxypropyl methyl cellulose (sometimes abbreviated "HPMC"); citric acid; dibasic sodium phosphate; sodium chloride; and purified water.

45. Beyond just naming ingredients, this label teaches a POSA that each of these ingredients was by 2002 a common pharmaceutical excipient, or inactive ingredient, that was suitable for nasal administration since they had all been used in at least one FDA-approved product—Astelin<sup>®</sup>. None of these ingredients was new in the pharmaceutical field. A POSA formulating any nasal composition would also know that these ingredients include at least one (i) preservative, (ii) suspending or thickening agent, (iii) tonicity-adjusting agent, and (iv) pH modifier or buffer to create a nasal solution for maximum absorption and comfort. Those additional materials are commonly used in nasal spray pharmaceutical products.

#### 1. Preservatives

46. Well before 2002 a POSA knew that preservatives were excipients that could help prevent degradation of the drug product and/or prevent and inhibit microbial contamination of the drug product. The prior art Astelin<sup>®</sup> formulation contains two ingredients that were known to act as preservatives: edetate disodium and benzalkonium chloride. *See* Wade & Weller, Handbook of Pharmaceutical Excipients (1994), at 27 (benzalkonium chloride); *id.* at 176 ("Edetic acid and edetates possess some antimicrobial activity but are most frequently used in

<sup>&</sup>lt;sup>1</sup> As I explain in paragraph 91, Example 1 of Astelin<sup>®</sup>'s patent, Hettche, discloses the formulation for 0.1% azelastine hydrochloride, which includes 1.25 g of benzalkonium chloride. Hettche, at 6:13. The solution is diluted to 10.05 kg = 10 Liters, which means there are 1.25 g of benzalkonium chloride per 10,050 g of solution. That is equivalent to 0.0124378 g of benzalkonium chloride per 100 g of solution, which is 0.01244 % w/w. A POSA would view 0.0124% w/w and 0.0125% w/v as essentially equivalent with regard to its preservative activity.

combination with other antimicrobial preservatives due to their synergistic effects."). Edetate disodium is also a chelating agent and antioxidant, i.e., it also helps preserve by removing ions from solution that can contribute to oxidative degradation of materials in aqueous solution. *Id.* (describing that edetates have been used to stabilize, among other things, corticosteroids). I discuss further these and other known preservatives below.

### 2. Suspending and thickening agents

47. It was also known that thickening agents were useful in drug products for nasal administration. These agents work because following administration, the formulation deposits on the tissue surfaces within the nasal cavity and it resides on the surface so the active ingredient can be absorbed. Formulations that are "thin"/low viscosity may only stay on the nasal tissue surfaces for a relatively short time and, instead, are cleared from the nasal cavity and subsequently swallowed. "Thicker" formulations may be able to stay within the nasal cavity for longer periods of time, and may improve the effectiveness of the drug(s). *E.g.*, U.S. Patent No. 5,164,194 ("Hettche"), at 4:51-66 ("[I]t is possible to add thickening agents to the solutions to prevent the solution from flowing out of the nose too quickly....").

48. The thickening agent in Astelin<sup>®</sup> is HPMC, which was in 2002, and is still today, commonly used as a pharmaceutical excipient. Wade & Weller, Handbook of Pharmaceutical Excipients (1994), at 229 (categorizing hydroxypropyl methylcellulose as a suspending agent and viscosity-increasing agent). Other thickening agents were also known for use in pharmaceutical preparations, specifically nasal sprays. As Hettche disclosed to a POSA in 1992, "Such thickening agents may, for example, be: cellulose derivatives (for example cellulose ether) in which the cellulose-hydroxy groups are partially etherified with lower unsaturated aliphatic alcohols and/or lower unsaturated aliphatic oxyalcohols (for example methyl cellulose, carboxymethyl cellulose, hydroxypropylmethylcellulose), ...." Hettche at 4:51-66; *see also* 

Pennington et al. (1988); Suzuki & Makino (1999). The combination of microcrystalline cellulose ("MCC") and carboxymethyl cellulose sodium ("CMC"), commercially sold under the brand name "Avicel," was a common thickening agent. Wade & Weller, Handbook of Pharmaceutical Excipients (1994), at 86 (describing the combinations of microcrystalline cellulose and carboxymethylcellulose sodium); Dolz et al. (1992), at 96-99 (explaining that these combinations "are extensively used in commercial preparations" as viscosity-increasing agents). I refer to that combination herein as MCC-CMC unless otherwise noted.

### **3.** Tonicity-adjusting agents (isotonization agents)

49. The NaCl, or sodium chloride, in Astelin<sup>®</sup> and other pharmaceutical formulations acts to adjust the tonicity of the formulation. *E.g.*, Hettche, at 4:31-35. An "isotonic" nasal solution drug product is one that has the same osmotic pressure as nasal secretions. *E.g.*, *id.* at 4:35-45. The practical effect of that equality in osmotic pressure is that the cells and tissue in the nasal cavities neither swell by imbibing water from the nasal spray, nor do they shrink due to water loss from the cells. Those types of changes could cause irritation in the nasal cavity.

50. Formulators of products for nasal administration thus generally preferred to make isotonic preparations, and they still do so today. *E.g.*, European Patent Application No. 0 780 127 (1997) ("Cramer"), at 3 ("Most preferably, the [combination] nasal composition is isotonic, i.e., it has the same osmotic pressure as blood and lacrimal fluid."); Hettche, at 4:36-38 ("The isotonization agents adjust the osmotic pressure of the formulations to the same osmotic pressure as nasal secretions."); PCT Publication No. WO 98/48839 (1998) ("Segal"), at 4 ("The [disclosed combination nasal] compositions are preferably isotonic. [Tonicity-adjusting] agents such as sugars and sodium chloride are known in the art and may be included in the subject compositions."). *See also* Remington's (2000), at 246-62. However, making an isotonic formulation was not required. A POSA would have known that non-isotonic nasal formulations

were also acceptable within certain ranges. *See* Allen (1997), at 220 ("The ideal tonicity is 300 mOsm/L; however, a range of 200 to 600 mOsm/L is acceptable.").

51. Hettche also discloses several other exemplary tonicity-adjusting agents that could be used with azelastine formulations, in addition to NaCl. Hettche at 4:31-35 ("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: saccharose, glucose, glycerine, sorbitol, 1,2-propylene glycol, NaCl.").

52. A POSA wanting to make an isotonic formulation also knew that the exact amount of a tonicity-adjusting agent necessary to obtain isotonicity with nasal secretions was determinable using appropriate parameter values by well-known mathematical formulas related to the freezing point of water. Remington's (2000), at 252-54. For instance, when a sufficient amount of a tonicity-adjusting agent is added to a solution such that it achieves a freezing-point depression of -0.52 degrees centigrade in comparison to pure water, the solution would be isotonic with human blood and lacrimal fluid. This comparison would also extend to nasal secretions. *Id*.

# C. Fluticasone propionate and Flonase<sup>®</sup>

53. Another product relevant to the desire to manufacture a combination azelastine HCl and fluticasone propionate combination product was Flonase<sup>®</sup>, which had fluticasone propionate as its active ingredient. I have reviewed the FDA-approved labeling for Flonase<sup>®</sup> dated 1998. Flonase<sup>®</sup> Label at 10. This label was available at this time to any prescriber, consumer, or researcher purchasing Flonase<sup>®</sup> and was generally available as the FDA-approved label for the drug product. The label states that the product was "indicated for the management of nasal symptoms of seasonal and perennial allergic and nonallergic rhinitis...." *Id.* at 4, *ll.* 139-40.

54. One portion of the label states as follows:

**DESCRIPTION:** Fluticasone propionate, the active ingredient of FLONASE Nasal Spray, is a synthetic corticosteroid with the chemical name of S-fluoromethyl  $6\alpha$ ,  $9\alpha$ -difluoro-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxo-17 $\alpha$ -propionyloxyandrosta-1,4-diene-17 $\beta$ -carbothioate and the following chemical structure:



Fluticasone propionate is a white to off-white powder with a molecular weight of 500.6. It is practically insoluble in water, freely soluble in dimethyl sulfoxide and dimethylformamide, and slightly soluble in methanol and 95% ethanol.

FLONASE Nasal Spray 50 mcg is an aqueous suspension of microfine fluticasone propionate for topical administration to the nasal mucosa by means of a metering, atomizing spray pump. FLONASE Nasal Spray also contains microcrystalline cellulose and carboxymethylcellulose sodium, dextrose, 0.02% w/w benzalkonium chloride, polysorbate 80, and 0.25% w/w phenylethyl alcohol, and has a pH between 5 and 7.

It is necessary to prime the pump before first use or after a period of non-use (1 week or more). After initial priming (six actuations), each actuation delivers 50 mcg of fluticasone propionate in 100 mg of formulation through the nasal adapter. Each bottle of FLONASE Nasal Spray provides 120 metered sprays. After 120 metered sprays, the amount of fluticasone propionate delivered per actuation may not be consistent and the unit should be discarded.

Id. at 1, ll. 8-26.

55. This provided significant information to a POSA about nasal spray formulations

containing fluticasone propionate.

56. The labeling indicates that the drug is practically insoluble in water, and that the drug product is an "aqueous suspension of microfine fluticasone propionate." The word "aqueous" indicates that the suspension includes water as a primary vehicle ingredient. In a suspension, the active drug is not entirely dissolved, but rather the system contains both drug in solution and solid drug suspended in the medium.

57. The fluticasone propionate is also described as "microfine," which tells a POSA

that the particle size of the solid fluticasone propionate has been reduced such that the diameter of the drug particles is in the low-micron size range. Ansel et al. (1995), at 255, defines the size of "micronized" particles to be under 10 microns ( $\mu$ m). A POSA would define both "micronized" and "microfine" particles to be in the same size ranges. Additionally, the patent that the manufacturer said covered Flonase<sup>®</sup>, "Phillips," U.S. Patent No. 4,335,121, explains that its composition is "micronized," which means it has a "particle size as defined in BPC 1973 pg. 911 for Ultra-Fine powder." Phillips at 34:47-49. That reference, in turn, 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  $\mu$ m and of which the diameter of none of the particles is greater than 50  $\mu$ m." Ansel et al. (1995), at 255, defines "ultrafine" and "micronized" the same, as particles under 10  $\mu$ m.

58. The labeling further discloses that the strength of the active ingredient is 50  $\mu$ g of fluticasone propionate in each 100-milligram spray. That means after initial priming, each actuation of the nasal delivery pump delivers 50  $\mu$ g of fluticasone propionate in 100 mg of formulation through the nasal adapter.

59. The label also describes the other ingredients in Flonase<sup>®</sup>. It contains microcrystalline cellulose (MCC) and carboxymethylcellulose sodium (CMC), dextrose, 0.02% w/w benzalkonium chloride, polysorbate 80, and 0.25% w/w phenylethyl alcohol. The labeling also indicates that it has a pH between 5 and 7.

60. I discussed above in connection with Astelin<sup>®</sup> why certain of the inactive ingredients were included in the dosage form. I do the same here with respect to certain ingredients in Flonase<sup>®</sup>.

### 1. Preservatives

61. Flonase<sup>®</sup>, like Astelin<sup>®</sup>, also contains preservatives including benzalkonium

chloride as well as another preservative called phenylethyl alcohol. Wade & Weller, Handbook of Pharmaceutical Excipients (1994), at 340 (categorizing phenylethyl alcohol as an antimicrobial preservative).

### 2. Thickening agents

62. Flonase<sup>®</sup>, like Astelin<sup>®</sup>, also contains thickening agents. They include microcrystalline cellulose (MCC) and carboxymethylcellulose sodium (CMC). *See* Wade & Weller, Handbook of Pharmaceutical Excipients (1994); *id.* at 78 (carboxymethylcellulose sodium); *id.* at 84 (microcrystalline cellulose). As explained above, the combination of those two substances was known and available to a POSA in at least one combination under the brand name Avicel. Wade & Weller, Handbook of Pharmaceutical Excipients (1994), at 86 (describing various MCC-CMC combinations as "Avicel RC-581; Avicel-591; Avicel CL-611"). For example, Dolz et al. (1992), at 96-99, described MCC-CMC combinations as "Avicel" and explained that combinations of these two excipients "are extensively used in commercial preparations" as gels and in other form.

# **3.** Tonicity-adjusting agents (isotonization agents)

63. Flonase<sup>®</sup>, like Astelin<sup>®</sup>, also contains tonicity-adjusting agents. In Flonase<sup>®</sup>, the agent is dextrose. Another name for dextrose, which would have been known to a POSA as of 2002, was D-glucose.

# 4. Surfactants

64. Flonase<sup>®</sup> also includes an ingredient called polysorbate 80. Polysorbate 80 was known before 2002 as a "surfactant." Wade & Weller, Handbook of Pharmaceutical Excipients (1994), at 375-76 (describing polysorbate 80 as a "nonionic surfactant"). Surfactants are "surface active agents" which are ingredients that can help hydrophobic/water-insoluble ingredients better interact with and disperse into an aqueous medium. In one of their functions,

they act at the interface between the hydrophobic material and water to decrease the surface free energy.

65. In the context of Flonase<sup>®</sup>, polysorbate 80 is used because, as the label indicates, fluticasone propionate is "practically insoluble" in water. *See* Remington's (2000), at 209. The polysorbate 80 is used to help the drug disperse in the aqueous medium so that it will remain suspended or be easily resuspended in order for an accurate dose of drug in solution and solid drug to be emitted from the sprayer following each pump actuation. Polysorbate 80 may also assist in pump performance which also contributes to the reproducibility of each emitted dose.

#### **D.** Additional Prior Art

66. In addition to the Flonase<sup>®</sup> and Astelin<sup>®</sup> labels noted above, there were numerous other sources of information about nasal sprays and how they were formulated prior to 2002. I provide summaries of a few of these references below to provide representative teachings. I am prepared to discuss these references in more detail if asked to do so.

### **1. Handbook of Pharmaceutical Excipients**

67. One reference, already cited above, is Wade & Weller, Handbook of Pharmaceutical Excipients (1994). This Handbook would have been familiar and readily available to the POSA prior to 2002. It was a standard reference text for formulators. The Handbook collects and presents information on known pharmaceutical excipients. The 1994 Handbook contains information on benzalkonium chloride (27-29); carboxymethylcellulose sodium (78-81); microcrystalline cellulose (84-87); edetic acid (EDTA) (176-79); hydroxypropyl methylcellulose (229-32); phenylethyl alcohol (340-41); and sorbitan fatty acid esters such as polysorbate 80 (375-78). It also includes descriptions of agents used to adjust tonicity such as glycerin, dextrose, NaCl, and others. *E.g., id.* at 204-06 (glycerin). The Handbook explains the functions of each excipient and typical concentrations of each—for example, 0.002-0.02% w/v

benzalkonium chloride (27); 1.2% w/v for Avicel CL-611, which is a MCC-CMC combination (86); about 0.01-0.1% w/v for edetic acid and edetates when used as antimicrobial preservative synergists (176); 0.25-0.5% w/v for phenylethyl alcohol (340); and sufficient glycerine (less than or equal to 2.6% v/v) to make an isotonic solution (204).

# 2. Hettche

68. One reference, which I noted above above, is the Hettche patent. Hettche teaches a nasal spray using azelastine in a weight/weight concentration of between 0.0005% to 2%, preferably between 0.001% to 1%, and most preferably 0.003 to 0.5%. 3:26-31. Hettche also teaches dosing ranges of azelastine, explaining that from "0.03 to 3 mg of azelastine base should be released per individual actuation." 2:20-23.

69. Hettche also discloses the use of numerous formulation ingredients such as, for example, preservatives (2:46–4:9), isotonization agents (4:31-35), thickening agents (4:51-66), and surfactants (4:14-29). More specifically with respect to preservatives, Hettche teaches benzalkonium chloride with a preferable concentration range of 0.005 to 0.05% weight/weight or weight/volume (3:3-25; 4:7-9) or a range of 0.002 to 0.02% weight/weight or weight/volume (3:64), edetate disodium with a concentration of 0.05% to 0.1% weight/weight or weight/volume (4:4-8), and teaches that the most preferred preservative combination is edetate disodium and benzalkonium chloride within the same concentration ranges (4:4-9). Hettche also teaches the preservative 2-phenylethanol (also known as phenyl ethyl alcohol, mentioned above) in a preferred concentration 0.2 to 2.0 weight/volume. 3:19-25.

70. Hettche also teaches the use of cellulose derivatives—and particularly carboxymethyl cellulose sodium—as thickening agents. 4:55-60.

71. Hettche also teaches that "isotonization agents adjust the osmotic pressure of the formulations to the same osmotic pressure as nasal secretions. For this purpose these substances

are in each case to be used in such amount that, for example, in the case of a solution, a reduction in the freezing point of 0.50° to 0.56° C. is attained in comparison to pure water." 4:36-42. This reflects the knowledge of a POSA that one can easily determine the appropriate amount of a given isotonization agent to obtain an isotonic formulation (if one requires an isotonic formulation) by measuring its effect on freezing point. A POSA would know to adjust the amount of the agent (raise or lower its concentration) in order to achieve this range of freezingpoint depression to obtain an isotonic preparation if one is desired.

72. Hettche discloses the use of saccharose, glucose, glycerine, sorbitol, 1,2propylene glycol, and NaCl as isotonization agents. 4:31-35.

# 3. Cramer

73. In addition to this prior art, several other references also discussed using various steroids and antihistamines in single, combination products. All of these would be known to a POSA.

74. One reference that would have been known to a POSA is "Cramer," European Patent Application No. 0 780 127 (1997). Cramer disclosed "nasal spray compositions comprising a safe and effective amount of a glucocorticosteroid and an antihistamine possessing leukotriene inhibiting properties." Cramer, at 1. It disclosed that fluticasone is an acceptable glucocorticosteroid, and azelastine and its salts are acceptable leukotriene inhibiting antihistamines. *Id.* at 3, *ll.* 15-18, 26-27. Cramer taught that this kind of combination composition had "improved effectiveness in the treatment of symptoms generally associated with either seasonal or perennial allergic rhinoconjunctivitis." *Id.* at 2, *ll.* 28-29.

75. Cramer taught a preferred concentration of glucocorticosteroid from about 0.01% to about 0.1% w/w (*id.* at 3, *l.* 20), and a preferred concentration of antihistamine from about

0.01% to about 1% w/w (*id.* at 3, *l.* 30).<sup>2</sup>

76. Cramer discloses in line with my opinions above that "[m]ost preferably, the nasal composition is isotonic, i.e., it has the same osmotic pressure as blood and lacrimal fluid." *Id*.at 3, *ll*. 49-50. Cramer thus also taught the use of tonicity-adjusting agents. *Id*. at 4, *ll*. 50-55.

77. Cramer also taught the use of thickening agents (*id*. at 4, *l*. 56–5, *l*. 5), surfactants (*id*. at 5, *ll*. 11-15), and preservatives (*id*. at 5, *ll*. 16-22) in these combination products.

78. Cramer taught more specifically that the preservatives for use in the combination products, including an azelastine/fluticasone product, could be a combination of benzalkonium chloride and EDTA, with a suitable weight/weight concentration of 0.001% to 2%. *Id.* at 5, *ll.* 19-21.

79. Cramer also discloses the use of thickening agents, including microcrystalline cellulose and carboxymethyl cellulose sodium (*id.* at 4, *l.* 58–5, *l.* 1), the use of surfactants including polysorbate 80 (*id.* at 5, *ll.* 12-13), and the use of isotonization agents including glycerin (*id.* at 6, *l.* 36). Example I of Cramer contains 1.2% w/v of a microcrystalline cellulose and carboxymethyl cellulose sodium combination (*id.* at 5, *l.* 47) and Example III contains 1.0% w/v of a similar cellulose derivative (*id.* at 6, *l.* 36). Example III contains 2.0% w/v of glycerin. *Id.* at 6, *l.* 35.

80. Cramer includes several examples of formulations that are suitable for nasal administration:

 $<sup>^{2}</sup>$  Cramer explains that all of its concentrations are by weight, that is, w/w, unless otherwise specified. Cramer, at 2. In the Examples, because Cramer specifies "q.s. to vol.," the concentrations are in w/v.

#### EXAMPLES

The following examples further describe and demonstrate embodiments within the scope of the present invention. The examples are given solely for the purpose of illustration and are not to be construed as limitations of the present invention, as many variations thereof are possible without departing from the spirit and scope of the invention.

#### Example I

The intranasally administered pharmaceutical composition of the present invention is prepared by combining the following components utilizing conventional mixing techniques similar to that described below.

Component	Wgt %
beclomethasone diproprionate, monohydrate	0.042
loratadine	0.200
avicel RC - 591 <sup>1</sup>	1.200
dextrose	5.100
polysorbate 80	0.025
benzalkonium chloride	0.040
phenylethyl alcohol	0.250
distilled water	q.s. to vol.

<sup>1</sup> microcrystalline cellulose and sodium carboxymethyl cellulose, supplied by FMC corporation.

In an appropriately sized vessel, the dextrose, polysorbate 80 and benzalkonium chloride are added one at a time to water with mixing, allowing each to dissolve or completely disperse before adding the next. To this is added, with mixing, a premixed slurry of the avicel and water. Upon forming a uniform solution, the becomethasone, loratadine

and phenylethyl alcohol are added. After all the ingredients are added, purified water is used to bring the batch to the appropriate weight.

Administration of approximately 0.4 grams of the composition is used for topical nasal application to provide relief from allergy or allergy-like symptoms.

#### Example II

The intranasally administered pharmaceutical composition of the present invention is prepared by combining the following components utilizing conventional mixing techniques similar to that described in Example I.

Component	Wgt %
flunisolide	0.025
cetirizine	0.200
propylene glycol	2.000
polyethylene glycol	1.000
sodium chloride	0.900
ethylenediamine tetraacetic acid	0.050
benzalkonium chloride	0.010
distilled water	q.s. to vol.

Administration of approximately 0.4 grams of the composition is used for topical nasal application to provide relief from allergy or allergy-like symptoms.

#### Example III

The intranasally administered pharmaceutical composition of the present invention is prepared by combining the
following components utilizing conventional mixing techniques similar to that described in Example I.

Component	Wgt %
triamcinolone acetonide	0.050
azelastine HCI	0.070
polysorbate 80	0.050
glycerin	2.000
hydroxypropyl methyl cellulose	1.000
sodium chloride	0.900
ethylenediamine tetraacetic acid	0.050
benzalkonium chloride	0.020
distilled water	q.s. to vol.

Administration of approximately 0.4 grams of the composition is used for topical nasal application to provide relief from allergy or allergy-like symptoms. Additionally, substantially similar results are also obtained using, in whole or in part, equivalent amounts of other glucocorticoid agents such as fluticasone, mometasone, budesonide, pharmaceutically acceptable salts thereof and mixtures thereof. Furthermore, the above described compositions may also contain a decongestant such as pseudoephedrine, phenylpropanolamine, phenylephrine, tetrahydrozoline, naphazoline, oxymetazoline, tramazoline, 5-(2-imidazolinylamino)benzimedazoles, optically active racemates thereof, pharmaceutically acceptable salts thereof and mixtures thereof. Those skilled in the art will quickly realize other suitable ingredients, diluents and dosage forms (or readily ascertain such using routine experimentation) which may further be incorporated into the above compositions without departing from the scope and spirit of the present invention.

81. The pH of the compositions in Cramer is preferably from about 4.5 to about 9, more preferably from about 6 to about 7. *Id.* at 2, *l*. 57.

#### 4. Segal

82. Segal, PCT Publication No. WO 98/48839 (1998), is another reference known to a POSA that discusses combination antihistamine/steroid nasal administration products. It discloses, among other things, "topically applicable nasal compositions comprising a therapeutically effective amount of a topical anti-inflammatory agent and a therapeutically effective amount of at least one agent suitable for topical administration" selected from a group consisting of, among other agents, a leukotriene inhibitor and an antihistamine. (Abstract.) The topical anti-inflammatory agents that Segal teaches are corticosteroids "known in the art to suppress inflammation." Segal, at 2, *ll.* 22-23. These include fluticasone propionate. *Id.* at 2, *l.* 25. Segal teaches that a suitable antihistamine is azelastine. *Id.* at 3, *ll.* 19-20. Segal teaches that "[t]he use of an additional therapeutic agent in combination with an anti-inflammatory agent provides additive and synergistic effects in the treatment of nasal and sinus conditions." *Id.* at 3, *ll.* 9-12.

83. According to Segal, "anti-inflammatory agents are utilized in dosages known in the art to be therapeutically effective upon nasal administration." *Id.* at 3, *ll.* 1-2. Segal also teaches the inclusion of other inactive ingredients, including those I discussed above:

The compositions of the present invention are formulated as aqueous solutions comprising an antiinflammatory agent and at least one additional therapeutic agent and further comprising a pharmaceutically acceptable nasal carrier.

The formulation of pharmaceutical compositions is generally known in the art and reference can be conveniently made to standard text such as Remington's Pharmaceutical Sciences, 1985, 17th ed., Mack Publishing Co., Easton, Pennsylvania.

Preferred nasal formulations are nose drops or nasal sprays containing a water buffered aqueous solution as a carrier. The compositions are preferably isotonic. Isotonic agents such as a sugars and sodium chloride are known in the art and may be included in the subject compositions.

The compositions of the present invention may also contain a humectant to increase viscosity and effect moisturization and ciliary vitality. Suitable humectants include glycerin, polyethylene glycol, propylene glycol and mixtures thereof.

Additional agents including pharmaceutically acceptable preservatives, stabilizers, flavoring agents, and pH adjusters are known in the art and may be included in the present compositions.

Id. at 3-4.

# 5. ADVAIR Diskus<sup>®</sup>

84. Before the priority date, fluticasone propionate had been formulated into a combination inhalation product with another drug substance for the treatment or prophylaxis of a condition for which the use of one or more steroids is indicated. Advair Diskus<sup>®</sup> (fluticasone propionate 100  $\mu$ g and salmeterol 50  $\mu$ g) is a combination product of fluticasone propionate and

salmeterol formulated as a metered-spray solution for inhalation. It was approved in 2000. Thus, before 2001, fluticasone propionate had been formulated into a combination inhalation product with another drug substance for the treatment or prophylaxis of a condition for which the use of one or more steroids is indicated.

# 6. Allen, The Art, Science, and Technology of Pharmaceutical Compounding

85. A POSA would also know Loyd V. Allen, The Art, Science, and Technology of Pharmaceutical Compounding (1998). Chapter 20 of this standard text describes "Ophthalmic, Otic, and Nasal Preparations," and discusses nasal preparations at pages 233-38. For example, these pages describe several methods of mixing both nasal solutions and nasal suspensions. *Id.* at 233-34. It discusses pH and buffering, stating that "[g]enerally, pH in the range of 4 to 8 is considered optimum." *Id.* at 235. It also discusses routine buffering systems. *Id.* It also discusses tonicity, explaining that "[a] tonicity of 300 mOsm/L is ideal, although a range of 200 to 600 mOsm/L is acceptable." *Id.* 

### V. FORMULATIONS BASED ON THE PRIOR ART

86. The next step in my analysis was to consider from the perspective of a POSA how they would have formulated an azelastine HCl and fluticasone propionate drug product for nasal administration, consistent with Dr. Schleimer's opinion that a POSA would have had several motivations for doing so and in light of the numerous pieces of prior art, described above, that would have been known to a POSA prior to 2002.

# A. Active ingredients

87. The first step in that analysis is considering what active ingredients to use. It is my opinion that a POSA would have determined immediately that both azelastine HCl and fluticasone propionate were available and suitable for use in the product. In other words, a POSA would have had no hesitation about trying to make the combination product with these two ingredients.

88. Both of these ingredients were known to be safe and effective in human patients who were suffering from allergic rhinitis. Both had been FDA-approved, and both had been commercially marketed as individual agents in either Astelin<sup>®</sup> or Flonase<sup>®</sup>. And, as confirmed by Dr. Accetta (see discussion below), both had been used in combination to treat allergic rhinitis.

89. It is true that some of the art I discussed above discloses that other antihistamines and steroids may also have been thought to be useful when making a combination anti-allergy product. But that is not inconsistent with my opinion that azelastine HCl and fluticasone propionate would likewise have been readily apparent as usable in a combination product.

#### **B.** Amounts of active ingredients

90. Recognizing that azelastine HCl and fluticasone propionate were available and useful in the proposed combination product, a POSA would have considered what amount of each was useful. The starting point again would have been the labeling for the FDA-approved products.

91. The Astelin<sup>®</sup> label says the nasal spray contains 0.1% azelastine HCl in an aqueous solution. The label further indicates that each metered spray delivers a mean volume of 0.137 mL containing 137 mcg (micrograms, also denoted as  $\mu$ g) of azelastine HCl. A POSA would know that this is a reference to the mass of azelastine HCl in each spray, and is the equivalent of 0.137 mg per spray.

92. This w/v concentration of 0.1% is effectively equivalent to a 0.1% w/w concentration. Example 1 of the Hettche reference, of which  $Astelin^{\ensuremath{\mathbb{R}}}$  is the commercial embodiment, contains all of the same ingredients as  $Astelin^{\ensuremath{\mathbb{R}}}$  with one insignificant modification.

Hettche teaches in Example 1 that the solution is diluted to 10.05 kg = 10 liters. Hettche, at 6:19. This means there is 10 g of azelastine (6:11) per 10,050 g of solution. This results in a w/w concentration of 10 g / 10,050 g = 0.000995 g of azelastine per 1 g of solution, which is equivalent to 0.0995 g of azelastine per 100 g of solution. Thus the w/w concentration is 0.0995% which is equivalent to 0.1% when rounded to one significant figure, and the example is titled "...with 0.1% azelastine hydrochloride." Moreover, the patent explains that the equivalent concentrations should be obtained either in w/v or in w/w, depending on the nature of the composition. Hettche, at 4:10-14 ("In the case of solutions/suspensions reference is always made to percent by weight/volume, in the case of solid or semi-solid formulations to percent by weight/weight of the formulation.").

93. The Flonase<sup>®</sup> label provides similar information for the amount of fluticasone propionate that had been proven effective. That label indicates that "each actuation delivers 50 mcg of fluticasone propionate in 100 mg" of the formulation. This is the equivalent to 0.05 mg per actuation (50  $\mu$ g = 0.05 mg), which is per 100 mg of formulation, and thus the weight/weight concentration is 0.05 mg/100 mg = 0.05% w/w. Because the density of an aqueous solution or suspension like those relevant in this prior art was known to a POSA to be reasonably approximated by the density of water, ~1 g/mL, the weight over volume concentration per actuation would have been known to be approximately 0.05 mg/0.1 g = 0.05 mg/0.1 mL = 0.5 mg/mL. Thus, for each mL of formulation, a POSA would have known that approximately 0.5 mg or 500 µg of fluticasone is delivered.<sup>3</sup>

94. There is no reason a POSA would deviate from these FDA-approved quantities

<sup>&</sup>lt;sup>3</sup> The Dymista<sup>®</sup> web site is not prior art and I did not consider it as part of my analysis of the prior art. However, I note that it confirms each spray of Flonase is 0.1 mL in volume, and the label indicates that each spray contains 50  $\mu$ g of drug. That is equal to 500  $\mu$ g /mL, just as the math known to a POSA in 2002 confirms. *See* http://dymista.com/spray-volume.php.

when considering how to formulate a combination product. They are quantities that are known to be safe and effective. It is my opinion that a POSA would be deterred from altering these quantities because doing so would potentially involve more time-consuming and expensive testing of safety and efficacy.

95. I have also reviewed the deposition testimony of Dr. Accetta, and understand that before 2002 he had prescribed azelastine HCl and fluticasone propionate nasal sprays to patients. He did so because it seemed "obvious" to him because allergists "were already using an oral antihistamine along with various steroid nasal sprays, and this seemed to be the next logical step in a patient who was not well-controlled using just a nasal steroid." Accetta Dep. Tr. 23:1-5. That is further evidence that a POSA at the time would have used the amounts of those active ingredients already provided in the commercially available formulations when trying to make a combination product.

# C. Inactive ingredients

96. The next step in formulating this combination nasal product would be to determine which inactive ingredients and in what amounts to use in the formulation.

97. A POSA would have used the Astelin<sup>®</sup> and Flonase<sup>®</sup> products as a starting point for identifying which excipients to use. Both product labels list the inactive ingredients that aided in the administration of both drugs. A POSA would also look at the prior art that I discuss above for teachings on suitable inactive ingredients. Several things would have been immediately apparent to a POSA from these materials.

#### 1. Water

98. Both Astelin<sup>®</sup> and Flonase<sup>®</sup> include water. The Astelin<sup>®</sup> label expressly lists purified water, and the Flonase<sup>®</sup> label indicates that the product is an aqueous suspension. Water is also described as an ingredient in each of the examples in Cramer. Put simply, a POSA

considering a nasal spray product would have considered purified water to be an important ingredient. For administration as a nasal spray, it would be expected that water was the major component of the formulation.

99. In terms of the amount of water to add, the exact amount will directly depend on the chosen volume of each spray. For instance, if a POSA chose to maintain the Astelin<sup>®</sup> amount of 0.137 mL per spray, then the amount of water needed would be the amount that provides that total volume and contains the desired amounts of active and inactive ingredients.

# 2. Flonase<sup>®</sup> ingredients

100. Second, a POSA would also note that fluticasone propionate is formulated as an aqueous suspension, not a solution, due to the fact that the active drug is practically insoluble in water. If anything, a POSA would know that stable suspensions of insoluble materials are somewhat more difficult to make than solutions containing more soluble materials. This would not deter a POSA from using that active ingredient or looking to the commercial product's, or a similar product's, label for guidance on how to formulate a combination product with azelastine HCl. To the contrary, a POSA would know that Flonase<sup>®</sup> provides the inactive ingredients that created a successful suspension of fluticasone propionate. That product would be particularly useful prior art to consider when determining the inactive components of the desired combination product.

# 3. Surfactant

101. Third, a POSA would know that polysorbate 80 was used in Flonase<sup>®</sup> as a surfactant to aid in the dispersability and suspendability of the formulation. If it were not there, one would expect the active ingredient could form agglomerates or separate out to such an extent that it would not be evenly distributed and would result in a variable amount of drug delivered in each spray.

102. Polysorbate 80 would thus be on the list of ingredients a POSA would think useful when making a nasal spray combination product including fluticasone propionate.

#### 4. **Preservatives**

103. Fourth, a POSA would know to include one or more preservatives in a formulation intended to be provided in a multi-use spray device. The preservative benzalkonium chloride was used in both Flonase<sup>®</sup> and Astelin<sup>®</sup> (as well as many other pharmaceutical products). Flonase<sup>®</sup> also contained phenyl ethyl alcohol. Those two ingredients would thus be immediately apparent to a POSA for use as preservatives in a combination nasal spray.

104. A POSA would also know that Astelin<sup>®</sup> contained edetate disodium. Examples in Cramer use benzalkonium chloride and either phenyl ethyl alcohol or ethylenediamine teraacetic acid, which is the acid form of edetate disodium.

105. A POSA would thus recognize that it would be acceptable and may be appropriate to use more than two preservatives, including any or all of EDTA, edetate disodium, benzalkonium chloride and/or phenyl ethyl alcohol in a formulation combining azelastine HCl and fluticasone propionate. Indeed, a POSA would recognize that edetate disodium was "most frequently used in combination with other antimicrobial preservatives due to their synergistic effects." Wade & Weller, Handbook of Pharmaceutical Excipients (1994), at 176. Similarly, phenyl ethyl alcohol "is generally used in combination with other preservatives." *Id.* at 340. Specifically, "Synergistic effects have been reported when combined with benzalkonium chloride, …" *Id.* 

106. As for the amounts of each to include in the formulation, the existing products are again a useful place that a POSA would look, as would be the Handbook of Pharmaceutical Excipients. More specifically:

107. As for benzalkonium chloride, Flonase<sup>®</sup> used 0.02% w/w of benzalkonium

chloride, and Astelin<sup>®</sup> used about 0.0125% w/v of that ingredient (125  $\mu$ g/mL), which, as explained above, is 0.0124% w/w, which is effectively the same concentration. Indeed, the Hettche patent explained that the appropriate concentrations should be obtained either in w/w or w/v, depending on the nature of the composition. Hettche, at 4:10-14 ("In the case of solutions/suspensions reference is always made to percent by weight/volume, in the case of solid or semi-solid formulations to percent by weight/weight of the formulation."). A POSA would thus think either of the amounts in the Flonase<sup>®</sup> or Astelin<sup>®</sup> formulation would be appropriate. *See also* Cramer, Example I (0.04% w/v); Example II (0.01% w/v); Example III (0.02% w/v); Wade & Weller, Handbook of Pharmaceutical Excipients (1994) at 27 ("In nasal and otic formulations a concentration of 0.002-0.02% [w/v] is used[.]").

108. Flonase<sup>®</sup> used 0.25% w/w of phenyl ethyl alcohol. Cramer also used this ingredient in that same amount in its Example 1, weight by volume. That is also an amount a POSA would therefore immediately think to use in the combination product. *See also* Wade & Weller, Handbook of Pharmaceutical Excipients (1994), at 340 ("Phenylethyl alcohol is used as an antimicrobial preservative in parenteral and ophthalmic formulations at 0.25-0.5% v/v concentration; it is generally used in combination with other preservatives."). Although Wade & Weller report v/v, the density of phenylethyl alcohol is known to be 1.02 g/cm<sup>3</sup>, and the density of solution will have a density slightly greater than water (1.0 g/cm<sup>3</sup>).

109. Cramer provides additional information about the amount of edetate disodium (used in Astelin<sup>®</sup>) that would be useful to a POSA. It discloses for use in combination steroid/antihistamine products that "[a] suitable concentration of the preservative will be from 0.001% to 2% based on the total weight [w/w], although there may be appreciable variation depending upon the agent selected." Example III, including azelastine, includes 0.05% w/v of

ethylenediamine tetraacetic acid. The 0.05%, which is squarely within the range presented by Cramer as ideal, is an obvious amount to use for a POSA interested in using edetate disodium as a preservative. What is more, according to the Handbook of Pharmaceutical Excipients (1994), "Typically, edetic acid and edetates are used in concentrations of 0.01-0.1% w/v as antimicrobial preservative synergists." Wade & Weller, Handbook of Pharmaceutical Excipients (1994), at 176. Elsewhere Wade & Weller state that "[t]ypically, edetic acid is used at a concentration of 0.1-0.15% w/v." *Id.* Finally, Hettche, the Astelin<sup>®</sup> patent, teaches edetate disodium with a concentration of 0.05% to 0.1% w/w or w/v. Hettche, at 4:4-8.

110. I also note, however, that appropriate and obvious amounts to use of these and other excipients will often be determined as part of the process of routine optimization to obtain the precise results a formulator desires. For instance, a POSA might begin a formulation with 0.0125% benzalkonium chloride as in Astelin<sup>®</sup>, because that amount was known to be effective in Astelin<sup>®</sup>. If that amount did not provide enough preservative functionality in the product under development, the POSA would know to increase the amount to, for instance, the 0.02% used in Flonase<sup>®</sup>. They would know whether and when they had used a sufficient amount to reach their particular goal based on results of preservative challenge testing, which is routine testing and is defined in the USP. USP 24/NF19 (2000). These excipients and others discussed below are results-driven, meaning that the precise amount will depend on the design parameters for the formulation. The process of finding those exact amounts is a matter of routine experimentation and optimization.

## 5. Thickening agents

111. A POSA would also note that Flonase<sup>®</sup> contains a combination of two cellulosic agents, microcrystalline cellulose (MCC) and sodium carboxymethyl cellulose (CMC), used for increasing viscosity and gel formation. The combination of these two materials, as of 2002, was
available in several commercial excipient blends as part of the Avicel family of products suitable for use in pharmaceutical products available from FMC. A POSA would understand that this combination is an obvious thickening agent to use in this combination drug formulation.

112. Astelin<sup>®</sup> uses another thickening agent called hypromellose. The use of this other ingredient in Astelin<sup>®</sup> would not present a reason for a POSA not to try using MCC and CMC in a combination product. It would be viewed as another available option to try as a thickening agent in the event there were any surprising incompatibilities with MCC and CMC in the desired combination formulation (I am not aware of any).

113. The labels for these products did not indicate exactly how much or which grade MCC-CMC should be used. But regarding the amounts of MCC-CMC or HPMC to include, both Cramer and the Handbook of Pharmaceutical Excipients (1994) provide useful information. Cramer states that "[t]he preferred concentration of the thickener will depend upon the agent selected. The important point is to use an amount which will achieve the selected viscosity." Cramer, at 5. For example, if a POSA wanted to achieve the same viscosity as Flonase<sup>®</sup>, she would adjust the levels of thickening agents until that was achieved.

114. Cramer's Example I also contains an example of a pharmaceutically acceptable formulation using an MCC-CMC combination at 1.2% w/v. The specification for Avicel RC-591 Bulletin (1994), at 7, explains that "[f]ormulations containing 1.2% RC-591 are well structured suspension vehicles, thixotropic, and have a finite yield value." A POSA would thus know that 1.2% w/v of a combination of MCC and CMC would be a suitable amount of suspending agent, and optimization of the precise amount to be used was routine. Additionally, a POSA would have other grades of Avicel available to use. Avicel RC-591 Bulletin (1994), at 15.

115. This would have been a useful starting point for a POSA designing a combination azelastine HCl/fluticasone propionate product. As noted above and reiterated by Cramer, however, the exact amount used in any given formulation would ultimately be determined when the desired viscosity is reached. Arriving at that viscosity by adjusting the amounts of the thickening agent was routine experimentation well before 2002.

#### 6. Tonicity-adjusting agents (isotonization agents)

116. The last excipient category used in the Flonase<sup>®</sup> suspension was dextrose, which was known at the time to be useful in adjusting tonicity. Astelin<sup>®</sup> uses a different such agent, sodium chloride. *See also, e.g.*, Remington's (2000), at 255 (explaining that dextrose and NaCl can both be used to make a solution isotonic). In addition to these two, several others were known to a POSA, as noted above. For instance, both Hettche and Cramer disclose azelastine formulations with a tonicity-adjusting agent called glycerin. Cramer, Example III; Hettche, at 4:31-35.

117. These tonicity-adjusting agents are another type of excipient where the exact amount included will depend on the amount which provides the desired tonicity level. This can be determined by known mathematical equations if appropriate parameter values are known, or the amount of tonicity-adjusting agent required can be determined through simple experimentation evaluating the freezing-point depression or, potentially, the vapor pressure lowering produced by the formulation. *See, e.g.*, Remington's at 258. If a POSA were to use glycerin, she would understand that a 2.6% v/v concentration was known to make water isotonic. *See id.* (listing 2.6% as the "iso-osmotic concentration" of glycerin). Also, 2.6% v/v is listed in the Handbook of Pharmaceutical Excipients (1994), at 204, for glycerin to be "iso-osmotic" with serum. Remington's (2000), at 262, also lists the isotonic value of glycerin as 0.3 g per 11.7 mL of water. Because water has a density of 1.0 g/mL, this translates to 0.3 g per 11.7 g of water for

an overall content of 0.3 g of glycerine per 12 g of total solution. This can be calculated as 0.3 g/12 g = 2.5% w/w. If there are other solutes in the formulation that affect tonicity, a POSA would know to use an amount less than 2.6% v/v or 2.5% w/w to achieve isotonicity. The precise amount to use would be determined by the routine experimentation described above.

#### 7. **pH of the formulation**

118. A POSA would also know that a formulation to be applied to the nasal mucosa should be maintained at a pH level compatible with the nasal mucosal surface. Allen (1998), at 235, discussed above, explains that "[g]enerally, pH in the range of 4 to 8 is considered optimum." Both the Flonase<sup>®</sup> and Astelin<sup>®</sup> products reported pHs of between 5 and 7, and 6.8 +/- 0.3, respectively. Often formulators select the final formulation pH based on the need for physiologic compatibility along with considerations of the solubility and stability characteristics of the formulation ingredients. Formulators evaluate the formulation pH following preparation and the maintenance of the pH during the storage shelf-life of the product. These evaluations are routine.

119. These were obviously acceptable ranges because they were used in successful commercialized products. The literature is consistent with these formulation pH values as well. Cramer reports that the pH of the compositions he described "is preferably from about 4.5 to about 9, more preferably from about 6 to about 7." Cramer, at 2. Hettche also reported adjusting the disclosed formulas to a pH value of 6 to 7.5, preferably 6.5 to 7.1. Hettche, at 5:6-7. One of its azelastine HCl nasal spray examples was said to have a pH value 6.8 +/- 0.3, just like Astelin<sup>®</sup>, the commercial embodiment of that patent. Hettche, at 6:23-24.

120. A POSA would thus have known that targeting a pH value for the combination product at 6.8, or anywhere between 5 and 7, and more broadly anywhere between 4 and 8, would have been acceptable.

121. Upon preparation, if a given formulation was well outside that range, a POSA also knew how to adjust the pH as appropriate using simple additions of acidic or basic pH adjusting materials or physiologically compatible buffers. Segal reported that "pH adjusters are known in the art and may be included in the present compositions." Segal, at 4; *see also* Hettche, at 5:1-7. One such pH adjuster was citric acid, and others were also known. Hettche, at 5:1-7.

#### 8. Particle size

122. A POSA would also have known that "[p]robably the most important single consideration in a discussion of suspensions is the size of the drug particles," Ansel et al. (1995) at 255, and that "[i]n most good pharmaceutical suspensions, the particle diameter is between 1 and 50  $\mu$ m," *id. See also id.* at 257 ("As shown by Stokes' equation, the reduction in the particle size of a suspensoid is beneficial to the stability of the suspension in that the rate of sedimentation of the solid particles is reduced as the particles are decreased in size.").

123. To formulate the combination product, a POSA would focus on the particle size of insoluble fluticasone (azelastine is more soluble, and does not have a particle size when in solution), and would attempt to achieve a "microfine" suspension as described in the Flonase<sup>®</sup> label. As discussed above, the Flonase<sup>®</sup> patent (Phillips) defines the particles as "micronized." Ansel et al. (1995) explain how to make a suspension of "micronized" or "ultrafine" particles under 10  $\mu$ m. Ansel et al. (1995), at 255 (describing the process for producing micronized particles under 10  $\mu$ m). The BPC (1973) reference, at 911, in turn explains that an ultra-fine power is "[a] powder of which the maximum diameter of 90 per cent of the particles is not greater than 5  $\mu$ m and of which the diameter of none of the particles is greater than 50  $\mu$ m."

124. The only other ingredient that might be considered to be in particle form is the MCC-CMC, and its particle sizes are all well below 10  $\mu$ m. *See* Avicel RC-591 Bulletin (1994),

at 4.

#### 9. Manufacturing process

125. The process for manufacturing a nasal suspension was well known in the art.

Allen (1998), at 234, explains two methods at a high level of generality:

234 Cha	pter 20	į
		17

Preparation of Nasal Products (cont.)	
Suspensions (Method 1)	
<ol> <li>Accurately weigh or measure each ingredient.</li> </ol>	
<ol><li>Dissolve/mix the ingredients in about three fourths of the qu for injection and mix well.</li></ol>	antity of sterile water
3. Add sufficient sterile water for injection to volume and mix	well.
<ol> <li>Take a sample of the suspension and determine the pH and factors.</li> </ol>	
5. Package in a suitable container for autoclaving.	
6. Autoclave, cool, and label.	
<ol><li>If a large number of suspensions are to be prepared, select be assayed and checked for sterility.</li></ol>	a random sample to
Suspensions (Method 2)	
1. Accurately weigh or measure each ingredient.	
2. Sterilize each ingredient using a suitable method.	
<ol><li>Dissolve/mix the ingredients in about three fourths of the que for injection and mix well.</li></ol>	antity of sterile water
4. Add sufficient sterile water for injection to volume and mix	well.
<ol><li>Take a sample of the suspension and determine the pH and factors.</li></ol>	
6. Package and label.	
<ol><li>If a large number of suspensions are to be prepared, select be assayed and checked for sterility.</li></ol>	a random sample to
126. Additionally, numerous patent references described	known mixing techniques
Cramer, for example, explains that any composition of a steroid	d and antihistamine can b

prepared "utilizing conventional mixing techniques," and describes the mixing process for its

Example I. Cramer, at 5. Several examples in Hettche, moreover, describe the method of

mixing nasal solutions or other products. Hettche, at cols. 6-7.

#### **D.** Summary

127. As explained below, it is my opinion that it would have been obvious to a person of ordinary skill in the art, prior to June 2002, how to formulate a product containing both azelastine HCl and fluticasone propionate. Formulating sprays was well known in the art prior to June 2002. Co-formulating fluticasone propionate with another active ingredient was also known prior to June 2002 (in the form of the insufflation powder Advair Diskus<sup>®</sup>). There were known and approved excipients that could be combined in any nasal formulation regardless of known or discovered incompatibilities with particular active ingredients.

128. Even more specifically, because formulating a nasal spray with fluticasone propionate was known in the art (Flonase<sup>®</sup>) and formulating a nasal spray with azelastine HCl was known in the art (Astelin<sup>®</sup>), in attempting to co-formulate azelastine HCl with fluticasone propionate, a POSA would have started with these known formulations. A POSA would begin with the Flonase<sup>®</sup> formulation because formulating a suspension is generally somewhat more difficult than formulating a solution when a drug has adequate solubility. The formulator would then add azelastine to the formulation using knowledge and skills of one versed in the art.

129. A formulator would have thought it obvious to start with the preservatives benzalkonium chloride and phenylethyl alcohol, which are the preservatives in Flonase<sup>®</sup>. Edetate disodium, a preservative included in Astelin<sup>®</sup>, could be considered as well because of its preservative effects as a chelating agent and its synergistic effects with other preservatives including benzalkonium chloride and phenylethyl alcohol. The concentrations with which a formulator would begin were specified in Flonase<sup>®</sup> (0.02% w/w benzalkonium chloride and 0.25% w/w phenylethyl alcohol). A formulator would also have known of the Handbook of Pharmaceutical Excipients which recites ranges for benzalkonium chloride of 0.002-0.02% w/v, and ranges for phenylethyl alcohol of 0.25-0.5% w/v. That reference also discloses 0.1-0.15%

w/v for edetic acid. The formulator could then pursue routine optimization methods to determine the optimum effective concentrations of each respective ingredient if necessary.

130. A formulator would have also thought it obvious to start with MCC-CMC, which was used in the Flonase<sup>®</sup> formulation, as the thickening/viscosity agent. The formulator following that product would have started with the 1.2% w/v for MCC-CMC described in the Handbook of Pharmaceutical Excipients and adjusted the concentration until the desired viscosity was reached.

131. A formulator would have also thought it obvious to start with the surfactant polysorbate 80, which was used in Flonase<sup>®</sup>. As explained above, a surfactant is included to help disperse and suspend insoluble active or inactive ingredients in the formulation. If it were not there, one would expect the active ingredient to clump together and/or settle out to such an extent that it would not be evenly distributed in a given spray.

132. Finally, a POSA would have thought it obvious to adjust the tonicity of the formulation to be near isotonic or otherwise within pharmaceutically acceptable tonicity ranges using standard agents. These would have included the agents used in Astelin<sup>®</sup> and Flonase,<sup>®</sup> or other agents. The tonicity-adjusting agent in Flonase<sup>®</sup> is dextrose and the tonicity-adjusting agent in Astelin<sup>®</sup> is NaCl. A POSA would also have thought it obvious to try other tonicity-adjusting agents, including glycerin. If glycerin were chosen, a POSA would have known that a 2.6% v/v solution of glycerin as reported in the Handbook of Pharmaceutical Excipients, or 2.5% w/w as reported in Remington's, produces an isotonic solution. Since there are other solutes in solution in the formulation, the POSA would know to add an amount of glycerin < 2.6% v/v or < 2.5% w/w to prepare an isotonic solution. The exact amount needed to achieve the desired tonicity level could be obtained by routine experimentation.

133. To the extent any of these excipients were incompatible in a co-formulated product, a POSA would have numerous other excipients from which to choose, many of which were listed in the Handbook of Pharmaceutical Excipients (1994) as well as numerous other prior art descriptions in the field of nasal sprays. Determining the ideal amounts of any of these excipients would, again, be a matter of routine optimization.

#### VI. THE ASSERTED PATENTS

134. The next step of my analysis was to review the asserted claims and note any differences between them and what was disclosed in the prior art. If there were differences, I asked myself whether a POSA prior to June 2002 would have thought bridging the gap between the prior art and the claims was obvious.

135. Based on my review of the asserted patents and the other materials discussed and referenced above, it is my opinion that a POSA would have found each of the asserted claims to be obvious over the prior art as of 2002 in view of the knowledge and experience of a POSA at the time of the purported inventions of the patents-in-suit.

136. In summary, my opinion is that all of the asserted claims are obvious. I agree with and accept the conclusion of Dr. Robert Schleimer that a POSA would have had motivation to combine azelastine HCl and fluticasone propionate in a single nasal spray with a reasonable expectation of success (and thus, that asserted claim 8 of the '723 patent is obvious in its entirety). It is also my opinion that it would have been obvious to that POSA how to formulate a combination product as described in the remaining asserted claims.

137. First, inasmuch as claims 29 of the '620 patent, and claims 10, 11, 13, 15, 16, 18-20, 22-24, 26 and 28-30 of the '428 patent, require specific concentrations of azelastine HCl and fluticasone propionate, I agree with Dr. Schleimer that these would have been obvious at least in light of the concentrations in Flonase<sup>®</sup> and Astelin<sup>®</sup> and related patent references—such as

Cramer, Segal, and Hettche. The concentrations of fluticasone in Flonase<sup>®</sup> and azelastine in Astelin<sup>®</sup> are squarely within the ranges asserted by the claims. Claim 14 of the '723 patent, which specifies concentrations of azelastine HCl and of fluticasone propionate or fluticasone valerate, is obvious for the same reasons.

138. Second, claim 11 of the '723 patent and claim 4 of the '620 patent require a particle size limitation of 10  $\mu$ m. These would have been obvious to a POSA because Flonase<sup>®</sup> included micronized fluticasone, which, according to the BPC (1973), would have been understood to be anywhere from 1-50 microns and typically have a distribution in which 90 per cent of the particles is not greater than 5  $\mu$ m. According to Ansel et al. (1995), micronized particles are those under 10  $\mu$ m. I also note that the specification does not disclose any surprising advantage to this particle size.

139. Third, claims 15 and 28 of the '428 patent require a specific pH range. As explained above, the acceptable pH range for nasal sprays was well known in the art prior to 2002, and the range of these claims are well within the known, acceptable range in the prior art. To the extent that the pH would need to be adjusted, however, such adjusters were known and common in the prior art. I also note that I have seen no evidence that a formulation with a pH within a disclosed, pharmaceutically acceptable prior art range but not fully within the claimed range performs any differently than a formulation within the narrower claimed range.

140. Finally, claims 25 and 28 of the '723 patent, claims 42-44 of the '620 patent, and all of the asserted claims of the '428 patent also require some combination of pharmaceutical preservatives, thickeners, isotonization agents, and a surfactant; require the combination of microcrystalline cellulose and carboxymethyl cellulose sodium; require glycerin; and/or require polysorbate 80. As explained above, these excipients were all well known in the art and would

have been obvious for a formulator to start with, and/or would have been obvious for a formulator to choose during formulation optimization.

141. Some of these claims further limit the concentration ranges of these various excipients. As explained in more detail above and below, all of these ranges encompass amounts well known in the prior art for the particular excipients and thus would have been obvious to a POSA.

#### A. Specification of the patents-in-suit

142. I have reviewed the specification of the asserted patents, and I am familiar with it in its entirety. The specification discloses that both azelastine and fluticasone were known to treat allergic rhinitis conditions through intranasal administration. *See* '723 patent at 1:30-34; 1:35-37. The specification discloses many variations of an aqueous azelastine and fluticasone formulation that combine excipients then known in the art. For example, like the prior art, the specification discloses preservatives and stabilizers used in nasal sprays.

> The formulations preferably contain a preservative and/or stabilizer. These include, for example: ethylene diamine tetraacetic acid (edetic acid) and its alkali salts (for example 35 dialkali salts such as disodium salt, calcium salt, calciumsodium salt), lower alkyl p-hydroxybenzoates, chlorhexidine (for example in the form of the acetate or gluconate) and phenyl mercury borate. Other suitable preservatives are: pharmaceutically useful quaternary ammonium compounds, 40 for example cetylpyridinium chloride, tetradecyltrimethyl ammonium bromide, generally known as "cetrimide", benzyldimethyl-[2-[2-[p-(1,1,3,3-tetramethyl-butyl)phenoxy] ethoxy]-ammonium chloride, generally known as "benzethonium chloride" and myristyl picolinium chloride. Each of 45 these compounds may be used in a concentration of 0.002 to 0.05%, for example 0.02% (weight/volume in liquid formulations, otherwise weight/weight). Preferred preservatives among the quaternary ammonium compounds are, however, alkylbenzyl dimethyl ammonium chloride and mixtures 50 thereof, for example the compounds generally known as "benzalkonium chloride."

'723 patent at 2:33-51. As with Hettche, the specification specifies that the concentrations of excipients may be obtained either weight/weight or weight/volume, depending on the nature of the composition.

#### 143. The specification further discloses tonicity-adjusting agents for intranasal sprays,

which were also known in the art:

It is optionally possible to use additional isotonization agents. Isotonization agents which may, for example, be used are: saccharose, glucose, glycerine, sorbitol, 1,2-propylene 25 glycol and NaCl.

'723 patent at 3:23-26. Moreover, the specification discloses thickening agents that are also

commonly used in nasal sprays:

Such thickening agents may, for example, be: cellulose derivatives (for example cellulose ether) in which the cellulose-hydroxy groups are partially etherified with lower unsaturated aliphatic alcohols and/or lower unsaturated aliphatic 45 oxyalcohols (for example methyl cellulose, carboxymethyl cellulose, hydroxypropylmethylcellulose), gelatin, polyvinylpyrrolidone, tragacanth, ethoxose (water soluble binding and thickening agents on the basis of ethyl cellulose), alginic acid, polyvinyl alcohol, polyacrylic acid, pectin and equiva-50 lent agents. Should these substances contain acid groups, the corresponding physiologically acceptable salts may also be used.

'723 patent at 3:42-53. The specification also discloses known surfactants used in aerosol nasal sprays:

A pharmaceutical aerosol formulation according to the present invention may further comprise one or more surfactants. Such surfactants can be included to stabilise the formulations and for lubrication of a valve system. Some of the most commonly used surfactants in aerosol formulations are oils 25 derived from natural sources, such as corn oil, olive oil, cottonseed oil and sunflower seed oil, and also phospholipids. Suitable surfactants can include lecithin, oleic acid or sorbitan oleate.

'723 patent at 5:21-29.

144. The specification also discloses a number of examples of the claimed invention. *See* '723 patent at 8:5–11:47. These examples all combine known antihistamines, known corticosteroids, and known excipients.

145. Except for Example 2, none of the Examples gives formulation instructions. Rather, the specification informs the POSA that these "formulations are prepared by techniques well known in the art." '723 patent at 8:1-2. In sum, the specification confirms my opinion that (1) all of the claimed excipients were known and used in nasal sprays; and (2) a POSA could have formulated the claimed compositions using these known excipients using "techniques well known in the art."

#### **B.** The Asserted Claims

146. I understand that plaintiffs assert Claims 8, 11, 14, 25, and 28 of the '723 patent;

Claims 4, 29, and 42-44 of the '620 patent; and Claims 10, 11, 13, 15, 16, 18-20, 22-24, 26, and

28-30 of the '428 patent.

#### 1. The '723 Patent (8, 11, 14, 25 and 28).

147. The '723 patent issued on April 24, 2012. Below are the asserted claims (in

bold), along with any claims on which they depend:

1. A method for the prophylaxis or treatment in a mammal of a condition for which administration of one or more antihistamines and/or one or more steroids is indicated, comprising intranasal administration to said mammal of a therapeutically effective amount of a pharmaceutical composition comprising (a) azelastine, or a pharmaceutically acceptable salt thereof; and (b) a pharmaceutically acceptable ester of fluticasone.

## 8. The method of claim 1, wherein said condition is allergic rhinitis.

10. The method of 1, wherein said pharmaceutical composition comprises a pharmaceutically acceptable ester of fluticasone in an amount from about 50 micrograms/ml to about 5 mg/ml of the composition.

## 11. The method of claim 10, wherein the pharmaceutical composition has a particle size of less than 10 $\mu$ m.

12. The method of claim 1, wherein said pharmaceutical composition is an aqueous suspension comprising from about 0.0005% to about 2% (weight/weight) of azelastine or a pharmaceutically acceptable salt of azelastine, and from about 0.0357% to about 1.5% (weight/weight) of pharmaceutically acceptable ester of fluticasone.

14. The method of Claim 12, wherein said pharmaceutical composition is an aqueous suspension comprising 0.1% or 0.15% (weight/weight) of azelastine HCl and from about 0.0357% to about 1.5% (weight/weight) of fluticasone propionate or fluticasone valerate.

17. The method of claim 1, wherein said pharmaceutical composition further comprises at least one isotonic agent selected from the group consisting of sodium chloride, saccharose, glucose, glycerine, sorbitol, 1,2-propylene glycol, and combinations thereof.

## 25. The method of claim 17, wherein said isotonic agent comprises glycerine.

28. The method of claim 1, wherein the pharmaceutical composition further comprises edetate disodium, glycerine, a thickening agent comprising microcrystalline cellulose and sodium carboxy methyl cellulose, polysorbate 80, benzalkonium chloride, phenyl ethyl alcohol, and purified water.

#### 2. The '620 Patent (4, 29, 42-44).

148. The '620 patent issued on May 1, 2012. Below are the asserted claims (in bold),

along with any claims on which they depend:

1. 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.

## 4. The pharmaceutical formulation of claim 1, wherein said formulation has a particle size of less than 10 μm.

5. The pharmaceutical formulation of claim 1, wherein said formulation is an aqueous suspension comprising from 0.0005% (weight/weight) to 2% (weight/weight) of said azelastine, or said pharmaceutically acceptable salt thereof, and from 0.0357% (weight/weight) to 1.5% (weight/weight) of said pharmaceutically acceptable ester of fluticasone.

6. The pharmaceutical formulation according to claim 5, comprising from 0.001% (weight/weight) to 1% (weight/weight) of said azelastine, or said pharmaceutically acceptable salt thereof,

and from 0.0357% (weight/weight) to 1.5% (weight/weight) of said pharmaceutically acceptable ester of fluticasone.

24. A pharmaceutical formulation comprising azelastine hydrochloride; and, fluticasone propionate, wherein said formulation is in the dosage form of as a nasal spray, and wherein said formulation is used in the treatment of conditions for which administration of one or more anti-histamine and/or one or more steroid is indicated.

26. The pharmaceutical formulation of claim 6, comprising 0.1% (weight/weight) of azelastine hydrochloride, and from 0.0357% to 1.5% (weight/weight) of fluticasone propionate.

## 29. The pharmaceutical formulation of claim 26, wherein said dosage form suitable for nasal administration comprises a nasal spray.

25. A nasal spray formulation comprising (i) azelastine, or a pharmaceutically acceptable salt thereof, (ii) a pharmaceutically acceptable ester of fluticasone, and (iii) a pharmaceutically acceptable carrier or excipient therefor.

42. The pharmaceutical formulation of claim 1, further comprising edetate disodium, glycerine, a thickening agent comprising microcrystalline cellulose and sodium carboxy methyl cellulose, polysorbate 80, benzalkonium chloride, phenyl ethyl alcohol, and purified water.

43. The pharmaceutical formulation of claim 24, further comprising edetate disodium, glycerine, a thickening agent comprising microcrystalline cellulose and sodium carboxy methyl cellulose, polysorbate 80, benzalkonium chloride, phenyl ethyl alcohol, and purified water.

44. The pharmaceutical formulation of claim 25, further comprising edetate disodium, glycerine, a thickening agent comprising microcrystalline cellulose and sodium carboxy methyl cellulose, polysorbate 80, benzalkonium chloride, phenyl ethyl alcohol, and purified water.

3. The '428 Patent (10, 11, 13, 15, 16, 18-20, 22-24, 26, 28-30).

149. The '428 patent issued on February 16, 2016. Below are the asserted claims (in

bold), along with any claims on which they depend:

1. A method for the treatment of seasonal allergic rhinitis, comprising administration of a therapeutically effective amount of nasal spray formulation comprising: from 0.001% (weight/weight) to 1% (weight/weight) of azelastine hydrochloride; from 0.0357% (weight/weight) to 1.5% (weight/weight) of fluticasone propionate; one or more preservatives; one or more thickening agents; one or more surfactants; and one or more isotonization agents.

9. The method of claim 1, wherein the formulation comprises edetate disodium, benzalkonium chloride, microcrystalline cellulose, carboxymethyl cellulose sodium, polysorbate 80, glycerine, and phenyl ethyl alcohol.

10. The method of claim 9, wherein the formulation comprises: from 0.002% (weight/weight) of 0.05% (weight/weight) of edetate disodium; 0.002% from (weight/weight) to 0.05% (weight/weight) of benzalkonium chloride; from 0.65% (weight/weight) to 3% (weight/weight) of a combination of microcrystalline cellulose and carboxymethyl cellulose sodium; and from 2.3% (weight/weight) to 2.6% (weight/weight) of glycerine.

The method of claim 1, wherein the formulation 11. comprises: 0.1% (weight/weight) azelastine hydrochloride; from 0.0357% (weight/weight) to 1.5% (weight/weight) of fluticasone propionate; from 0.002% (weight/weight) to 0.05% (weight/weight) edetate disodium: from of 0.002% (weight/weight) to 0.02% (weight/weight) of benzalkonium chloride; from 0.65% (weight/weight) to 3% (weight/weight) of a combination of microcrystalline and carboxymethyl cellulose sodium; polysorbate 80; 2.3% (weight/weight) of glycerine; and 0.25% (weight/weight) of phenyl ethyl alcohol.

13. The method of claim 1, wherein the formulation is contained in a nasal spray product; and wherein from 0.03 mg to 3 mg of azelastine hydrochloride and from 0.05 mg to 0.15 mg of fluticasone propionate is released per individual actuation of the nasal spray product.

14. A method for minimizing symptoms of seasonal allergic rhinitis, comprising administration of a therapeutically effective amount of a nasal spray formulation comprising: from 0.001% (weight/weight) to 1% (weight/weight) of azelastine hydrochloride; 0.0357% (weight/weight) from to 1.5% (weight/weight) of fluticasone propionate; one or more preservatives; one or more thickening agents; one or more

surfactants; and one or more isotonization agents.

15. The method of claim 14, wherein the formulation has a pH of 4.5 to about 6.5.

16. The method of claim 14, wherein the formulation is an aqueous suspension.

18. The method of claim 14, wherein the one or more thickening agents comprise microcrystalline cellulose and carboxymethyl cellulose sodium.

**19.** The method of claim 14, wherein the one or more surfactants comprise polysorbate 80.

20. The method of claim 14, wherein the one or more isotonization agents comprise from 2.3% (weight/weight) to 2.6% (weight/weight) of glycerine.

22. The method of claim 14, wherein the formulation comprises edetate disodium, benzalkonium chloride, microcrystalline cellulose, carboxymethyl cellulose sodium, polysorbate 80, glycerine, and phenyl ethyl alcohol.

23. The method of claim 22, wherein the formulation comprises: from 0.002% (weight/weight) to 0.05% (weight/weight) disodium: 0.002% of edetate from (weight/weight) to 0.05% (weight/weight) of benzalkonium chloride; from 0.65% (weight/weight) to 3% (weight/weight) of a combination of microcrystalline cellulose and carboxymethyl cellulose sodium; and from 2.3% (weight/weight) to 2.6% (weight/weight) of glycerine.

24. The method of claim 14, wherein the formulation comprises: 0.1% (weight/weight) azelastine hydrochloride; from 0.0357 (weight/weight) to 1.5% (weight/weight) of fluticasone propionate; from 0.002% (weight/weight) to 0.05% (weight/weight) of edetate disodium: from 0.002% (weight/weight) to 0.02% (weight/weight) of benzalkonium chloride; from 0.65% (weight/weight) to 3% (weight/weight) of a combination of microcrystalline and carboxymethyl cellulose sodium; polysorbate 80; 2.3% (weight/weight) of glycerine; and 0.25% (weight/weight) of phenyl ethyl alcohol.

26. The method of claim 14, wherein the formulation is contained in a nasal spray product; and wherein from 0.03 mg

to 3 mg of azelastine hydrochloride and from 0.05 mg to 0.15 mg of fluticasone propionate is released per individual actuation of the nasal spray product.

28. A method for the treatment of seasonal allergic rhinitis, comprising administration of a therapeutically effective amount of nasal spray formulation comprising: from 0.001% (weight/weight) to 1% (weight/weight) of azelastine hydrochloride; from about 50 µg/mL to about 5 mg/mL of fluticasone propionate; from 0.002% (weight/weight) to 0.05% (weight/weight) of benzalkonium chloride; from 0.002% (weight/weight) to 0.05% (weight/weight) of edetate disodium; glycerine; polysorbate; and a thickening agent; wherein the formulation has a pH of 4.5 to about 6.5; and wherein the formulation is an aqueous suspension.

29. The method of claim 28, wherein the formulation is contained in a nasal spray product; and wherein from 0.03 mg to 3 mg of azelastine hydrochloride and from 0.05 mg to 0.15 mg of fluticasone propionate is released per individual actuation of the nasal spray product.

30. The method of claim 28, wherein the thickening agent comprises microcrystalline cellulose and carboxymethyl cellulose sodium.

#### VII. THE ASSERTED CLAIMS WOULD HAVE BEEN OBVIOUS TO A POSA.

#### A. Combinations of azelastine and fluticasone

150. To the extent that all of the claims depend on a combination of azelastine and fluticasone, I agree with the conclusions of Dr. Schleimer that these ingredients would have been obvious to combine or, at a minimum, it would have been obvious to try to combine them. Thus, claim 8 of the '723 patent, claiming a combination of azelastine and fluticasone for the treatment of the condition allergic rhinitis, is obvious in its entirety. It is also my opinion that the aspect of each claim covering a combination of azelastine HCl and fluticasone propionate is obvious for the same reasons. I base these opinions on the Astelin<sup>®</sup> and Flonase<sup>®</sup> labels, alone or in combination with Hettche and/or the Phillips patent.

#### **B.** Concentrations of azelastine and fluticasone

151. To the extent that claims 29 of the '620 patent, and claims 10, 11, 13, 15, 16, 18-20, 22-24, 26 and 28-30 of the '428 patent, require specific concentrations of azelastine HCl and fluticasone propionate, I agree with Dr. Schleimer that these would have been obvious in light of the numerous prior art disclosing effective therapeutic concentrations of both azelastine and fluticasone. I hold the same opinion.

152. Specifically, my opinion is that if a POSA had a motivation to combine azelastine and fluticasone in a combined nasal spray, these claimed concentration ranges would have been obvious over Flonase<sup>®</sup> and Astelin<sup>®</sup>, whose concentrations, as explained in Dr. Schleimer's report and by me above, are squarely within the ranges of the asserted claims. There would have been no reason for a POSA to look beyond Flonase<sup>®</sup> and Astelin<sup>®</sup>. If a POSA did choose to look beyond these, however, several patent references—including Cramer, Hettche, and Segal in particular—also disclosed similar ranges as in the asserted claims. I therefore independently agree with Dr. Schleimer's conclusions that these references, too, would have made it obvious for a POSA to choose the concentration ranges of the asserted claims. These particular limitations are obvious in view of the Astelin<sup>®</sup> and Flonase<sup>®</sup> labels, alone or in combination with Cramer, Hettche, and Segal.

153. Claim 14 of the '723 patent, which requires specific concentration ranges of azelastine HCl and of fluticasone propionate or fluticasone valerate, is obvious for the same reasons. That claim also specifies an aqueous suspension, which was well known in the art. *See*, *e.g.*, Flonase<sup>®</sup> Label at 1 (specifying that Flonase<sup>®</sup> is an "aqueous suspension of microfine fluticasone propionate").

154. Thus, in addition to claim 8 of the '723 patent, claim 14 of the '723 patent and claim 29 of the '620 patent are obvious in their entirety.

#### C. Pharmaceutical excipients

155. Claim 25 of the '723 patent specifies the tonicity-adjusting agent glycerin. Claim 28 of the '723 patent also specifies glycerin; the preservatives edetate disodium, benzalkonium chloride, and phenyl ethyl alcohol; the thickening agent MCC-CMC; the surfactant polysorbate 80; and purified water. Claims 42–44 of the '620 patent specify the same preservatives, thickening agent, surfactant, and tonicity-adjusting agent as claim 28 of the '723 patent. Claim 18 of the '428 patent specifies a method of using an azelastine and fluticasone composition "wherein one or more thickening agents comprise microcrystalline cellulose and carboxymethyl cellulose sodium." Claim 19 of the '428 patent specifies a method of using an azelastine and fluticasone composition "wherein the one or more surfactants comprise polysorbate 80." Claim 22 of the '428 patent specifies the same preservatives, thickening agent, surfactant, and isotonization agent as claim 28 of the '723 patent. Claim 30 of the '428 patent is a further limitation on asserted claim 28 of the '428 patent, with the additional limitation that "the thickening agent comprises microcrystalline cellulose sodium."

156. Each of these claims is obvious at least over Flonase<sup>®</sup> and Astelin<sup>®</sup>, alone or in combination with Wade & Weller, The Handbook of Pharmaceutical Excipients (1994). As explained above, the Handbook of Pharmaceutical Excipients teaches that *each* of the above excipients was well known in the art. The Handbook specified the function of these excipients and also normal concentration ranges. *See* Wade & Weller at 27-29 (benzalkonium chloride); *id.* at 78-81 (carboxymethylcellulose sodium); *id.* at 84-87 (microcrystalline cellulose); *id.* at 176-79 (edetic acid (EDTA)); 204-06 (glycerin); *id.* at 340-41 (phenylethyl alcohol); *id.* at 375-78 (polysorbate 80 and similar sorbitan fatty acid esters).

157. Additionally, Flonase<sup>®</sup> contained benzalkonium chloride, phenylethyl alcohol, carboxymethylcellulose sodium, microcrystalline cellulose, and polysorbate 80. Astelin<sup>®</sup>

contained benzalkonium chloride and EDTA. Thus, each of the above claims are obvious over Flonase<sup>®</sup> and Astelin<sup>®</sup> inasmuch as they use these excipients known in the art to be formulated successfully with fluticasone and/or azelastine.

158. The only excipient not present in either commercial formulation is glycerin, which was a known tonicity-adjusting agent available for use in nasal formulations. *See* Wade & Weller, Handbook of Pharmaceutical Excipients (1994), at 204-06.

159. Numerous other prior art references before June 2002 further demonstrate that the use of each excipient mentioned in these claims was well known in the art.

160. Cramer discloses that the pharmaceutical composition of Example I includes microcrystalline cellulose and sodium carboxymethyl cellulose. Cramer, at 5, *l*. 53.

161. Cramer teaches that the preferred preservative system of the compositions comprise a combination of benzalkonium chloride and disodium EDTA. *Id.* at *ll.* 19-20. Example III of Cramer includes glycerin, benzalkonium chloride, and polysorbate 80. *Id.* at 6, *ll.* 34-41. Cramer also discloses phenyl ethyl alcohol as a suitable preservative. *Id.* at 5, *ll.* 17-18. Cramer also discloses the use of thickening agents, including specifically microcrystalline cellulose and carboxymethyl cellulose sodium. *Id.* at 4, *l.* 58–5, *l.* 1. Thus, these claims are obvious over Cramer as well as Astelin<sup>®</sup> and Flonase<sup>®</sup>.

162. Hettche teaches the use of preservatives (2:46–4:9), tonicity-adjusting agents (4:31-35), thickening agents (4:51-66), and surfactants (4:14-29). More specifically, Hettche teaches benzalkonium chloride (3:3-25; 4:7-9) and edetate disodium (4:4-8). Hettche also discloses phenylethyl alcohol in (3:19-25), cellulose derivatives—and particularly carboxymethyl cellulose sodium—as thickening agents (4:55-60), sorbitol (4:34), and that glycerin is a preferable solvent (2:39) and tonicity-adjusting agent (4:34). Thus, each of the

above claims is independently obvious over Hettche as well as Astelin<sup>®</sup> and Flonase<sup>®</sup>.

163. Claim 28 of the '428 patent is a method for the treatment of allergic rhinitis using a combination of azelastine and fluticasone with specific concentrations of edetate disodium and benzalkonium chloride. Among other limitations, this claim also specifies the use of "glycerine; polysorbate; and a thickening agent." This particular limitation of claim 28 of the '428 patent is obvious over Wade & Weller, Handbook of Pharmaceutical Excipients (1994), over Flonase<sup>®</sup>, or over some combination of the two, for the same reasons specified above. This claim is independently obvious over either Cramer or Hettche, for the same reasons specified above.

#### **D.** Concentrations of pharmaceutical excipients

164. Claims 10, 11, 23, 24, and 28 of the '428 patent further specify a concentration range for edetate disodium of 0.002% to 0.05% w/w. These limitations are obvious over Wade & Weller, Handbook of Pharmaceutical Excipients (1994), at 176, which explains that 0.01-0.1% w/v for edetic acid and edetates when used as antimicrobial preservative synergists. The slight expansion of the range on one end and slight narrowing on the other would be obvious if a POSA determined, using routine optimization techniques, that less edetate disodium was necessary. Finally, these claims are independently obvious over Hettche, which teaches edetate disodium with a concentration of 0.05% to 0.1% w/w (4:4-8), thus encompassing the higher range of these claims.

165. Claims 10, 23, and 28 of the '428 patent further specify a concentration range for benzalkonium chloride of 0.002% to 0.05% w/w. Claims 11 and 24 specify a concentration range of 0.002% to 0.02% w/w. These limitations are obvious over either of Astelin<sup>®</sup> or Flonase<sup>®</sup>. The former contains 0.0124% w/w benzalkonium chloride (0.125% w/v), the latter 0.02% w/w benzalkonium chloride. These are squarely within the ranges of the asserted claims. These claims are also independently obvious over Hettche, which teaches benzalkonium chloride

with a preferable concentration of 0.005 to 0.05% w/w (3:3-25; 4:7-9) or a range of 0.002 to 0.02% w/w (3:64), thus encompassing the full range of these claims. These limitations are also obvious over Wade & Weller, Handbook of Pharmaceutical Excipients (1994), at 27, which specifies a typical concentration range of benzalkonium chloride as 0.002-0.02% w/v. Slightly expanding the range to 0.05% if necessary for optimization would be obvious.

166. All of the above claims involving concentration ranges of benzalkonium chloride and edetate disodium are also independently obvious over Cramer, which teaches that the preferred preservative system of the compositions comprise a combination of both of those ingredients with a suitable combined concentration of 0.001% to 2% w/w, thereby encompassing all of the above claims. Cramer, at 5, *ll.* 19-21. I am not aware of any evidence that narrowing the claimed limitations as claimed results in any difference other than the amount of benzalkonium chloride.

167. Claims 10, 11, 23, and 24 of the '428 patent further specify a concentration range of a combination of MCC-CMC between 0.65% to 3.0% w/w. These claims are obvious over Cramer, Example I of which contains 1.2% w/v of a MCC-CMC combination (p. 5, *l*. 47) and Example III of which contains 1.0% w/v of a similar cellulose derivative (p. 6, *l*. 36). They are also obvious over the Avicel RC-591 Bulletin (1994), at 7, which explains that a 1.2% w/v concentration of that MCC-CMC combination creates "well structured suspension vehicles" that are "thixotropic." A POSA thus would have started with a 1.2% w/v concentration and adjusted the concentration to obtain the desired viscosity using known optimization methods. Because 1.2% w/v is approximately 1.2% w/w given the density of the formulation is approximately that of water, these teachings fall squarely within the claimed range of 0.65% to 3.0% w/w. Additionally, and as explained above, the patent specification specifies that the particular concentration ranges should be obtained weight/weight or weight/volume, depending on the nature of the composition.

168. Claims 10, 20, and 23 of the '428 patent further specify a concentration range for glycerin between 2.3% to 2.6% w/w. Claims 11 and 24 of the '428 patent specify a concentration of 2.3% w/w. These concentrations and ranges are obvious over Wade & Weller, Handbook of Pharmaceutical Excipients (1994), at 204, which specifies a concentration of 2.6% v/v of glycerin for isotonic solutions. Additionally, these concentrations and ranges are independently obvious over Remington's (2000), at 258 (listing 2.6% as the "iso-osmotic concentration" of glycerin). Further, as explained above, Remington's (2000), at 262, also lists the isotonic value of glycerin as 0.3 g per 11.7 mL of water; because water has a density of 1.0 g/mL, this translates to 0.3 g/11.7 g of water, or 0.025 g/1 g of solution, which is 2.5% w/w. Moreover, as also explained above, reducing the concentration below 2.6% in the presence of other solutes affecting tonicity would be obvious to a POSA. The precise reduction necessary to achieve isotonicity was determined by routine experimentation, for example by freezing-point depression.

169. Claims 11 and 24 of the '428 patent further specify a concentration of phenyl ethyl alcohol of 0.25% w/w. These claims are obvious over Flonase<sup>®</sup>, which has a concentration of phenyl ethyl alcohol of 0.25% w/w—identical to these claims. Additionally, these claims are independently obvious over Wade & Weller, Handbook of Pharmaceutical Excipients (1994), at 340, which teaches that the typical concentration range for phenylethyl alcohol is 0.25% to 0.5% w/v. Additionally, this concentration is obvious over Cramer, Example I of which discloses a composition with 0.25% (w/v) of phenyl ethyl alcohol. Cramer, at 5, *l*. 51. As explained above, because the density of phenyl ethyl alcohol is 1.02 g/cm<sup>3</sup>—approximately the density of water—

these concentrations are essentially equivalent to 0.25% w/w.

170. All of these limitations (and the claims they are a part of) would have been obvious to a POSA in light of the Astelin<sup>®</sup> and Flonase<sup>®</sup> labels alone or in combination with Wade & Weller, Cramer, Remington's, and/or Hettche.

#### E. Particle size and pH

171. Claim 11 of the '723 patent and claim 4 of the '620 patent require a particle size limitation of 10  $\mu$ m. This would have been obvious over Flonase<sup>®</sup>, which contained "microfine" fluticasone. As explained above, a POSA would have known that this referred to a "micronized" particle, as explained in the Flonase<sup>®</sup> patent (Phillips), and "micronized" is defined by Ansel et al. (1995) as particles under 10  $\mu$ m.

172. Claims 15 and 28 of the '428 patent require a specific pH range of 4.5 to 6.5. These claims are also obvious over Allen (1998) because, as explained above, the range of acceptable pH was well known in the art prior to 2002 to be between 4 and 8, and the range of these claims are well within the known, acceptable range of pH in the prior art. Most likely, the pH of the composition would inherently be somewhere within that range, and this claim reflects nothing more than an inherent quality of the composition. To the extent that the pH would need to be adjusted, however, such adjusters were known and common in the prior art. *See* Allen (1998), at 235.

#### F. Conclusion

173. In sum, my opinion is that each limitation of every asserted claim is obvious over some combination of Astelin<sup>®</sup>, Flonase<sup>®</sup>, Wade & Weller, Handbook of Pharmaceutical Excipients (1994), and Remington's (2000). Each of these limitations and claims is independently obvious over some combination of prior patent references, and Cramer, Hettche, Segal, and Phillips in particular. The pH claims are additionally obvious over Allen (1998).

#### VIII. ANALYSIS OF ALLEGED UNEXPECTED RESULTS

174. The above opinions are based on my review of the prior art, as discussed above. I also have reviewed certain materials that were not publicly available before 2002. Those materials did not influence my opinions on obviousness. However, to the extent the alleged inventors suggest that they encountered any difficulties in formulating a combination product, it is my opinion that any such difficulties were either not difficulties or would have been easily surmounted by a POSA with routine experimentation. I also offer opinions below on the question of whether the Cramer reference offers an enabling description of how to make pharmaceutically acceptable nasal sprays combining two active ingredients. I understand that plaintiffs carry the burden of proving secondary considerations, and so I reserve the right to respond to any expert reports from the plaintiffs on unexpected results or other secondary considerations.

#### A. No Formulation Difficulties

175. I have been informed that a named inventor of the asserted patents, Geena Malhotra, described at her deposition certain obstacles that she says she faced when first trying to make a combination azelastine HCl/fluticasone propionate nasal spray product.

176. One issue Ms. Malhotra said she encountered was determining what tonicityadjusting agent to use. She explained that the dextrose used in the Flomist<sup>®</sup> product—Cipla's counterpart to Flonase<sup>®</sup>—was incompatible with azelastine because the azelastine does not readily dissolve in dextrose. She also said that dextrose could not be replaced by the tonicity agent in the available azelastine product (Astelin<sup>®</sup>), NaCl, because that was known to be incompatible with Avicel (MCC-CMC) in the fluticasone product. Malhotra Dep. Tr. 116:3-19; 117:3-17. Thus, she needed to find a different tonicity agent, and she settled on glycerin. *Id.* at 117:19-20.

177. Irrespective of these particular ingredients and potential incompatibilities, it is quite common for various ingredients, both active and inactive, to be incompatible. But a POSA as of 2002 could have used any of several possible excipients for any particular function should an incompatibility arise. Indeed, as discussed at length above, there were several tonicity-adjusting agents known to a POSA. Thus, as part of standard pharmaceutical development practices in 2002, a POSA would simply have tried another tonicity-adjusting agent if dextrose or NaCl for whatever reason did not work in a combined formulation. Glycerin would have been one of the obvious and readily available options because it had been used before to adjust tonicity. This selection of optimal excipients is standard practice; I consider it part of routine experimentation. It does not involve anything that would have been considered inventive to a POSA.

178. Additionally, the patents-in-suit here suggest that there is no significant incompatibility between NaCl and MCC-CMC. Example 1 of the '428 patent is a formulation identified as an illustration of the invention. It contains both NaCl and Avicel RC 591, which includes CMC and MCC. These ingredients are therefore compatible enough to be useful as pharmaceutical formulations, according to plaintiffs' own patent. Regardless, if there were incompatibilities it would have required only routine excipient selection and optimization to correct, as explained above.

179. The second issue Malhotra mentioned was that there was some level of difficulty getting the formulation sequence right. Malhotra Dep. Tr. 127:19-22. However, she also described finding the most optimal sequence as "optimization," which is routine and happens often in pharmaceutical development. *Id.* at 133:8-22. Obtaining the optimal manufacturing sequence for a given pharmaceutical product is well within the level of ordinary skill in the art.

The specification of the patents is consistent with this opinion when it says, as mentioned that "[i]n examples where only the ingredients of formulations according to the present invention are listed, these formulations are prepared by techniques well known in the art." In other words, not even the inventors thought they needed to teach anything new about preparation techniques beyond what was already common knowledge in the prior art.

#### **B.** Replication of Cramer Example III

180. I am also aware that Ms. Malhotra submitted a declaration to the Patent Office during prosecution of the patents-in-suit arguing that Example III in the Cramer reference discussed above is "inoperable and unacceptable as a pharmaceutical formulation in a dosage form suitable for nasal administration." CIP\_DYM\_60302. Ms. Malhotra states that "Example 3 of Cramer was reproduced according to the following table of ingredients and process of preparation," and then lists various ingredients and process steps. As an initial matter, the ingredients listed in her declaration are not the same as those in Cramer Example III. Ms. Malhotra used disodium EDTA, while Cramer Example III calls for EDTA.

181. I have also seen evidence contrary to the conclusions she draws about Example III. Specifically, I have reviewed the expert report and exhibits of Dr. Ram Govindarajan. I understand that he was asked to formulate the composition in Example III, having been told nothing other than to follow any instructions or guidance included in the document, and to otherwise proceed as an ordinarily skilled pharmaceutical formulator would have proceeded in June 2002 after reading Cramer. I understand from his report that he was directed not to take any step or use any equipment that was not known and readily available to an ordinarily skilled pharmaceutical formulator in 2002. He was then asked to do the following if he was able to make a pharmaceutical formulation as described in Example III:

a. Observe whether Example III forms a suspension, solution, or something else.

- i. If Example 3 does form a suspension, observe whether that suspension settles.
  - 1. If it settles, observe whether it is difficult to re-suspend.
  - 2. If it settles, opine on whether the settling as unacceptable for a pharmaceutical product.
- b. Measure the osmolality in mOsm/kg.
- c. Put the resulting composition in a nasal pump with a suitable actuator. Observe if the composition comes out as a spray, a jet, or something else.

182. I have reviewed Dr. Govindarajan's laboratory notebook pages, which begin on June 10, 2016. I see that he prepared Example III three times. He describes the precise ingredients, instruments, and process steps he used in his efforts. The first formulation he made was 100 mL of the composition labeled 1345-004. He made the following conclusions about that composition on June 13, 2016:

the pen d

Govindarajan Notebook, at 7.

183. Dr. Govindarajan then made a second formulation, this time by dissolving the EDTA in the aqueous phase with the aid of heat, and a slurry of glycerin, polysorbate 80, and triamcinolone were added to the aqueous phase containing the remaining ingredients, followed by homogenization and making up of the volume. The resulting composition was labeled 1345-008. He made the following conclusions about it on June 14, 2016:

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Id. at 10.

184. Finally, he made a 500 mL formulation on June 16, 2016, for which he again recorded all of the process steps. This was referred to as 1345-011. *Id.* at 11-15. He completed his testing on June 18, 2016. That means in a period of 8 days, and not full days spent on this project, Dr. Govindarajan was able to make three formulations using the ingredients of Example III. He made the following conclusions about the 1345-011 composition:



*Id.* at 15. The measured osmolality of this formulation was 529 mOsm/kg. *Id.* I have also seen the videos of the actuation of the final formulation he placed in nasal devices.

185. I can draw several conclusions from his work. First, he made a more accurate replication of Example III than Ms. Malhotra did insofar as he used EDTA, instead of disodium EDTA. Second, it is my opinion that the process steps he used are how a POSA would have made the formulation on or before June 2002. These are all steps that were known to a POSA at that time.

186. Third, all of his conclusions contradict Ms. Malhotra's conclusions about Cramer

and Example III. Dr. Govindarajan found that Example III results in a product that is "readily & uniformly resuspendible" (Govindarajan Lab Notebook, at 15), while Ms. Malhotra incorrectly reported to the Patent Office that Example III is "very difficult to redisperse" and thus has "unacceptable difficulty in resuspending...." CIP\_DYM60303. Dr. Govindarajan also found that "the product could be delivered as a fine spray using a nasal spray pump" (Govindarajan Lab Notebook, at 15), and the videos he took of the spray confirm this. Ms. Malhotra incorrectly found that Example III was discharged as an "unacceptable jet rather than desired spray mist...." CIP\_DYM\_60303. Finally, Dr. Govindarajan's results showed an osmolality of 529 mOsm/kg. While this is not isotonic, it is not an "unacceptable osmolality" as Ms. Malhotra suggested to the Patent Office. As noted above, the reported tonicity of this product is well within ranges that were deemed "acceptable" for nasal administration in the prior art. *See* Allen (1998) at 220. Moreover, at least one product with an osmolality of 742 mOsm/kg was approved for intranasal administration as of 1992. Imitrex (sumatriptan) Nasal Spray Label, at 9.

187. I thus disagree with Ms. Malhotra's position that Cramer's Example III is "inoperable and unacceptable as a pharmaceutical formulation in a form suitable for nasal adminstration." CIP\_DYM60304. To the contrary, using knowledge well within the grasp of a POSA in June 2002, Example III can be made with ease, and results in a formulation that is in every measured respect fully suitable as a pharmaceutical for adminstration as an intranasal spray.

#### IX. CONCLUSION

188. In conclusion, it is my opinion that each asserted claim of the patents-in-suit is obvious in its entirety.

#### X. DECLARATION

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.

Date: June 30, 2016

By: Mauren D. Drovan

Maureen Donovan, Ph.D.

# EXHIBIT A

#### **Curriculum Vitae**

#### Maureen D. Donovan, Ph.D.

Office Address:	University of Iowa College of Pharmacy 115 S. Grand Ave Iowa City, IA 52242 maureen-donovan@uiowa.edu 319-335-9697
Education:	University of Minnesota College of Pharmacy

Minneapolis, Minnesota Bachelor of Science in Pharmacy, 1983 University of Michigan College of Pharmacy Horace H. Rackham School of Graduate Studies

Horace H. Rackham School of Graduate Studies Ann Arbor, Michigan Ph.D. (Pharmaceutics), 1989

#### PROFESSIONAL EXPERIENCE

2013-present	Associate Dean for Undergraduate Programs College of Pharmacy University of Iowa Iowa City, IA
2008-2013	<b>Division Head</b> Division of Pharmaceutics and Translational Therapeutics University of Iowa College of Pharmacy Iowa City, IA
2008-present	<b>Professor</b> Division of Pharmaceutics and Translational Therapeutics University of Iowa College of Pharmacy Iowa City, IA
1996-2008	Associate Professor University of Iowa College of Pharmacy Division of Pharmaceutics Iowa City, IA
1989-1996	Assistant Professor University of Iowa College of Pharmacy Division of Pharmaceutics Iowa City, IA
1991	<b>Visiting Scholar</b> SmithKline Beecham Pharmaceuticals King of Prussia, PA
1986-88	<b>Staff Pharmacist</b> Clark Professional Pharmacy Ypsilanti, MI

#### ADDITIONAL POSITIONS AND MEMBERSHIPS

2011-present	Visiting Professor, Tongji School of Pharmacy, Tongji Medical University, Wuhan, China
2010-present	Member, Environmental Health Sciences Research Center, University of Iowa
2009-10	Member, Nanoscience and Nanotechnology Institute at the University of Iowa.

#### PUBLICATIONS

#### <u>Thesis</u>

Donovan, Maureen D. The Molecular Weight Permeability Dependence of the Absorption of Polyethylene Glycols in the Nasal and Gastrointestinal Mucosa and Its Correlation to Size Dependent Diffusion. Ph.D. Thesis, The University of Michigan, 1989.

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"Nose to Brain Delivery of Cimetidine in Rats" Maya George, Maureen Donovan. AAPS Annual Meeting, Washington DC. 2011. (http://abstracts.aaps.org/published/ContentInfo.aspx?conID=27252)

"CYP1A2 Mediated Metabolism of Melatonin by the Nasal Mucosa" Varsha Dhamankar, Maureen Donovan. AAPS Annual Meeting, Washington DC. 2011. (http://abstracts.aaps.org/published/ContentInfo.aspx?conID=26519)

"Pharmacoimaging of Drug Disposition after Intranasal Administration" Laura B. Ponto, Susan Walsh, Jiangeng Huang, Christine Mundt, John Sunderland, Maureen Donovan. AAPS Annual Meeting, Washington DC. 2011.

(http://abstracts.aaps.org/published/ContentInfo.aspx?conID=26420)

"Surface Modification and Size Dependence of Nanoparticle Translocation in the Nasal Mucosa" Nan Chen, Maureen Donovan. AAPS Annual Meeting, Washington DC. 2011. (http://abstracts.aaps.org/published/ContentInfo.aspx?conID=26234)

"Permeability Characteristics of Non-Functionalized Cellulose Membranes Prepared From Dimethyl Sulfoxide Paraformaldehyde Solvent System- Influence of Degree of Polymerization of Cellulose" Bhavik Bhatt, Maureen Donovan, Douglas Flanagan, Vijay Kumar. AAPS Annual Meeting, Washington DC. 2011.

(http://abstracts.aaps.org/published/ContentInfo.aspx?conID=27142)

"Expression of Drug Transporters in Animal Models Used for Nasal Absorption Characterization" Manar Al-Ghabeish, Todd Scheetz, Mahfoud Assem, Maureen Donovan. AAPS Annual Meeting, Chicago, IL 2012. (http://abstracts.aaps.org/published/ContentInfo.aspx?conID=1838)

"A Mass Transport Model for Concurrent Diffusion and Metabolism of Drugs across the Nasal Mucosa" Varsha Dhamankar, Stephen Stamatis, Maureen Donovan. AAPS Annual Meeting, Chicago IL 2012. (http://abstracts.aaps.org/published/ContentInfo.aspx?conID=893)

"Use of PET Imaging to Measure Nucleoside Transporter-Mediated Distribution from the Nasal Mucosa" Laura Ponto, Jiangeng Huang, Susan Walsh, Michael Acevedo, Christine Mundt, John Sunderland, Maureen Donovan. AAPS Annual Meeting, Chicago, IL 2012. (http://abstracts.aaps.org/published/ContentInfo.aspx?conID=1329)

"Effect of Marijuana Smoking on Global Cerebral Blood Flow in Chronic and Occasional Users." Rakesh Awasthi, Daniel O'Leary, Jonathan Koeppel, R Nguyen, Maureen Donovan, Laura Ponto. AAPS Annual Meeting & Exposition, San Antonio TX, November, 2013.

"Expression and Activity of LAT-2: An L-Type Amino-Acid Transporter in the Olfactory and Respiratory Nasal Mucosa". Ana Ferreira, Maureen Donovan. AAPS Annual Meeting & Exposition, San Antonio TX, November, 2013.

"Uptake of Quantum Dots Across the Nasal Mucosa". Bhanu Bejgum, Maureen Donovan. AAPS Annual Meeting & Exposition, San Antonio TX, November, 2013.

"Expression of the LAT-2 Transporter in the Nasal Mucosa and Its Role in the Uptake of Gabapentin." Nan Ferreira and Maureen Donovan. AAPS Annual Meeting and Exposition, San Diego, CA November, 2014.

"Uptake and Transport Pathways for Ultrafine Nanoparticles (Quantum Dots) in the Nasal Mucosa." Bhanu Bejgum and Maureen Donovan. AAPS Annual Meeting and Exposition, San Diego, CA November, 2014

"PBPK Simulation of Brain Tetrahydrocannabinol (THC) and Metabolites Based on Fitting to Plasma Concentrations following IV Administration of a Surfactant/Ethanolic Solution." Rakesh Awasthi, Michael Bolger, Maureen Donovan, and Laura Boles Ponto. AAPS Annual Meeting and Exposition, San Diego, CA November, 2014

"Characterization of Atrazine Transport across Nasal Respiratory and Olfactory Mucosa". Wisam Al Bakri and Maureen Donovan. AAPS Annual Meeting and Exposition, San Diego, CA November, 2014

"Assessment of Deposition Patterns of Nasal Sprays in Children Using an In Vitro MRI-Based Nasal Cast Model" Namita Sawant and Maureen Donovan. AAPS Annual Meeting and Exposition, Orlando, FL, October, 2015

"An Effect-Compartment Modeling Approach to Relate the Plasma Concentrations of  $\Delta^9$ tetrahydrocannibinol (THC) and Active Metabolite to the Observed Psychoactive Effects". Rakesh Awasthi, Guohua An, Maureen Donovan, Laura Ponto. . AAPS Annual Meeting and Exposition, Orlando, FL, October, 2015

"Atrazine Permeation across the Nasal Mucosa: Formulation Effects of Commercial Herbicide Products". Wisam Al Bakri and Maureen Donovan. . AAPS Annual Meeting and Exposition, Orlando, FL, October, 2015

"Synergistic Behavior of LAT-2 and other Amino Acid or Cation Transporters in the Nasal Uptake of Gabapentin" Ana Ferreira and Maureen Donovan. . AAPS Annual Meeting and Exposition, Orlando, FL, October, 2015

#### INVITED PRESENTATIONS

"The Molecular Weight Dependence of Gastrointestinal and Nasal Absorption" Ciba-Geigy Corp. Ardsley, NY May 1, 1989.

"Nasal Drug Delivery: Molecular Weight and Formulation Effects" SmithKline Beecham Pharmaceuticals, Upper Merion, PA March 15, 1991.

"Drug Absorption into CSF and Plasma following Intranasal Administration" Glaxo Inc., Research Triangle Park, NC March 28, 1993.

"Presystemic Metabolism following Intranasal Delivery" First International Conference on Pharmaceutical and Food Sciences and Technology - Symposium on Drug Delivery Systems Chicago, IL August 26, 1993.

"Nasal Drug Delivery: Local vs. Systemic Effects" University of Connecticut School of Pharmacy Storrs, CT October 28, 1993.

"Local Effects following Intranasal Drug Administration" Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT October 29, 1993.

"Evaluation of Intranasal Dosage Forms Using *In Vitro* Systems" Miles Laboratories, Inc., Elkhart, IN November 8, 1993.

"Predicting Nasal Bioavailability and Toxicity Using *In Vitro* and *In Vivo* Animal Models" Syntex, Inc. Palo Alto, CA June 9, 1994.

"Career Opportunities in Pharmaceutics" 12th Annual Sumposium on Pharmaceutical Sciences Graduate Programs, Merrillville, IN October 15, 1994.

"Nasal Drug Delivery: Mucosal and Formulation Effects on Systemic Distribution and Bioavailability" Parke-Davis/Warner Lambert Pharmaceutical Research Division Ann Arbor, MI October 17, 1994.

"Nasal Drug Delivery: Local vs. Systemic Effects" Alza, Inc. Palo Alto, CA November 4, 1994.

"Limitations to Drug Permeability Due to Mucus Layers" Eli Lilly & Co. Indianapolis, IN April 10, 1996

"Metabolism and Residence Time Effects on Nasal Drug Delivery" Indianapolis/Cincinatti Pharmaceutical Discussion Group Indianapolis, IN April 10, 1996

"Drug Delivery to a Virtual Space: Development of Vaginal Formulations" Gilead Sciences, Inc. Foster City, CA September 6, 1996

"Drug Disposition into the CNS following Nasal Delivery" Nastech Pharmaceutical Company Hauppauge, NY October 4, 1996

"Preferential Drug Delivery to the CNS: Myth or Fact?" American Association of Pharmaceutical Scientists October 29, 1996

"Nasal Drug Delivery" American Association of Pharmaceutical Scientists October 31, 1996.

"Nasal Drug Delivery: Mucosal and Formulation Effects on Nasal Bioavailability" The West Company, January 6, 1997.

"Drug Delivery to a Ciliated Mucosal Surface: Trying to Trick Mother Nature" Aguoron Pharmaceuticals, Inc. March 28, 1997.

"Non-immunologic Complications of Nasal Drug Delivery" Nasal and Pulmonary Drug Delivery, Conference V, Stockholm, Sweden, September 30, 1997

"Nasal Drug Delivery: Formulation and Mucosal Surface Effects" Unigene, Inc. August, 1998

"Evaluation of Vaginal Drug Delivery System Efficacy", Women's Health Symposium, University of Iowa, March, 1999.

"Drug Disposition into the CNS Following Nasal Delivery" West Pharmaceutical Services, Inc. August, 2000

"Nasal Drug Delivery: Mucosal and Formulation Effects on Nasal Bioavailability" Bristol Myers Squibb, May, 2001

"Nasal Drug Delivery: Mucosal and Formulation Effects on Systemic Distribution and Bioavailability" Pharmacia Corporation, 2001

"Biopharmaceutics Curriculum at the University of Iowa: What to Include and Why" AACP Teachers of Pharmaceutics Seminar. American Association of Pharmaceutical Scientists Annual Meeting. Toronto, CA November 10, 2002.

"Carrier Mediated Processes as an Explanation for Selective Nose to Brain Transport" Uppsala University, Uppsala Sweden. March, 2003.

"Intranasal Deposition: Effect of Particle Size, Velocity, and Nasal Anatomy" AAPS Workshop on Particle Size Analysis. Alexandria, VA May 2, 2003

"Gender Differences in Medication Response: Drugs and Delivery Systems" 11<sup>th</sup> Annual Congress on Women's Health, Hilton Head, SC June 2, 2003.

"The Pharmaceutics Curriculum: Integrating Physical Concepts with Clinical Practice" AACP Annual Meeting, July 20, 2003.

"Gender and Racial Differences in Pharmacologic Response: Drug Delivery Systems" Expert Meeting on Improving the Use and Safety of Medications in Women Through Gender and Race Analysis. Sponsored by the Agency for Healthcare Research and Quality, April 19, 2004.

"Nose to Brain Delivery: An Optimistic Pessimist's Analysis" Respiratory Drug Delivery X Conference, Boca Raton, FL, May, 2006

"Nasal Drug Delivery: Passing the Sniff Test" Affymax, Inc. Palo Alto, CA September 22, 2006

"Using Biological Properties and Permeability to Select Routes of Administration" University of Michigan, October, 2006.

"Drug Delivery: Utilizing Chemistry, Biology and Materials Science to Improve Human Health" Department of Biomedical Engineering, University of Iowa, April, 2007 "Nasal Drug Delivery: Passing the Sniff Test" Pallatin, Inc.Cranbury, NJ April, 2007

"Some Do and Others Don't: Understanding Nose to Brain Delivery of Therapeutic Agents" University of Oklahoma College of Pharmacy, May, 2007.

"Prolonging Nasal Residence Time: Bioadhesive Polymers and Their Interactions with the Nasal Mucosa" NovaBay Pharmaceuticals, Inc. Emeryville, CA, April, 2008.

"Nasal Drug Delivery: Passing the Sniff Test" Centocor Pharmaceuticals, Palo Alto, CA February, 2009

"Alternative Routes of Delivery: Significance, Selection and Success" Glaxo SmithKline Consumer Products, Parsipanny, NJ March, 2009.

"Drug Transport Processes and Limitations in the Olfactory Mucosa" University of Michigan College of Pharmacy Science Symposium : Physical Chemistry in the Age of Molecular and Cellular Biology. October 15, 2010

"Size and Surface Characteristics Influencing Nanoparticle Uptake and Transport through the Olfactory Mucosa. Environmental Health Sciences Research Center, University of Iowa October 22, 2010.

"Size and Surface Properties Determining Nanoparticulate Uptake in the Nasal Mucosa" University of Iowa Environmental Health Sciences Research Center Retreat. January 10, 2011.

"Alternative Routes of Delivery: Significance, Selection and Success" Tongji Medical College School of Pharmacy, Huazhong University of Science and Technology, Wuhan, China. November 19, 2011.

"Materials and Methods for the Controlled Release of Ophthalmic Medications" Department of Ophthalmology Fourth Military Medical University, Xi'an, China. November 21, 2011.

"Some Do and Others Don't. Understanding Nose to Brain Transport of Therapeutic Agents" University of Iowa Department of Chemical and Biochemical Engineering. February 23, 2012.

"Career and Life Lessons Learned" University of Iowa Chapter of Women in Science and Engineering. February 26, 2012.

"The Nose to Brain Transport Pathway: Navigating the Entrance and Exit Ramps" Duquesne University College of Pharmacy. March 29, 2012.

"The Olfactory Neuroepithelial Barrier as a Delivery Pathway to the CNS" Gordon Research Conference on The Barrier Function of Mammalian Skin. August 21, 2013.

Using the Olfactory Neuroepithelium as a Delivery Pathway to the CNS. China Pharmaceutical Association, Wuhan, China, October 25, 2013.

Using the Olfactory Neuroepithelium as a Delivery Pathway to the CNS. Shiyan, China. October 28, 2013.

Abuse Deterrent Drug Products: Formulations and Drug Product Equivalence. University of Iowa College of Pharmacy. Cold Night, Hot Topics Symposium January 23, 2014.

Translational Medicine and Drug Development. University of Iowa Institute for Clinical and Translational Science. October, 2014.

In Vitro Assessment of Nasal Deposition Patterns in the Pediatric Population. NIPTE/FDA Science Meeting, Shady Grove, MD. April, 2015.

The Promise of Nose to Brain Transport: It's Not Nice (or Easy) to Fool Mother Nature. Eli Lilly & Co. May, 2015

Molecules and Macromolecules, Nano and Microparticles: Does the Olfactory System Provide a Drug Delivery Pathway to the Brain? Iowa State University Nanovaccine Initiative Annual Meeting. May, 2015

#### CE Presentations

"Drug Delivery Systems: An Application of Technology" Trends in Health Care CE Conference Iowa City, IA October 8, 1989.

#### **GRADUATE STUDENTS**

#### Ph.D. Degree Conferred

Yu-Min (Francis) Chung The Limiting Effects of Mucosal Metabolism on Systemic Bioavailability				
from the Nasal Cavity, May, 1995				

Pavan G. Bhat	Drug Binding and Permeation in Normal and Cystic Fibrosis Mucus Solutio		
	May, 1996		

- Mengping Zhou Drug and Formulation Induced Toxicity and Clearance Alterations in the Nasal Cavity, August, 1996
- Kang-Jye Chou Physicochemical Properties Controlling Transport into the CSF following Intranasal Drug Administration, August, 1997
- Ye (Bill) Huang Characterization of the Rheological Properties of In Situ Gelling Systems and Their Potential Use in Nasal Drug Delivery, August, 1997.
- Pei Fen Chou Roghair The Influence of Formulation Osmotic Pressure on Nasal Bioavailability, July, 2001
- Karunya Kandimalla Carrier Mediated Transport of Small Molecules across Bovine Olfactory Mucosa: Implications in Nose to Brain Drug Delivery, May, 2004
- Ankur Shah Viscoelastic Gels Resistant to Mucociliary Clearance: Rheological and Chemical Optimization for Prolonged Mucosal Contact, July, 2005
- Nagendra V. Chemuturi The Characterization of Biomolecular Processes Controlling Dopamine Transport Across the Nasal Mucosa, December, 2005
- Mow Yee Foo Deposition Patterns of Sprays in the Human Nasal Airway: Interactions Among Formulation, Device, Anatomy, and Administration Techniques. Dec. 2007.
- Chen-Ming Lee Nanoparticle Mobility in Viscoelastic Media. July, 2008

- Hefei Zhang Identification of Membrane Transporters to Facilitate Intranasal Drug Delivery Using Tissue-based and Pharmacokinetic Approaches. July, 2009
- Joanne Reiland Analysis of Cell Culture Models of Mammary Transport, July, 2009.
- Varsha Dhamankar Role of Concurrent Metabolism and Saturable Uptake on Distribution Following Nasal Administration. May, 2013
- Maya George The Role of Organic Cation Transporters in the Nasal Uptake and Brain Distribution of Organic Cation Substrates. May, 2013
- Nan Chen Size and Surface Properties Determining Nanoparticle Uptake and Transport in the Nasal Mucosa. July, 2013.
- Manar Al-Ghabeish Drug Transports in the Nasal Epithelia and Their Contributions in Drug Delivery. December, 2013.

Master's Degree Conferred

Hsiao-Hui (Daisy) Wu Comparison of Drug Permeation Rates through the Nasal Mucosae of Three Animal Species, August, 1994.

- Diane Venice Factors Influencing the Viscoelastic Behavior of a (Poly)Acrylic Acid Gel System, December, 1995.
- Daniel Cullinan (non-thesis) August, 1997
- Jeffrey Scott (non-thesis) July, 2000
- Kavita Khanvilkhar (non-thesis) December, 2001

Saroj Vangani (non-thesis) December, 2003

Saurabh Agarwal (non-thesis) August, 2004

Anita Gondi (non-thesis) December, 2005

Salem Elghami (non-thesis) May, 2011

Juan Carlos Soza Rios (non-thesis) May, 2012

- Wided Najahi-Missaoui (non-thesis) December, 2013
- Krupal Robeshkumar Maity Targeting the Trigeminal Nerve System for Orofacial Pain Treatment May, 2013
- Wisam Albakri Characterization of Atrazine Transport Across Nasal Respiratory and Olfactory Mucosae, May, 2014

#### Current Students (and tentative Ph.D. dissertation title)

Bhanu Bejgum – Ultrafine Nanoparticle Uptake and Transport in the Nasal Mucosa (expected completion: December, 2015)

Anna Ferreira – Identification and Function of Amino Acid Transporters in the Nasal Mucosa (expected completion: September, 2015)

Rakesh Awasthi – Pharmacokinetic Modeling of THC Disposition for Improved Estimation of Duration of Marijuana Pharmacodynamic Effects (expected completion: December, 2015)

Namita Sawant – Nasal Deposition Patterns in Pediatric Nasal Airways (pre-comp)

Laxmishanti Chede – Intranasal Amantadine as an Adjuctive Parkinson's Therapy (pre-comp)

Wisam Al-Bakri – Enhanced CNS Distribution of Pesticides following Inhalation Exposure (pre-comp)

Ammar Al-Khafaji (HCED Scholar, 2014-16)

Mohammed Al Barki (HCED Scholar, 2014-16)

Zainab Bakri (HCED Scholar, 2014-16\_

Post-Doctoral Fellows

Jiangeng Huang, Ph.D. – Pharmacokinetic Evaluation of Nose to Brain Transport (2010-12)

#### Visiting Scholars

Bjorn Jansson, Uppsala University, October - December, 2001

Jon Haraldsson, Uppsala University, January – May, 2004

Juan Pablo Cerasano, Neurosurgeon, Argentina, June - October, 2011

Bryan Gonzalez, University of Puerto Rico. SROP Scholars Program – June – August, 2012

Jiaqiang Xu, Tongji Medical College, Hubei University of Science and Technology– Dec 2011-March 2012; Sept 2012-Sept 2014.

Johnny Xu, Tongji Tongji Medical College, Hubei University of Science and Technology – March, 2014-June 2104.

#### Pharm.D. Student Trainees

Michael Arndorfer, 1990-1992 Kristen Swantz, 1992-94 Kelsey Mohs (P4 Research Rotation), September, 2013 Ashley Beckman, 2014-2015 Amanda Rixen, 2014-2015

#### **GRANTS AND AWARDS**

Investigation of the Limiting Role of Mucus in the Diffusion of Drug Molecules in the Lower Respiratory Tract The University of Iowa College of Pharmacy BRSG Seed Grant \$6000, 1989.

Research gift from the Proctor and Gamble Co. \$5000, 1989.

Molecular Weight Dependent Absorption following Intraperitoneal, Intramuscular, and Subcutaneous Administration Parenteral Drug Association Faculty Development Grant Program \$15,000, 1990-91.

The Limiting Effects of Mucosal Metabolism on Systemic Bioavailability from the Nasal Cavity The University of Iowa College of Pharmacy BRSG Seed Grant \$5000, 1990.

Research gift from SmithKline Beecham Pharmaceuticals \$5000, 1990.

CSF vs. Plasma Drug Concentration following Intranasal Administration American Association of Colleges of Pharmacy Grant Program for Young Investigators \$5000, 1991.

*The Use of a PABA-Peptide (Bentiromide) as a Nasal Absorption Marker* Pharmaceutical Manufacturers Association Undergraduate Research Fellowships Program \$5000, 1991.

Research gift from SmithKline Beecham Pharmaceuticals \$5000, 1991.

*Physicochemical Properties Controlling Transport into the CSF Following Intranasal Administration* Glaxo, Inc. \$15,000, 1991.

*Investigation of Epithelial Damage and Repair in the Nasal Mucosa* Rugby Darby Group Companies, Inc. \$30,000, 1991.

Eli Lilly & Co. Young Investigator Award \$20,000, 1992-93.

National Institutes of Health, National Institute of Allergy and Infectious Disease, DAIDS NO1-Al-95040. T.F. Chin (principal investigator). M.D. Donovan and D. R. Flanagan, co-investigators Funds available \$210,000 (January, 1994 - September 1995).

Abbott Laboratories, Development of an Otic Formulation, March - November, 1997, \$25,000

Mimetix, Inc. *Development of Sustained Release Vaginal Formulations* M.D. Donovan and D.E. Wurster, co-investigators, \$13,000, 1997.

Battelle, Inc. *Formulation Development of Solutions for Inhalation* M.D. Donovan and D.R. Flanagan, co-investigators, \$120,000, 1997-1999.

Pharmacia & Upjohn *Preformulation and Formulation of a Veterinary Injectable Dosage Form.* \$64,500, 1998 - 1999.

Aguoron Pharmaceuticals *Dissolution Characterization of Poorly Soluble Drugs*. D.E. Wurster (PI) and MD Donovan (co-investigator) \$75,000, 1998-2000

Meyer Nutraceuticals *Dissolution Characterization of a Targeted Release Oral Dosage Form* \$50,000, 1999-2000.

Pharmaceutical Research & Manufacturers of America Foundation. *Improved In Vitro Drug Release Testing Methods for Dosage Forms Administered to Limited Volume Sites.* \$5000, 2001.

Pinney & Associates Formulation and Evaluation of Nasal Dosage Forms, \$113,000, 2001

Bristol Myers Squibb *Bioavailability and Toxicologic Evaluation of Nasal Dosage Forms*. \$108,750, 2002

Ross Products Development of Gel Formulations. \$ 310,600, 2002-2006.

The University of Iowa Collaborative Interdisciplinary Projects Cell Culture Models for Drug Transport across Mammary Epithelium. co-investigator: Sarah England, Ph.D. \$24,975, 2004

National Cancer Institute, Division of Cancer Treatment and Diagnosis, Developmental Therapeutics Program *Manufacturing of Oral and Topical Dosage Forms* PI: Rolland Poust, Ph.D. (task order contract), \$250,000 (annual) 2005-2011 ((MDD, 5% effort)

Abbott Laboratories Investigation of Mucosal Transport \$60,000, 2005

Abbott Laboratories *Bioavailability of Sustained Release Injectables* \$20,000, DR Flanagan (PI), 2006

NIH/NIDCD R01 DC008374 Bypassing the Blood Brain Barrier: Modulation of Transporters in the Nasal Mucosa, \$1,500,000, (Donovan, PI), 2007-2012. ARRA Supplement \$127,500 (2009)

Glaxo Smith Kline Consumer Products In Vitro Formulation Evaluation, \$85,000, 2009-11.

Novartis Pharmaceuticals Corporation "*Novartis Pharmaceuticals Student Internships*". \$108,318, 2010.

Acquisition of a Dispersive Raman Spectrometer with Confocal Microscope. Roy J. Carver Charitable Trust. \$125,000, 2010

Novartis Pharmaceuticals Corporation "*Novartis Pharmaceuticals Student Internships*". \$123,000 2011.

Nanoparticle Distribution from the Olfactory Epithelium to the Brain Institute for Clinical Translational Science – University of Iowa \$50,000 2012-13

Enhanced CNS Exposure to Glyphosate following Inhalation Resulting from Olfactory Uptake Center for Health Effects of Environmental Contamination- University of Iowa \$30,000 2013

Pediatric Nasal Dosage Forms: In Vitro Characterization of Intranasal Deposition Patterns in Children for Optimal Delivery and Performance. NIPTE/US FDA U01 \$84,500 2013-2015.

Exposure Characterization following Nasal Inhalation of Narcotic-Containing Drug Products. Mallinckrodt Pharmaceuticals \$65,000 2013-15.

#### TEACHING RESPONSIBILITIES

Pharmacy Orientation, Pharmacy 46:014 (2 s.h.) Spring 1990 - 1993 Drug Delivery Systems: Principles and Applications, Pharmacy 46:202/46:232/46:110,111/46:238/239 (3 s.h.) Fall 1990, 1992, 1994; 2009, 2011 ,2013 Spring, 1997, 1999, 2001, 2005, 2007, 2009, 2011, 2012, 2014

Introduction to Pharmaceutical Care 46:049 Fall 1993 - 1996 lecture on Dosage Forms for Colds and Allergies

Introduction to Pharmaceutical Sciences 46:050 Spring 1994, 1995 (15 lectures; course coordinator)

Therapeutic and Diagnostic Systems 46:145 (2 s.h.) Fall 1995 – Fall, 2002

Principles of Equilibrium Processes 46:050 Spring 1996 (15 lectures; course coordinator))

Pharmaceutics Seminar 46:231 (2 s.h.) 1997-2003 (co-coordinator) 2012-present (coordinator)

Professional Practice 46:143 Fall 1997- 2000 8 lectures on Parenteral Dosage Forms

Pharmacy Projects (Calculations) 46:050 (2 s.h.) Spring 1997

Pharmacy Honors Seminar 46:102 (1 s.h.) 1998-2001 (coordinator)

Pharmaceutics I: Solutions 46:123 Fall 2001-2004 (20 lectures)

Pharmaceutics II: Solids and Semi-solids 46:124 Spring 2002-2009 (30 lectures); 2010 (8 lectures), 2011 (15 lectures), 2012 (10 lectures), 2014 (8 lectures); 2015 (6 lectures)

Pharmaceutics III: Pharmacokinetics and Biopharmaceutics 46:138 Spring 2002, Fall 2002, 2003 (15 lectures); Fall 2009-15 (25 lectures)

Parenteral Products and Technology 46:173 Fall 2002 (6 lectures)

Pharmacy Practice Laboratory I Fall 2004-2015 (25 - 35 contact hours)

Pharmacy Practice Laboratory II Spring 2005-2009 (10 contact hours)

Pharmacy Practice Laboratory III Fall 2004, 2005 (24 contact hours), 2007 (8 contact hours)

Pharmacy Practice Laboratory IV Spring 2004-11 (7 contact hours) Pharmacy Practice Laboratory V Fall 2004, 2006, 2007 (8 contact hours)

Introductory Practice Experience I (preceptor) 2007-2009

First Year Seminar: Health in a Bottle – Drug Development in the 21<sup>st</sup> Century (1 sh) 46:029 Fall 2009-13

Pharmacy Projects Fall 2014, Spring 2015 – Ashley Beckman Fall 2014, Spring 2015 – Amanda Rixen

#### EDITORIAL ADVISORY BOARD MEMBERSHIPS

Molecular Pharmaceutics (American Chemical Society), 2013-present

Journal of Pharmaceutical Innovation (Springer), 2010.

#### **REVIEW AND ADVISORY PANEL MEMBERSHIPS**

NIH/CSR – Small Business: Drug Discovery for Aging, Neuropsychiatric and Neurologic Disorders. ZRG1-ETTN-M(11) February, 2015.

NIH/CSR – Small Business: Drug Discovery for Aging, Neuropsychiatric and Neurologic Disorders. ZRG1-ETTN-M(11) October, 2014.

NIH/CSR – Small Business: Drug Discovery for Aging, Neuropsychiatric and Neurologic Disorders. ZRG1-ETTN-M(11) June, 2014.

NIH/CSR – Small Business: Drug Discovery for Aging, Neuropsychiatric and Neurologic Disorders. ZRG1-ETTN-M(11) February, 2014.

NIH/NIDCD – Chemosensory Fellowship Application Review. ZDC1 SRB-Y (68) February, 2014.

NIH/NIDCD – Chemosensory Fellowship Application Review. ZDC1 SRB-Y (52) June, 2013.

NIH/NCI – Special Emphasis Panel – Development of Radiation Modulators for Radiotherapy. ZCA1 SRLB-V (C1) March 21, 2013.

NIH/NCI – Special Emphasis Panel – Development of Radiation Modulators for Use During Radiotherapy. ZCA1-SRLB-V (C2) March 27-28, 2012.

NIH/NIAID – Special Emphasis Panel – Therapeutics for Neurotropic Biodefense Toxins and Pathogens. February 3, 2012.

NIH/CSR – Special Emphasis Panel (mail review) – Translational Research in Aging. ZAG1 ZIJ M1 February, 2012.

FDA Pharmaceutical Science and Clinical Pharmacology Advisory Committee – Ad hoc member (2012-present)

NIH/NCI – Special Emphasis Panel – Cancer Targeted Discovery and Development (CTDD) Network. November 14-15, 2011.

NIH/NCRR Special Emphasis Panel – Centers for Biomedical Research Excellence (COBRE), June 22-23, 2011.

NIH/NCI – Special Emphasis Panel – Preclinical Pharmacokinetic and Pharmacologic Studies. ZCA1 SRLB-V(C1)S September 30, 2010.

NIH/NIEHS – Special Emphasis Panel – Engineered Nanomaterials: Linking Physical and Chemical Properties to Biology. ZES1-SET-V 03 June 8-9, 2010.

NIH/CSR – Special Emphasis Panel – Emerging Technologies and Training in Neurosciences/ Neuropharmacology SBIR ZRG1 ETTN C-11, 2008, Chair 2009-2011

Society for Women's Health Research, Board of Directors, 2007-2009.

Invited reviewer, Leaders Opportunity Fund, Canada Foundation for Innovation, April, 2007

NIH/CSR – Special Emphasis Panel – Brain Disorders and Clinical Neurosciences/ Neuropharmacology SBIR ZRG1 BDCN A(11); 2006-2007

NIH/CSR Special Emphasis Panel (SBIR) – Pharmacology and Diagnostics for Neuropsychiatric Disorders, BDCN F(11); 2005-2006

NSF Scientific Review Panel (SBIR) - 2004

#### **PROFESSIONAL SERVICE ACTIVITIES**

# Society for Women's Health Research

Board of Directors (2007-2009)

#### American Association of Pharmaceutical Scientists

Program Review Team – Distance Learning, 2004-2005 Program Review Team – Students, 2003 Program Review Team – Books, 2003 AAPS Treasurer (1998-2000) AAPS Publications Board Member (1998-2000) AAPS Diversity Task Force-Mentoring Subcommittee Chair (1994-1995) PDD Section Secretary-Treasurer (1993-1995) AAPS Finance Committee (1991-95) PPDM Travelships-Graduate Student Committee (1993) Poster Session Moderator Las Vegas, NV (1991) Pharmaceutics and Drug Delivery Section Nominations Committee (1990-91) Pharmaceutics and Drug Delivery Section Paper Screening Committee (1990, 1992) Representative to AACP sponsored "Pharmacy in the 21<sup>st</sup> Century Conference" (1989) Pharmaceutics and Drug Delivery Section Membership Committee (1989, 1990, chair 1991, 1992) AAPS Long Range Planning Committee (1987,1988) University of Iowa AAPS Student Chapter Adviser (1995-present)

#### American Association of Colleges of Pharmacy

Pharmaceutics Section Strategic Planning Initiative – Concepts Committee (2015)

Review Panel Member (Teachers of Pharmaceutics) 2006 Annual Meeting Program Committee (2005-06) Academic Leadership Fellow (2004-05) Review Panel Chair (Pharmaceutics – Biological) New Investigators Program (2003) Chair, Section of Teachers of Pharmaceutics, 1998-99 Vice Chair, Section of Teachers of Pharmaceutics, 1997-98

#### American Pharmaceutical Association

APS Poster Session Committee (1984-85) Student American Pharmaceutical Association 1980-83 SAPhA Special Grant Chairman (1982)

#### Kappa Epsilon Pharmaceutical Fraternity

Alpha chapter pledge trainer 1982 Province E co-director 1982 Alpha chapter president 1983 Gamma Chapter Advisor 1990-1998

### Rho Chi Pharmaceutical Honor Society

University of Iowa, chapter advisor (2005 2009) Chapter secretary/treasurer (1982-83)

# Crohn's and Colitis Foundation of America - Eastern Iowa Chapter

Board of Trustee's member 1992-95

#### Mortar Board Honor Society

Iowa Alumnae Chapter

Treasurer 1994-96 Vice-president 1996-97 President 1997-98

#### Phi Kappa Phi Honor Society

#### ADMINISTRATIVE ACTIVITIES

University of Iowa Assignments
Graduate College Post-Doc Professional Development Program – Grant Reviews and Study Sections Panelist (2014)
Graduate College Post-Doc Professional Development Program – Insights from Faculty Search Committees Panelis (2013)
Task Force on Graduate Education (2009-10).
Women Faculty Development Conference, Planning Committee Member (2009-15)
Advisory Board Member, Nanoscience and Nanotechnology Institute at the University of Iowa (2006-2010)
University of Iowa Animal Care and Use Committee (2006-09)
Faculty Senate (2006-09)
Gender Equity Task Force (2005)

James F. Jakobsen Graduate Forum Faculty Judge (2004, 2006, 2007) University of Iowa Presidential Search Committee (2002) Task Force on Post-doctoral Scholars – Graduate College (2001-2003) University of Iowa Strategic Planning Committee (1998-2000) University of Iowa Animal Care and Use Committee (1997-2003) Graduate Council (University of Iowa Graduate College) (1996-99) Advisory Committee in the Biological Sciences (University of Iowa) (1996-97)

College of Pharmacy Assignments Accreditation Steering Committee (2014-2016) Administration sub-committee chair Curriculum Committee (ad hoc) (2014-present) College Council (2010-present) Pharmaceutical Sciences Department Chair Search Committee (2010-12) Executive Committee (2008-present) Accreditation Steering Committee (2008-2010) Facilities and Budget sub-committee chair College of Pharmacy Dean Search Committee (2006-07) Admissions Committee Chair (2006-08) Rho Chi Honor Society Faculty Advisor (2005-present) College of Pharmacy Accreditation Steering Committee Students sub-committee chair (2002-2004) Division of Pharmaceutics Search Committee (2001) Pharmaceutics Vice-Chair for Professional and Undergraduate Curriculum (2000-2003) Ad Hoc Task Force for Clinical Track Appointments (College of Pharmacy) (1999-2000) Task Force for Development of B.S. in Pharmaceutical Sciences Program (1999-2001) Ad Hoc Pharmaceutics Curriculum Review Committee (1999) Advisor, College of Pharmacy Honors Program (1998-2001) Task Force on the Development of Educational Outcomes (1997) Graduate Studies Committee (College of Pharmacy) (1996 - 1999) Division of Medicinal and Natural Products Chemistry Search Committee (1996) Division of Pharmaceutics Faculty Search Committees (2) (1993-95) College of Pharmacy Dean Search Committee (1991) Faculty Secretary (College of Pharmacy) (1990-93) Pharmaceutical Service Director Search Committee (1990-91) Undergraduate Career Opportunities and Placement (1990 (chair), 1991-92) Building and Space Utilization Committee (1989-91) Safety Committee (1989, 1992)

# HONORS AND AWARDS

Teacher of the Year, University of Iowa College of Pharmacy, 2005

American Association of Colleges of Pharmacy Academic Leadership Fellow (2004-05)

Treasurer, American Association of Pharmaceutical Scientists 1998-2000

Pharmaceutics and Drug Delivery Section Section Secretary-Treasurer, AAPS, 1993-1995

American Association of Colleges of Pharmacy, Chair, Section of Teachers of Pharmaceutics, 1998-99

Eli Lilly Young Investigator Award in Pharmaceutics, 1992-93

<u>Fellowships (Graduate)</u> Horace H. Rackham Predoctoral Fellow 1987-88 American Foundation for Pharmaceutical Education Fellow 1985-88 1987 Abbott Pharmaceutics Fellow Nellie Wakeman Fellowship (Kappa Epsilon) 1985

#### Nominations

National Dean's List 1980-81 Who's Who Among Students in American Universities and Colleges Outstanding Young Women of America Who's Who in Science and Engineering Outstanding Mentor, University of Iowa Graduate College, 2003

# **MEMBERSHIPS**

American Association of Pharmaceutical Scientists American Association of Colleges of Pharmacy American Society for Pharmacology and Experimental Therapeutics The Controlled Release Society

# EXHIBIT D

Description	Begin Bates	End Bates
Advair Diskus Prescribing Information	APOTEX_AZFL 0059181	APOTEX_AZFL 0059242
Ansel, H., et al., Oral Suspensions, Emulsions, Magmas, and Gels,		
Chapter 7, Pharmaceutical Dosage Forms and Drug Delivery	ADOTEV AZEL 0122747	ADOTEX AZEL 0122700
Systems, pp. 253-285	APOTEX_AZFL 0132747	APOTEX_AZFL 0132780
Apotex's Initial Invalidity Contentions Pursuant to the Court's Default Standard for Discovery (Aug. 12, 2015)	N/A	N/A
Avicel® RC-951 Microcrystalline Cellulose and		
Carboxymethylcellulose Sodium, NF, BP, Pharmaceutical Emulsions		
and Suspensions Stabilization Technology for Liquid and Semi-Solid		
Dosage Forms (1994)	APOTEX_AZFL 0132781	APOTEX_AZFL 0132800
British Pharmaceutical Codex, p. 977 (1973)	APOTEX_AZFL 0132801	APOTEX_AZFL 0132803
Center for Drug Evaluation and Research Application Number: 20-		
114/S006 Astelin® Final Printed Label	APOTEX_AZFL 0059081	APOTEX_AZFL 0059097
Center for Drug Evaluation and Research, Application Number: 20-		
121/S009 Flonase® Final Printed Label	APOTEX_AZFL 0060185	APOTEX_AZFL 0060207
Declaration of Geena Malhotra for Application No. 10/518,016 (July 6, 2005)	CIP DYM 00060301	CIP DYM 00060350
Deposition Transcript of Donald Accetta (May 6, 2016)	N/A	 N/A
Deposition Transcript of Geena Malhotra (April 25, 2016)	N/A	N/A
Dolz, M., et al., Rheological Behaviour of Microcrystalline Cellulose		
Hydrogels, Journal of Dispersion Science and Technology Vol. 13		
Number 1, pp. 96-99 (1992)	APOTEX_AZL 0132557	APOTEX_AZL 0132579
Draft Development Report for Azelastine Hydrochloride and		
Fluticasone Propionate Nasal Spray for U.S. Market (April 2008)	CIP_DYM_00004654	CIP_DYM_00004757
Draft Development Report for Azelastine Hydrochloride and Fluticasone Propionate Nasal Spray for U.S. Market (July 31, 2007)	CIP DYM 00461986	CIP DYM 00462122
Dymista® web site (http://dymista.com/spray-volume.php)	APOTEX_AZFL 0132804	APOTEX_AZFL 0132805

# Materials Considered for the Initial Expert Report of Maureen Donovan

Description	Begin Bates	End Bates
European Patent Application No. 0 780 127 (1997) (Cramer)	APOTEX_AZFL 0052951	APOTEX_AZFL 0052960
Guidance for Industry, Nasal Spray and Inhalation Solution,		
Suspension, and Spray Drug Products - Chemistry, Manufacturing, and Controls Documentation (July 2002)	N/A	N/A
Guidance for Industry, Nasal Spray and Inhalation Solution,		
Suspension, and Spray Drug Products - Chemistry, Manufacturing,		
and Controls Documentation (May 1999)	N/A	N/A
Imitrex Nasal Spray Prescribing Information	APOTEX_AZFL 0132818	APOTEX_AZFL 0132842
Loyd V. Allen, The Art, Science, and Technology of Pharmaceutical Compounding, Chapter 20 (1998)	APOTEX AZFL 0132304	APOTEX AZFL 0132325
Lund, C.G., et al. The Preparation of Solutions Isoosmotic with	APOTEA_AZFL 0152504	APOTEX_AZEL 0132323
Blood, Tears, and Tissue, Contributions from the Danish		
Pharmacopoeia Commission (1947)	APOTEX_AZFL 0130722	APOTEX_AZFL 0130895
PCT Publication No. WO 97/01337	APOTEX_AZFL 0059010	APOTEX_AZFL 0059024
PCT Publication No. WO 97/46243	APOTEX_AZFL 0055458	APOTEX_AZFL 0055475
PCT Publication No. WO 98/48839 (Segal)	APOTEX_AZFL 0059025	APOTEX_AZFL 0059037
Pennington, A.K., et al. The Influence of Solution Viscosity on		
Nasal Spray Deposition and Clearance, International Journal of Pharmaceutics, Vol. 43 pp. 221-224 (1988)	APOTEX AZFL 0132938	APOTEX AZFL 0132941
Remington: The Science and Practice of Pharmacy, Chapter 16	ATOTEA_ALTE 0152756	AI OILA_ALI L 0132341
Solutions and Solubility (2000)	APOTEX_AZFL 0132974	APOTEX_AZFL 0132992
Remington: The Science and Practice of Pharmacy, Chapter 18,		
Tonicity, Osmoticity, Osmolality, and Osmolarity (2000) Suzuki Y., et al, Mucosal Drug Delivery Using Cellulose Derivatives	APOTEX_AZFL 0130673	APOTEX_AZFL 0130689
as a Functional Polymer, Journal of Controlled Release, Vol. 62 pp.		
101-107 (1999)	APOTEX_AZFL 0133012	APOTEX_AZFL 0133018
U.S. Patent Application Publication No. 2004/0242638 A1	APOTEX_AZFL 0053415	APOTEX_AZFL 0053417
U.S. Patent No. 4,335,121 (Phillips)	APOTEX_AZFL 0133019	APOTEX_AZFL 0133041

Description	Begin Bates	End Bates
U.S. Patent No. 5,164,194 (Hettche)	APOTEX_AZFL 0054360	APOTEX_AZFL 0054365
U.S. Patent No. 8,163,723	CIP_DYM_0054179	CIP_DYM_0054192
U.S. Patent No. 8,168,620	CIP_DYM_0054193	CIP_DYM_0054206
U.S. Patent No. 9,259,428	MEDA_APTX03490368	MEDA_APTX03490383
U.S. Pharmacopoeia, The National Formulary, 24/NF19 (2000)	APOTEX_AZFL 0132333	APOTEX_AZFL 0132337
Wade, A., et al., Handbook of Pharmaceutical Excipients (1994)	APOTEX_AZFL 0132041	APOTEX_AZFL 0132077
Expert Report of Robert P. Schleimer, PH.D. and the documents cited		
therein	N/A	N/A
Expert Report of Ram Govindarajan, PH.D. and the documents cited		
therein	N/A	N/A