

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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ARGENTUM PHARMACEUTICALS LLC  
Petitioner

v.

CIPLA LTD.  
Patent Owner

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

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*Inter Partes* Review No.: IPR2017-00807

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**DECLARATION OF ROBERT P. SCHLEIMER, Ph.D.**

## **TABLE OF CONTENTS**

I.	Introduction .....	1
II.	My Background And Qualifications .....	1
III.	List Of Documents Considered In Formulating My Opinion .....	2
IV.	Summary of Opinions .....	5
V.	Person Of Ordinary Skill In The Art .....	6
VI.	The '620 Patent .....	6
VII.	Claim Construction .....	8
VIII.	The Claims of the '620 Patent are Not Entitled to the Earliest Effective Filing Date .....	9
IX.	Technical Background.....	10
X.	Claims 1 and 25 are Anticipated .....	12
A.	Claim Limitation 1.1: "A pharmaceutical formulation comprising".....	12
B.	Claim Limitation 1.2: "azelastine, or a pharmaceutically acceptable salt thereof" .....	13
C.	Claim Limitation 1.3: "a pharmaceutically acceptable ester of fluticasone" .....	13
D.	Claim Limitation 1.4: "wherein said pharmaceutical formulation is in a dosage form suitable for nasal administration." .....	14
E.	Claim Limitation 25.1: "A nasal spray formulation comprising" .....	14
F.	Claim Limitation 25.2: "(i) azelastine, or a pharmaceutically acceptable salt thereof," .....	15
G.	Claim Limitation 25.3: "(iii) a pharmaceutically acceptable ester of fluticasone," .....	15
H.	Claim Limitation 25.4: "and (iii) a pharmaceutically acceptable carrier or excipient therefor." .....	15
I.	Segal discloses all claim elements as arranged in Claims 1 and 25 ..	16
J.	Segal is enabling prior art .....	16
XI.	Claims 1, 5-6, 24-26, and 29, were Obvious as of at least June 2002 .....	17
A.	The cited references disclose all of the claim elements.....	18

B.	It was well known that steroids and antihistamines were effective at treating allergic rhinitis together.....	21
C.	Fluticasone propionate was the most potent glucocorticoid for treating the late phase response of allergic rhinitis.....	25
D.	Azelastine was the most effective antihistamine on the market.....	26
E.	Oral antihistamines were combined with intranasal steroids .....	29
F.	Administration of nasal antihistamine and nasal steroid to treat allergic rhinitis was recommended .....	30
G.	A co-formulation of fluticasone and azelastine has been disclosed ..	34
H.	Combining fluticasone and azelastine into a single product would have improved patient compliance .....	36
I.	Fluticasone was previously co-formulated with other drugs.....	36
J.	Clinical studies disclosed benefits to combining antihistamines and corticosteroids .....	38
XII.	Absence of Secondary Considerations of Nonobviousness.....	41
A.	No teaching away.....	41
B.	There was no long-felt but unmet need satisfied by the '620 Patent.	44
C.	No evidence of unexpected results compared to the closest prior art .....	49
D.	A POSA would appreciate the teachings of Cramer .....	54
XIII.	Conclusion.....	57

I, Robert Schleimer, do declare as follows:

**I. Introduction**

1. I am over the age of eighteen (18) and otherwise competent to make this declaration.

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

**II. My Background And Qualifications**

3. My area of expertise is in the field of allergy and immunology. At Northwestern University's Feinberg School of Medicine, I am presently the Chief of the Division of Allergy-Immunology in the Department of Medicine, the Roy and Elaine Patterson Professor of Medicine, and a Professor of Medicine in the Division of Allergy-Immunology. I am also a Professor in the Departments of Microbiology-Immunology and Otolaryngology - Head and Neck Surgery. My research areas include the mechanisms of pathogenesis and treatment of a variety

of allergic and inflammatory diseases associated with allergy, including chronic rhinosinusitis, asthma, hay fever, rhinitis, food allergy and others. I also study the mechanisms of action of anti-inflammatory glucocorticoids, with a focus on the molecular and cellular mechanisms underlying disease and steroid action as well as developing strategies for new treatments.

4. I obtained a Bachelor of Arts in Biology from the University of California, San Diego in 1974 and a Ph.D. from the University of California, Davis in Pharmacology, Toxicology, and Immunology in 1979.

5. Additionally, I have been a named author on over 300 scientific papers, served as an editor or on the editorial board of ten different journals, and I have trained a large number of graduate and undergraduate students as well as postdoctoral fellows. I am currently on the Editorial Boards of the American Journal of Respiratory Cell and Molecular Biology, the Journal of Allergy, and Allergology International.

6. My *curriculum vitae* is attached as Ex. 1051 to this document.

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

### **III. List Of Documents Considered In Formulating My Opinion**

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

<b>Ex #</b>	<b><u>Exhibit</u></b>
1001	U.S. Patent No. 8,168,620 (“’620 patent”)
1002	Prosecution History of U.S. Patent No. 8,168,620
1006	UK Patent Application GB 0213739.6
1007	U.S. Patent No. 5,164,194 (“Hettche”)
1008	Physician’s Desk Reference, Astelin® Label, rev.1/99, 3147-3148 (54 <sup>th</sup> ed. 2000) (“Astelin® Label”)
1009	U.S. Patent No. 4,335,121 (“Phillipps”)
1010	Flonase® Label (1998)
1011	European Patent Application No. 0780127 (“Cramer”)
1012	PCT Publication No. WO 98/48839 to Segal (“Segal”)
1015	Falser, N., <i>et al.</i> , “Comparative efficacy and safety of azelastine and levocabastine nasal sprays in patients with seasonal allergic rhinitis.” ARZNEIMITTELFORSCHUNG, 51(5):387-93 (2001)
1016	Kusters, S., <i>et al.</i> , “Effects of Antihistamines on Leukotriene and Cytokine Release from Dispersed Nasal Polyp Cells.” ARZNEIM-FORSCH/DRUG RES., 52(2): 97-102 (Feb. 2002)
1017	Stellato, C., <i>et al.</i> , An in vitro Comparison of Commonly Used Topical Glucocorticoid Preparations, J. ALLERGY CLIN. IMMUNOL., Vol. 104, No. 3, Part 1, 623-629 (Sept. 1999)
1018	Johnson, M., Development of fluticasone propionate and comparison with other inhaled corticosteroids, J. Allergy Clin. Immunol., Vol. 101, No. 4, Part 2, S434-S439 (1998)
1019	Dykewicz, Mark S., <i>et al.</i> , “Diagnosis and management of rhinitis: complete guidelines of the joint task force on practice parameters in allergy, asthma and immunology,” ANNALS OF ALLERGY, ASTHMA & IMMUNOLOGY, Vol. 81, 478-518 (1998)
1020	Stoloff, R., <i>et al.</i> , “Combination Therapy with Inhaled Long-Acting $\beta_2$ -Agonists and Inhaled Corticosteroids: A Paradigm Shift in Asthma Management,” PHARMACOTHERAPY, Vol. 22, No. 2, 212-226 (Feb. 2002)
1021	Berger, W. E. <i>et al.</i> , “Double-blind trials of azelastine nasal spray

	monotherapy versus combination therapy with loratadine tablets and beclomethasone nasal spray in patients with seasonal allergic rhinitis,” ANNALS OF ALLERGY, ASTHMA & IMMUNOLOGY, Vol. 82, 535-541 (1999)
1022	Cauwenberge, P. et al., “Consensus statement on the treatment of allergic rhinitis,” ALLERGY, Vol. 55: 116-134 (2000)
1023	Spector, S., “Ideal Pharmacology for Allergic Rhinitis,” J. ALLERGY CLIN. IMMUNOL., Vol. 103, No. 3, Part 2, S386-87 (1999)
1024	Bousquet et al., Management of Allergic Rhinitis and Its Impact on Asthma, JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY, Vol. 108, No. 5 (2001)
1025	Markham, A., et al., “Inhaled Salmeterol-Fluticasone Propionate Combination, A Review of its Use in Persistent Asthma,” DRUGS 60(5) 1207-1233 (Nov. 2000)
1030	Advair Diskus Prescribing Information (2000)
1031	Juniper, E., "First-line Treatment of Seasonal (Ragweed) Rhinoconjunctivitis)," Canadian Medical Association Journal, Vol. 156, No. 8, April 1997, 1123-31.
1034	Ratner, P., et al., “A Comparison of the Efficacy of Fluticasone Propionate Aqueous Nasal Spray and Loratadine, Alone and in Combination, for the Treatment of Seasonal Allergic Rhinitis,” JOURNAL OF FAMILY PRACTICE, Vol. 47, No. 2, 118-125 (Aug. 1998)
1035	Drouin, M., et al. “Adding Loratadine to Topical Nasal Steroid Therapy Improves Moderately Severe Seasonal Allergic Rhinoconjunctivitis.” ADVANCES IN THERAPY, 12(6): 340-349; 1995.
1036	Simpson, R., Budesonide and terfenadine, separately and in combination, in the treatment of hay fever, ANNALS OF ALLERGY, Vol. 73 497-502 (Dec. 1994)
1038	Brooks, C. et al. “Spectrum of Seasonal Allergic Rhinitis Symptom Relief with Topical Corticoid and Oral Antihistamine Given Singly or in Combination.” AM. J. RHINOL., Vol. 10, 193-196 (1996)
1039	Juniper, E F., et al., “Comparison of beclomethasone dipropionate aqueous nasal spray, astemizole, and the combination in the prophylactic treatment of ragweed pollen-induced rhinoconjunctivitis,” JOURNAL OF

	ALLERGY AND CLINICAL IMMUNOLOGY, Vol. 83, No. 3, Cover page, Publications page, 627-633 (Mar. 1989)
1040	Benincasa, C. & Lloyd, R.S., “Evaluation of Fluticasone Propionate Aqueous Nasal Spray Taken Alone and in Combination with Cetirizine in the Prophylactic Treatment of Seasonal Allergic Rhinitis,” DRUG INVEST., Vol. 8, Issue 4, 225-233 (1994)
1041	Galant, S. and Wilkinson, R., “Clinical Prescribing of Allergic Rhinitis Medication in the Preschool and Young School-Age Child.” BIODRUGS, 15(7): 453-463; 2001
1042	Schleimer, R., “Glucocorticosteroids: Their Mechanisms of Action and Use in Allergic Diseases,” ALLERGY PRINCIPLES & PRACTICE, 638-660 (1998)
1045	Ratner, Paul H., et al., “Combination therapy with azelastine hydrochloride nasal spray and fluticasone propionate nasal spray in the treatment of patients with seasonal allergic rhinitis,” ANNALS OF ALLERGY, ASTHMA & IMMUNOLOGY, VOL. 100, 74-81 (2008)
1047	NASACORT AQ Prescribing Information (2013)
1050	Ratner, Paul H., et al., “A double-blind, controlled trial to assess the safety and efficacy of azelastine nasal spray in seasonal allergic rhinitis,” Journal of Allergy and Clinical Immunology, Vol. 94, No. 5, 818-825 (1994)

#### IV. Summary of Opinions

9. Based on my investigation and analysis and for the reasons set forth below, it is my opinion that claims 1 and 25 of the '620 patent are anticipated by PCT Publication No. WO 98/48839 to Segal (“Segal”).

10. In addition, claims 1, 5-6, 24-26, and 29 of the '620 patent would

have been obvious to one of ordinary skill in the art at the time of the alleged invention in view of the combined teachings of U.S. Patent No. 5,164,194 (“Hettche”), U.S. Patent No. 4,335,121 (“Phillipps”), and Segal.

**V. Person Of Ordinary Skill In The Art**

11. I understand that as of June 14, 2002, a person of ordinary skill in the art (“POSA”) would “be aware of all the pertinent prior art” at that time.

12. A hypothetical POSA would be part of a multidisciplinary team including a clinician/scientist and formulator. As a clinician/scientist in this field, a POSA typically would have had an M.D., Pharm. D. or Ph.D. in the field of allergy/immunology and/or pharmacology (or the equivalent), and have at least three years of experience in the treatment of, or research for treatments, of allergic rhinitis, including with nasally administered steroids and antihistamines.

**VI. The ’620 Patent**

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

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

15. Independent claim 1 of the '620 patent recites:

“A pharmaceutical formulation comprising: azelastine, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable ester of fluticasone, wherein said pharmaceutical formulation is in a dosage form suitable for nasal administration.”

16. The specification of the '620 patent states:

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

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

Ex. 1001, 1:20-30.

## **VII. Claim Construction**

17. I understand from counsel that the claim terms of an unexpired patent subject to *inter partes* review are given the broadest reasonable construction in light of the specification of the patent.

18. The '620 patent discloses the term “conditions” in the context of the phrase “treatment of conditions for which administration of one or more anti-histamine and/or one or more steroid is indicated.” Ex. 1001, cl. 24. I understand that Petitioner contends in this proceeding that the broadest reasonable construction of the term “conditions” is “disease(s) or illness(es).” I agree with this construction given that the specification of the '620 patent itself refers to “conditions” in the context of nasal spray treatments of “allergy-related conditions” using antihistamines and corticosteroids like azelastine and fluticasone respectively. Ex. 1001, 1:20-30. The specification mentions the treatment of “seasonal or perennial allergic rhinitis,” “seasonal and perennial allergic conjunctivitis,” as well as “nasal and ocular inflammatory conditions.” *Id.*, 1:21-28.

19. I also note that nothing in the specification or the prosecution history of the '620 patent specifically limits “conditions” to only the specific diseases or illnesses listed in those documents.

20. Accordingly, for purposes of this proceeding, I understand

“conditions” to mean “disease(s) or illness(es).”

**VIII. The Claims of the '620 Patent are Not Entitled to the Earliest Effective Filing Date**

21. I understand from counsel that a patent claim is not entitled to rely on the filing date of an earlier-filed patent application unless the earlier-filed patent application contains an adequate written description of the claimed invention. I understand from counsel that an adequate written description of a claimed genus requires more than a generic statement of an invention's boundaries and instead requires the disclosure of either a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can 'visualize or recognize' the members of the genus. I am told that an adequate written description requires a precise definition, such as by structure, formula, chemical name, physical properties, or other properties, of species falling within the genus sufficient to distinguish the genus from other materials.

22. It is my opinion that at least Claims 1, 4-6, 25, 42, 44 of the '620 Patent are not adequately described in GB 0213739.6 because GB 0213739.6 lacks written description support for the genus term “pharmaceutically acceptable ester of fluticasone.”

23. GB 0213739.6 discloses, generally, “an ester” of fluticasone in claim

5, and provides only one specific example—“fluticasone propionate”—in claim 6. Ex. 1006, cl.5, cl.6. Moreover, GB 0213739.6 provides no additional examples, no qualitative guidance, no definition, no test, and no structure-function relationship for what it considered “pharmaceutically acceptable” esters of fluticasone. The broad genus of “an ester” of fluticasone in claim 5 of GB 0213739.6, and one specific example of “fluticasone propionate” in claim 6 of GB 0213739.6, are insufficient for a POSA to ‘visualize or recognize’ all the members of the genus “pharmaceutically acceptable ester of fluticasone” (other than fluticasone propionate).

24. Therefore, it is my opinion that all claims of the ’620 patent that are not specifically limited to fluticasone propionate are not entitled to the filing date of GB 0213739.6.

## **IX. Technical Background**

25. Rhinitis is a disorder characterized by the inflammation of the mucous membrane inside the nose. Nasal symptoms often include sneezing, itching, rhinorrhea (runny nose), and nasal congestion. Frequently, symptoms may spread to the eyes, ears, and throat, and post-nasal drainage may occur as well. Allergic rhinitis (“AR”), or hay fever, is one of the more common causes of rhinitis.

26. Allergic rhinitis is an inflammation in the nose that results from the immune system responding to specific allergens or antigenic environmental

factors, such as pollen, pet dander, dust, or mold. Allergic rhinitis is widely considered to be the most common of all allergic disorders, affecting over 40 million Americans.

27. It is well known that allergic rhinitis responses occur in two separate phases: an early phase response (“EPR”) and a late phase response (“LPR”). The EPR occurs immediately after the patient is exposed to the allergen. Once exposed, mast cells in the nose release mediators, including histamine, tryptase, prostaglandin D<sub>2</sub> and the cysteinyl leukotrienes. Ex. 1041, 455. These inflammatory mediators cause early phase symptoms.

28. The LPR occurs roughly 4-8 hours after allergen exposure. *Id.* This phase is characterized by mast cells releasing mediators into the tissue at the site, which will cause a more prolonged response. The LPR is characterized by profound infiltration and activation of migrating and resident cells. The LPR is often described as a chronic inflammatory-type response, which is thought to be responsible for the persistent symptoms of allergic rhinitis. *Id.* The symptoms usually associated with LPR include EPR symptoms as well as nasal obstruction and enhanced sensitivity to allergens in the nasal mucosa. *Id.*

29. Many different drugs have been used to prevent or minimize the symptoms of AR. Antihistamines, both oral and intranasal, intranasal steroids,

decongestants, cromolyn, and leukotriene receptor antagonists are the most commonly used.

**X. Claims 1 and 25 are Anticipated**

30. I understand from counsel that a patent claim is “anticipated” if all elements of the claim are disclosed in a single prior art reference in the same way the elements are arranged in the claim. I further understand that where a reference provides broad disclosure of a larger group of, *e.g.*, combinations, as well as specific preferences for the combinations, the reference still anticipates so long as all claim elements are disclosed as arranged in the claim. I am also told that the prior art reference must be enabling (*i.e.*, allowing a POSA to make and use the claimed invention without undue experimentation) in order to anticipate the claim.

31. Segal is an international patent application filed by Warner Lambert Company and was published on November 5, 1998. Ex. 1012. It is my expert opinion that Segal anticipates Claims 1 and 25.

**A. Claim Limitation 1.1: “A pharmaceutical formulation comprising”**

32. Segal discloses “topically applicable nasal compositions comprising a therapeutically effective amount of a topical antiinflammatory agent and a therapeutically effective amount of at least one agent suitable for topical nasal administration and selected from the group consisting of a vasoconstrictor, a neuramidinase [sic] inhibitor, an anticholinergic agent, a leukotriene inhibitor, an

antihistamine, an antiallergic agent, an anesthetic, and a mucolytic agent.” Ex. 1012, 2:10-15; *see also id.* cl.1. The term “therapeutically effective amount” and the listed active ingredients are pharmaceuticals. Therefore, Segal discloses a “pharmaceutical formulation” as claimed in the ’620 patent.

**B. Claim Limitation 1.2: “azelastine, or a pharmaceutically acceptable salt thereof”**

33. Segal states that “suitable antihistamines” can include “azelastine.” *Id.*, 3:19-20. Likewise, Segal’s claim 4, which depends from Segal’s claim 1, discloses the combination of an antihistamine, like azelastine, with a topical anti-inflammatory agent. Therefore, Segal discloses azelastine as part of the combination nasal composition.

**C. Claim Limitation 1.3: “a pharmaceutically acceptable ester of fluticasone”**

34. Segal discloses fluticasone as part of the combination nasal composition. Segal identifies “fluticasone propionate” as one of the “preferred” antiinflammatory agents of the invention. *Id.*, 2:22-26. Likewise, Segal’s claim 2 recites fluticasone propionate as one of the topical anti-inflammatory agents in the combination nasal composition. *Id.*, cl. 2. Therefore, Segal discloses fluticasone propionate as part of the combined nasal composition.

**D. Claim Limitation 1.4: “wherein said pharmaceutical formulation is in a dosage form suitable for nasal administration.”**

35. Segal states: “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. . . . Preferred nasal formulations are nose drops or nasal sprays containing a water buffered aqueous solution as a carrier.” Ex. 1012, 3:29-4:5; *see also id.* cl.15 (depending from Segal claim 1 or 11). Thus, Segal’s pharmaceutical formulation is a nasal spray, which thus is suitable for nasal administration.

**E. Claim Limitation 25.1: “A nasal spray formulation comprising”**

36. Segal states: “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. . . . Preferred nasal formulations are nose drops or nasal sprays containing a water buffered aqueous solution as a carrier.” Ex. 1012, 3:29-4:5; *see also id.* cl.15 (depending from Segal claim 1 or 11). Thus, Segal’s pharmaceutical formulation is a nasal spray, which thus is suitable for nasal administration.

**F. Claim Limitation 25.2: “(i) azelastine, or a pharmaceutically acceptable salt thereof,”**

37. Segal states that “suitable antihistamines” can include “azelastine.” *Id.*, 3:19-20. Likewise, Segal’s claim 4, which depends from Segal’s claim 1, discloses the combination of an antihistamine, like azelastine, with a topical anti-inflammatory agent. Therefore, Segal discloses azelastine as part of the combination nasal composition.

**G. Claim Limitation 25.3: “(iii) a pharmaceutically acceptable ester of fluticasone,”**

38. Segal discloses fluticasone as part of the combination nasal composition. Segal identifies “fluticasone proprionate” as one of the “preferred” antiinflammatory agents of the invention. *Id.*, 2:22-26. (As would be recognized by one of skill in the art, “proprionate” is merely an alternative spelling of “propionate” and has the same meaning.) Likewise, Segal’s claim 2 recites fluticasone proprionate as one of the topical anti-inflammatory agents in the combination nasal composition. *Id.*, cl. 2. Therefore, Segal discloses fluticasone propionate as part of the combined nasal composition.

**H. Claim Limitation 25.4: “and (iii) a pharmaceutically acceptable carrier or excipient therefor.”**

39. Segal discloses that the preferred “nasal formulations are nose drops or nasal sprays containing a water buffered aqueous solution as a carrier.” *Id.*, 4:4-

5.

**I. Segal discloses all claim elements as arranged in Claims 1 and 25**

40. Segal's disclosure of "azelastine" (Ex. 1012, 3:19-20) is identified as a suitable "antihistamine," which is listed as one of the components of the "topically applicable nasal compositions" of the "present invention" under the "SUMMARY OF INVENTION." This same "SUMMARY OF INVENTION" lists "topical antiinflammatory agent" as another component of the same nasal compositions of the present invention, a "preferred embodiment" of which Segal says is "fluticasone propionate." Ex. 1012, 2:22-26. Segal also refers to the "compositions of the present invention" as being preferably formulated as a "nasal spray[]" containing a water buffered aqueous solution as a carrier." Ex. 1012, 3:29-4:5. Therefore, Segal teaches to formulate a nasal spray containing azelastine, fluticasone propionate, and water in the same solution.

**J. Segal is enabling prior art**

41. Segal was enabling at least as of June 2002. The '620 patent expressly states that "where only the ingredients of formulations according to the present invention are listed, these formulations are prepared by techniques well known in the art." Ex. 1001, 7:67-8:2. The only ingredients in claims 1 and 25 are azelastine, fluticasone ester, and a carrier—all of which were disclosed by Segal, and therefore the combination of these ingredients could be "prepared by

techniques well known in the art.” Examples of such prior art include Hettche (Ex. 1007), the Astelin® Label (Ex. 1008), Phillipps (Ex. 1009), and the Flonase® Label (Ex. 1010).

**XI. Claims 1, 5-6, 24-26, and 29, were Obvious as of at least June 2002**

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

43. I understand that when considering the obviousness of an invention, one should also consider whether there are any secondary considerations that support the nonobviousness of the invention. I understand that secondary considerations of nonobviousness include failure of others, copying, unexpectedly superior results, perception in the industry, commercial success, and long-felt but unmet need.

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

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

**A. The cited references disclose all of the claim elements**

45. Hettche, Phillipps, and Segal describe pharmaceutical formulations and nasal compositions. *See* Ex. 1007, 2:10-11; Ex. 1009, Abstract; Ex. 1012, 2:10-15. Like Segal (see Section X above), Hettche discloses “azelastine or a physiologically acceptable salt” and Phillipps discloses fluticasone propionate, which is a pharmaceutically acceptable ester of fluticasone. Ex. 1007, Abstract; Ex. 1009, cl.13. All three references disclose the use of a nasal spray. *See* Ex. 1007, 2:12-17; Ex. 1009, 33:12-13; Ex. 1012, 4:4-5.

46. Claims 5, 6, and 26 call for specific amounts of azelastine and fluticasone propionate. Claim 29 specifies that the formulation of claim 26 is a nasal spray. The elements of each of these claims are disclosed or would have

been obvious over the disclosure of Hettche, Phillipps, and Segal.

47. Claim 5 specifies 0.0005% to 2% (weight/weight) of azelastine in the formulation, and claim 6 specifies 0.001% to 1% of azelastine (weight/weight) in the formulation. Hettche discloses azelastine formulations having identical amounts: “0.0005 to 2 [claim 5], preferably 0.001 to 1 [claim 6], in particular 0.003 to 0.5% (weight/weight) of azelastine.” Ex. 1007, 3:26-32. Hettche also discloses that the amounts would be recalculated as necessary for any salt of azelastine. *Id.*, 3:31-34. Finally, Hettche teaches a working example of a nasal spray with 0.1% azelastine hydrochloride, which is identical to the amount in claim 26. *Id.*, 6:7-35. Thus, the azelastine concentrations of claims 5, 6, and 26 are identically disclosed in Hettche.

48. Claims 5 and 6 also state that the pharmaceutically acceptable ester of fluticasone be present at a concentration of 0.0357% to 1.5% (weight/weight). Claim 26 specifies 0.0357% to 1.5% of fluticasone propionate. Phillipps describes pharmaceutical formulations having 0.001 to 5.0% weight or 0.01 to 0.25% proportion of the active androstane compound in the topical compositions, such as fluticasone propionate, including powders for inhalation or insufflation having 0.1% to 0.2% androstane such as fluticasone propionate. Ex. 1009, 33:23-32. Phillipps provides an example that is an aerosol spray containing 0.059% w/w of

active ingredient. *Id.*, Example (C), 34:55-62. As this formulation is presented shortly after the preparation for fluticasone propionate and a general discussion of how to prepare formulations of the invention (*Id.*, 32:34-34:11), it is clear that fluticasone propionate may be used as the active ingredient. Phillipps therefore describes several concentrations of fluticasone within the range disclosed in Claims 5, 6, and 26. In my opinion, it would have been obvious to select the amounts of fluticasone propionate disclosed by Phillipps to provide relief of allergic rhinitis in combination with azelastine, including amounts within Phillipps' preferred ranges that wholly or partially overlap with the claimed ranges.

49. As noted above, each of Hettche, Phillipps and Segal disclose nasal sprays. Therefore, they also disclose the elements of claim 29.

50. Claim 24 defines a pharmaceutical formulation that includes azelastine hydrochloride and fluticasone propionate as a nasal spray "used in the treatment of conditions for which administration of one or more anti-histamine and/or one or more steroid is indicated." As discussed above for claim 1, Hettche, Phillipps, and Segal disclose pharmaceutical nasal sprays. Ex. 1007, 2:12-17; Ex. 1009, 33:12-13; Ex. 1012, 4:4-5. In addition, they all disclose formulations used to treat a condition, such as allergic rhinitis, that either an antihistamine or steroid is used to treat. Ex. 1007, 1:29-52; Ex. 1009, 1:4-5; Ex. 1012, 2:20-26, 3:19-20.

Hettche also discloses the use of azelastine salts such as the hydrochloride (Ex. 1007, 2:3-5), while Phillipps discloses fluticasone propionate. Ex. 1009, cl. 13.

51. Similar to claim 24, claim 25 describes a nasal spray formulation with azelastine or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable ester of fluticasone, and a pharmaceutically acceptable carrier or excipient therefor. As stated above for claim 1, Hettche, Phillipps, and Segal individually or together disclose a nasal spray with azelastine and fluticasone propionate. Also, Hettche, Phillips and Segal all disclose water as a pharmaceutically acceptable carrier for their formulations. Ex. 1007, Example 1; Ex. 1009, 33:12-13; Ex. 1012, 4:4-5.

**B. It was well known that steroids and antihistamines were effective at treating allergic rhinitis together**

52. As of June 2002, intranasal or topical corticosteroids were well known as the most effective treatment available for allergic rhinitis. The ARIA Guidelines, which are prepared by international experts in allergy and immunology, concluded that intranasal glucocorticosteroids should be regarded as highly effective first-line treatment for allergic rhinitis. Ex. 1024, S234. Intranasal corticosteroids treat patients suffering from moderate to severe symptoms and can be effective in treating persistent symptoms as well. *Id.* Clinical studies, such as one performed by Berger in 1999, have also shown that an antihistamine or a nasal

corticosteroid alone could be used as first-line therapy, but “for those patients whose symptoms are not adequately controlled by either treatment often a combination of both an antihistamine with an intranasal corticosteroid is prescribed.” Ex. 1021, 536.

53. Steroids were well known to be effective in treating the LPR. As stated above, allergic rhinitis is a chronic inflammatory allergic disease and the LPR is characterized as the chronic inflammatory-type response. Intranasal corticosteroids were known to be well suited to reverse this process by inhibiting a variety of pro-inflammatory cytokines, which ultimately decrease this specific response. Ex. 1041, 459. However, using topical steroids to treat AR can require one week or longer before the EPR is inhibited. Ex. 1024, S231-S232.

54. Even though topical steroids are considered by most leading experts to be the most effective treatment for AR, they have a slow onset of action. Steroids can oftentimes take days before the patient realizes any improvement in symptom relief. Ex. 1010, 2. Many patients suffering from AR desire treatments that work more quickly to combat AR symptoms. This delayed onset of action causes many patients to either stop treatment or to perceive that they do not work well at controlling the symptoms of AR.

55. Antihistamines, or H<sub>1</sub>-receptor antagonists, were well known to be the

most effective at treating the EPR of allergic rhinitis. *See, e.g.*, Ex. 1035, 341-42.

Notably, topical antihistamines possess the quickest onset of action, which can improve nasal symptoms as quickly as 15 minutes after use. Ex. 1024, S230.

Nasal antihistamines were known to have the quickest onset of action as they act directly at the target organ.

56. Oral antihistamines and nasal antihistamines were available as of June 2002. It was well known to a skilled artisan that intranasal antihistamines presented several advantages over oral antihistamines. As stated above, intranasal antihistamines have faster onsets of action. Ex. 1024, S222. In addition, intranasal antihistamines possess fewer side effects than their oral counterparts because they are applied topically to the nose in smaller total doses. Therefore, a targeted application avoids the larger doses that are required of oral antihistamines. The reduction of systemic side effects clearly makes intranasal antihistamines superior to oral antihistamines. *Id.* Intranasal antihistamines also have been shown to inhibit the release of inflammatory mediators and have an effect on both the late phase and the early phase. Even though intranasal antihistamines are not as effective on LPR as steroids, intranasal antihistamines possess many advantages over oral antihistamines, such as partially relieving nasal congestion. Ex. 1021, 536.

57. In my opinion, a POSA would have known that treating both the EPR and the LPR of AR would provide the most effective management of allergic rhinitis symptoms. The optimal treatment was known to be achieved by managing the symptoms associated with both EPR and LPR. Ex. 1023, S387.

58. Among the drugs that were available to treat AR, only antihistamines and steroids combined adequately treated both the EPR and LPR. As stated earlier, drugs such as decongestants, cromolyn sodium, and anticholinergics were available to treat allergic rhinitis. However, Spector emphasized that many decongestants were not as effective as other treatments because they did not relieve other symptoms of allergic rhinitis besides congestion. Ex. 1023, S386. Decongestants also can cause adverse effects such as hypertension and heart problems. Ex. 1024, S237. Cromolyn sodium, a mast cell stabilizer, is unpopular because it has to be administered for several weeks before optimal relief of symptoms is realized. Ex. 1023, S386. It is also widely known that mast cell stabilizers, though somewhat effective, have to be used many times a day in order to manage symptoms. The frequency at which mast cell stabilizers need to be administered alone can cause problems with compliance among patients suffering from AR. *Id.* Anticholinergics like ipratropium are also not effective in managing symptoms other than rhinorrhea. *Id.*, S386-S387. Spector teaches that the ideal drug would treat the

EPR and LPR, and only conjunctive use of antihistamines and steroids effectively fits that profile. *Id.* at S387. Spector thus lays out what a skilled artisan would have known about the most complete and effective treatment for AR.

**C. Fluticasone propionate was the most potent glucocorticoid for treating the late phase response of allergic rhinitis**

59. Fluticasone propionate was well known as the most potent intranasal steroid on the market as of June 2002. A study done in my own laboratory, which was published in 1999, showed that fluticasone propionate was more potent than mometasone furoate, budesonide, beclomethasone dipropionate, triamcinolone acetonide, and hydrocortisone. Ex. 1017, 623. Other studies have also shown that fluticasone propionate was the most potent topical glucocorticoid available. One such study showed that fluticasone propionate was 1.5 to 3-fold more potent than 17-BMP, mometasone furoate, and budesonide and 10-fold more potent than triamcinolone acetonide and flunisolide. Ex. 1018, Table III.

60. Intranasal delivery of steroids was developed to avoid systemic side effects of steroids when used to treat AR and related conditions. In fact, guidelines for the diagnosis and management of rhinitis by a nationally recognized team of experts<sup>1</sup> state that nasally inhaled corticosteroids “are generally not associated with significant systemic side effects in adults.” Ex. 1019, 506. Phillipps itself

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<sup>1</sup> Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology.

similarly indicates that that the disclosed topically (*i.e.*, nasally) administered androstanes, which include fluticasone propionate, have minimal ability to cause undesired systemic side effects. Ex. 1009, 1:48-55.

61. As explained above, fluticasone propionate was known to be the most potent corticosteroid out of the many available on the market as of June 2002, and intranasal administration was standard to avoid systemic side effects. Based on the foregoing, it is my opinion that a POSA would have had a reason to use fluticasone propionate to treat the LPR of allergic rhinitis. Indeed, fluticasone propionate was the most potent and the most popular intranasal steroid.

**D. Azelastine was the most effective antihistamine on the market**

62. As stated earlier, intranasal antihistamines were known to be better than oral antihistamines, since they were safer and had additional anti-inflammatory effects not shared by oral antihistamines. Most importantly, intranasal antihistamines do not have the systemic side effects that often result from utilizing oral antihistamines.

63. As of June 2002, only azelastine and levocabastine were the only intranasal antihistamines approved by the FDA for intranasal use. For this reason, a POSA would have been drawn to these two products to treat the EPR of allergic rhinitis. As to the choice between these two products, a POSA would have known that azelastine compared favorably to levocabastine. In a clinical study done by

Falser, azelastine was found to be statistically superior to levocabastine. Ex. 1015, 387. Falser showed that azelastine provided significantly better symptom relief as evidence by the reduction in total symptom score and nasal sum scores. *Id.*, 391-392. In fact, global efficacy was judged by physicians as either ‘very good’ or ‘good’ for **90%** of azelastine patients compared to **74%** of the levocabastine group. *Id.*, 387. Similarly, **92%** of azelastine patients and **76%** of levocabastine patients judged the treatment to be either ‘very good’ or ‘good.’ *Id.*

64. Patients found that symptom relief occurred as fast as 15 minutes after taking azelastine. *Id.*, 392. No adverse events were registered and azelastine proved to be better tolerated than levocabastine. *Id.* Notably, none of the patients in the Falser clinical study reported a single case of taste disturbance even though taste is often reported as an adverse event after taking azelastine. *Id.* Falser concluded that the “reduced potential for sedation, combined with the rapid onset of action and minimal overall dosage of the nasal spray may be considered an advantage over other antihistamines, particularly first-generation compounds...” *Id.*, 393.

65. Hettche discloses that azelastine nasal spray has additional advantages, including the avoidance of tiredness that arises in other applications, elimination or relief of reddening and irritation of the *eye* so that the additional use

of eye drops is frequently unnecessary, and either no or barely perceptible bitter taste, even when sprayed azelastine ran down into the pharynx. Ex. 1007, 1:44-48, 53-55; 1:63-2:2. A POSA would understand that the tiredness referred to by Hettche is a common occurrence with some antihistamines and is a systemic effect resulting from oral administration of antihistamines. *See, e.g.*, Ex. 1024, S222, S229-230, S253. Consistent with Hettche, the Dykewicz Guidelines indicate that less than 11% of patients report such sedation, and only about 20% report a bitter taste after using azelastine. Ex. 1019, 505. Just as with Hettche, Berger also disclosed that azelastine nasal spray managed a "complex of symptoms associated with seasonal allergic rhinitis, including...itchy and watery eyes." Ex. 1021, 536. Moreover, another study performed by Ratner in 1994 found that intranasally administered azelastine improved eye symptoms possibly through systemic action. Ex. 1050, 823-824.

66. Kusters demonstrated that azelastine inhibited leukotriene mediators by 86% compared to 20% for levocabastine. Ex. 1016, 100. Kusters showed that azelastine was unique in being able to reduce nasal congestion in patients suffering from AR. *Id.*, 98 A POSA would know that steroids, not antihistamines, are effective at relieving nasal congestion. Azelastine stands apart from other antihistamines in being able to suppress the symptoms of sneezing, itching, watery

secretion, as well as congestion. *Id.* Kusters also demonstrated that histamine H<sub>1</sub>-receptor antagonists combined with topical steroids are the “treatment of choice” in allergic rhinitis. *Id.* Notably, a POSA would have been motivated to not only use azelastine instead of other antihistamines, but also to combine azelastine with topical steroids to provide the ideal treatment for AR.

67. Azelastine stands apart from other topical antihistamines due to its ability to affect inflammatory cells and mediators in addition to histamine. Ex. 1021, 539. Therefore, azelastine nasal spray’s treatment of both the histamine-related EPR symptoms as well as some of the LPR effects of seasonal allergic rhinitis made it an obvious choice to combine with intranasal steroids to improve AR symptom relief.

**E. Oral antihistamines were combined with intranasal steroids**

68. A POSA would have recognized that oral antihistamines and intranasal steroids were commonly prescribed in combination. Numerous clinical studies have suggested such a combination.

69. For example, a 1995 study tested loratadine and beclomethasone, and found that combining the two improved the treatment of patients with allergic rhinitis. Ex. 1035, 343-46. A person of ordinary skill would have recognized that combining antihistamines and intranasal steroids provided additional relief beyond each of the monotherapies.

70. Another study published in 1996 found that combining an antihistamine and steroid resulted in “additive symptom suppression almost across the board.” Ex. 1038, 198. Specifically, Brooks found that with itching and sneezing, which showed the greatest increment of benefit from combination treatment, the combination treatment showed that both drugs contributed to symptom control. *Id.*, 198-199. Combining an antihistamine and a corticosteroid provided relief beyond the benefits of each individual drug. The additive effects alone would have motivated a POSA to consider combining antihistamines and steroids to treat allergic rhinitis. Moreover, Brooks found that “patients preferred combined treatment by a substantial margin,” which suggested that patients found that combination therapy provided “quicker and overall better control of sneezing and itching.” *Id.*, 199. Accordingly, a POSA would have known that antihistamines and steroids have complementary mechanisms of action that allow for quicker relief and better control as a result of the additive effects of both drugs.

**F. Administration of nasal antihistamine and nasal steroid to treat allergic rhinitis was recommended**

71. Leading experts in the field recommended the co-administration of nasal antihistamines and nasal steroids to treat the symptoms of allergic rhinitis. As stated earlier, the ARIA guidelines are generated by leading experts from around the world and have been very useful for practicing physicians in the United

States. The ARIA guidelines, published in 2001, recommended a “stepwise approach” to treating moderate to severe allergic rhinitis beginning with an intranasal glucocorticosteroid as a “first line treatment.” Ex. 1024, S251.

However, if the steroid does not effectively manage the disease, the ARIA guidelines suggest adding an antihistamine to improve symptom relief. *Id.*

Accordingly, a POSA would have been motivated to co-administer a nasal antihistamine in combination with a nasal steroid, as suggested by the ARIA guidelines.

72. Dykewicz also would have led a POSA to combine nasal antihistamines and steroids to treat allergic rhinitis. Dykewicz contains complete guidelines for diagnosis and management of rhinitis developed by the Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology, representing the American Academy of Allergy, Asthma and Immunology, the American College of Allergy, Asthma and Immunology and the Joint Council on Allergy, Asthma and Immunology. Ex. 1019, 478. Dykewicz (citing Juniper, Ex. 1031) reported that “at least 50% of patients needed to take both nasal corticosteroids and oral antihistamines to adequately control symptoms of seasonal allergic rhinitis.” *Id.*, 506. Moreover, Dykewicz also would have motivated a POSA to co-formulate an antihistamine and a steroid because it found that “compliance is enhanced

when...fewer number of daily doses is required.” *Id.*, 512. The guidelines also instructed practitioners that intranasal antihistamines, like Astelin® (*i.e.*, intranasal azelastine), “are appropriate for use as a first line treatment for the symptoms of allergic rhinitis, or as part of combination therapy with nasal corticosteroids.” *Id.*, 505. Both the ARIA and Dykewicz guidelines recommended combination therapy of antihistamines and steroids, and a POSA would have been motivated to follow such a recommendation.

73. Berger taught that “azelastine nasal spray can be used either in place of oral antihistamines or in combination with intranasal corticosteroids.” Ex. 1021, 540. Since azelastine affects both the EPR and the LPR of allergic rhinitis, a POSA would be motivated to not replace azelastine with less effective oral antihistamines, but to take advantage of the additive effects of combining azelastine with a potent corticosteroid, like fluticasone, to treat AR. Berger found that “an antihistamine alone or a nasal corticosteroid alone can be used as first-line therapy for the treatment of seasonal allergic rhinitis, and for those patients whose symptoms are not adequately controlled by either treatment often a combination of both an antihistamine with an intranasal corticosteroid is prescribed.” Ex. 1021, 536.

74. Cauwenberge recommended the use of both antihistamines and

steroids to treat allergic rhinitis symptoms. Cauwenberge is a consensus statement on the treatment of allergic rhinitis by the European Academy of Allergology and Clinical Immunology. Ex. 1022. Cauwenberge taught that if inadequate control was achieved with nasal corticosteroids as a first-line therapy, then “nasal steroids and antihistamines (oral and/or topical [*i.e.*, nasal]) is recommended.” *Id.*, 125.

75. Regarding nasal corticosteroids, Cauwenberge noted that “fluticasone propionate is available for children of 4 years and over,” while other topical corticosteroids could only be used “in children over the age of 5 years.” *Id.*, 124. Furthermore, in a list of local treatment options, only fluticasone propionate could be used in children as young as 3 years of age. *Id.*

76. Regarding antihistamines, Cauwenberge noted that topical treatment with “azelastine and levocabastine” had a “similar efficacy profile to oral antihistamines with the advantage of a significantly faster onset of action on both nasal and ocular symptoms.” *Id.*, 119. Cauwenberge discloses that azelastine and levocabastine topically administered at recommended doses do not show any significant sedative effect. *Id.*, 120.

77. Based on the foregoing, a POSA would have been motivated to combine azelastine and fluticasone into a single nasal spray product to treat seasonal allergic rhinitis.

**G. A co-formulation of fluticasone and azelastine has been disclosed**

78. European Patent Application No. 0780127A1 (“Cramer”) disclosed a pharmaceutical composition for nasal administration that was comprised of a glucocorticoid and a leukotriene inhibiting antihistamine. Ex. 1011. Cramer was filed by Procter & Gamble Co. and was published on June 25, 1997.

79. Cramer discloses that “the present invention relates to pharmaceutical compositions for nasal administration comprising: a) a safe and effective amount of glucocorticoid selected from the group consisting of beclomethasone, flunisolide, triamcinolone, **fluticasone**, mometasone, budesonide, pharmaceutical acceptable salts thereof and mixtures thereof; b) a safe and effective amount of a leukotriene inhibiting antihistamine selected from the group consisting of cetirizine, loratadine, **azelastine**, pharmaceutical acceptable salts thereof, optically active racemates thereof and mixtures thereof; and c) an intranasal carrier.” *Id.*, 2:34-45. Cramer states that “the present inventor has found that by combining a nasal corticosteroid with a leukotriene inhibiting antihistamine, improved intranasal compositions result, providing improved relief of symptoms generally associated with either seasonal or perennial allergic rhinoconjunctivitis.” *Id.*, 2:25-27. Among the above-listed glucocorticoids, a POSA would have been drawn to fluticasone’s potency and would have considered fluticasone as the best choice among those glucocorticoids. Likewise, among the above-listed antihistamines, a

POSA would have chosen azelastine because it was the only antihistamine that was FDA-approved and was the most potent antihistamine on the market.

80. As described above in Section X, Segal also discloses a co-formulated nasal spray containing both azelastine and fluticasone. Segal's express motivation to co-formulate a nasal spray containing multiple therapeutic ingredients was to avoid the disadvantages of administering multiple agents separately. Ex. 1012, 1:12-13 ("The use of multiple topical nasal preparations to administer multiple therapeutic agents suffers from significant disadvantages"), 2:2-3 ("Patient compliance may be compromised by the inconvenience of applying multiple spray products or nose drops"), 1:18-20 ("Multiple topical nasal preparations cannot be effectively administered simultaneously" because "the delivery volume per actuation is limited to the volume that will be retained in the nostril without premature drainage.") If the liquid from multiple nasal sprays drains from the nostril prematurely, there may not be sufficient contact time with the nasal membrane to assure adequate dosing of the nasal therapeutic. *Id.*, 15-17. Segal further explains that "[t]he use of an additional therapeutic agent," such as an "antihistamine," "in combination with an antiinflammatory agent provides additive and synergistic effects in the treatment of nasal and sinus conditions. *Id.*, 3:9-12, 3:19-20.

**H. Combining fluticasone and azelastine into a single product would have improved patient compliance**

81. A combination fluticasone and azelastine product would have been expected to improve patient compliance because the additive effects of both drugs would have provided patients with faster and more complete relief. In addition, combining two drugs into one nasal spray would have made it more convenient for patients to administer the treatment each time.

82. Segal expressly taught: “Patient compliance may be compromised by the inconvenience of applying multiple spray products or nose drops.” Ex. 1012, 2:2-3; *id.*, 3:4-9 (touting the benefits of “the convenient administration of an antiinflammatory agent and at least one additional therapeutic agent,” including an “antihistamine,” “in a single topical nasal composition”). The guidelines for diagnosis and management of rhinitis state that “[c]ompliance is enhanced when: (1) a fewer number of daily doses is required ....” Ex. 1019, 512. Similarly, Stoloff disclosed in February 2002 that combining fluticasone propionate with a faster acting bronchodilator in a single product would “simplify and increase patient adherence to an asthma treatment plan.” Ex. 1020, 224.

**I. Fluticasone was previously co-formulated with other drugs**

83. A person of ordinary skill in the art would have recognized that fluticasone had been combined with  $\beta_2$ -agonists to successfully treat asthma. Ex.

1020, 212. Stoloff reported that by combining fluticasone with a faster acting bronchodilator, the “complementary mechanisms of action” of these two drugs achieved “a superior level of asthma control.” Ex. 1020, 223.

84. The success of the asthma inhalation device, ADVAIR®, demonstrates that fluticasone has been combined with other drugs to improve compliance. It was well known that despite being one of the best drugs to treat asthma, fluticasone had a slow onset of action. As stated above, this problem caused patient compliance issues. ADVAIR® was known to have been successful in remedying compliance issues by combining fluticasone with a faster acting bronchodilator. Ex. 1030; Ex. 1025, 1213. It is my expert opinion that a person of ordinary skill in the art would have known that a combination product with fluticasone and a faster acting antihistamine would also simplify and increase patient adherence to an allergic rhinitis treatment plan. Since azelastine has been shown to possess an onset of action as fast as 15 minutes, a person of ordinary skill in the art would have taken advantage of the complementary mechanisms of action of fluticasone and azelastine to better treat symptoms of allergic rhinitis. By combining these two drugs, a POSA could expect to have a preparation that works within 15 minutes due to the fast action of the antihistamine and yet also have the superior antiinflammatory profile of the intranasal steroid.

**J. Clinical studies disclosed benefits to combining antihistamines and corticosteroids**

85. As discussed above, many clinical studies have been performed regarding the efficacy of combining oral antihistamines and steroids to treat allergic rhinitis. Those studies have shown that there are advantages to combining the two drugs.

86. One such example is a study conducted in 1994 utilizing budesonide and terfenadine in the treatment of hay fever. Ex. 1036. This study did not test the efficacy of azelastine or fluticasone, but it did find a statistically significant improvement in sneezing with the combined treatment when compared to the individual monotherapies. *Id.*, 499. Because sneezing is one of the most common symptoms of allergic rhinitis, this study would motivate a POSA to combine antihistamines and steroids to more effectively treat AR.

87. Drouin also demonstrated that there was statistically significant improvement in total symptom scores on the seventh day of the study. Ex. 1035, 344 Table 2. The study also showed that there was a significant improvement in the patients' total nasal symptom scores on day 3, which demonstrated how quickly the combined treatment was able to manage the nasal symptoms of allergic rhinitis. *Id.* Drouin 1995 also demonstrated that there was significant improvement in the hallmark symptoms of sneezing and itching when compared to

the steroid monotherapy. *Id.* This study concluded that the conjunctive use of the oral antihistamine loratadine and the intranasal steroid beclomethasone was more effective than using the steroid alone. A person of ordinary skill in the art would find these results to be indicative of the efficacy of using combination therapy to treat AR.

88. As stated above, Brooks found that combining an antihistamine and steroid resulted in “additive symptom suppression almost across the board.” Ex. 1038, 198. Brooks demonstrated that with itching and sneezing, which showed the greatest increment of benefit from combination treatment, the combination treatment showed that both drugs contributed to symptom control. *Id.*, 198-199. This means that combining an antihistamine and a corticosteroid provided relief beyond the benefits of each individual drug. Moreover, Brooks found that “patients preferred combined treatment by a substantial margin,” which suggested that patients found that combination therapy provided “quicker and overall better control of sneezing and itching.” *Id.*, 199. Accordingly, a POSA would have known that antihistamines and steroids have complementary mechanisms of action that allow for quicker relief due to the antihistamine and better control as a result of the additive effects of both drugs. A POSA would know that there are noticeable benefits to combining antihistamines and corticosteroids.

89. Juniper studied the health-related quality of life (“HRQL”) “by initiating treatment of seasonal (ragweed) rhinoconjunctivitis with a nasal steroid (fluticasone) backed up by a nonsedating antihistamine (terfenadine) or whether it is better to start with the antihistamine and add the nasal steroid when necessary.” Ex. 1031, 1123. Notably, Juniper concluded that regardless “of the treatment [fluticasone propionate or terfenadine], at least 50% of patients will need to take both types of medication in combination to control symptoms adequately.” Ex. 1031, 1123. By recommending the use of “2 different types of medication in combination to achieve optimal HRQL,” Juniper would have motivated a POSA to combine antihistamines and steroids to improve the quality of life of AR patients. Ex. 1031, 1130.

90. Ratner compared the efficacy of fluticasone propionate and loratadine alone and in combination to treat seasonal allergic rhinitis. Ex. 1034, 121-122. Ratner demonstrated that the combination of fluticasone with loratadine showed statistically significant improvement for patient-rated total nasal symptom scores over the fluticasone propionate monotherapy. *Id.*

91. These studies show that there are distinct advantages to using combination therapy to treat allergic rhinitis. A POSA would be motivated to combine the most efficacious and potent steroid and antihistamine—fluticasone

and azelastine—to effectively treat allergic rhinitis.

## **XII. Absence of Secondary Considerations of Nonobviousness**

92. I understand that in considering the obviousness of an invention, one must also consider whether there are any secondary considerations that support the nonobviousness of the invention. I understand that secondary considerations of nonobviousness include failure of others, copying, unexpectedly superior results, perception in the industry, commercial success, and long-felt but unmet need.

### **A. No teaching away**

93. I understand that the prior art must be viewed “as a whole” when considering whether the prior art “taught away” from an invention. I also understand that a reference does not teach away if it merely expresses a general preference for an alternative invention but does not criticize, discredit, or otherwise discourage investigation into the invention claimed.

94. Here, I do not believe that the prior art taught away from combining azelastine and fluticasone into a nasal spray. To the contrary, the prior art as a whole taught *toward* this combination, and the combination of these two classes of drugs, intranasal steroids and antihistamines, was the norm rather than the exception.

95. As discussed above, Simpson, Drouin, Brooks, Juniper 1997, and Ratner 1998 all showed that there were distinct advantages to combining an

antihistamine and a steroid in the treatment of allergic rhinitis. While there are some studies that show combining an intranasal steroid and oral antihistamine to treat allergic rhinitis has no distinct advantage, the above studies support the benefits of such combinations. Studies not illustrating an advantage include a study performed by Juniper in 1989 which showed that the combination of intranasal steroid beclomethasone and oral antihistamine astemizole “provided no better control” than the intranasal steroid alone. Ex. 1039, Abstract; 629 (“Subjects were instructed to take the [astemizole] tablet in the morning...”). Another example is a study performed by Benincasa showed that there was “no significant difference in efficacy” between using a combination of oral cetirizine and nasal fluticasone propionate and using the nasal fluticasone propionate alone. Ex. 1040, Abstract. However, these early studies did not consider intranasal antihistamines. In contrast, many more studies have illustrated the benefits of combining a steroid and antihistamine. Ex. 1036, 499 (combination showed “statistically significant” improvement over monotherapies for “sneezing”); Ex. 1035, 348 (combination “improves the treatment of patients”); Ex. 1038, 199 (“study confirms the overall effectiveness” of steroid/oral AH combination); Ex. 1031, Abstract (“at least 50% of patients will need to take both types of medication in combination to control symptoms adequately”); Ex. 1034, 123 (“combination

was considered more effective according to some patient ratings”). Even for these oral antihistamine/intranasal steroid combinations, the totality of the art falls short of criticizing, discrediting, or discouraging the combination of a steroid and antihistamine in general.

96. In addition, these studies do not reflect on a POSA’s expectation in combining an intranasal antihistamine and an intranasal steroid. A POSA would still have been motivated to combine two intranasal drugs for multiple reasons, such as to improve patient compliance. Ex. 1012, 2:2-3; Ex. 1019, 512; Ex. 1021, 540 (instructing using azelastine nasal spray in combination with intranasal corticosteroids). Moreover, intranasally administered antihistamines (such as azelastine) possess advantages over oral antihistamines, such as lower required dosages and a reduction or elimination of systemic side effects associated with many oral antihistamines. *See, e.g.*, Ex. 1007, 1:53-55; 2:23-31. In particular, intranasal antihistamines were understood to provide a significantly faster onset of action than oral antihistamines. *See, e.g.*, Ex. 1022, 118 Table 2. The intranasal combination of azelastine and fluticasone propionate was particularly emphasized in the art. For example, Cauwenberge advises using nasal corticosteroids in combination with nasal antihistamines (Ex. 1022, 125) and highlights intranasal fluticasone propionate and intranasal azelastine as suitable for use (*id.*, 124). Segal

itself discloses the intranasal formulation containing both fluticasone propionate and azelastine. Ex. 1012, 2:23-26, 3:19-20. Therefore, even if the efficacy of a specific oral antihistamine/intranasal steroid combination was not shown to be superior in a specific study, such a result would not counter a POSA's understanding to combine an intranasal antihistamine and an intranasal steroid nor would such a result detract from the expected advantages of the intranasal combination.

**B. There was no long-felt but unmet need satisfied by the '620 Patent**

97. In obtaining the '620 Patent, the Patent Owner submitted a declaration by Dr. Sujeet Rajan that stated the claimed combination satisfied a long-felt unmet need for patients and healthcare practitioners in managing the symptoms of allergic rhinitis and non-allergic vasomotor rhinitis. Ex. 1002, 406, 407(¶ 7). However, such a need was met prior to 2002 because (1) the combined use of both azelastine and an ester of fluticasone conjunctively was well known and practiced before 2002 to manage the symptoms of allergic rhinitis and non-allergic vasomotor rhinitis and (2) topical nasal compositions including a combination of azelastine and an ester of fluticasone were previously disclosed in the art. The Rajan declaration does not acknowledge this knowledge and use – in fact, Dr. Rajan focuses on oral antihistamines rather than addressing well-known nasal antihistamine sprays. *Id.*, 408 ¶ 11. As I explain below, only by ignoring the

knowledge and art can Dr. Rajan propose any “long-felt but unmet” need.

98. Leading experts and clinical practitioners in the field recommended the co-administration of nasal antihistamines and nasal steroids to treat the symptoms of rhinitis prior to 2002. As previously noted, the ARIA guidelines, recommended using an intranasal glucocorticosteroid as a “first line treatment.” Ex. 1024, S251. However, if the steroid alone does not effectively manage the disease, the ARIA guidelines instruct adding an antihistamine to improve symptom relief. *Id.*

99. Prescribing and using both intranasally delivered azelastine and nasal corticosteroids was common practice prior to 2002, as shown by Dykewicz and Berger. As noted above, Dykewicz contains complete guidelines for diagnosis and management of rhinitis developed by the Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology. Ex. 1019, 478. The guidelines instruct practitioners that intranasal antihistamines, like Astelin®, “are appropriate for use as first line treatment for the symptoms of allergic rhinitis, or as part of combination therapy with nasal corticosteroids.” *Id.*, 505 (emphasis added). Similarly, Berger advises that “azelastine nasal spray can be used either in place of oral antihistamines or in combination with intranasal corticosteroids.” Ex. 1021, 540 (emphasis added). Berger further instructed that the combination of azelastine

nasal spray and an intranasal corticosteroid is often prescribed for patients whose symptoms are not adequately controlled by either treatment alone. *Id.*, 536.

100. The advantages of using a combination of nasally administered azelastine and nasally administered fluticasone propionate is highlighted by Cauwenberge (Ex. 1022). Cauwenberge, introduced above (§ 74), states that if inadequate control is achieved with nasal corticosteroids as a first-line therapy, then “nasal steroids and antihistamines (oral and/or topical [*i.e.*, nasal]) is recommended.” Ex. 1022, 125. Cauwenberge specifically notes that fluticasone propionate may be used in children as young as 3 years of age while other topical corticosteroids may only be used in children over the age of 5 years. *Id.*, 124. Cauwenberge also points out that topical treatment with azelastine provided a similar efficacy profile to oral antihistamines with the advantages of “a significantly faster onset of action on both nasal and ocular symptoms” (*id.*, 119) but without any significant sedative effect (*id.*, 120).

101. As shown above, combining nasal corticosteroids and nasal antihistamines was a common practice, where the advantages of nasally administered azelastine and nasally administered fluticasone propionate were particularly emphasized. Against this backdrop of concurrent treatment regimens, it is unsurprising that convenient nasal spray formulations including both

azelastine and fluticasone were known and published prior to 2002.

102. As noted above (§§78-79) Cramer discloses pharmaceutical compositions for nasal administration that include a glucocorticoid such as fluticasone and a leukotriene inhibiting antihistamine such as azelastine. While Cramer disclosed several such combination formulations, a POSA would have been drawn to fluticasone's potency and would have considered fluticasone as the best choice among those glucocorticoids. Likewise, a POSA would have chosen azelastine because it was the only intranasal antihistamine disclosed by Cramer that was FDA-approved and also was the most potent intranasal antihistamine on the market.

103. Segal (Ex. 1012; published in 1998) similarly describes a co-formulated nasal spray containing both azelastine and fluticasone in the treatment of nasal and sinus conditions. Segal describes topically applicable nasal compositions that include "a therapeutically effective amount of a topical antiinflammatory agent and a therapeutically effective amount of at least one of a vasoconstrictor, a neuramidinase [sic] inhibitor, an anticholinergic agent, a leukotriene inhibitor, an antihistamine, an antiallergic agent, an anesthetic, and a mucolytic agent." Ex. 1012, 2:10-15. Segal identifies fluticasone propionate as a preferred anti-inflammatory agent (*id.*, 2:22-25) and azelastine as a preferred

antihistamine (*id.*, 3:19-20). Segal further highlights that such co-formulation allows for more convenient use by patients over using two or more products independently. *Id.*, 2:2-3.

104. The art and knowledge of the time clearly refute Dr. Rajan's assertion of a long-felt but unmet need. Dr. Rajan strangely excludes any discussion of nasal antihistamines, and instead solely discusses combining oral antihistamines with nasal corticosteroids and the unfavorable side effects due to the systemic nature of oral antihistamines. Ex. 1002, 408-409 (¶¶11-13). In contrast to Dr. Rajan's discussion, the art and practicing guidelines of the time specifically advised using nasal antihistamines in combination with nasal corticosteroids due to nasal antihistamines exhibiting significantly faster onset of action on nasal symptoms but without any significant sedative effect or the systemic effects of oral antihistamines. Ex. 1007, 1:53-55; 2:23-31; Ex. 1022, 120, 124. Moreover, both Cramer and Segal provide nasal co-formulations of fluticasone and azelastine, where Segal specifically highlights that such co-formulation allows for more convenient use by patients. Segal, 2:2-3; *compare with* Ex. 1002, 408-409(¶¶ 13, 15). Thus, the "long-felt but unmet need" asserted by Dr. Rajan was met prior to, and independently of, the '620 Patent.

**C. No evidence of unexpected results compared to the closest prior art**

105. I understand that “unexpectedly superior results” can be evidence of nonobviousness if the patent owner shows that the results are greater than those that would have been expected from the closest prior art and that the results have a significant and practical advantage. It is also my understanding that unexpectedly superior results must be commensurate in scope with the claims.

106. No unexpected advantages were shown by the Patent Owner for the ’620 Patent’s claimed formulations. I understand that the Patent Owner submitted a declaration by Dr. Joachim Maus that purported to establish surprising and unexpected advantages from the co-formulation of azelastine hydrochloride and fluticasone propionate. Ex. 1002, 306-312. However, Dr. Maus’ conclusions are flawed because he does not compare the co-formulation against concurrent use of fluticasone propionate (*e.g.*, Flonase®) and azelastine hydrochloride (*e.g.*, Astelin®) that was present in the art, nor does Dr. Maus address that the combination of fluticasone and azelastine was previously known via Cramer and Segal (where Segal specifically recites using fluticasone propionate).

107. In his declaration, Dr. Maus compares fluticasone propionate *monotherapy* and azelastine hydrochloride *monotherapy* to the co-formulation of fluticasone propionate and azelastine hydrochloride (referred to as the

“combination therapy”). *Id.*, 307-308(¶ 8). Dr. Maus evaluated the total nasal symptom score (“TNSS”) for each and reported:

A 50% response was achieved by 49.1 % of the combination therapy patients, versus 37.4% of the azelastine hydrochloride monotherapy patients, 38.2% of the fluticasone propionate monotherapy patients, and 28.3% of the placebo patients.

*Id.*, 308(¶ 10). Dr. Maus further stated that a response was achieved statistically and significantly earlier with the combination therapy than with either monotherapy alone. *Id.*, 308(¶ 11). Dr. Maus also reported data obtained from the Rhinoconjunctivitis Quality of Life Questionnaire (“RQLQ”; *id.*, 309(¶¶12-14)) where the combination reduced the score of the “Eye Symptoms” domain of RQLQ by a greater margin than either monotherapy alone (*id.*, 310 (¶ 16)). Similar results were seen for reduction of individual ocular symptoms. *Id.*, 309-310 (¶ 15). Dr. Maus then asserts that a number of studies on combining nasal steroids with oral antihistamines provided minimum to no clinical benefit, including quoting a sentence of Salib *et al.* *Drug Safety* 26:863-893 (2003), to assert the advantages of the combination would have been unexpected. *Id.*, 310-311 (¶¶ 18-23).

108. Dr. Maus’ declaration relies on the premise that a nasal spray containing both fluticasone propionate and azelastine hydrochloride was unknown

prior to 2002. As discussed previously, this is false – both Cramer and Segal disclose such combination nasal sprays. Further, as discussed previously, Segal discloses each and every component of claims 1 and 25. As stated in more detail above, Segal discloses “azelastine” and “fluticasone propionate” in a “nasal spray” for the treatment of “allergic rhinitis.” Ex. 1012, 2:22-25, 3:20, 4:4-5.

Accordingly, unexpected results should be examined in comparison to the nasal compositions disclosed by Segal.

109. Furthermore, Dr. Maus ignores that it was common clinical practice to prescribe both an intranasal antihistamine and an intranasal corticosteroid, where fluticasone and azelastine were the preferred choices for such concurrent therapy. *Supra* ¶¶52-67, 102-104. Even if Dr. Maus could avoid the disclosed combination nasal sprays of Cramer and Segal, Dr. Maus incorrectly implies that the appropriate comparison is only with a monotherapy of fluticasone propionate or azelastine hydrochloride. However, because concurrent therapy was commonly practiced in the art, in order to show any unexpected or significantly advantageous results of the co-formulation of these two drugs over actual practice, a POSA would require comparison of concurrent intranasal therapy with fluticasone propionate and azelastine hydrochloride against the combination intranasal therapy.

110. As shown by Ratner 2008 (Ex. 1045), had Dr. Maus tested the correct comparison it would be clear there were no significant differences. Ratner studied the efficacy of using Flonase® and Astelin® independently versus using the nasal sprays concurrently. Ex. 1045, 75-76. In addition to other data, Ratner reports the TNSS and RQLQ for each course of therapy. *Id.* Ratner reports that after 2 weeks, concurrent use of Flonase® and Astelin® provided greater than 40% relative improvement in TNSS scores as compared with either agent alone. *Id.*, 77. Further, Figure 2 of Ratner (along with its associated text) illustrates that a response was achieved statistically and significantly earlier with the combination than with either agent alone. *Id.*, 78. Ratner also reports that the improvements in RQLQ overall scores was greater for the combination (*id.*), and Table 3 shows that improvement in the “Eye Symptoms” domain for the combination was also greater than monotherapy with either Flonase® and Astelin® (*id.*, 79).

111. Ratner 2008 shows that the level of improvement of the combination over the monotherapies (38% improvement) is roughly the same when concurrently (but separately) using Flonase® and Astelin® (40% improvement). *Id.*, 77. In fact, Ratner reports nearly identical benefits for concurrent therapy as Dr. Maus reported for the co-formulation of azelastine and fluticasone propionate claimed by the '620 Patent. Based on this more appropriate comparison, it is clear

the combination of intranasal fluticasone propionate and intranasal azelastine hydrochloride in the '620 is not superior to the concurrent use of intranasal fluticasone propionate and intranasal azelastine hydrochloride.

112. Moreover, any improvement over the individual monotherapies would have been expected by a POSA based on the complementary mechanisms of action of fluticasone propionate and azelastine hydrochloride. Ex. 1011, 2:25-27; Ex. 1012, 3:9-12; Ex. 1023, S386-S387. Dr. Maus' assertion of an unexpected improvement relies on references discussing the concurrent use of oral antihistamines and intranasal corticosteroids, not the concurrent use of intranasal antihistamines and intranasal corticosteroids. Ex. 1002, 310-311 (¶¶ 19-21). Specifically, a POSA would understand the Dr. Maus' quoted sentence of the Salib review article merely observes that the author is unaware of any studies providing evaluation of the concurrent use of intranasal antihistamines and intranasal corticosteroids, not that there were such studies and no advantages were shown. Ex. 1002, 311 (¶ 22); 375; 398. As discussed previously, the art shows that a POSA understood it was common practice in the art to prescribe both an intranasal antihistamine and an intranasal corticosteroid in patients where a monotherapy failed to adequately control symptoms, and the art further shows that fluticasone and azelastine were the preferred choices for such concurrent therapy. *Supra* ¶¶

98-103, and Sections XI(B)-(D), (F)-(H).

**D. A POSA would appreciate the teachings of Cramer**

113. Cramer's Example III provides a composition for intranasal administration that includes azelastine hydrochloride (a pharmaceutically acceptable salt of the antihistamine azelastine) and the corticosteroid triamcinolone acetonide. Ex. 1011, 6:26-51. I understand that during the prosecution of the '620 patent, the Patent Owner submitted a declaration by inventor Ms. Geena Malhotra, alleging that Example III of Cramer was "inoperable" and "unacceptable" (Ex. 1002, 284-287 (¶¶ 6, 9)) and that no appropriate comparison could be made to the '620 claims (*id.*, 287 (¶ 10)). I understand from counsel that the '620 patent was issued on the basis of secondary considerations that did not involve the testing performed by Ms. Malhotra. *See id.*, 143-146.

114. In any event, Ms. Malhotra's analysis is flawed because Cramer's Example III would be expected to be operable to manage the symptoms of allergic rhinitis and non-allergic vasomotor rhinitis based on the understanding of each component. I understand from counsel that additional flaws in Ms. Malhotra's analysis are described by another expert retained by Argentum.

115. Cramer's Example III includes azelastine hydrochloride and triamcinolone acetonide. Azelastine was FDA-approved as a nasal spray and was the most potent antihistamine on the market (*supra* Section XI(D)), and Nasacort

AQ® Nasal Spray, first marketed in 1996, included triamcinolone acetonide (Ex. 1047, 21). Because each of these active ingredients was known to manage symptoms of allergic rhinitis and non-allergic vasomotor rhinitis, a POSA would readily expect the combination of Cramer's Example III also be active and therefore operable.

116. Ms. Malhotra ignores this pharmacologically recognized activity. Instead, Ms. Malhotra focuses on physical characteristics that, in her opinion, make Cramer's Example III desirable as a nasal spray. Ex. 1002, 286-287 (¶9). Yet Cramer does not describe Example III as a nasal spray but as an intranasal administration composition. Cramer, 6:27-28, 43-44. Cramer explicitly states that such compositions may be in a variety of nasal dosage forms that are not nasal sprays, such as drops, suspensions, ointments, and gels. *Id.*, 3:43-45. Ms. Malhotra does not investigate or even discuss any of these dosage forms when deeming Cramer's Example III "inoperable." See 1002, 284-287. It is apparent from Ms. Malhotra's discussion that her opinion does not reflect on whether the composition will manage symptoms, but rather whether it conforms to her definition of a "preferable" nasal spray composition. A POSA's understanding of the operability of Cramer's Example III in managing symptoms would not be so restricted. Thus, Ms. Malhotra's conclusion that Cramer's Example III is

Patent No. 8,168,620

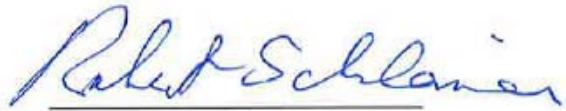
Declaration in Support of *Inter Partes* Review

“inoperable” conflicts with the understanding of a POSA.

### **XIII. Conclusion**

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

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



Robert P. Schleimer, Ph.D.

Dated: February 2, 2017