UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ARGENTUM PHARMACEUTICALS LLC
Petitioner

v.

CIPLA LTD.
Patent Owner

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

Inter Partes Review No. IPR2017-00807

PETITION FOR *INTER PARTES* REVIEW
UNDER 35 U.S.C. §§ 311-319 AND 37 C.F.R. § 42.100 *ET SEQ.*

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Page(s)

Cases

Statutes

Other Authorities

TABLE OF EXHIBITS

Ex #	Exhibit
1001	U.S. Patent No. 8,168,620 ("'620 patent")
1002	Prosecution History of U.S. Patent No. 8,168,620
1003	Declaration of Dr. Robert Schleimer
1004	Declaration of Dr. Maureen Donovan
1005	*Meda Pharms. Inc. v. Apotex Inc.*, 14-cv-1453 (D. Del. May 12, 2016) (Claim Construction Memorandum and Order)
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, pp.3147-3148 (54th 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")
1013	British Pharmaceutical Codex (1973)
1014	U.S. Patent Publication No. 20040136918 ("Garrett")
1015	Falser, N., *et al.*, "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., *et al*., "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., et al., 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., et al., "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., et al., "Combination Therapy with Inhaled Long-Acting ß2-Agonists and Inhaled Corticosteroids: A Paradigm Shift in Asthma Management," PHARMACOTHERAPY, Vol. 22, No. 2, 212-226 (Feb. 2002)
1021	Berger, W. E. et al., "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)
1026	
1027	Ansel, et al., Pharmaceutical Dosage Forms and Drug Delivery Systems, ch. 7 (6th ed. 1995)
1028	
1029	
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.

1032	
1033	Wade & Weller, HANDBOOK OF PHARMACEUTICAL EXCIPIENTS (1994)
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)
1037	
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, astemizone, 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, pp.638-660 (1998)
1043	
1044	

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)
1046	IMITREX Prescribing Information (2013)
1047	NASACORT AQ Prescribing Information (2013)
1048	Rabago, David, et al., "Efficacy of daily hypertonic saline nasal irrigation among patients with sinusitis: A randomized controlled trial," The Journal of Family Practice, Vol. 51, No. 12, 1049-1055 (2002)
1049	Budavari, S., et al. (Ed), "Edetate Disodium," The Merck Index, Eleventh Edition, 550 (1989)
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)
1051	Curriculum Vitae of Dr. Robert Schleimer
1052	Curriculum Vitae of Dr. Maureen Donovan
1053	Patent Certification for U.S. Patent No. 5,164,194 - Astelin® Nasal Spray (2000)
1054	"Avicel® RC-591 Microcrystalline Cellulose and Carboxymethylcellulose Sodium, NF, BP," FMC Corporation (1994)

Petitioner Argentum Pharmaceuticals LLC ("Petitioner") petitions for *inter partes* review ("IPR") of U.S. Patent No. 8,168,620 ("'620 patent) (Ex.1001), purportedly owned by CIPLA Ltd. ("Patent Owner").

I. MANDATORY NOTICES UNDER 37 C.F.R. § 42.8

A. Real Parties-In-Interest under 37 C.F.R. § 42.8(b)(1)

Argentum Pharmaceuticals LLC; Intelligent Pharma Research LLC; APS GP LLC; APS GP Investors LLC; and KVK-TECH, Inc.

B. Related Matters under 37 C.F.R. § 42.8(b)(2)

(1) *Meda Pharms. Inc. v. Apotex Inc.,* 14-cv-01453 (D. Del.); (2) *Meda Pharms. Inc. v. Teva Pharms.*, 15-cv-00785 (D. Del.); (3) *Meda Pharms. Inc. v. Perrigo UK Finco Ltd.*, 16-cv-00794 (D. Del.). Petitioner is not a party to any of those cases.

C. Lead and Backup Counsel under 37 C.F.R. § 42.8(b)(3)

Lead Counsel	Backup Counsel	Backup Counsel
Michael R. Houston, Ph.D. Reg. No. 58,486 Foley & Lardner LLP	Joseph P. Meara, Ph.D. Reg. No. 44,932 James P. McParland, Ph.D. Reg. No. 69,440 Foley & Lardner LLP	Tyler C. Liu Reg. No. 72,126 Argentum Pharmaceuticals LLC

D. Service Information under 37 C.F.R. § 42.8(b)(4)

Foley & Lardner LLP, 3000 K St. NW, Suite 600, Washington, DC. 20008. Petitioner consents to service by email at: ARG-dymista@foley.com.

II. REQUIREMENTS FOR IPR UNDER 37 C.F.R. § 42.104

A. Grounds For Standing under 37 C.F.R. § 42.104(a)

Petitioner certifies that the '620 patent is available for IPR and that Petitioner is not barred or estopped from requesting an IPR challenging the claims on the grounds identified in this petition.

B. Identification of Challenge under 37 C.F.R. § 42.104(b)

Petitioner requests cancellation of claims 1, 4-6, 24-26, 29, 42-44 of the '620 patent on the following grounds (pre-AIA):

Ground	Claims	Basis	Reference(s)
1	1, 25	§ 102(b)	Segal
2	1, 4-6, 24-26, 29	§ 103	Hettche, Phillipps, and Segal
3	42-44	§ 103	Hettche, Phillipps, Segal, Flonase® Label

III. SUMMARY OF ARGUMENT

The claims of the '620 patent are invalid for anticipation as well as obviousness over numerous prior art references in the field. The '620 patent

merely claims the co-formulation of two FDA-approved drugs, fluticasone and azelastine, for their known use and with known excipients. Well before the priority date of the '620 patent, both drugs had been marketed individually as Astelin (azelastine hydrochloride) and Flonase (fluticasone propionate) nasal sprays for treating allergic rhinitis. Even the patentee admits that these drugs were well-known for this use, that the excipients were known, and that techniques for preparing the formulations were well-known. *See* Ex. 1001, 1:20-29, 8:1-2. Not only are these admissions from the '620 patent binding on Patent Owner as a matter of law, they are further confirmed by the overwhelming prior art evidence detailed in the instant petition, along with clear motivations to combine and a reasonable expectation of success.

The scientific literature had already acknowledged the complementary mechanisms of action of these two classes of drugs in achieving a superior level of asthma control and increasing quality of life, including a public statement from the European Academy of Allergology and Immunology in 2000 recommending a combination of nasal steroids and antihistamines for treating allergic rhinitis. The beneficial effect from the combined drugs was hardly surprising given that a similar complementary effect had already been observed when fluticasone was combined with other inhalable asthma medications.

While Patent Owner ultimately obtained allowance of the '620 patent claims based on declarations attesting to unexpected results, commercial success and long-felt but unmet need, closer inspection shows these arguments to be flawed. Patent Owner's own evidence reveals that the combined drug formulation actually performed no better than concurrent monotherapies of fluticasone and azelastine, highlighting that the main shortcoming of the monotherapy approach was nothing more than achieving patient compliance—hardly a surprising discovery. Patent Owner's evidence also failed to establish a nexus between the claimed invention and the alleged success and unmet need.

In any event, such arguments are moot in view of the anticipation of the claims by the Segal reference. The instant petition also establishes an insurmountable *prima facie* case of obviousness based on the well-known drugs, and the well-known uses, formulations, and techniques for making their combination.

IV. THE '620 PATENT

A. Overview

The '620 patent is listed in the FDA's Orange Book as covering DYMISTA®, a nasal spray incorporating fluticasone propionate (a corticosteroid), and azelastine (an antihistamine). The Orange Book states that the '620 patent will

expire on February 24, 2026. The '620 patent issued from U.S. Patent Application No. 10/518,016, which purports to be 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"), filed on June 14, 2002 (the earliest possible effective date).

Claim 1 of the '620 patent recites a two-component pharmaceutical formation suitable for nasal administration:

> 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.

According to the specification of the '620 patent, each of the two claimed components (azelastine and fluticasone) were "known" to be used as a "nasal spray" in the treatment of "allergy-related conditions," including "allergic rhinitis":

> 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 cyclosenide.

Ex. 1001, 1:20-30 (emphasis added).

To combine these two ingredients, the '620 patent admits: "where only the ingredients of formulations according to the present invention are listed, these formulations are prepared by techniques well known in the art." *Id.* at 7:67-8:2 (emphasis added).

B. Prosecution History

The '620 patent issued after numerous rounds of rejection-and-response before two different examiners. Ultimately, the second examiner allowed the claims based entirely on three declarations submitted by the applicant: the Chopra Declaration (commercial success), Rajan Declaration (long unmet need), and Maus Declaration (unexpected results). *See* Ex. 1002, 143-146 (Reasons of Allowability). Applicant submitted these three declarations solely "[a]s evidence of … secondary considerations" of nonobviousness. *Id.*, 226. However, nowhere in the "Reasons for Allowability" (*id.,* 143-145) did the examiner identify any claim element that was missing in the Cramer reference (EP 0780127), despite

having found Cramer to anticipate most of the claims in the last-issued Office Action (*id.*, 510-512).

V. CLAIM CONSTRUCTION

Claim 24 contains the term "**conditions**." The term appears within 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. For purposes of this IPR, and consistent with the court's order in *Meda Pharms. Inc. v. Inc.* (Ex. 1005, 5), Petitioner proposes that the broadest reasonable construction of the term "conditions" is "**disease(s) or illness(es)**." Ex. 1003, ¶18.

The specification of the '620 patent expressly refers to "conditions" when discussing the well-known prior art nasal spray treatments of "allergy-related conditions" using antihistamines (including azelastine hydrochloride) and corticosteroids (including fluticasone). Ex. 1001, 1:20-33. It mentions allergic conditions such as "seasonal or perennial allergic rhinitis," "seasonal and perennial allergic conjunctivitis" and "nasal and ocular inflammatory conditions." *Id.* While "conditions" must be broad enough to encompass the foregoing specific diseases or illnesses mentioned, nothing in the specification or prosecution history limits "conditions" to only those specific diseases or illnesses themselves. Ex. 1003, ¶19.

The Board may take judicial notice of the fact that the District Court has construed "conditions," consistent with the foregoing, to mean "disease(s) or illness(es)," while rejecting a narrower construction proffered by Patent Owner that would have limited it to "allergic reactions." Ex. 1005, 5. The broadest reasonable interpretation of "conditions" should be at least as broad as the District Court's, which applies the narrower *Phillips* standard. Ex. 1003, ¶20.

VI. LACK OF ENTITLEMENT TO FOREIGN PRIORITY DATE

The prior art cited in the Grounds below all constitute § 102(b) pre-AIA prior art, even if all claims of the '620 patent were entitled to the effective filing date of the earliest priority application, GB 0213739.6 (filed June 14, 2002). Nevertheless, to preserve the issue for trial, Petitioner hereby disputes the entitlement of claims 1, 4-6, 25, 42, and 44 to any effective date earlier than June 13, 2003.

Raising priority issues in an IPR involves "identifying, specifically, the features, claims, and ancestral applications allegedly lacking § 112, first paragraph, written description and enabling disclosure support for the claims based on the identified features." *Polaris Wireless, Inc. v. TruePosition, Inc.*, IPR2013-00323, Paper 9 at 29; *see also SAP America, Inc. v. Pi-Net Int'l, Inc.*, IPR2014-00414, Paper 11 at 13-14. The test for sufficiency under the written description

requirement is whether the application disclosure relied on reasonably conveys to a POSA that the inventors had possession of the claimed subject matter. *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc). The USPTO never considered priority during prosecution of the '620 patent, and therefore no presumption of priority applies. *PowerOasis, Inc. v. T-Mobile USA*, 522 F.3d 1299, 1305 (Fed. Cir. 2008) (explaining that when neither the Office nor the Board has considered priority, there is no presumption that patent claims are entitled to the effective filing date of an earlier-filed application).

Here, the genus term "**pharmaceutically acceptable ester of fluticasone**" lacks written description support in the GB 0213739.6 application. GB 0213739.6 does not demonstrate possession of the genus "pharmaceutically acceptable ester of fluticasone." In fact, GB 0213739.6 only discloses, generally, "an ester" of fluticasone in claim 5, and provides only one specific example—"fluticasone propionate"—in claim 6. Ex. 1006, cls. 5-6. 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. Ex. 1003, ¶¶22-23.

Under *Ariad*, "an adequate written description of a claimed genus requires more than a generic statement of an invention's boundaries." 598 F.3d at 1350. "[A] sufficient description of a genus 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." *Id.* at 1351. "[A]n 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." *Id.* "[F]unctional claim language can meet the written description requirement when the art has established a correlation between structure and function." *Id.*

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 under *Ariad* to convey possession of the functional genus "pharmaceutically acceptable ester of fluticasone" in the '620 patent. Therefore, all claims of the '620 patent not specifically limited to fluticasone propionate are not entitled to the filing date of GB 0213739.6. Therefore, claims 1, 4-6, 25, 42, 44 have an effective filing date no earlier than June 13, 2003.

VII. LEVEL OF SKILL AND KNOWLEDGE IN THE ART

As of either June 14, 2002 or June 13, 2003, a hypothetical POSA would "be aware of all the pertinent prior art" at the time of the alleged invention, (*Custom Accessories, Inc. v. Jeffrey-Allan Indus*., 807 F.2d 955, 963 (Fed. Cir. 1986)),

including specialized knowledge applicable to various aspects of the claimed invention. *See, e..g*., *AVX Corp. v. Greatbatch, Ltd*., IPR2014-00697, Paper 60 at 3 (PTAB Jan. 11, 2016).

A hypothetical POSA would typically have been part of a multidisciplinary team. The team would have included a clinician and a formulator. The clinician of ordinary skill would have "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 additional years of experience in the treatment, or research for treatment, of allergic rhinitis, including the use of nasally administered steroids and antihistamines." Ex. 1003 ¶12. The formulator of ordinary skill would have been "a pharmaceutical formulator with at least a bachelor's degree in chemistry, biology, chemical engineering or pharmaceutical science and 3-5 years of experience in formulation development of nasal dosage forms, although the formulator could have more advanced degrees with fewer years of experience; and would have had familiarity with pharmaceutical excipients and their uses." Ex. 1004 ¶14-15.

The following prior art references, summarized below, would have further established a POSA's skill and understanding of the art. *See In re GPAC Inc*., 57 F.3d 1573, 1579 (Fed. Cir. 1995) (noting that the level of ordinary skill can be evidenced by the prior art references themselves).

A. Hettche (Ex. 1007)

U.S. Patent No. 5,164,194 ("Hettche"), issued in 1982, is the patent that covers Astelin®. Ex. 1053, 1; *see also* Ex. 1004, ¶24-25. Hettche discloses and claims: "A method for the treatment of irritation or disorders of the nose and eye which comprises applying directly to nasal tissues or to the conjunctival sac of the eyes a medicament which contains a member selected from the group consisting of azelastine and its physiologically acceptable salts." Ex. 1007, cl.1. Example 1 teaches a nasal spray with 0.1% azelastine hydrochloride, wherein "0.14 mg of azelastine hydrochloride are sprayed into the nose per actuation in the form of the solution." *Id.*, 6:8-35. Excipients compatible with azelastine include edetic acid disodium salt (4:5; 6:12), glycerine (2:35-39; 4:31-34), thickening agents (4:51-66), benzalkonium chloride (2:68-3:25), 2-phenylethanol (3:19-25), and water (2:35-36; 6:11; 6:48-49). Ex. 1004, ¶¶24-31.

B. Astelin® Label (Ex. 1008)

The Astelin® Label was published in the 2000 Physician's Desk Reference and shows a revision date of "1/99." Ex. 1008, 3148. It describes a nasal spray that contains a concentration of azelastine hydrochloride of 0.1% w/v and the preservative benzalkonium chloride. *Id.*, 3147. Additional components include edetate disodium, hydroxypropyl methyl cellulose, citric acid, dibasic sodium phosphate, sodium chloride, and purified water. *Id.* The nasal spray is indicated

for "treatment of the symptoms of seasonal allergic rhinitis." *Id.*, 3148; Ex. 1004, ¶¶21-23.

C. Phillipps (Ex. 1009)

U.S. Patent No. 4,335,121 ("Phillipps") was issued in 1982 and covers Flonase®. Ex. 1010, 8. Phillipps claims fluticasone propionate, which is described by its chemical name, S-fluoromethyl 6α, 9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxyandrosta-1,4-diene-17β-carbothioate." Ex. 1009, cl.13. The formulation is suitable for topical administration using "sprays, (e.g. for the nose, throat, lung or skin)." *Id.*, 32:55-60. They "are intended for administration on a prophylactic basis to humans suffering from allergic and/or inflammatory conditions of the nose, throat or lungs such as asthma and rhinitis, including hay fever." *Id.*, 33:40-44. Phillipps states that the "steroid is micronised (particle size as defined in BPC 1973 pg. 911 for Ultra-Fine powder)." *Id.*, 34:47-48. The "BPC 1973" reference, in turn, defines an ultra-fine powder as a "powder of which the maximum diameter of 90 per cent of the particles is not greater than 5 μm and of which the diameter of none of the particles is greater than 50 μm." Ex. 1013, 911; Ex. 1004, ¶¶ 36-39.

D. Flonase® Label (Ex. 1010)

Flonase® Label was published at least as of the December 1998 revision date shown on the face of the label. Ex. 1010, 9. It describes a nasal spray

containing an aqueous suspension of "microfine" particles of fluticasone propionate at a concentration of 0.5% w/w. *Id.*, 1; Ex. 1004, ¶¶26-29. The suspension also contains microcrystalline cellulose and carboxymethylcellulose sodium, dextrose, 0.02% w/w benzalkonium chloride, polysorbate 80, and 0.25% w/w phenylethyl alcohol. *Id.*

E. Cramer (Ex. 1011)

European Patent Application No. 0780127 ("Cramer") published in 1997 to the Proctor & Gamble Company, and was titled "A nasal spray containing a steroid and a [sic] antihistamine." Ex. 1011, 1. Cramer is directed to "pharmaceutical compositions for nasal administration comprising: a) a safe and effective amount of a glucocorticoid selected form 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 (emphasis added). Cramer 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.

Cramer's express motivation to co-formulate a steroid/antihistamine nasal spray was to provide "improved symptomatic relief with increased user acceptance and compliance." *Id.*, 2:23-24.

F. Segal (Ex. 1012)

PCT Publication No. WO 98/48839 ("Segal") was assigned to the Warner-Lambert Company and published in 1998. Like Cramer, Segal also describes a co-formulated nasal spray containing both azelastine and fluticasone. Segal provides "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 inhibitor, an anticholinergic agent, a leukotriene inhibitor, an antihistamine, an antiallergic agent, an anesthetic, and a mucolytic agent." Ex. 1012, 2:10-15. Among the preferred antiinfammatory agents, Segal identifies "**fluticasone proprionate**". *Id.*, 2:22-26 (emphasis added). Among the "[s]uitable antihistamines," Segal identifies "**azelastine**." *Id.*, 3:18-20 (emphasis added). Segal's express motivation to co-formulate a nasal spray containing multiple therapeutic ingredients was to avoid the disadvantages of administering multiple agents separately. *Id.*, 1:12-2:5 ("Patient compliance may be compromised by the inconvenience of applying multiple spray products or nose drops.").

VIII. CLAIM-BY-CLAIM EXPLANATION OF GROUNDS FOR UNPATENTABILITY

Claims 1, 4-6, 24-26, 29, 42-44 of the '620 patent are unpatentable for the reasons detailed below.

A. Ground 1: Claims 1 and 25 are anticipated by Segal

Segal is prior art under 35 U.S.C. §102(b) (pre-AIA) because Segal published on November 5, 1998, more than a year before the earliest possible priority date of the '620 patent.

A single reference anticipates a claim if it discloses each and every element "arranged as in the claim." *Net MoneyIN, Inc. v. VeriSign, Inc*., 545 F.3d 1359, 1370 (Fed. Cir. 2008). Where a reference discloses a genus, if a POSA can envision each and every species of the genus, the genus anticipates the species. *In re Petering*, 301 F.2d 676, 681 (CCPA 1962); *In re Schaumann*, 572 F.2d 312, 315-16 (CCPA 1978). Indeed, "the description of 'specific preferences in connection with a generic formula' is determinative in an analysis of anticipation under 35 USC 102." *Merck v. Biocraft*, 874 F.2d 804, 808 (Fed. Cir. 1989) (quoting *In re Petering*). "To serve as an anticipating reference, a reference must enable that which it is asserted to anticipate." *Elan Pharms., Inc. v. Mayo Found. for Med. Educ. & Research*, 346 F.3d 1051, 1375 (Fed. Cir. 2003). Segal meets these criteria.

Segal anticipates claims 1 and 25 because it not only discloses a nasal formulation having both a topical anti-inflammatory and an antihistamine but discloses specific preferences for each type of drug in its nasal formulations. Ex. 1012, 2:10-15, cl. 1; Ex. 1003, ¶32. Segal teaches fluticasone propionate as a preferred embodiment of the topical anti-inflammatory agent, along with azelastine as a suitable antihistamine. Ex. 1012, 2:23-26, 3:19-20, cls. 1, 2, 4; Ex. 1003, ¶¶33-34, 37-38. Segal also discloses that preferred nasal formulations are nasal drops or sprays. Ex. 1012, 3:29-4:5; Ex. 1003, ¶¶35-36. In addition to all the elements of claim 1, claim 25 further requires a nasal spray formulation comprising a pharmaceutically acceptable carrier or excipient. Segal meets this limitation by teaching a formulation containing a "water buffered aqueous solution as a carrier" (*Id.*, 4:4-5), which is a pharmaceutically acceptable carrier or excipient (Ex. 1004, ¶39).

There is no question that Segal was enabling at the time of invention. Ex. 1003, ¶41. The '620 patent expressly admits 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. This admission is binding on Patent Owner for purposes of anticipation. *Constant v. Advanced Micro-Devices Inc*., 848 F.2d 1560, 1570 (Fed. Cir. 1988) ("A statement

in a patent that something is in the prior art is binding on the applicant and patentee for determinations of anticipation and obviousness."). 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."

Even if Patent Owner had not admitted that the formulations of claims 1 and 25 could be prepared using known techniques, a POSA reading Segal would have recognized as much. First, Segal disclose that the combination of drugs may be formulated as a nasal spray containing a "water buffered aqueous solution as carrier," along with standard excipients well known in the art. Ex. 1012, 3:29-4:19; Ex. 1003, ¶39. Second, fluticasone propionate and azelastine were already available in FDA-approved aqueous nasal spray formulations (Flonase® and Astelin®). Ex. 1008, Ex. 1010. As explained by Dr. Donovan, a POSA, being aware of these FDA-approved commercial formulations could readily have prepared a combined formulation of the two drugs together without undue experimentation. Ex. 1004, ¶¶35,59-61; *see also infra*, Section VIII(C).

Claim 1 of Segal calls for a topical antiinflammatory agent, and one of seven types of therapeutic agents, of which an antihistamine is one. Claim 2 limits the anti-inflammatory agent to six compounds, of which fluticasone proprionate is one.

Finally, claim 4 limits the antihistamine to one of nine compounds, of which azelastine is one. Thus, taking claims 1, 2 and 4 together, Segal discloses at most 54 discrete compositions, of which the combination of fluticasone proprionate and azelastine is one. Given the limited number of combinations identified, a POSA would have easily envisioned the "species" (*i.e.* the combination of fluticasone proprionate and azelastine) from the "genus" of claim 1 of Segal, such that Segal anticipates claims 1 and 25 of the '620 patent. *In re Petering*, 301 F.2d at 681.

As shown in the claim chart below, Segal discloses each and every element of claims 1 and 25 and therefore anticipates them. Ex. 1003, ¶40.

'620 Patent Claims	**Segal (Ex. 1012)**
1. A pharmaceutical formulation comprising:	"The present invention provides 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 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.
azelastine, or a pharmaceutically acceptable salt thereof, and	"Suitable antihistamines are diphenhydramine, chlorpheniramine, cetirizine terfenadine, fenofexadine, astemizole norastemizole, azelastine, and azatidine." Ex. 1012, 3:19-20; *see also id.* cl.4 (depending from Segal claim 1).
a pharmaceutically acceptable ester of fluticasone,	"In a preferred embodiment the topical antiinflammatory agent is beclomethasone diproprionate, budesonide, dexamethasone,

	mometasone furoate, fluticasone proprionate or triamcinolone acetonide." Ex. 1012, 2:23-26; *see also id.* cl.2 (depending from Segal claim 1).
wherein said pharmaceutical formulation is in a dosage form suitable for nasal administration.	"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).

25. A nasal spray formulation comprising	"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).
(i) azelastine, or a pharmaceutically acceptable salt thereof,	"Suitable antihistamines are diphenhydramine, chlorpheniramine, cetirizine terfenadine, fenofexadine, astemizole norastemizole, azelastine, and azatidine." Ex. 1012, 3:19-20; *see also id.* cl.4 (depending from Segal claim 1).
(ii) a pharmaceutically acceptable ester of fluticasone,	"In a preferred embodiment the topical antiinflammatory agent is beclomethasone diproprionate, budesonide, dexamethasone, mometasone furoate, fluticasone proprionate or triamcinolone acetonide." Ex. 1012, 2:23-26; *see also id.* cl.2 (depending from Segal claim 1).
and (iii) a pharmaceutically acceptable carrier or	"Preferred nasal formulations are nose drops or nasal sprays containing a water buffered aqueous solution as a carrier." Ex. 1012, 4:4-5.

excipient therefor.	

B. Ground 2: Claims 1, 4-6, 24-26, 29 are obvious over Hettche, Phillipps, and Segal

As admitted in the '620 patent, "azelastine … hydrochloride" and "fluticasone" were each "known" for use in "nasal sprays" or for nasal use to "treat allergy-related conditions," including "allergic rhinitis." Ex. 1001, 1:20-36. The challenged claims are obvious because the '620 patent simply combined these two active ingredients, along with known excipients, using known techniques, to yield predictable results. *See KSR Int'l Co. v. Teleflex Inc*., 550 U.S. 398, 416 (2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results."). The '620 patent is also obvious because it merely uses a known technique—adding fluticasone propionate to a faster acting therapeutic—in the same way fluticasone had been used in the past to improve similar products (*e.g.*, Advair®, a fixed-dose combination spray containing fluticasone propionate and the β2-agonist salmeterol for the treatment of asthma, a condition related to allergic rhinitis). *See KSR* at 417 ("[I]f a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond that person's skill."). The combination of azelestine and fluticasone propionate is

therefore nothing more than "the predictable use of prior art elements according to their established functions." *Id.*

1. All claim elements were known

As discussed below and shown in the accompanying claim charts, all the elements of claims 1, 4-6, 24-26 and 29 were present in the prior art more than a year prior to the effective filing date of the '620 patent.

a. Claims 1 and 4

Hettche, Phillipps, and Segal teach the use of pharmaceutical formulations and nasal compositions. See Ex. 1007, 2:10-11; Ex. 1009, Abstract, 33:40-44; Ex. 1012, 2:10-15. Hettche discloses "azelastine or a physiologically acceptable salt," Phillipps teaches fluticasone propionate, a pharmaceutically acceptable ester of fluticasone, and Segal teaches both. Ex. 1007, Abstract; Ex. 1009, cl.131; Ex. 1012, 2:23-26, 3:20, cls. 1, 2, 4. All three references disclose the use of a nasal spray. See Ex. 1007, 2:12-17; Ex. 1009, 33:12-13, 40-44; Ex. 1012, 4:4-5; Ex. 1003 ¶45.

---

[1] The compound "S-fluoromethyl 6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxyandrosta-1,4-diene-17β-carbothioate" is the "chemical name" for "Fluticasone propionate." Ex. 1010, 1.

Claim 4 of the '620 patent specifies the formulation to have a particle size of less than 10 μm. Phillipps discloses examples in which the particle size of fluticasone propionate is micronized to be an ultrafine powder as defined by the BPC, British Pharmaceutical Codex (BPC). The BPC defines such "powder of which the maximum diameter of 90 per cent of the particles is not greater than 5 μm." Ex. 1009, 34:37-39; Ex. 1013, 911; Ex. 1004, ¶¶43-45.

b. Claims 5-6, 26, and 29

Claim 5 requires the formulation to have 0.0005% to 2% (weight/weight) of azelastine, and claim 6 requires 0.001% to 1% of azelastine (weight/weight). Claims 5 and 6 further require that the pharmaceutically acceptable ester of fluticasone be present at a concentration of 0.0357% to 1.5% (weight/weight). Claim 26 further calls for 0.1% (weight/weight) of azelastine hydrochloride and 0.0357% to 1.5% of fluticasone propionate. Claim 29 further calls for a nasal spray. None of these additional limitations render the claims patentably distinct over the prior art. Ex. 1003 ¶46.

Concentration of Azelastine: Hettche expressly discloses a formulation comprising "0.0005 to 2 [identical to claim 5's range], preferably 0.001 to 1 [identical to claim 6's range], in particular 0.003 to 0.5% [encompassing claim 26's range] (weight/weight) of azelastine." Ex. 1007, 3:26-34. Hettche also discloses that the amounts would be recalculated as necessary for any salt of

azelastine. *Id.* Finally, Hettche teaches a working example of a nasal spray with 0.1% azelastine hydrochloride, identical to claim 26. *Id.*, 6:7-35. Thus, the azelastine concentrations required by Claims 5, 6, and 26 are identically disclosed in the art. Ex. 1003 ¶47.

Concentration of Fluticasone: Phillipps teaches pharmaceutical formulations having 0.01 to 0.25% androstane, such as fluticasone propionate, including powders for inhalation or insufflation having 0.1% to 0.2% androstane such as fluticasone propionate. Ex. 1009, 33:27-32. Phillipps further discloses a liquid aerosol spray containing 0.059% w/w of active ingredient, which is the androstane of Example 39, fluticasone propionate. Ex. 1009, 34:55-62. Thus, Phillipps teaches a concentration of fluticasone within the range disclosed in Claims 5, 6, and 26. Ex. 1003 ¶48. Moreover, no criticality of these ranges is disclosed in the '620 patent. Therefore, it would have been obvious to select the amount of fluticasone propionate disclosed by Phillipps to provide relief of allergic rhinitis in combination with azelastine. *See In re Peterson*, 315 F.3d 1325, 1329-30 (Fed. Cir. 2003)(finding obviousness when the ranges of a claimed composition overlap the ranges disclosed in the prior art).

Nasal Spray: Hettche, Phillipps, and Segal all call for the formulation to be administered as a nasal spray. Ex. 1007, 2:12-17; Ex. 1009, 32:57-60, 33:12-13, 40-44; Ex. 1012, 4:4-5; Ex. 1003 ¶49; Ex. 1004, ¶¶50-51.

c. Claims 24 and 25

Claim 24 requires a pharmaceutical formulation comprising azelastine hydrochloride and fluticasone propionate as a nasal spray used to treat 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, 32:57-60, 33:12-13; Ex. 1012, 4:4-5. In addition, they all disclose formulations used to treat a condition (*i.e.*, disease or illness) that either an antihistamine or steroid is used to treat, such as allergic rhinitis. Ex. 1007, 1:29-52; Ex. 1009, 1:3-4; 33:40-44; Ex. 1012, 2:20-26, 3:19-20. Moreover, Hettche discloses azelastine salts that include the hydrochloride (Ex. 1007, 3:48-49), while Phillipps discloses fluticasone propionate. Ex. 1009, cl. 13; Ex. 1003, ¶50. Thus, Hettche, Phillipps, and Segal separately and in combination disclose pharmaceutical formulations used to treat conditions for which administration of one or more anti-histamine and/or one or more steroid is indicated, with Hettche disclosing azelastine hydrochloride, Phillipps disclosing fluticasone propionate, and Segal disclosing both. Ex. 1003, ¶51.

Claim 25 requires 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 and together disclose a nasal spray with azelastine and fluticasone propionate. Moreover, 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; Ex. 1003, ¶51.

The following claim chart maps the claim elements to the teachings in the prior art.

'620 Patent Claims	**Hettche (Ex. 1007), Phillipps (Ex. 1009), and Segal (Ex. 1012)**
1. A pharmaceutical formulation comprising:	"[M]edical formulations which are adapted to direct application to nasal and eye tissues." Ex. 1007, 2:10-11. "Pharmaceutical compositions containing the compounds of formula I and methods for the use of the compounds are described and claimed." Ex. 1009, Abstract. "The present invention provides topically applicable nasal compositions …." Ex. 1012, 2:10-15.
azelastine, or a pharmaceutically acceptable salt thereof,	"A medicament for nasal use or for use in the eye which contains as active ingredient azelastine or a physiologically acceptable salt." Ex. 1007, Abstract. "Suitable antihistamines are diphenhydramine, chlorpheniramine, cetirizine terfenadine, fenofexadine, astemizole norastemizole, azelastine, and azatidine." Ex. 1012, 3:19-20.
and a pharmaceutically acceptable ester of fluticasone,	"A compound as claimed in claim 1 which is S-fluoromethyl 6α, 9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxyandrosta-1,4-diene-17β-carbothioate." Ex. 1009, cl.13. The compound "S-

	fluoromethyl 6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxyandrosta-1,4-diene-17β-carbothioate" is the "chemical name" for "Fluticasone propionate." Ex. 1010, 1. "In a preferred embodiment the topical antiinflammatory agent is beclomethasone diproprionate, budesonide, dexamethasone, mometasone furoate, fluticasone proprionate or triamcinolone acetonide." Ex. 1012, 2:23-26.
wherein said pharmaceutical formulation is in a dosage form suitable for nasal administration.	"The preferred embodiment of the invention is a sterile and stable aqueous solution of azelastine or one or more of its salts which can be used . . . , in a particularly preferred embodiment, in the form of a spray (preferably a nasal spray)." Ex. 1007, 2:12-17. Examples of various types of preparation for topical administration include…sprays, (e.g. for the nose, throat, lung or skin)…" Ex. 1009, 32:57-60. "Spray compositions may for example be formulated as aqueous solutions or suspensions …." *Id.*, 33:12-13. "Preferred nasal formulations are nose drops or nasal sprays containing a water buffered aqueous solution as a carrier." Ex. 1012, 4:4-5.

4. The pharmaceutical formulation of claim 1,	See Claim 1 above.
wherein said formulation has a particle size of less than 10 μm.	"The active ingredient[fluticasone propionate] is micronised (particle size as defined in BPC 1973 pg. 911 for Ultra-Fine powder)." Ex. 1009, 34:63-65. The cited "BPC 1973" reference defines an ultra-fine powder as a "powder of which the maximum diameter of 90 per cent of the particles is not greater than 5 μm and of which the diameter of none of the particles is greater than 50 μm." Ex. 1013, 911.

5. The pharmaceutical formulation of claim	See Claim 1 above.

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	"The preferred embodiment of the invention is a sterile and stable aqueous solution of azelastine or one or more of its salts …." Ex. 1007, 2:12-14. "The formulations of the invention (solutions, suspensions as well as oily solutions or suspensions, ointments, emulsions, creams, gels, dosage aerosols) contain 0.0005 to 2, preferably 0.001 to l, in particular 0.003 to 0.5% (weight/weight) of azelastine (related to the free azelastine base). Should the azelastine be present as a salt, the amounts should be recalculated as necessary to give the amounts of azelastine itself mentioned above." 1007, 3:26-34. "Nasal spray or nasal drops or eye drops with 0.1% azelastine hydrochloride as active ingredient." Ex. 1007, 6:8-9.
from 0.0357% (weight/weight) to 1.5% (weight/weight) of said pharmaceutically acceptable ester of fluticasone.	"Spray compositions may for example be formulated as aqueous solutions…. for most types of [pharmaceutical] preparations advantageously the proportion [of androstane compound in the formulation] used will be within the range from 0.005 to 0.5%, and preferably from 0.01 to 0.25%. However, with powders for inhalation or insufflation, the proportion used will be within the range of from 0.1% to 2%." Ex. 1009, 33:12-13, 27-32. Phillipps also discloses an aerosol spray containing 0.059% w/w of active ingredient, which can be Example 39, *i.e.*, fluticasone propionate. Ex. 1009, 34:55-62.

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

acceptable salt thereof, and	
from 0.0357% (weight/weight) to 1.5% (weight/weight) of said pharmaceutically acceptable ester of fluticasone.	See Claim 5 above.

24. A pharmaceutical formulation comprising	"[M]edical formulations which are adapted to direct application to nasal and eye tissues." Ex. 1007, 2:10-11. "Pharmaceutical compositions containing the compounds of formula I and methods for the use of the compounds are described and claimed." Ex. 1009, Abstract. "The present invention provides topically applicable nasal compositions …." Ex. 1012, 2:10-15.
azelastine hydrochloride; and,	"A medicament for nasal use or for use in the eye which contains as active ingredient azelastine or a physiologically acceptable salt." Ex. 1007, Abstract. "Possible acid components for azelastine salts are, for example: hydrohalic acids (HCl, HBr)…." *Id.* 3:48-49.
fluticasone propionate,	"A compound as claimed in claim 1 which is S-fluoromethyl 6α, 9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxyandrosta-1,4-diene-17β-carbothioate." Ex. 1009, cl.13. The compound "S-fluoromethyl 6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxyandrosta-1,4-diene-17β-carbothioate" is the "chemical name" for "Fluticasone propionate." Ex. 1010, 1. "In a preferred embodiment the topical antiinflammatory agent is beclomethasone diproprionate, budesonide, dexamethasone, mometasone furoate, fluticasone proprionate or

	triamcinolone acetonide." Ex. 1012, 2:23-26.
wherein said formulation is in the dosage form of as a nasal spray,	"The preferred embodiment of the invention is a sterile and stable aqueous solution of azelastine or one or more of its salts which can be used . . . , in a particularly preferred embodiment, in the form of a spray (preferably a nasal spray)." Ex. 1007, 2:12-17. Examples of various types of preparation for topical administration include…sprays, (e.g. for the nose, throat, lung or skin)…" Ex. 1009, 32:57-60. "Spray compositions may for example be formulated as aqueous solutions or suspensions …." *Id.*, 33:12-13. "Preferred nasal formulations are nose drops or nasal sprays containing a water buffered aqueous solution as a carrier." Ex. 1012, 4:4-5.
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.	"Azelastine also has anti-allergic and antihistamine properties." Ex. 1007, 1:29-30. "Elimination or marked relief has thus been achieved … in allergy-related rhinitis…" *Id.* 1:39-40. "Other indications for the application/use of the invention are, for example: non-specific conjunctivitis, allergy-related conjunctivitis, allergic blepharoedema, catarrhal conditions in the eye or nose, coryza." *Id.* 1:49-52. "The present invention relates to anti-inflammatory steroids of the androstane series." Ex. 1009, 1:4-5. "The formulations for administration by inhalation or insufflation are intended for administration on a prophylactic basis to humans suffering from allergic and/or inflammatory conditions of the nose, throat or lungs such as asthma and rhinitis…." *Id*. 33:40-44. "The present compositions are useful for the treatment of nasal and sinus conditions, for example allergic rhinitis or the common cold." Ex. 1012, 2:20-21. "The topical antiinflammatory agents in the compositions of the present invention are corticosteroids known in the art to suppress inflammation . . . The topical antiinflammatory agent is … fluticasone

	proprionate…." *Id.* 2:22-26. "Suitable antihistamines are … azelastine…." *Id.* 3:19-20.

25. A nasal spray formulation comprising	"The preferred embodiment of the invention is a sterile and stable aqueous solution of azelastine or one or more of its salts which can be used . . . , in a particularly preferred embodiment, in the form of a spray (preferably a nasal spray)." Ex. 1007, 2:12-17. Examples of various types of preparation for topical administration include…sprays, (e.g. for the nose, throat, lung or skin)…" Ex. 1009, 32:57-60. "Spray compositions may for example be formulated as aqueous solutions or suspensions …." *Id.*, 33:12-13. "Preferred nasal formulations are nose drops or nasal sprays containing a water buffered aqueous solution as a carrier." Ex. 1012, 4:4-5.
(i) azelastine, or a pharmaceutically acceptable salt thereof,	"The preferred embodiment of the invention is a sterile and stable aqueous solution of azelastine or one or more of its salts which can be used . . . , in a particularly preferred embodiment, in the form of a spray (preferably a nasal spray)." Ex. 1007, 2:12-17. "Suitable antihistamines are diphenhydramine, chlorpheniramine, cetirizine terfenadine, fenofexadine, astemizole norastemizole, azelastine, and azatidine." Ex. 1012, 3:19-20.
(ii) a pharmaceutically acceptable ester of fluticasone,	"A compound as claimed in claim 1 which is S-fluoromethyl 6α, 9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxyandrosta-1,4-diene-17β-carbothioate." Ex. 1009, cl.13. The compound "S-fluoromethyl 6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxyandrosta-1,4-diene-17β-carbothioate" is the "chemical name" for "Fluticasone propionate." Ex. 1010, 1. "In a preferred embodiment the topical antiinflammatory agent is beclomethasone diproprionate, budesonide, dexamethasone,

	mometasone furoate, fluticasone proprionate or triamcinolone acetonide." Ex. 1012, 2:23-26.
and (iii) a pharmaceutically acceptable carrier or excipient therefor.	"The following are dissolved, in the following order, into 9.00 kg of water: 10 g of azelastine hydrochloride…." Ex. 1007, Example 1, 6:10-11. "The solution obtained is diluted to 10.05 kg = 10 liters with water." *Id.*, Example 1, 6:19-20. "[P]umps with nasal spray inserts are, for example used, which spray about 0.14 ml of solution per actuation." *Id.*, Example 1, 6:26-28. "Spray compositions may be formulated as aqueous suspensions or solutions." Ex. 1009, 33:12-13. "Preferred nasal formulations are nose drops or nasal sprays containing a water buffered aqueous solution as a carrier." Ex. 1012, 4:4-5.

26. The pharmaceutical formulation of claim 6, comprising	See Claim 6 above.
0.1% (weight/weight) of azelastine hydrochloride, and from 0.0357% to 1.5% (weight/weight) of fluticasone propionate.	See Claim 5 above.

29. The pharmaceutical formulation of claim 26,	See Claim 26 analysis above.
wherein said dosage form suitable for nasal administration comprises a nasal spray.	"The preferred embodiment of the invention is a sterile and stable aqueous solution of azelastine or one or more of its salts which can be used . . . , in a particularly preferred embodiment, in the form of a spray (preferably a nasal spray)." Ex. 1007, 2:12-17. Examples of various types of preparation for topical

	administration include…sprays, (e.g. for the nose, throat, lung or skin)…" Ex. 1009, 32:57-60. "Spray compositions may for example be formulated as aqueous solutions or suspensions …." *Id.*, 33:12-13. "Preferred nasal formulations are nose drops or nasal sprays containing a water buffered aqueous solution as a carrier." Ex. 1012, 4:4-5.

2. Reasons to select and to combine azelastine and fluticasone

a. Selection

A POSA looking to improve treatment for allergic rhinitis (AR) would have selected azelastine hydrochloride as the preferred antihistamine, and would have selected fluticasone propionate as the preferred corticosteroid, for combination into a single fixed-dose nasal spray, as explained below. Hettche discloses that azelastine hydrochloride nasal spray could be used to treat allergic rhinitis and teaches the commercial formulation marketed as Astelin® nasal spray. Ex. 1007, 1:34-43, 6:7-31 (Example 1). As of June 2002, Astelin® nasal spray was the safest and most potent FDA-approved nasal antihistamine available. Ex. 1003, ¶¶63-64, 67. In a comparison to the only other FDA-approved nasal antihistamine available at that time—levocabastine—azelastine was "statistically superior in efficacy as well as in safety." Ex. 1015, 387, see also 391-92 (azelastine provides significantly better symptom relief as evidence by the reduction in total symptom score and nasal sum scores); Ex. 1003, ¶63. In another study, azelastine was found

to inhibit leukotriene mediator by 86%, compared to 20% for levocabastine and was unique among antihistamines in being able to reduce nasal congestion. Ex. 1016, Fig.2, 99-100; Ex. 1003, ¶66. As disclosed in Hettche, 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; Ex. 1003, ¶65; Ex. 1050, 823-24.

Similarly, as of June 2002, fluticasone propionate (disclosed by Phillips and marketed as Flonase® nasal spray) combats allergic rhinitis (Ex. 1010 and was the most potent FDA-approved corticosteroid available. Ex. 1017, 623 (fluticasone propionate most potent among mometasone furoate, budesonide, beclomethasone dipropionate, triamcinolone acetonide, and hydrocortisone); Ex. 1018, S434 (fluticasone propionate most potent among 17-BMP, mometasone furoate, budesonide, triamcinolone acetonide and flunisolide); Ex. 1003, ¶59, 61.

Moreover, a POSA had a reason to retain these drugs as nasal sprays, rather than reformulating them into oral forms, given the known advantages of nasal (topical) administration. As noted above, azelastine nasal spray avoids the tiredness associated with other applications (e.g., oral dosage forms), as well as often obviating the need for separate eye drops, and eliminating or minimizing the

bitter taste of the drug. Ex. 1007, 1:44-48, 53-55; 1:63-2:2; Ex. 1003, ¶65. Further, nasally administered "azelastine reduces nasal congestion, … which dis[t]inguishes azelastine from oral antihistamines…." Ex. 1016, 98. Similarly, Phillipps indicates that that the disclosed topically (i.e., nasally) administered androstanes, which includes fluticasone propionate, have minimal ability to cause undesired systemic side effects. Ex. 1003, ¶60; Ex. 1009, 1:48-55; see also Ex. 1019, 506 (recognizing nasally inhaled corticosteroids "are generally not associated with significant systemic side effects in adults").

b. Motivation to combine

In addition to Segal's express teaching to combine azelastine and fluticasone propionate into a single nasal product (supra Ground 1), a POSA would have had at least three additional reasons for combining azelastine and fluticasone propionate. First, the clinical use of antihistamines and corticosteroids together for treating allergic rhinitis was well established before June 2002. For example, in 1998, a Joint Task Force representing five different medical associations in the areas of allergy, asthma, and immunology published guidelines for diagnosis and management of rhinitis, stating that intranasal antihistamines "are appropriate for use as first line treatment for the symptoms of allergic rhinitis, or as part of combination therapy with nasal corticosteroids or oral antihistamines." Ex. 1019, 505; Ex. 1003, ¶72. Azelastine hydrochloride was specifically identified as a

suitable intranasal antihistamine. Id. In a 1999 publication, the authors noted, "for those patients whose symptoms [of AR] are not adequately controlled by either treatment often a combination of both an antihistamine with an intranasal corticosteroid is prescribed." Ex. 1021, 536; Ex. 1003, ¶73. Likewise, in 2000, the European Academy of Allergology and Immunology published a consensus statement on the treatment of allergic rhinitis saying "a combination of nasal steroids and antihistamines (oral and/or topical [e.g., nasal]) is recommended" if "the patient presents with severe symptoms or if the treatment with nasal steroids in the case of moderate disease does not have an adequate effect." Ex. 1022, Fig.1, 125; Ex. 1003, ¶74-76. Consequently, in February 2002, Kusters stated that "[h]istamine H1-receptor antagonists together with topical steroids are the treatment of choice in allergic rhinitis." Ex. 1016, 98; Ex. 1003, ¶66.

Second, a POSA would have wanted to take advantage of the known complementary mechanisms of action of azelastine and fluticasone working together. Ex. 1003, ¶70. For example, it was known that "[t]he ideal therapeutic agent for managing the symptoms of seasonal allergic rhinitis (SAR) would be one that effectively addresses the pathophysiology of both the early-phase reaction (EPR) and the late-phase reaction (LPR)." Ex. 1023, S386; Ex. 1003, ¶¶57-58. "[T]he ideal pharmacologic therapy would be a drug that possessed not only H1-receptor antagonist activity but also anti-inflammatory activity." Id., S387.

Together, azelastine and fluticasone achieve exactly that. "Azelastine hydrochloride is an H1-receptor antagonist with anti-inflammatory properties," and topical H1-antihistamines have a "rapid onset of action (less than 15 minutes)." Ex. 1021, 535; Ex. 1024, S226, S230; Ex. 1003, ¶55. "Fluticasone has long-term effects on the nasal response to histamine in perennial allergic rhinitis," but has "a slower onset of action than H1-antihistamines, usually less than 12 hours, and maximum efficacy develops over days and weeks." Ex. 1024, S231-S232; Ex. 1003, ¶¶53-54. Cramer 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." Ex. 1011, 2:25-27; Ex. 1003, ¶¶78-79.

Taking advantage of complementarity of mechanisms of action of two therapeutics was a known technique in the art, and had even been implemented by incorporating fluticasone propionate in the product Advair® (fluticasone propionate and salmeterol). Ex. 1003, ¶¶83-84. Stoloff reported that by combining fluticasone with a faster acting bronchodilator (salmeterol), the "complementary mechanisms of action" of these two drugs achieved "a superior level of asthma control." Ex. 1020, 223. See Ex. 1025, p.1213 ("Based on evidence of a complementary effect, and the fact that compliance with inhaled asthma medication is generally poor, salmeterol and fluticasone propionate have

been combined in a single inhalation device."). Thus, a POSA would have been encouraged by the beneficial result seen in Advair® to combine fluticasone propionate with another active ingredient, and azelastine would have been the obvious choice for the treatment of allergic rhinitis based on Spector and Berger. Ex. 1003, ¶¶52, 58, 73.

Third, a POSA would have expected a combined azelestine/fluticasone nasal spray to improve patient compliance over use of the individual monotherapies. As Segal expressly taught: "Patient compliance may be compromised by the inconvenience of applying multiple spray products or nose drops." Ex. 1012, 2:2-3. Multiple topical nasal preparations are not merely inconvenient, but "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." Id., 1:18-20. 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; Ex. 1003, ¶80. Co-formulation of a topical anti-inflammatory agent and an additional therapeutic agent that is an antihistamine in a single nasal spray provides a convenient alternative that does not suffer from the foregoing disadvantages. Id., 3:3-9.

Increasing patient compliance through the increased convenience of coformulation was also known in the art. As mentioned above, 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; Ex. 1003, ¶82.

3. Known techniques to make the co-formulation

The '620 patent admits that the "formulations according to the present invention … are prepared by techniques well known in the art." Ex. 1001, 7:67-8:2 (emphasis added). In none of the Examples containing both azelastine hydrochloride and fluticasone propionate does the '620 patent describe any synthesis, processing, or mixing techniques whatsoever. Id., Examples 3, 5, 9, 10. Therefore, given the '620 patent's "well known in the art" admission and its complete silence regarding processing techniques, a POSA is presumed to have been able to formulate and make the claimed compositions. See In re Epstein, 32 F.3d 1559, 1658 (Fed. Cir. 1994) ("Board's observation that appellant did not provide the type of detail in his specification that he now argues is necessary in prior art references supports the Board's finding that one skilled in the art would have known how to implement the features of the references").

Azelastine hydrocholoride and fluticasone proprionate were disclosed and claimed in the prior art U.S. patents to Hettche (Ex. 1007) and Phillipps (Ex.

1009), and the various excipients are described throughout those two patents. Accordingly, a POSA was presumptively enabled to make a formulation containing those components. See Amgen Inc. v. Hoechst Marion Roussel, 314 F.3d 1313, 1355 (Fed. Cir. 2003) (holding that "a presumption arises that both the claimed and unclaimed disclosures in a prior art patent are enabled").

Moreover, as a practical matter, a POSA would have known that, in water, azelastine hydrochloride is "sparingly soluble" (as it is in Astelin®, Ex. 1008, 3147) and fluticasone propionate remains in "suspension" (as it does in Flonase®, Ex. 1010, 1), and that these two ingredients together in water would retain their respective behaviors without any problems (exactly as in Dymista®). Ex. 1004, ¶67. Neither Segal nor Cramer mentioned any special mixing techniques or observed any problems when combining azelastine and fluticasone. See generally Ex. 1011; Ex. 1012.

While Patent Owner alleged during prosecution of the '620 Patent that Example III of Cramer (combining azelastine with a different steroid) was "inoperable" and "unacceptable" (Ex. 1002, 284-287), because each of the active ingredients in Example III 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 Ex. 1003, ¶ 115. In fact, it is clear Patent Owner's opinion does not reflect on whether the composition

will manage symptoms, but rather whether it conforms to a personal definition of a "preferable" nasal spray composition. Id., ¶ 116. A POSA's understanding of the operability of Cramer's Example III in managing symptoms would not be so restricted. Id. Indeed, while Patent Owner alleged the hypertonicity of Example III made it unacceptable as a nasal spray (Ex. 1002, 287 (¶ 9)), Patent Owner ignored FDA-approved intranasal drugs with higher tonicity and daily hypertonic saline treatments for inflamed sinuses. Ex. 1004, ¶ 71; 1046, 9, 26-27. Moreover, modifying Cramer's Example III into a "preferred" nasal composition would have been a routine undertaking for a POSA, as evidenced by Cramer itself (Ex. 1004, ¶¶ 65-71) as well as being admitted by Patent Owner (Ex. 1001, 7:67-8:2). See Pharmastem Therapeutics, Inc. v. Viacell, Inc., 491 F.3d 1342, 1362 (Fed. Cir. 2007) ("Admissions in the specification regarding the prior art are binding on the patentee for purposes of a later inquiry into obviousness.").

4. Combination yields predictable results

Combining azelastine and fluticasone in a nasal spray yields predictable results. Indeed, the results were actually predicted by the prior art. Both Cramer and Segal taught that a single dual-ingredient spray (containing both an antihistamine and corticosteroid) is superior to the individual monotherapies. Cramer states: "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." Ex. 1011, 2:25-27 (emphasis added). Cramer discloses "fluticasone" as a nasal glucocorticoid and "azelastine" as a leukotriene inhibiting antihistamine. Id., 2:36-44; Ex. 1003¶78-79. Segal states: "The use of an additional therapeutic agent in combination with an antiinflammatory agent provides additive and synergistic effects in the treatment of nasal and sinus conditions." Ex. 1012, 3:9-12 (emphasis added). Segal discloses "fluticasone proprionate" as an antiiflammatory agent and "azelastine" as a suitable antihistamine, and the disclosures of Stellato and Falser provide motivation for choosing these two ingredients from the relatively small number of options disclosed in Segal. Id., 2:25, 3: 3-4, 3:15-20; Ex. 1017, 623; Ex. 1015, 387; Ex. 1003¶¶59, 63.

Moreover, the improvement of such a combination over monotherapy by azelastine or fluticasone alone was recognized as evidenced by art teaching the co-administration of nasal sprays to enhance the treatment of rhinitis. As discussed in Section VIII(B)(2)(b) and further by Dr. Schleimer, guidelines provided by various leading entities in the field directed practitioners to prescribe concurrent use of an intranasal steroid and an intranasal antihistamine. Ex. 1003, ¶¶ 98-100; Ex. 1021, 536; Ex. 1022, Fig. 1, 125. Such concurrent use was prescribed where monotherapy alone did not provide an adequate effect. Ex. 1022, Fig.1, 125.

These guidelines highlighted the advantages of using a combination of nasally administered azelastine and nasally administered fluticasone propionate. Ex. 1003, ¶100; Ex. 1022, 119-120, 124. Because the concurrent use of both azelastine nasal spray and fluticasone propionate nasal spray was recognized to provide an improved therapeutic effect, these prior art guidelines demonstrate that a POSA would reasonably expect the advantages provided by a combination nasal spray containing both active ingredients. Ex. 1003, ¶¶80-84, 98-100.

The combined effect of azelastine and fluticasone would also have been predicted based on the prior success of Advair®, a combination metered-spray solution containing fluticasone propionate and the β2-agonist salmeterol for the treatment of asthma, a condition related to allergic rhinitis. Ex. 1003, ¶84; Ex. 1020, 223 ("Scientific and clinical data support complementary mechanisms of action of these two classes of drugs in achieving a superior level of asthma control and increasing quality of life ….); Ex. 1025, 1213 ("Based on evidence of a complementary effect, … salmeterol and fluticasone propionate have been combined in a single inhalation device.").

C. Ground 3: Claims 42-44 are obvious over Hettche, Phillipps, Segal, and Flonase® Label

Claims 42-44 are unpatentable under 35 U.S.C. §103(a) over Hettche, Phillipps, Segal, and the Flonase® Label. As claims 42-44 depend from claims 1,

24 and 25, respectively, the combination of Hettche, Phillipps and Segal is relied on for the reasons explained above in Section VIII(B) (including the understanding and knowledge of a POSA). The Flonase® Label was published in 1998. Therefore, each of Hettche, Phillipps, Segal, and the Flonase® Label is prior art under 35 U.S.C. §102(b), pre-AIA.

Claims 42-44 would have been obvious because they claim known excipients used for their known purposes and are expressly taught for use with azelastine and/or fluticasone propionate by the cited references.

- Edetate disodium is disclosed in Hettche as a preservative (Ex. 1007, 2:46-50) and described as preferably used with the preservative, benzalkonium chloride (*Id.*, 4:4-6). Ex. 1004,¶¶ 52-55; s*ee also* Ex. 1033, 176 (describing the preservative function of edetate disodium and other edetates).
- Glycerine is described in Hettche as a preferable solvent for azelastine hydrochloride and as an isotonization agent in water (Ex. 1007, 2:35-39, 4:33-35). Ex. 1004, ¶56; *see also* Ex. 1033, 204 (describing glycerine as a "tonicity agent"). As described by Segal, it may also be used in nasal formulations as a humectant. Ex. 1012, 4:8-10.
- Microcrystalline cellulose and carboxymethylcellulose sodium are present in Flonase® (Ex. 1010, 1) and disclosed as "thickening agents" in Hettche (Ex. 1007,

4:51-60 (cellulose derivatives)). Ex. 1004, ¶¶57-60; *see also* Ex. 1033, 78, 84 (describing carboxymethylcellulose sodium as a "suspending agent" and "viscosity-increasing agent,"). Together they are widely used as in pharmaceutics for their dual suspension and thickening properties. 1004, ¶59.

- Polysorbate 80 is present in Flonase® (Ex. 1010, 1) where it serves as a "nonionic surfactant" (Ex. 1033, 375-76) that helps to disperse the fluticasone propionate. Ex. 1004, ¶¶61-62.

- Benzalkonium chloride is present in Flonase® (Ex. 1010, 1) and described as a preservative suitable for azelastine formulations by Hettche (Ex. 1007, 2:68-3:4). Ex. 1004, ¶¶ 52-55; *see also* Ex. 1033, 27 (describing benzalkonium chloride as an "antimicrobial preservative"). It is preferably used in combination with disodium edetate in azelastine nasal formulations. Ex. 1007, 4:4-6.

- Phenylethyl alcohol is present in Flonase® (Ex. 1010, 1) where it serves as an "antimicrobial preservative" (Ex. 1033, 340). Hettche also disclosed it as an excipient to be used in combination with benzalkonium chloride (Ex. 1007, 19-26). Ex. 1004, ¶¶ 52-55.

Purified water is the vehicle for Flonase® and Segal, and serves that function in Dymista®. Ex. 1010, 1; Ex. 1012, 4:4-5; Ex. 1004, ¶¶ 63-64.

Given that it was obvious to combine azelastine hydrochloride and fluticasone propionate in a single nasal formulation (*supra* Section VIII(B)) , a

POSA would have been especially motivated to look to and employ the excipients listed in the FDA-approved nasal sprays for both drugs and described in the corresponding patents, Hetche and Phillipps. The excipients were well known in the art, and were being used for the exact same functions as in the individual nasal formulations. *Id.,* ¶¶34-35. A POSA would thus have had a reasonable expectation of success in co-formulating azelastine hydrochloride and fluticasone propionate into a single nasal spray.

Nasal sprays must be preserved against microbial contamination. Ex. 1004 ¶52. Both Flonase and Astelin incorporate preservatives and a POSA would have recognized the need for preservatives in a combined formulation. Ex. 1004 ,¶ 52-55. Flonase utilizes well-known benzalkonium chloride in combination with phenylethyl alcohol, whereas Astelin uses benzalkonium chloride and edetic acid, disodium. Ex. 1010, 1, 1008, 3147; Ex. 1004, ¶53. Hettche discloses that the combination of benzalkonium chloride and edetic acid disodium is particularly preferred for azelastine formulations, and also that phenyl ethyl alcohol may be used in combination with benzalkonium chloride. Ex. 1007 4:4-6; Ex. 1004, ¶53. A POSA would be motivated to utilize these three preservatives as they were all successfully used in the nasal formulations of the individual drugs and Hettsche also indicated the suitability of phenylethyl alcohol in conjunction with benzalkonium chloride for preservation of azelastine formulations. Further a

POSA would have desired to take advantage of the potential synergistic effects of edetic acid disodium as part of the preservative formulation and would not have been concerned about using it conjunction with fluticasone propionate. Ex. 1004, ¶¶54-55.

Tonicity adjusters are widely used to adjust the isotonicity of formlations and typically have very little impact on the formulation as a whole. In seeking a tonicity adjuster for use in an azelastine/fluticasone propionate coformulation, a POSA would have been drawn to glycerine. It is a well-known example of such agents, has other beneficial functions as solvent and humectant, and is disclosed by Hettche as suitable for use with azelastine formulations. Ex. 1004, 50.

A POSA would have been motivated to include both microcrystalline cellulose and carboxymethylcellulose sodium that are present in Flonase® because together they serve as suspending and thickening agents for the suspension of fluticasone propionate and have been disclosed as useful in azelastine-containing nasal sprays. Ex. 1010, ¶1; Ex. 1007; 4:51-60; Ex. 1004, 57-60.

Similarly a POSA would have been motivated to use polysorbate 80 from the Flonase formulation in a combined formulation with azelastine hydrochloride. Polysorbate 80 is a surfactant that helps disperse the suspension of fluticasone propionate. Ex. 1010, 1. Hettche also indicates that that polyethoxylated sorbitan

fatty acid esters (of which polysorbate 80 is one) are suitable for use in azelastine formulations. Ex. 1007, 4:14-19; Ex. 1004, 55-56.

A POSA would also be motivated to use purified water in a nasal spray. Water is used in both Astelin® and Flonase®, and is disclosed for use in the nasal formulations of Hettche and Phillipps. Ex. 1008, 3147; Ex. 1010, 1; Ex. 1007, 6:19-21; Ex. 1009, 33:12-13, 32:66-34:1, 34:30-40; Ex. 1004 ¶57.

Thus, a POSA would have been motivated to combine the Flonase® and Astelin® excipients (including those suggested by Hettche) with each other because they were known to be compatible with both active drugs and would have been used for the same functions as in the individual formulations. Ex. 1004, ¶¶65-67. *See Senju Pharm. Co. v. Apotex, Inc.*, 717 F. Supp. 2d 404, 424 (D. Del. 2010) ("[O]ne skilled in the art concerned with [obtaining a certain result] would reasonably expect to achieve this goal by adding a known compatible…excipient…").

Because the excipients listed above were known for use with commercial formulations of azelastine and fluticasone propionate, a POSA would have been motivated to employ them in a combined nasal spray formulation with a reasonable expectation of success. Ex. 1004, ¶¶65-67. A POSA would have known how to prepare a formulation that contains the above excipients using "techniques well known in the art," as the '620 patent expressly admits. Ex. 1001, 7:67-8:2. *See*

Pharmastem, 491 F.3d at 1362 (admissions are binding for purposes of obviousness).

In addition to Patent Owner's admission, the art shows that a POSA was well-educated in such techniques, and knew the effects of particular excipients in the formulation and how the concentration of such excipients may be adjusted for a desired effect and/or substituted with a different excipient to obtain the desired effect. Ex. 1004 ¶¶65-67; *see also id.* ¶¶41-64. Such techniques also included adjusting the tonicity/osmolality of the formulation. Ex. 1004 ¶¶ 56, 71. Furthermore, the prior art cited in this Petition acknowledges a POSA would consider such techniques routine. For example, Cramer teaches that a fluticasone corticosteroid may be combined with azelastine hydrochloride instead of triamcinolone acetonide, further that a POSA is of the skill to modify Example III into any suitable dosage form. Ex. 1011, 6:44-52; Ex. 1004 ¶ 68.

Given that each excipient in claims 42-44 performs the "same function it had been known to perform" in Hettche, Segal and the Flonase® Label separately, the claimed combination is obvious. *KSR*, 550 U.S. at 417 (combination obvious where the patent "simply arranges old elements with each performing the same function it had been known to perform"); *see also Great Atl. & Pac. Tea Co. v. Supermarket Equip. Corp.*, 340 U.S. 147, 151 (1950) ("[M]ere aggregation of a number of old parts or elements which, in the aggregation, perform or produce no

new or different function or operation than that theretofore performed or produced by them, is not a patentable invention.")

In addition, a POSA would reasonably expect the benefits and advantages provided by the nasal formulations of claims 42-44 for similar reasons as discussed in Ground 2. *See* Section VIII(B)(4).

As shown in the claim chart below, each of claims 42, 43, and 44 recites identical additional excipients, all of which are taught for use with the claimed drugs in the cited references.

'620 Patent Claims	**Hettche (Ex. 1007), Phillipps (Ex. 1009), Segal (Ex. 1012), and Flonase® Label (Ex. 1010)**
42, 43, 44. The pharmaceutical formulation of claim [1, 24, 25], further comprising	See Claims 1, 24, and 25 above.
edetate disodium,	"The solutions or formulations preferably contain preservatives and stabilizers. These include, for example: ethylene diamine tetra-acetic acid (edetic acid) and their alkali salts (for example dialkali salts such as disodium salt…" Ex. 1007, 2:46-50. "Nasal spray or nasal drops or eye drops with 0.l % azelastine hydrochloride as active ingredient. The following are dissolved, in the following order, into 9.00 kg of water: 10 g of azelastine hydrochloride, 5 g of edetic acid disodium salt…." Ex. 1007, Example 1, 6:8-12. "The preservative used is preferably a combination of edetic acid (for example as the disodium salt) and benzalknonium chloride." *Id.*, 4:4-6.

glycerine,	"Solvents which may preferably be used for the formulations of the invention are: water, saturated aliphatic mono and polyvalent alcohols which contain 2-3 carbon atoms (for example ethanol, isopropanol, 1,2-propylene glycol, glycerine) …" Ex. 1007, 2:35-39. "In the case of dosage forms containing water, it is optionally possible to use additional isotonization agents. Isotonization agents which may, for example, be used are: … glycerine…." Ex. 1007, 4:31-34. "The compositions of the present invention may also contain a humectant to increase viscosity and effect moisturization and ciliary vitality. Suitable humectants include glycerin…" Ex. 1012, 4:8-10.
a thickening agent comprising microcrystalline cellulose and sodium carboxy methyl cellulose,	"[I]t is possible to add thickening agents to the solutions to prevent the solution from flowing out of the nose too quickly…. 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, carboxy methyl cellulose…." Ex. 1007, 4:51-60. "FLONASE Nasal Spray also contains microcrystalline cellulose and carboxymethylcellulose sodium…." Ex. 1010, 1.
polysorbate 80,	"Further auxiliary substances which may, for example, be used for the formulations of the invention are: … sorbitan fatty acid esters such as sorbitan trioleate, polyethoxylated sorbitan fatty acid esters (for example polyethoxylated sorbitan trioleate)…." Ex. 1007, 4:14-19. "FLONASE Nasal Spray also contains … polysorbate 80…." Ex. 1010, p.1.
benzalkonium chloride,	"Preferred preservatives among the quaternary ammonium compounds are … the compounds generally known as 'benzalkonium chloride.'" Ex. 1007, 2:68-3:4. "The preservative used is preferably a combination of edetic acid (for example as the disodium salt) and benzalknonium chloride." *Id.*, 4:4-6.

	"Nasal spray or nasal drops or eye drops with 0.l % azelastine hydrochloride as active ingredient. The following are dissolved, in the following order, into 9.00 kg of water: 10 g of azelastine hydrochloride, … 1.25 g of alkyl-benzyldimethylammonium chloride (benzalkonium chloride)…." Ex. 1007, Example 1, 6:8-15. "FLONASE Nasal Spray also contains … benzalkonium chloride…." Ex. 1010, 1.
phenyl ethyl alcohol,	"'Benzalkonium chloride' … may optionally be used in combination with 0.2 to 2.0, for example 0.4% (weight/ volume) of 2-phenylethanol." Ex. 1007, at 3:19-25. "FLONASE Nasal Spray also contains … 0.25% w/w phenylethyl alcohol…." Ex. 1010, 1.
and purified water.	"The following are dissolved, in the following order, into 9.00 kg of water: 10 g of azelastine hydrochloride…." Ex. 1007, Example 1, 6:10-11. "The solution obtained is diluted to 10.05 kg = 10 liters with water. The solution is filtered through a membrane filter of pore size 0.2 μm." *Id.*, Example 1, 6:19-21. "Preferred nasal formulations are nose drops or nasal sprays containing a water buffered aqueous solution as a carrier." Ex. 1012, 4:4-5. "Astelin® Nasal Spray … contains … purified water." Ex. 1008, 3147.

IX. NO SECONDARY CONSIDERATIONS OF NONOBVIOUSNESS

If Patent Owner does present secondary evidence of nonobviousness in its preliminary response, the Board should refuse consideration of that evidence, and institute trial, because "detailed consideration of [a patentee's] secondary consideration evidence may not be undertaken until [the petitioner] has had an

opportunity to test it." *Amneal Pharms. v. Supernus Pharms*., IPR2013-00368, at 12-13 (PTAB Dec. 17, 2013) (granting IPR despite submission of district court evidence of secondary considerations in preliminary response). Nevertheless, there are no secondary considerations of nonobviousness that could overcome the strong *prima facie* case presented here.

A. No Teaching Away

The "prior art as a whole" must be viewed when considering a patentee's "teaching away" argument, not merely individual references. *Merck v. Gnosis*, 808 F.3d 829, 834 (Fed. Cir. 2015). Moreover, "[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." *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc*., 567 F.3d 1314, 1327 (Fed. Cir. 2009).

Here, no references taught a POSA to avoid, or otherwise discouraged, combining a steroid and an antihistamine, much less fluticasone and azelastine specifically. A number of studies of particular oral antihistamine/intranasal steroid combinations recited benefits from such combinations, while a few found no particular benefit but also no disadvantage. Ex. 1003 ¶92.

In fact, for a intranasal antihistamine/intranasal steroid, the prior art as a whole taught *toward* co-formulating such a combination, especially the

combination of azelastine and fluticasone propionate. *Id*.; *see* Ex. 1012, 2:23-26, 3:19-20; Ex. 1022 at 124-125. A POSA further understood intranasal antihistamines such as azelastine exhibited faster onset of action and lower side effects than oral antihistamines. Ex. 1003 ¶92. Therefore, even if the efficacy of a specific oral antihistamine/intranasal steroid combination was not superior in a specific study, this would not deter a POSA's desire to combine azelastine and fluticasone propionate nor would such a result detract from the expected advantages of the intranasal combination. *Id*.

B. No unexpected results compared to closest prior art

As argued in Grounds 1 and 2, Segal discloses combining both "azelastine" and "fluticasone proprionate" in a "nasal spray" for the treatment of "allergic rhinitis." Ex. 1012, 2:22, 2:23-26, 3:19-20, 4:4-5. Thus, Patent Owner must produce evidence of unexpected results relative to the co-formulation disclosed by Segal.

Alternatively, should the Board disagree that Segal is the closest prior art, then Petitioner proposes that the concurrent use of both fluticasone propionate (Flonase®) and azelastine (Astelin®) is the closest prior art. Ex. 1003 ¶100; Ex. 1022, Fig.1, 125-126 ("combination of nasal steroids and antihistamines (oral and/or topical) is recommended"); Ex. 1024, S251 ("It is advised to use intranasal glucocorticosteroids as a first-line treatment" and to "add" "H1-antihistamines if

the major symptoms are sneezing, itching or rhinorrhea"). During prosecution, Patent Owner submitted a declaration by Joachim Maus, who claimed that Dymista® was unexpectedly superior to fluticasone propionate *monotherapy* and azelastine *monotherapy*. Ex. 1002, 312; Ex. 1003 ¶¶97-98. This analysis is flawed because the relevant comparator for Dymista® is not each monotherapy in isolation, but rather the concurrent use of fluticasone propionate (Flonase®) and azelastine (Astelin®). Ex. 1003 ¶100. Studies by Ratner show that the improvement over the monotherapies is essentially the same for both Dymista® (38% improvement) and the concurrent use of both of Flonase® and Astelin® (40% improvement). Ex. 1003 ¶¶101-102; Ex. 1045, 77 & Table 2. Thus, when the comparison is more appropriately directed to the monotherapies combined,, Ratner's results actually show that Dymista® is not superior to the concurrent use of Flonase® and Astelin®. Ex. 1003 ¶ 102. Moreover, any improvement over the individual monotherapies was expected based on the complementary mechanisms of action of the two drugs, which had already been suggested by the prior art. Ex. 1003 ¶103; Ex. 1011, 2:25-27; Ex. 1012, 3:9-12; Ex. 1023, S386.

C. No long-felt unmet need in the art

The art and knowledge at the time when the '620 patent was filed clearly refute any assertion of a long-felt but unmet need. While Patent Owner submitted a declaration by Dr. Sujeet Rajan attesting as such (Ex. 1002 at 408-409(¶¶11-13)),

this declaration excludes any discussion of combining nasal antihistamines with nasal corticosteroids and instead solely discusses combining oral antihistamines with nasal corticosteroids. Ex. 1003 ¶¶88, 95. 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 the side effects of oral antihistamines. Ex. 1003 ¶¶89-94. Moreover, Segal expressly teaches nasal co-formulations of fluticasone and azelastine, and specifically highlights that such co-formulation allows for more convenient use by patients. Ex. 1003 ¶¶94-95; Ex. 1012, 2:2-3; *but see* Ex. 1002, 408-409(¶¶13, 15). Thus, the "long-felt but unmet need" asserted by Patent Owner was met prior to, and independently of, the '620 patent. Ex. 1003 ¶95.

D. Blocking patents negate secondary considerations

Although a POSA would have found it desirable and technically feasible to combine azelastine hydrochloride and fluticasone propionate into a single nasal spray, the POSA would have been legally blocked by the Phillipps and Hettche patents from commercializing such a product until May 2011. This undercuts any nexus to alleged "commercial success" or "unmet need."

Phillipps, which issued in 1982 and expired in May 2004, covers fluticasone propionate. Ex. 1009, cl.13. Phillipps broadly covered the compound for any use and was not limited to formulations consisting solely of fluticasone propionate.

Hettche covers a "method for the treatment of irritation or disorders of the nose and eye which comprises applying directly to nasal tissues or to the conjunctival sac of the eyes a medicament which *contains* a member selected from the group consisting of azelastine and its physiologically acceptable salts." Ex. 1007, cl.1 (emphasis added). Hettche issued in 1992 and expired in May 2011. The word "contains" is an open-ended term synonymous with "comprising" and thus does not limit the claim to medicaments consisting solely of azelastine and its physiologically acceptable salts. *See Mars Inc. v. H.J. Heinz Co*., 377 F.3d 1369, 1376, 71 USPQ2d 1837, 1843 (Fed. Cir. 2004) ("[L]ike the term 'comprising,' the terms 'containing' and 'mixture' are open-ended.").

Petitioner is not aware of any licenses granted to any third parties by the owners of the Phillipps and Hettche patents. Therefore, a POSA would have been blocked from commercializing a combined azelastine hydrochloride/fluticasone propionate product as of the priority dates of the '620 patent (2002-2003). This fact significantly undermines any argument of commercial success of Dymista®. *See Galderma Labs., L.P. v. Tolmar, Inc*., 737 F.3d 731, 740 (Fed. Cir. 2013) ("Where market entry by others was precluded due to blocking patents, the

inference of non-obviousness of the asserted claims, from evidence of commercial success, is weak.") (alternations and internal quotations omitted).

E. Commercial success evidence is weak and lacks nexus

If Patent Owner nonetheless attempts to argue that Dymista® is a commercial success, the burden is on Patent Owner to show a nexus between any objective indicia of nonobviousness and the "specific invention claimed." *King Pharms., Inc. v. Eon Labs, Inc.*, 616 F.3d 1267,1281 (Fed. Cir. 2010). During prosecution, Patent Owner submitted a self-serving declaration by its employee, Mr. Nikhil Chopra, which argued that Duonase®, an embodiment of the '620 patent in India, was a commercial success in India. Ex. 1002, 277. Mr. Chopra's analysis is flawed given that there was no evidence of the marketing spent on promoting Duonase® in India, and no mention of Duonase®'s price or the price of competitors' products. *Wm. Wrigley*, 683 F.3d at 1363 (rejecting commercial success argument when numerous factors such as marketing efforts were not accounted for).

Moreover, Patent Owner bears the burden to show "significant sales in a relevant market." *Ecolochem Inc. v. S.Cal. Edison Co.*, 227 F.3d 1361, 1377 (Fed. Cir. 2000). However, Mr. Chopra failed to define the relevant market and merely compared Duonase® to other drugs containing fluticasone propionate and azelastine hydrochloride. This comparison thus ignores other drugs useful in the

treatment of allergic rhinitis. As to Dr. Chopra's evidence of absolute sales, this information does not show commercial success without additional evidence "as to what sales would normally be expected in the market." *Ex parte Jellá*, 90 USPQ2d 1009, 1012 (BPAI 2008) (precedential). Since Mr. Chopra did not produce any record evidence of what level of sales should have been expected to which the actual sales of Duonase® can be compared, and because the evidence of Duonase®'s market share is flawed, Patent Owners have not borne the burden of production on commercial success. *Torrent Pharms. v. Novartis AG*, IPR2014-00784, Paper 12, at 30 (PTAB Sept. 24, 2015). In any event, even a highly successful product cannot alone overcome the strong showing of obviousness that Petitioner has made in this case. *Media Techs. Licensing, LLC v. Upper Deck Co.*, 596 F.3d 1334, 1339 (Fed. Cir. 2010).

X. NO BASIS TO DENY THE PETITION UNDER 35 U.S.C. § 325(D)

The instant IPR petition is the first time the '620 patent has been challenged in the Office since the patent issued. During original prosecution, the examiner never cited Segal, Hettche, Phillipps, or the Flonase® Label in any Office action rejection, nor did the examiner discuss those references in the "Reasons for Allowability." Ex. 1002, 143-46. Moreover, the instant IPR petition addresses specifically why the "secondary considerations" declarations submitted during

prosecution lack legal and factual merit. Accordingly, there is no basis to deny the instant petition under 35 U.S.C. § 325(d) based on any allegation that the same or substantially the same prior art or arguments was previously presented to the Office.

CONCLUSION

For the foregoing reasons, Petitioner respectfully requests that trial be instituted and that the challenged claims be canceled.

Respectfully submitted,

Dated: February 2, 2017

By: */Joseph P. Meara/*

Reg. No. 44,932

Counsel for Petitioner

CERTIFICATE OF COMPLIANCE

The undersigned certifies that this brief complies with the type-volume limitations of 37 CFR § 42.24(a)(1)(i). This brief (including figure labels and annotations) contains 12,617 words as calculated by the "Word Count" feature of Microsoft Word 2010, the word processing program used to create it, and manual counting of the annotations in the figures.

The undersigned further certifies that this brief complies with the typeface requirements of 37 CFR § 42.6(a)(2)(ii) and typestyle requirements of 37 CFR § 42.6(a)(2)(iii). This brief has been prepared in a proportionally spaced typeface using Microsoft Word 2010 in Times New Roman 14 point font.

By: */Joseph P. Meara/*

Reg. No. 44,932

Counsel for Petitioner

CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of the foregoing Petition for *Inter Partes* Review and all Exhibits and other documents filed together with the Petition were served on February 2, 2017, by delivering a copy via Express mail directed to the attorneys of record for the '620 Patent at the following address:

CONLEY ROSE, P.C.
5601 GRANITE PARKWAY, SUITE 500
PLANO TX 75024

Patent Owner's correspondence address of record '620 Patent

Mark Fox Evens, Esq.
Dennies Varughese, Esq.
Uma N. Everett, Esq.
Sterne, Kessler, Goldstein & Fox P.L.L.C.
1100 New York Ave. NW Suite 600
Washington, DC 20005

Additional address known to Petitioner as likely to effect service

By: */Joseph P. Meara /*

Joseph P. Meara
Counsel for Petitioner