UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GLAXOSMITHKLINE CONSUMER HEALTHCARE HOLDINGS (US), LLC,
Petitioner

v.

CIPLA LTD.,
Patent Owner

Case No. IPR2020-00368
U.S. Patent No. 8,163,723

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 8,163,723

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I. INTRODUCTION

Petitioner GlaxoSmithKline Consumer Healthcare Holdings (US) LLC ("Petitioner" or "GSK") requests *inter partes* review ("IPR") of all claims 1-28 ("the challenged claims") of U.S. Patent No. 8,163,723 ("*'723 Patent*"; Ex. 1002) assigned to Cipla Ltd. ("Patent Owner" or "Cipla") under 35 U.S.C. §§ 311-319 and 37 C.F.R. § 42.100 *et seq*. This Petition demonstrates that there is a reasonable likelihood that Petitioner will prevail in proving, by a preponderance of the evidence, that the challenged claims are unpatentable over the prior art. Petitioner certifies that the *'723 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.

II. IDENTIFICATION OF CHALLENGE AND PRECISE RELIEF REQUESTED

The challenged claims are unpatentable and should be cancelled based on the following grounds:

Ground	Claim(s)	Basis
1	1-28	Obvious over *PDR 1999* (Ex. 1010) in view of *Segal* (Ex. 1012)
2	1-28	Obvious over *Cramer* (Ex. 1011) in view of *PDR 1999* (Ex. 1010)

III. PRIORITY DATE

The purported priority date of the *'723 Patent* is June 14, 2002, based on Great Britain Patent Application No. GB 0213739.6. (*'723 Patent*, (30); *id.*, 1:4-15.) Because the undisputed publication date of each reference relied upon in this Petition is well before that date, Petitioner takes no position for purposes of this Petition regarding the sufficiency of this priority claim and refers to June 14, 2002 as "the priority date."

IV. LEVEL OF ORDINARY SKILL

The application field for the '*723 Patent* is pharmaceutical formulations for allergy/immunology. A person having ordinary skill in the art ("POSA") as of the priority date would have been part of a multidisciplinary team including a clinician/scientist and formulator. (*Schleimer*, ¶ 21; *Donovan*, ¶ 21.) The clinician/scientist would have had an M.D., a Pharm. D., or a Ph.D. in the field of allergy/immunology and/or pharmacology (or the equivalent), and at least three years of experience in treating or researching the treatment of allergic rhinitis, including with nasally administered steroids and antihistamines. (*Schleimer*, ¶ 22.) The formulator would have had a bachelor's degree in chemistry, biology, chemical engineering, pharmaceutics, or a related field, and three to five years of experience in developing nasal dosage forms. (*Donovan*, ¶ 23.) A higher level of

education or specific skill might make up for less experience, and vice versa. (*Schleimer*, ¶ 22; *Donovan*, ¶ 23.)

V. THE CHALLENGED CLAIMS ARE UNPATENTABLE

A. Summary

The challenged claims are directed to methods of using formulations comprising azelastine and fluticasone. (*'723 Patent*, claims.) Nasal sprays comprising each of these ingredients were known in the prior art and approved by the U.S. Food and Drug Administration ("FDA") as safe and effective for allergic rhinitis (*PDR 1999*). Co-formulation of the two ingredients into a single formulation, and the benefits of such co-formulations, were also known in the prior art (*Segal*; *Cramer*). A POSA would have been motivated to combine these prior art teachings to arrive at the claimed invention with a reasonable expectation of success, rendering the claims unpatentable as obvious under 35 U.S.C. § 103.

B. Ground 1: Obviousness over *PDR 1999* in View of *Segal*

1. Independent Claim 1

Claim 1 recites "[a] method for the prophylaxis or treatment in a mammal of a condition for which administration of one or more anti-histamines and/or one or more steroids is indicated, comprising intranasal administration to said mammal of a therapeutically effective amount of a pharmaceutical composition comprising (a) azelastine, or a pharmaceutically acceptable salt thereof; and (b) a

pharmaceutically acceptable ester of fluticasone." Claim 1 would have been obvious over *PDR 1999* in view of *Segal*. (*Schleimer*, ¶¶ 111, 113; *Donovan*, ¶ 90.)

a) Scope of the Prior Art

PDR 1999 in view of *Segal* teaches all the limitations of claim 1. (*Schleimer*, ¶ 114.) *PDR 1999* discloses prescribing information for Astelin® Nasal Spray and Flonase® Nasal Spray (*Schleimer*, ¶ 41, 64; *Donovan*, ¶¶ 28, 45), and was publicly available to and in actual use by researchers no later than the first week of April 2000 (*Greenhill*, ¶ 15). *PDR 1999* discloses that Astelin® is a pharmaceutical composition "for intranasal administration" that comprises "azelastine hydrochloride," which is a pharmaceutically acceptable salt of azelastine, and "is indicated for the treatment of the symptoms of seasonal allergic rhinitis," which is a condition for which administration of one or more antihistamines is indicated. (*PDR 1999*, 3191-3192; *Schleimer*, ¶ 114.) *PDR 1999* thus teaches a method for treating a condition for which administration of one or more antihistamines is indicated using a pharmaceutical composition for intranasal administration comprising a pharmaceutically acceptable salt of azelastine. (*PDR 1999*, 3191-3192; *Schleimer*, ¶ 114.)

PDR 1999 discloses that Flonase® is a pharmaceutical composition for "intranasal" administration that comprises "fluticasone propionate," which is a

pharmaceutically acceptable ester of fluticasone, and "is indicated for the management of the nasal symptoms of seasonal and perennial allergic rhinitis," which is a condition for which administration of one or more steroids is indicated. (*PDR 1999*, 1122-1124; *Schleimer*, ¶ 115.) *PDR 1999* thus teaches a method for treating a condition for which administration of one or more steroids is indicated using a pharmaceutical composition for intranasal administration comprising a pharmaceutically acceptable ester of fluticasone. (*PDR 1999*, 1122-1124; *Schleimer*, ¶ 115.)

Segal discloses pharmaceutical compositions for intranasal administration "comprising a topical anti-inflammatory agent," such as "fluticasone propionate," and "at least one additional therapeutic agent," such as "azelastine." (*Segal*, 2:18-20, 2:23-26, 3:19-20, 4:20-24; *Schleimer*, ¶ 116.) *Segal*'s formulations "are useful for the treatment of nasal and sinus conditions, for example allergic rhinitis," which is a condition for which administration of one or more antihistamines and/or one or more steroids is indicated. (*Segal*, 2:20-21; *Schleimer*, ¶ 116.) *Segal* thus discloses a method for treating a condition for which administration of one or more antihistamines and/or one or more steroids is indicated using a pharmaceutical composition for intranasal administration comprising azelastine and a pharmaceutically acceptable ester of fluticasone. (*Segal*, 2:18-21, 2:23-26, 3:19-20, 4:20-24; *Schleimer*, ¶ 116.)

b) Motivation to Modify

A POSA would have been motivated to modify the teachings of *PDR 1999* in view of *Segal* to arrive at the claimed invention. (*Schleimer*, ¶ 117.) As discussed above under "Scope of the Prior Art" (section V.B.1.a), *PDR 1999* teaches (1) a method of treating a condition for which administration of one or more antihistamines is indicated using a pharmaceutical composition for intranasal administration comprising a pharmaceutically acceptable salt of azelastine, and (2) a method for treating a condition for which administration of one or more steroids is indicated using a pharmaceutical composition for intranasal administration comprising a pharmaceutically acceptable ester of fluticasone. (*PDR 1999*, 1122-1124, 3191-3192; *Schleimer*, ¶ 118.) *Segal* teaches a method for treating a condition for which administration of one or more antihistamines and/or one or more steroids is indicated using a pharmaceutical composition for intranasal administration comprising both azelastine and a pharmaceutically acceptable ester of fluticasone. (*Segal*, 2:18-21, 2:23-26, 3:19-20, 4:20-24; *Schleimer*, ¶ 118.)

A POSA would have been motivated to modify these teachings of *PDR 1999* in view of *Segal* to co-formulate the ingredients into a pharmaceutical composition for intranasal administration because *Segal* teaches the benefits of such a co-formulation. (*Segal*, 1:12-2:3, 3:3-12; *Schleimer*, ¶ 118.) For example, *Segal* discloses that co-formulation "allow[s] the convenient administration of an

antiinflammatory agent and at least one additional therapeutic agent in a single topical nasal composition," and "provides additive and synergistic effects in the treatment of nasal and sinus conditions." (*Segal*, 3:3-12; *Schleimer*, ¶ 118.) *Segal* also discloses that co-formulation overcomes "significant disadvantages" of administering the ingredients separately, such as limits on "[t]he volume of liquid that can effectively be applied nasally," requirements for "sufficient contact time [with] the surface area of the nostril," limits on "the delivery volume per actuation," "patient inconvenience," and compromised "[p]atient compliance." (*Segal*, 1:12-2:3; *Schleimer*, ¶ 118.)

A POSA would have been motivated to use azelastine hydrochloride and fluticasone propionate specifically, because *PDR 1999* teaches that both were FDA-approved as safe and effective for allergic rhinitis, a condition for which administration of one or more antihistamines and/or one or more steroids is indicated. (*PDR 1999*, 1122-1124, 3191-3192; *Schleimer*, ¶ 119.)

The teachings of *PDR 1999* in view of *Segal* are supported by similar prior art disclosures. (*Drouin*, 341, 347; *Brooks*, 199; *Dykewicz*, 505; *Berger*, 536; *Cauwenberge*, 119-120, 125; *Spector*, 387; *Bousquet*, S189-S192; *Schleimer*, ¶¶ 120-122.) For example, a POSA would have been motivated to co-formulate the ingredients to "maximize" therapeutic and clinical efficacy (*Drouin*, 341, 347), and to "better and sooner" remit symptoms (*Brooks*, 199). (*Schleimer*, ¶ 120.) A

POSA would have known as of the priority date, as exemplified in the prior art, that azelastine and fluticasone should be co-administered when one did not adequately control symptoms. (*E.g.*, *Dykewicz*, 505 ("[Intranasal antihistamines] are appropriate…as part of combination therapy with nasal corticosteroids…."); *Berger*, 536 ("[F]or those patients whose symptoms are not adequately controlled…often a combination of both an antihistamine with an intranasal corticosteroid is prescribed."); *Cauwenberge*, 125 ("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, a combination of nasal steroids and antihistamines (oral and/or topical) is recommended…."); *Schleimer*, ¶ 122.)

A POSA would have also been motivated to co-formulate the two ingredients because a POSA would have known, as exemplified in the prior art, that their mechanisms of action are complementary. (*Spector*, S387; *Cauwenberge*, 119-120; *Bousquet*, S189-S192; *Schleimer*, ¶ 121.) A POSA would have known as of the priority date, as exemplified in the prior art, that allergic rhinitis includes an early-phase reaction and a late-phase reaction, and that "[o]ptimal treatment…can be achieved only by managing both." (*Spector*, S387; *Schleimer*, ¶ 121.) A POSA would have also known, as exemplified in the prior art, that early-phase reaction symptoms "are most effectively managed by an H_1-receptor antagonist," such as azelastine, and that late-phase reaction symptoms

"are best managed with a corticosteroid," such as fluticasone propionate. (*Spector*, S387; *see also Cauwenberge*, 119-120 (disclosing that azelastine is a "highly specific H_1-receptor antagonist" and that fluticasone propionate is a "topical corticosteroid[]"); *Bousquet*, S189-S192 (disclosing that allergic rhinitis includes an early-phase reaction and a late-phase reaction); *Schleimer*, ¶ 121.)

c) Reasonable Expectation of Success

A POSA would have had a reasonable expectation of success in modifying *PDR 1999* in view of *Segal* to arrive at the claimed invention. (*Schleimer*, ¶ 123.) *PDR 1999* teaches that both Astelin® and Flonase® were FDA-approved as safe and effective for allergic rhinitis. (*PDR 1999*, 1122-1124, 3191-3192; *Schleimer*, ¶ 125.) A POSA would have reasonably expected based on this teaching in *PDR 1999* that a pharmaceutical composition for intranasal administration comprising the two ingredients would likewise be useful for treating allergic rhinitis, a condition for which one or more antihistamines and/or one or more steroids is indicated. (*PDR 1999*, 1122-1124, 3191-3192; *Schleimer*, ¶ 125.)

A POSA would have also had a reasonable expectation of success based on *Segal*'s disclosures that co-formulations of the ingredients "provide[] additive and synergistic effects in the treatment of nasal and sinus conditions," "can be conveniently administered nasally to a human subject…to elicit the desired therapeutic effect," and "may be administered in the form of a nasal spray or nose

drops." (*Segal*, 3:9-12, 4:20-24; *Schleimer*, ¶ 124.) The reasonable expectation of success for the modification of *PDR 1999* in view of *Segal* is supported by similar prior art disclosures, as discussed above under "Motivation to Modify" (section V.B.1.b). (*Schleimer*, ¶ 126.)

A POSA would have also had a reasonable expectation of success in preparing the pharmaceutical compositions of the claim. (*Donovan*, ¶ 158.) For example, *PDR 1999* discloses pharmaceutical compositions for "intranasal" administration comprising "azelastine hydrochloride" or "fluticasone propionate." (*PDR 1999*, 1122-1124, 3191-3192; *Donovan*, ¶ 155.) A POSA would have had a reasonable expectation of success in preparing a co-formulation of the two ingredients based on this disclosure in *PDR 1999*. (*PDR 1999*, 1122-1124, 3191-3192; *Donovan*, ¶ 155.) A POSA would have also had a reasonable expectation of success in preparing the pharmaceutical compositions of the claim based on *Segal*'s disclosure that "[t]he formulation of pharmaceutical compositions is generally known in the art and reference can be conveniently made to standard text such as [*Remington*]." (*Segal*, 4:1-3; *Donovan*, ¶ 156.) Moreover, the *'723 Patent* acknowledges that all of its examples involving azelastine and fluticasone "are prepared by techniques well known in the art." (*'723 Patent*, 7:67-8:2, Examples 1, 3-14; *Donovan*, ¶ 159.)

2. Dependent Claim Limitations

Claims 2-28 are dependent claims that recite limitations as discussed below. (*Schleimer*, ¶ 108; *Donovan*, ¶ 87.) Each of these dependent claims would have been obvious over *PDR 1999* in view of *Segal* for the reasons discussed above for independent claim 1 (section V.B.1) and for the reasons discussed below. (*Schleimer*, ¶ 111; *Donovan*, ¶ 90.)

a) Azelastine Hydrochloride (Dependent Claim 2); Fluticasone Propionate (Dependent Claim 3)

Claims 2 and 3, which depend from claim 1, recite "azelastine HCl" and "fluticasone propionate," respectively. Using azelastine hydrochloride and/or fluticasone propionate in the compositions of the claims would have been obvious. (*Schleimer*, ¶¶ 131, 135.)

PDR 1999 discloses that Astelin® comprises "azelastine hydrochloride" as its active ingredient, and that Flonase® comprises "fluticasone propionate" as its "active ingredient." (*PDR 1999*, 1122, 3191; *Schleimer*, ¶¶ 131, 135.) *Segal* discloses that "fluticasone propionate" is "the anti-inflammatory agent" in a "preferred embodiment" of its co-formulation, which may also comprise "azelastine." (*Segal*, 2:23-26, 3:19-20; *Schleimer*, ¶ 135.) A POSA would have been motivated to use azelastine hydrochloride and/or fluticasone propionate, and had a reasonable expectation of success, based on these disclosures in *PDR 1999*

and *Segal*, and for the reasons discussed above for independent claim 1 (section V.B.1). (*Schleimer*, ¶¶ 131, 135.)

b) Concentrations of Azelastine and Fluticasone (Dependent Claims 10, 12-14)

Claim 10, which depends from claim 1, recites that the pharmaceutically acceptable ester of fluticasone is "in an amount from about 50 micrograms/ml to about 5 mg/ml of the composition."[1] Claim 12, which depends from claim 1, recites "from about 0.0005% to about 2% (weight/weight) of azelastine or a pharmaceutically acceptable salt of azelastine, and from about 0.0357% to about 1.5% (weight/weight) of a pharmaceutically acceptable ester of fluticasone." Claim 13, which depends from claim 12, recites "from about 0.001% to 1% (weight/weight) of azelastine or a pharmaceutically acceptable salt of azelastine, and from about 0.0357% to about 1.5% (weight/weight) of a pharmaceutically acceptable ester of fluticasone." Claim 14, which depends from claim 12 recites "0.1% or 0.15% (weight/weight) of azelastine HCl and from about 0.0357% to about 1.5% (weight/weight) of fluticasone propionate or fluticasone valerate." Using these concentrations of azelastine hydrochloride and fluticasone propionate

[1] Micrograms may be abbreviated as "mcg" or "µg"; milligrams may be abbreviated as "mg"; milliliters may be abbreviated as "mL" or "ml"; and grams may be abbreviated as "g." (*Schleimer*, ¶ 26; *Donovan*, ¶ 26.)

(or more broadly, a pharmaceutically acceptable salt of azelastine and a pharmaceutically acceptable ester of fluticasone) in the compositions of the claims would have been obvious. (*Schleimer*, ¶¶ 170, 181, 190, 199.)

PDR 1999 discloses that Astelin® "contains 0.1% azelastine hydrochloride," which is within the claimed ranges for claims 12 and 13 and the same as a claimed concentration for claim 14. (*PDR 1999*, 3191; *Schleimer*, ¶¶ 181, 190, 199.) *PDR 1999* discloses that Flonase® comprises "0.05% (w/w)" fluticasone propionate, which is within the claimed ranges for claims 12-14. (*PDR 1999*, 1122; *Schleimer*, ¶¶ 182, 191, 200.) The concentration of 0.05% (w/w) fluticasone propionate that is disclosed in *PDR 1999* equals 0.5 mg/mL, which is within the claimed range of from about 50 µg/mL (or 0.05 mg/mL) to about 5 mg/mL of fluticasone propionate for claim 10. (*PDR 1999*, 1122; *Schleimer*, ¶ 170.)

A POSA would have been motivated to use the claimed concentrations of azelastine hydrochloride and fluticasone propionate (or more broadly, a pharmaceutically acceptable salt of azelastine and a pharmaceutically acceptable ester of fluticasone), and had a reasonable expectation of success, based on these disclosures in *PDR 1999*, and for the reasons discussed above for independent claim 1 (section V.B.1). (*Schleimer*, ¶¶ 172, 184, 193, 202.) Moreover, the '*723 Patent* does not disclose that the claimed concentrations of azelastine

hydrochloride and fluticasone propionate are critical. (*See generally '723 Patent*; *Schleimer*, ¶¶ 183, 192, 201.)

c) Nasal Drops, Nasal Spray, Insufflation Powder (Dependent Claims 4, 5, 6)

Claims 4, 5, and 6 each depend from independent claim 1 and recite, respectively, that the pharmaceutical composition is in the form of "a nasal spray," "nasal drops," and "an insufflation powder." Preparing the compositions of the claims as a nasal spray, nasal drops, or an insufflation powder would have been obvious. (*Schleimer*, ¶¶ 139, 143, 148; *Donovan*, ¶ 92.) *PDR 1999* discloses that both Astelin® and Flonase® are "nasal sprays." (*PDR 1999*, 1122, 3191; *Schleimer*, ¶ 139.) *Segal* discloses that its "compositions may be administered in the form of a nasal spray or nasal drops." (*Segal*, 4:23-24; *Schleimer*, ¶¶ 139, 143.) A POSA would have known as of the priority date, as exemplified in the prior art such as *Remington*, that "insufflations" are "powders" that are also an acceptable "dosage form" for pharmaceuticals. (*Remington*, 1598-1599, 1601; *Donovan*, ¶ 93.) A POSA would have also known, as exemplified in the prior art such as *Hettche*, that compositions comprising azelastine or pharmaceutically acceptable salts thereof may be formulated as an "insufflatable powder." (*Hettche*, 2:12-17, 3:37-39, 3:48-55, 5:51-53; *Donovan*, ¶ 94.) A POSA would have been motivated to prepare the composition as a nasal spray, nasal drops, or an insufflation powder,

and had a reasonable expectation of success, based on these disclosures in *PDR 1999* and *Segal*, and for the reasons discussed above for independent claim 1 (section V.B.1). (*Donovan*, ¶ 95; *Schleimer*, ¶¶ 139, 143, 148.)

d) Human (Dependent Claim 7)

Claim 7 depends from independent claim 1 and recites that the "mammal is a human." Using the compositions of the claims in a human would have been obvious. (*Schleimer*, ¶ 152.) *PDR 1999* teaches that both Astelin® and Flonase® were FDA-approved as safe and effective for treating allergic rhinitis in humans. (*PDR 1999*, 1122-1124, 3191-3192; *Schleimer*, ¶ 152.) A POSA would have been motivated to use the composition in a human, and had a reasonable expectation of success, based on these disclosures in *PDR 1999*, and for the reasons discussed above for independent claim 1 (section V.B.1). (*Schleimer*, ¶ 153.)

e) Allergic Rhinitis (Dependent Claim 8); Allergic Conjunctivitis (Dependent Claim 9)

Claims 8 and 9 depend from independent claim 1 and recite, respectively, that the condition is "allergic rhinitis" or "allergic conjunctivitis." Using the compositions of the claims for allergic rhinitis and/or allergic conjunctivitis would have been obvious. (*Schleimer*, ¶¶ 157, 164.) *PDR 1999* discloses that both Astelin® and Flonase® are indicated for "allergic rhinitis." (*PDR 1999*, 1122, 3191; *Schleimer*, ¶¶ 157-158, 164.) *Segal* discloses that its formulations "are

useful for the treatment of nasal and sinus conditions, for example allergic rhinitis or the common cold." (*Segal*, 2:20-21; *Schleimer*, ¶¶ 159, 164.) A POSA would have known as of the priority date, as acknowledged by the *'723 Patent*, that both azelastine hydrochloride and fluticasone could treat both "seasonal or perennial allergic rhinitis" and "seasonal and perennial allergic conjunctivitis." (*'723 Patent*, 1:30-34; *Schleimer*, ¶ 165.) A POSA would have been motivated to use the formulation for allergic rhinitis and/or allergic conjunctivitis, and had a reasonable expectation of success, based on these disclosures in *PDR 1999* and *Segal* and this knowledge, and for the reasons discussed above for claim 1 (section V.B.1). (*Schleimer*, ¶¶ 160, 166.)

f) Particle Size (Dependent Claim 11)

Claim 11, which depends from claim 10, recites "wherein the pharmaceutical composition has a particle size of less than 10 μm." Using a particle size of less than 10 μm for the compositions of the claims would have been obvious. (*Donovan*, ¶ 98; *Schleimer*, ¶ 177.) *PDR 1999* discloses that "Flonase® Nasal Spray is an aqueous suspension of microfine fluticasone propionate." (*PDR 1999*, 1122; *Donovan*, ¶ 99.) A POSA would have known as of the priority date, as exemplified in the prior art such as *Ansel*, that "[i]n most good pharmaceutical suspensions, the particle diameter is between 1 and 50 μm," and

that the term "microfine" in the Flonase® Nasal Spray label refers to drug particles of under 10 μm. (*Ansel*, 255; *Donovan*, ¶ 99.)

A POSA would have also known, as exemplified in the prior art such as *Phillipps*, that formulations comprising fluticasone propionate may have a micronized particle size (*Phillipps*, 34:47-49, 34:63-65, 35:12-15 (citing *BPC*, 911 in each instance)), i.e., one where "the maximum diameter of 90 per cent of the particles is not greater than 5 μm," and "the diameter of none of the particles is greater than 50 μm" (*BPC*, 911). (*Donovan*, ¶ 100.) A POSA would have been motivated to use a particle size of less than 10 μm for the composition, and had a reasonable expectation of success, based on these disclosures in *PDR 1999* and this knowledge, and for the reasons discussed above for claim 1 (section V.B.1). (*Id.*, ¶ 101; *Schleimer*, ¶ 177.)

g) Aqueous Suspension (Dependent Claims 12-14)

Claim 12, which depends from claim 1, and claims 13 and 14, which each depends from claim 12, recite "aqueous suspension." Preparing the compositions of the claims as an aqueous suspension would have been obvious. (*Donovan*, ¶ 103; *Schleimer*, ¶¶ 186, 195, 204.) *PDR 1999* discloses that Flonase® "is an aqueous suspension." (*PDR 1999*, 1122; *Donovan*, ¶ 104.) A POSA would have known as of the priority date, as exemplified in the prior art such as *Remington*, that "suspensions" are a "useful" "dosage form…prepared…by suspending the

drug…in an appropriate medium." (*Remington*, 1492; *Donovan*, ¶ 105.) A POSA would have been motivated prepare the composition an aqueous suspension, and had a reasonable expectation of success, based on these disclosures in *PDR 1999* and this knowledge, and for the reasons discussed above for independent claim 1 (section V.B.1). (*Donovan*, ¶ 107; *Schleimer*, ¶¶ 186, 195, 204.)

h) pH (Dependent Claims 22, 23)

Claims 22 and 23, which depend from claim 1, recite that the pH is "from 3 to 7" and "from 4.5 to about 6.5," respectively. Using a pH in these ranges for the compositions of the claims would have been obvious. (*Donovan*, ¶ 109; *Schleimer*, ¶¶ 244, 249.) *PDR 1999* discloses that Astelin® has "pH 6.8 ± 0.3," and that Flonase® "has a pH between 5 and 7," each of which overlaps with the claimed ranges. (*PDR 1999*, 1122, 3191; *Donovan*, ¶¶ 110-111.) *Segal* discloses that "pH adjusters are known in the art and may be included." (*Segal*, 4:12-14; *Donovan*, ¶ 112.) A POSA would have been motivated to use a pH of from 4.5 to about 6.5 (or more broadly, from 3 to 7), and had a reasonable expectation of success, based on these disclosures in *PDR 1999* and *Segal*, and for the reasons discussed above for independent claim 1 (sections V.B.1). (*Donovan*, ¶ 113; *Schleimer*, ¶¶ 244, 249.)

i) Surfactant (Dependent Claims 15, 24)

Claim 15, which depends from claim 1, recites a surfactant "selected from the group consisting of a polysorbate surfactant, a poloxamer surfactant, and combinations thereof." Claim 24, which depends from claim 15, recites that "said surfactant comprises a polysorbate." Using a surfactant comprising a polysorbate (or more broadly, as recited) in the compositions of the claims would have been obvious. (*Donovan*, ¶ 115; *Schleimer*, ¶¶ 206, 251.) *PDR 1999* discloses that Flonase® comprises polysorbate 80, which is a polysorbate that acts as a surfactant. (*PDR 1999*, 1122; *Donovan*, ¶¶ 116-117.) A POSA would have been motivated to use a surfactant comprising a polysorbate (or more broadly, as recited), and had a reasonable expectation of success, based on these disclosures in *PDR 1999* and this knowledge, and for the reasons discussed above for independent claim 1 (section V.B.1). (*Donovan*, ¶ 118; *Schleimer*, ¶¶ 209, 254.)

j) Concentration of Surfactant (Dependent Claim 16)

Claim 16 depends from claim 15 and recites "from about 50 micrograms to about 1 milligram of said surfactant per ml of the formulation." Using from about 50 micrograms to about 1 milligram of surfactant per milliliter of the formulation in the compositions of the claims would have been obvious. (*Donovan*, ¶ 120; *Schleimer*, ¶ 214.) *PDR 1999* discloses that Flonase® comprises polysorbate 80, which is a polysorbate that acts as a surfactant. (*PDR 1999*, 1122; *Donovan*,

¶¶ 121-122.) A POSA would have known as of the priority date, as exemplified in the prior art such as the *Handbook*, that the polysorbate 80 disclosed in *PDR 1999* could be used in a concentration ranging from 0.1 to 15% (or about 1-150 mg/mL), which overlaps with the claimed range. (*Handbook*, 417; *PDR 1999*, 1122; *Donovan*, ¶ 122.) A POSA would have been motivated to use from about 50 micrograms to about 1 milligram of surfactant per milliliter, and had a reasonable expectation of success, based on these disclosures in *PDR 1999* and this knowledge, and for the reasons discussed above for independent claim 1 (section V.B.1). (*Donovan*, ¶ 123; *Schleimer*, ¶ 214.)

k) Glycerin (Dependent Claims 17, 25)

Claim 17, which depends from claim 1, recites a tonicity adjusting agent[2] "selected from the group consisting of sodium chloride, saccharose, glucose, glycerine, sorbitol, 1,2-propylene glycol, and combinations thereof." Claim 25, which depends from claim 17, recites that the tonicity adjusting agent "comprises glycerine." Using a tonicity adjusting agent comprising glycerin (or more broadly, as recited) in the compositions of the claims would have been obvious. (*Donovan*, ¶ 125; *Schleimer*, ¶¶ 219, 259.) *PDR 1999* discloses that Astelin® comprises

[2] "Tonicity adjusting agent," "isotonic agent," and "isotonization agent" have the same meaning to a POSA. (*Donovan*, ¶ 26.)

"sodium chloride," which acts as a tonicity adjusting agent. (*PDR 1999*, 3191; *Donovan*, ¶ 126.) *Segal* discloses that "[i]sotonic agents such as…sugars and sodium chloride are known in the art and may be included," and that its compositions may contain "glycerin." (*Segal*, 4:5-11; *Donovan*, ¶ 127.) A POSA would have known as of the priority date, as exemplified in the prior art such as the *Handbook*, that the glycerin disclosed in *Segal* may function as a tonicity adjusting agent and be selected instead of the sodium chloride disclosed in *PDR 1999* and *Segal*. (*Segal*, 4:5-11; *PDR 1999*, 3191; *Handbook*, 220; *Donovan*, ¶¶ 126-128.) A POSA would have been motivated to use a tonicity adjusting agent comprising glycerin (or more broadly, as recited), and would have had a reasonable expectation of success, based on these disclosures in *PDR 1999* and *Segal* and this knowledge, and for the reasons discussed above for independent claim 1 (section V.B.1). (*Donovan*, ¶ 129; *Schleimer*, ¶¶ 219, 259.)

l) Preservative (Dependent Claims 20, 26)

Claim 20 depends from claim 18 and recites a preservative "selected from the group consisting of edetic acid and its alkali salts, lower alkyl p-hydroxybenzoates, chlorhexidine, phenyl mercury borate, benzoic acid or a salt thereof, a quaternary ammonium compound, sorbic acid or a salt thereof, and combinations thereof." Claim 26 depends from claim 18 and recites that the "preservative comprises edetate disodium and benzalkonium chloride." Using a

preservative comprising edetate disodium and benzalkonium chloride (or more broadly, as recited) in the compositions of the claims would have been obvious. (*Donovan*, ¶ 131; *Schleimer*, ¶¶ 234, 264.) *PDR 1999* discloses that Astelin® comprises "benzalkonium chloride" and "edetate disodium," and that Flonase® comprises "benzalkonium chloride" and "phenylethyl alcohol." (*PDR 1999*, 1122, 3191; *Donovan*, ¶ 132.) *Segal* discloses that "[a]dditional agents including pharmaceutically acceptable preservatives…are known in the art and may be included." (*Segal*, 4:12-14; *Donovan*, ¶ 133.) A POSA would have been motivated to use a preservative comprising edetate disodium and benzalkonium chloride (or more broadly, as recited), and had a reasonable expectation of success, based on these disclosures in *PDR 1999* and *Segal*, and for the reasons discussed above for independent claim 1 (section V.B.1). (*Donovan*, ¶ 134; *Schleimer*, ¶¶ 234, 264.)

m) Thickening Agent (Dependent Claims 21, 27)

Claim 21, which depends from claim 18, recites a suspending agent or thickening agent "selected from the group consisting of cellulose derivatives, gelatin, polyvinylpyrrolidone, tragacanth, ethoxose, alginic acid, polyvinyl alcohol, polyacrylic acid, pectin, and combinations thereof." Claim 27, which depends from claim 18, recites "cellulose derivatives." Using a thickening agent comprising cellulose derivatives (or more broadly, as recited) in the compositions

of the claims would have been obvious. (*Donovan*, ¶ 137; *Schleimer*, ¶¶ 239, 269.) *PDR 1999* discloses that Astelin® comprises "hydroxypropyl methyl cellulose" and that Flonase® comprises "microcrystalline cellulose" and "carboxymethylcellulose sodium," all of which are cellulose derivatives that act as thickening agents. (*PDR 1999*, 1122, 3191; *Donovan*, ¶¶ 138-139.) A POSA would have been motivated to use a thickening agent comprising cellulose derivatives (or more broadly, as recited), and had a reasonable expectation of success, based on these disclosures in *PDR 1999* and this knowledge, and for the reasons discussed above for independent claim 1 (section V.B.1). (*Donovan*, ¶ 140; *Schleimer*, ¶¶ 239, 269.)

n) Buffer (Dependent Claim 19)

Claim 19 depends from claim 18 and recites "a citric acid-citrate buffer." Using a citric acid-citrate buffer in the compositions of the claims would have been obvious. (*Donovan*, ¶ 142; *Schleimer*, ¶ 229.) *PDR 1999* discloses that Astelin® comprises "citric acid" and "dibasic sodium phosphate," which together act as a buffer. (*PDR 1999*, 3191; *Donovan*, ¶ 143.) *Segal* discloses that "[p]referred nasal formulations are nose drops or nasal sprays containing a water buffered aqueous solution as a carrier." (*Segal*, 4:4-5; *Donovan*, ¶ 144.) A POSA would have known as of the priority date, as exemplified in the prior art such as *Perrin*, that the citric acid and dibasic sodium phosphate that are disclosed in *PDR 1999* may act as

a buffer across a pH range of about 2.2 to 8.0, and that a citric acid-citrate buffer may be useful across a pH range of about 3.0 to 6.2. (*Perrin*, 132, Table 10.14, 153, Table 10.45 (abbreviating dibasic sodium phosphate as Na_2HPO_4); *PDR 1999*, 3191; *Donovan*, ¶ 143.) A POSA would have used a citric acid-citrate buffer as claimed instead of the citric acid and dibasic sodium phosphate that is disclosed in *PDR 1999* as a matter of routine experimentation. (*PDR 1999*, 3191; *Donovan*, ¶ 143.) A POSA would have been motivated to use a citric acid-citrate buffer, and had a reasonable expectation of success, based on these disclosures in *PDR 1999* and *Segal* and this knowledge, and for the reasons discussed above for independent claim 1 (section V.B.1). (*Donovan*, ¶ 145; *Schleimer*, ¶ 229.)

o) Buffer, Preservative, Suspending Agent, Thickening Agent (Dependent Claim 18)

Claim 18 depends from claim 1 and recites "at least one additional component selected from the group consisting of a buffer, a preservative, a suspending agent, a thickening agent, and combinations thereof." Using at least one of these excipients in the compositions of the claims would have been obvious for the reasons discussed above under "preservative," "thickening agent," and/or "buffer" (sections V.B.2.l-n). (*Donovan*, ¶ 147; *Schleimer*, ¶ 224.)

p) Identified Excipients (Dependent Claim 28)

Claim 28, which depends from independent claim 1, recites "edetate disodium, glycerine, a thickening agent comprising microcrystalline cellulose and sodium carboxy methyl cellulose, polysorbate 80, benzalkonium chloride, phenyl ethyl alcohol, and purified water." Using these excipients in the compositions of the claims would have been obvious. (*Donovan*, ¶ 149; *Schleimer*, ¶ 274.)

PDR 1999 discloses that Astelin® "contains benzalkonium chloride (125 mcg/mL), edetate disodium, hydroxypropyl methyl cellulose, citric acid, dibasic sodium phosphate, sodium chloride, and purified water." (*PDR 1999*, 3191; *Donovan*, ¶ 150.) *PDR 1999* discloses that Flonase® "contains microcrystalline cellulose and carboxymethylcellulose sodium, dextrose, 0.02% w/w benzalkonium chloride, polysorbate 80, and 0.25% w/w phenylethyl alcohol." (*PDR 1999*, 1122; *Donovan*, ¶ 151.) *PDR 1999* thus discloses edetate disodium, benzalkonium chloride, microcrystalline cellulose and carboxymethyl cellulose sodium, polysorbate 80, phenyl ethyl alcohol, and purified water. (*Donovan*, ¶¶ 150, 151.) A POSA would have known as of the priority date, as exemplified in the prior art such as the *Remington*, that glycerin may be selected as a tonicity adjusting agent instead of the sodium chloride disclosed in *PDR 1999*. (*Remington*, 1467; *PDR 1999*, 3191; *Donovan*, ¶ 150.) *Segal* discloses co-formulations comprising "[i]sotonic agents"; "humectants" such as "glycerin"; and

"[a]dditional agents including pharmaceutically acceptable preservatives, stabilizers, flavoring agents, and pH adjusters." (*Segal*, 4:6-14; *Donovan*, ¶ 152.)

A POSA would have been motivated to use edetate disodium, glycerin, a thickening agent comprising microcrystalline cellulose and sodium carboxy methyl cellulose, polysorbate 80, benzalkonium chloride, phenyl ethyl alcohol, and purified water, and had a reasonable expectation of success, based on these disclosures in *PDR 1999* and *Segal* and this knowledge, and for the reasons discussed above for independent claim 1 (sections V.B.1). (*Donovan*, ¶ 153; *Schleimer*, ¶ 274.) Moreover, a POSA would have known as of the priority date, as exemplified in the prior art such as the *Handbook*, that the claimed excipients may be used in pharmaceutical formulations for the same functions that they are used in the compositions of the claims. (*See generally Handbook*; *Donovan*, ¶ 154.)

C. Ground 2: Obviousness over *Cramer* in View of *PDR 1999*

1. Independent Claim 1

Claim 1 recites "[a] method for the prophylaxis or treatment in a mammal of a condition for which administration of one or more anti-histamines and/or one or more steroids is indicated, comprising intranasal administration to said mammal of a therapeutically effective amount of a pharmaceutical composition comprising (a) azelastine, or a pharmaceutically acceptable salt thereof; and (b) a

pharmaceutically acceptable ester of fluticasone." Claim 1 would have been obvious over *Cramer* in view of *PDR 1999*. (*Schleimer*, ¶¶ 277, 279; *Donovan*, ¶ 162.)

a) Scope of the Prior Art

Cramer in view of *PDR 1999* teaches all the limitations of claim 1. (*Schleimer*, ¶ 280.) *Cramer* discloses "pharmaceutical formulations for nasal administration comprising…a safe and effective amount of a glucocorticoid," such as "fluticasone," and "a safe and effective amount of a leukotriene inhibiting antihistamine," such as "azelastine" or "pharmaceutically acceptable salts thereof." (*Cramer*, 2:36-44; *Schleimer*, ¶ 280.) *Cramer* discloses that its compositions may be used "for the treatment of symptoms associated with seasonal or perennial allergic rhinoconjunctivitis," which encompasses treating allergic rhinitis, a condition for which one or more antihistamines and/or one or more steroids is indicated. (*Cramer*, 2:47-51; *Schleimer*, ¶ 280.) *Cramer* thus teaches a method for treating a condition for which one or more antihistamines and/or one or more steroids is indicated using a pharmaceutical composition for intranasal administration comprising both azelastine or a pharmaceutically acceptable salt thereof and fluticasone. (*Cramer*, 2:36-44, 2:47-51; *Schleimer*, ¶ 280.)

Cramer's Example 3 discloses an "intranasally administered pharmaceutical composition" comprising "azelastine HCl" (or azelastine hydrochloride), which is

a pharmaceutically acceptable salt of azelastine, and "triamcinolone acetonide," which is a pharmaceutically acceptable ester of triamcinolone. (*Cramer*, 6:26-51; *Schleimer*, ¶ 280.) *Cramer* discloses that "substantially similar results are also obtained using, in whole or in part, equivalent amounts of other glucocorticoid agents such as fluticasone…." (*Cramer*, 6:44-46; *Schleimer*, ¶ 280.) *Cramer*'s Example 3 discloses that "the composition is used for topical nasal application to provide relief from allergy or allergy-like symptoms," which encompasses treating allergic rhinitis, and that "[t]hose skilled in the art will quickly realize other suitable ingredients, diluents and dosage forms (or readily ascertain such using routine experimentation)." (*Cramer*, 6:43-51; *Schleimer*, ¶ 280.) *Cramer*'s Example 3 thus teaches a method for treating a condition for which one or more antihistamines and/or one or more steroids is indicated using a pharmaceutical composition for intranasal administration comprising both a pharmaceutically acceptable salt of azelastine and fluticasone. (*Cramer*, 6:26-51; *Schleimer*, ¶ 280.)

PDR 1999 discloses that Astelin® is a pharmaceutical composition for "intranasal administration" that comprises "azelastine hydrochloride," which is a pharmaceutically acceptable salt of azelastine, and "is indicated for the treatment of the symptoms of seasonal allergic rhinitis," which is a condition for which administration of one or more antihistamines is indicated. (*PDR 1999*, 3191-3192; *Schleimer*, ¶ 281.) *PDR 1999* thus teaches a method for treating a condition for

which administration of one or more antihistamines is indicated using a pharmaceutical composition for intranasal administration comprising a pharmaceutically acceptable salt of azelastine. (*PDR 1999*, 3191-3192; *Schleimer*, ¶ 281.)

PDR 1999 discloses that Flonase® is a pharmaceutical composition for "intranasal" administration that comprises "fluticasone propionate," which is a pharmaceutically acceptable ester of fluticasone, and "is indicated for the management of the nasal symptoms of seasonal and perennial allergic rhinitis," which is a condition for which administration of one or more steroids is indicated. (*PDR 1999*, 1122-1124; *Schleimer*, ¶ 282.) *PDR 1999* thus discloses a method for treating a condition for which administration of one or more steroids is indicated using a pharmaceutical composition for intranasal administration comprising a pharmaceutically acceptable ester of fluticasone. (*PDR 1999*, 1122-1124; *Schleimer*, ¶ 282.)

b) Motivation to Modify

A POSA would have been motivated to modify the teachings of *Cramer* in view of *PDR 1999* to arrive at the claimed invention. (*Schleimer*, ¶ 283.) As discussed above under "Scope of the Prior Art" (section V.C.1.a), *Cramer* teaches a method for treating a condition for which one or more antihistamines and/or one or more steroids is indicated using a pharmaceutical composition for intranasal

administration comprising both a pharmaceutically acceptable salt of azelastine and fluticasone. (*Cramer*, 6:26-51; *Schleimer*, ¶ 284.) *PDR 1999* discloses methods of treating a condition for which one or more antihistamines and/or one or more steroids is indicated using a pharmaceutical composition for intranasal administration comprising a pharmaceutically acceptable salt of azelastine or a pharmaceutically acceptable ester of fluticasone. (*PDR 1999*, 1122-1124, 3191-3192; *Schleimer*, ¶ 284.)

A POSA would have been motivated to modify these teachings of *Cramer* in view of *PDR 1999* to co-formulate a pharmaceutically acceptable salt of azelastine with a pharmaceutically acceptable ester of fluticasone into a pharmaceutical composition for intranasal administration because *Cramer* teaches the benefits of such a co-formulation. (*Cramer*, 2:25-27, 3:39-40, 6:26-51; *Schleimer*, ¶ 284.) For example, *Cramer* discloses that "combining a nasal corticosteroid," such as "fluticasone," "with a leukotriene inhibiting antihistamine," such as "azelastine and pharmaceutically acceptable salts thereof," results in "improved intranasal compositions…, providing improved relief of symptoms." (*Cramer*, 2:25-27, 2:36-44; *Schleimer*, ¶ 284.) *Cramer* discloses that co-formulations "can be conveniently administered nasally to warm-blooded animals to elicit the desired therapeutic response," and that its Example 3 co-formulations specifically may be

administered intranasally "to provide relief from allergy or allergy-like symptoms." (*Cramer*, 3:39-40, 6:26-51; *Schleimer*, ¶ 284.)

A POSA would have been motivated to use azelastine hydrochloride and fluticasone propionate specifically, because *PDR 1999* teaches that both were FDA-approved as safe and effective for allergic rhinitis, a condition for which administration of one or more antihistamines and/or one or more steroids is indicated. (*PDR 1999*, 1122-1124, 3191-3192; *Schleimer*, ¶ 285.)

These teachings of *Cramer* in view of *PDR 1999* are supported by similar prior art disclosures. (*Drouin*, 341, 347; *Brooks*, 199; *Dykewicz*, 505; *Berger*, 536; *Cauwenberge*, 119-120, 125; *Spector*, 387; *Bousquet*, S189-S192; *Schleimer*, ¶¶ 286-288.) For example, a POSA would have been motivated to co-formulate the ingredients to "maximize" therapeutic and clinical efficacy (*Drouin*, 341, 347), and to "better and sooner" remit symptoms (*Brooks*, 199). (*Schleimer*, ¶ 286). A POSA would have known as of the priority date, as exemplified in the prior art, that the ingredients should be co-administered when one did not adequately control symptoms. (*E.g.*, *Dykewicz*, 505 ("[Intranasal antihistamines] are appropriate…as part of combination therapy with nasal corticosteroids or oral antihistamines."); *Berger*, 536 ("[F]or those patients whose symptoms are not adequately controlled…often a combination of both an antihistamine with an intranasal corticosteroid is prescribed."); *Cauwenberge*, 125 ("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, a combination of nasal steroids and antihistamines (oral and/or topical) is recommended…."); *Schleimer*, ¶ 288.)

A POSA would have also been motivated to co-formulate the ingredients because a POSA would have known as of the priority date, as exemplified in the prior art, that their mechanisms of action are complementary. (*Spector*, 387; *Cauwenberge*, 119-120; *Bousquet*, S189-S192; *Schleimer*, ¶ 287.) A POSA would have known as of the priority date, as exemplified in the prior art, that allergic rhinitis includes an early-phase reaction and a late-phase reaction, and that "[o]ptimal treatment…can be achieved only by managing both." (*Spector*, S387; *Schleimer*, ¶ 287.) A POSA would have also known, as exemplified in the prior art, that early-phase reaction symptoms "are most effectively managed by an H_1-receptor antagonist," such as azelastine, and that late-phase reaction symptoms "are best managed with a corticosteroid," such as fluticasone propionate. (*Spector*, S387; *see also Cauwenberge*, 119-120 (disclosing that azelastine is a "highly specific H_1-receptor antagonist" and that fluticasone propionate is a "topical corticosteroid[]"); *Bousquet*, S189-S192 (disclosing that allergic rhinitis includes an early-phase reaction and a late-phase reaction); *Schleimer*, ¶ 287.)

c) Reasonable Expectation of Success

A POSA would have had a reasonable expectation of success in modifying the teachings of *Cramer* in view of *PDR 1999* to arrive at the claimed invention. (*Schleimer*, ¶ 289.) *Cramer* discloses that co-formulations result in "improved intranasal compositions…, providing improved relief of symptoms," and "can be conveniently administered nasally to warm-blooded animals to elicit the desired therapeutic response." (*Cramer*, 2:25-27, 3:39-40; *Schleimer*, ¶ 290.) *Cramer*'s Example 3 co-formulations may be administered intranasally "to provide relief from allergy or allergy-like symptoms," and "substantially similar results" are obtained using fluticasone. (*Cramer*, 6:26-51; *Schleimer*, ¶ 290.)

A POSA would have also had a reasonable expectation of success based on *PDR 1999*'s teaching that both Astelin® and Flonase® were FDA-approved as safe and effective for allergic rhinitis. (*PDR 1999*, 1122-1124, 3191-3192; *Schleimer*, ¶ 291.) A POSA would have reasonably expected based on this teaching in *PDR 1999* that a pharmaceutical composition for intranasal administration comprising the two ingredients would likewise be useful for treating allergic rhinitis, a condition for which one or more antihistamines and/or one or more steroids is indicated. (*PDR 1999*, 1122-1124, 3191-3192; *Schleimer*, ¶ 291.) These teachings of *Cramer* in view of *PDR 1999* are supported by similar prior art

disclosures, as discussed above under "Motivation to Modify" (section V.C.1.b). (*Schleimer*, ¶ 292.)

A POSA also would have had a reasonable expectation of success in preparing the compositions of the claim based, for example, on *Cramer*'s disclosure that co-formulations may be "prepared by combining the…components utilizing conventional mixing techniques." (*Cramer*, 5:40-41; 6:8-9, 28-29; *Donovan*, ¶¶ 235, 239.) *Cramer* discloses that the ingredients can be "formulat[ed]…into a nasal dosage form, together with a nontoxic pharmaceutically acceptable nasal carrier," which "are known to those skilled in the art and are also fully disclosed in [*Remington*]." (*Cramer*, 3:39-43; *Donovan*, ¶ 236.)

A POSA would have also had a reasonable expectation of success in preparing the compositions of the claim based on *PDR 1999*'s disclosure of pharmaceutical compositions for "intranasal" administration comprising "azelastine hydrochloride" or "fluticasone propionate." (*PDR 1999*, 1122-1124, 3191-3192; *Donovan*, ¶ 237.) Moreover, the *'723 Patent* acknowledges that all of its examples involving azelastine and fluticasone "are prepared by techniques well known in the art." (*'723 Patent*, 7:67-8:2, Examples 1, 3-14; *Donovan*, ¶ 240.)

2. Dependent Claim Limitations

Claims 2-28 are dependent claims that recite limitations as discussed below. (*Schleimer*, ¶ 108; *Donovan*, ¶ 87.) Each of these dependent claims would have been obvious over *Cramer* in view of *PDR 1999* for the reasons discussed above for independent claim 1 (section V.C.1) and for the reasons discussed below. (*Schleimer*, ¶ 277; *Donovan*, ¶ 162.)

a) Azelastine Hydrochloride (Dependent Claim 2); Fluticasone Propionate (Dependent Claim 3)

Claims 2 and 3, which depend from claim 1, recite "azelastine HCl" and "fluticasone propionate," respectively. Using azelastine hydrochloride and/or fluticasone propionate in the compositions of the claims would have been obvious. (*Schleimer*, ¶¶ 297, 302.)

Cramer discloses that its compositions may comprise "azelastine" or a "pharmaceutically acceptable salt[] thereof," and *Cramer*'s Example 3 uses "azelastine HCl." (*Cramer*, 2:36-44, 6:26-51; *Schleimer*, ¶ 297.) *Cramer* discloses that the "most useful" glucocorticoids for its co-formulations "include those selected from the group consisting of beclomethasone, flunisolide, triamcinolone, fluticasone, mometasone, budesonide, pharmaceutically acceptable salts thereof and mixtures thereof." (*Cramer*, 3:15-18; *Schleimer*, ¶ 302.) *Cramer*'s Example 3 discloses a co-formulation comprising triamcinolone

acetonide, which is an ester of a glucocorticoid agent, and that "substantially similar results are also obtained using, in whole or in part, equivalent amounts of other glucocorticoid agents such as fluticasone…." (*Cramer*, 6:26-51; *Schleimer*, ¶ 302.) *PDR 1999* discloses that Astelin® comprises "azelastine hydrochloride" as its active ingredient, and that Flonase® comprises "fluticasone propionate" as its "active ingredient." (*PDR 1999*, 1122, 3191; *Schleimer*, ¶¶ 298, 303.) A POSA would have been motivated to use azelastine hydrochloride and/or fluticasone propionate, and had a reasonable expectation of success, based on these disclosures in *Cramer* and *PDR 1999*, and for the reasons discussed above for independent claim 1 (section V.C.1). (*Schleimer*, ¶¶ 298, 303.)

b) Concentrations of Azelastine and Fluticasone (Dependent Claims 10, 12-14)

Claim 10, which depends from claim 1, recites that the pharmaceutically acceptable ester of fluticasone is "in an amount from about 50 micrograms/ml to about 5 mg/ml of the composition." Claim 12, which depends from claim 1, recites "from about 0.0005% to about 2% (weight/weight) of azelastine or a pharmaceutically acceptable salt of azelastine, and from about 0.0357% to about 1.5% (weight/weight) of a pharmaceutically acceptable ester of fluticasone." Claim 13, which depends from claim 12 recites, "from about 0.001% to 1% (weight/weight) of azelastine or a pharmaceutically acceptable salt of azelastine,

and from about 0.0357% to about 1.5% (weight/weight) of a pharmaceutically acceptable ester of fluticasone." Claim 14, which depends from claim 12, recites "0.1% or 0.15% (weight/weight) of azelastine HCl and from about 0.0357% to about 1.5% (weight/weight) of fluticasone propionate or fluticasone valerate." Using these concentrations of azelastine hydrochloride and fluticasone propionate (or more broadly, a pharmaceutically acceptable salt of azelastine and a pharmaceutically acceptable ester of fluticasone) in the compositions of the claims would have been obvious. (*Schleimer*, ¶¶ 338, 350, 361, 372.)

Cramer discloses that "the antihistamine component is preferably present at a concentration of from about 0.01% to about 4%, more preferably from about 0.01% to about 1%," which overlaps with the claimed ranges of claims 12 and 13 and encompasses a claimed concentration of claim 14. (*Cramer*, 3:28-30; *Schleimer*, ¶¶ 350, 361, 372.) *Cramer* discloses that "the glucocorticoid component is preferably present at a concentration of from about 0.001% to about 0.2%, more preferably from about 0.01% to about 0.1%," which overlaps with the claimed ranges of claims 12-14. (*Cramer*, 3:19-20; *Schleimer*, ¶¶ 351, 362, 373.) The concentrations of from about 0.001% to about 0.2%, more preferably from about 0.01% to about 0.1%, that are disclosed in *Cramer* equals about 0.01-2 mg/mL, more preferably about 0.1-1 mg/mL, which overlap with the claimed

range of about 50 mcg/mL (or 0.05 mg/ml) to about 5 mg/mL of fluticasone propionate for claim 10. (*Cramer*, 3:19-20; *Schleimer*, ¶ 338.)

PDR 1999 discloses that Astelin® "contains 0.1% azelastine hydrochloride," which is within the claimed range for claims 12 and 13 and the same as the claimed concentration for claim 14. (*PDR 1999*, 3191; *Schleimer*, ¶¶ 352, 363, 374.) *PDR 1999* discloses that Flonase® comprises "0.05% (w/w)" fluticasone propionate, which is within the claimed ranges for claims 12-14. (*PDR 1999*, 1122; *Schleimer*, ¶¶ 353, 364, 375.) The concentration of 0.05% (w/w) fluticasone propionate that is disclosed in *PDR 1999* equals 0.5 mg/mL, which is within the claimed range for claim 10. (*PDR 1999*, 1122; *Schleimer*, ¶ 339.)

A POSA would have been motivated to use the claimed concentrations of azelastine hydrochloride and fluticasone propionate (or more broadly, a pharmaceutically acceptable salt of azelastine and a pharmaceutically acceptable ester of fluticasone), and had a reasonable expectation of success, based on these disclosures in *Cramer* and *PDR 1999*, and for the reasons discussed above for independent claim 1 (section V.C.1). (*Schleimer*, ¶¶ 341, 355, 366, 377.) Moreover, the '*723 Patent* does not disclose that the claimed concentrations of azelastine hydrochloride and fluticasone propionate are critical. (*See generally '723 Patent*; *Schleimer*, ¶¶ 340, 354, 365, 376.)

c) Nasal Drops, Nasal Spray, Insufflation Powder (Dependent Claims 4, 5, 6)

Claims 4, 5, and 6 each depend from independent claim 1 and recite, respectively, that the pharmaceutical composition is in the form of "a nasal spray," "nasal drops," and "an insufflation powder." Preparing the compositions of the claims as a nasal spray, nasal drops, or an insufflation powder would have been obvious. (*Schleimer*, ¶¶ 307, 311, 316; *Donovan*, ¶ 164.) *Cramer* discloses that its compositions may be formulated as a nasal "spray" or nasal "drops." (*Cramer*, 3:43-45; *Schleimer*, ¶¶ 307, 311.) *PDR 1999* discloses that both Astelin® and Flonase® are "nasal sprays." (*PDR 1999*, 1122, 3191; *Schleimer*, ¶ 307.) A POSA would have known as of the priority date, as exemplified in the prior art such as *Remington*, that "insufflations" are "powders" that are also an acceptable "dosage form" for pharmaceuticals. (*Remington*, 1598-1599, 1601; *Donovan*, ¶ 165.) A POSA would have also known, as exemplified in the prior art such as *Hettche*, that compositions comprising azelastine or pharmaceutically acceptable salts thereof may be formulated as an "insufflatable powder." (*Hettche*, 2:12-17, 3:37-39, 3:48-55; 5:51-53; *Donovan*, ¶ 166.)

A POSA would have been motivated to prepare the composition as a nasal spray, nasal drops, or an insufflation powder, and had a reasonable expectation of success, based on these disclosures in *Cramer* and *PDR 1999*, and for the reasons

discussed above for independent claim 1 (section V.C.1). (*Donovan*, ¶ 167; *Schleimer*, ¶¶ 307, 311, 316.)

d) Human (Dependent Claim 7)

Claim 7 depends from independent claim 1 and recites that the "mammal is a human." Using the compositions of the claims in a human would have been obvious. (*Schleimer*, ¶ 318.) *PDR 1999* teaches that both Astelin® and Flonase® were FDA-approved as safe and effective for treating allergic rhinitis in humans. (*PDR 1999*, 1122-1124, 3191-3192; *Schleimer*, ¶ 320.) A POSA would have been motivated to use the composition in a human, and had a reasonable expectation of success, based on these disclosures in *PDR 1999*, and for the reasons discussed above for independent claim 1 (section V.C.1). (*Schleimer*, ¶ 321.)

e) Allergic Rhinitis (Dependent Claim 8); Allergic Conjunctivitis (Dependent Claim 9)

Claims 8 and 9 depend from independent claim 1 and recite, respectively, that the condition is "allergic rhinitis" or "allergic conjunctivitis." Using the compositions of the claims for allergic rhinitis and/or allergic conjunctivitis would have been obvious. (*Schleimer*, ¶¶ 328, 334.) *Cramer* discloses that its compositions may be used "for the treatment of symptoms associated with seasonal or perennial allergic rhinoconjunctivitis," which encompasses both treating allergic rhinitis and treating allergic conjunctivitis. (*Cramer*, 2:47-51; *Schleimer*, ¶¶ 325,

332.) *PDR 1999* discloses that both Astelin® and Flonase® are indicated for "allergic rhinitis." (*PDR 1999*, 1122, 3191; *Schleimer*, ¶¶ 326-327, 332.) A POSA would have known as of the priority date, as acknowledged by the *'723 Patent*, that both azelastine hydrochloride and fluticasone could treat both "seasonal or perennial allergic rhinitis" and "seasonal and perennial allergic conjunctivitis." (*'723 Patent*, 1:30-34; *Schleimer*, ¶ 333.) A POSA would have been motivated to use the composition for allergic rhinitis and/or allergic conjunctivitis, and had a reasonable expectation of success, based on these disclosures in *Cramer* and *PDR 1999* and this knowledge, and for the reasons discussed above for independent claim 1 (section V.C.1). (*Schleimer*, ¶¶ 328, 334.)

f) Particle Size (Dependent Claim 11)

Claim 11, which depends from claim 10, recites "wherein the pharmaceutical composition has a particle size of less than 10 μm." Using a particle size of less than 10 μm for the compositions of the claims would have been obvious. (*Donovan*, ¶ 170; *Schleimer*, ¶ 346.) *PDR 1999* discloses that "Flonase® Nasal Spray is an aqueous suspension of microfine fluticasone propionate." (*PDR 1999*, 1122; *Donovan*, ¶ 171.) A POSA would have known as of the priority date, as exemplified in the prior art such as *Ansel*, that "[i]n most good pharmaceutical suspensions, the particle diameter is between 1 and 50 μm," and

that the term "microfine" in the Flonase® Nasal Spray label refers to drug particles of under 10 μm. (*Ansel*, 255; *Donovan*, ¶ 171.)

A POSA would have also known, as exemplified in the prior art such as *Phillipps*, that formulations comprising fluticasone propionate could have a micronized particle size (*Phillipps*, 34:47-49, 34:63-65, 35:12-15 (citing *BPC*, 911)), i.e., one where "the maximum diameter of 90 per cent of the particles is not greater than 5 μm," and "the diameter of none of the particles is greater than 50 μm" (*BPC*, 911). (*Donovan*, ¶ 172.) A POSA would have been motivated to use a particle size of less than 10 μm, and had a reasonable expectation of success, based on these disclosures in *PDR 1999* and this knowledge, and for the reasons discussed above for claim 1 (section V.C.1). (*Id.*, ¶ 173; *Schleimer*, ¶ 346.)

g) Aqueous Suspension (Dependent Claims 12-14)

Claim 12, which depends from claim 1, and claims 13 and 14, which each depend from claim 12, recite "aqueous suspension." Preparing the compositions of the claims as an aqueous suspension would have been obvious. (*Donovan*, ¶ 175; *Schleimer*, ¶¶ 357, 368, 379.) *Cramer* discloses that its compositions "are preferably provided as isotonic aqueous solutions, suspensions or viscous compositions." (*Cramer*, 3:8-9; *Donovan*, ¶ 176.) *PDR 1999* discloses that Flonase® "is an aqueous suspension." (*PDR 1999*, 1122; *Donovan*, ¶ 177) A POSA would have known as of the priority date, as exemplified in the prior art

such as *Remington*, that "suspensions" are a "useful" "dosage form…prepared…by suspending the drug (if it is insoluble in pharmaceutically or therapeutically acceptable solvents) in an appropriate medium." (*Remington*, 1492; *Donovan*, ¶ 178.) A POSA would have been motivated to prepare the composition as an aqueous suspension, and had a reasonable expectation of success, based on these disclosures in *Cramer* and *PDR 1999* and this knowledge, and for the reasons discussed above for claim 1 (section V.C.1). (*Donovan*, ¶ 180; *Schleimer*, ¶¶ 357, 368, 379.)

h) pH (Dependent Claims 22, 23)

Claims 22 and 23, which depend from claim 1, recite that the pH is "from 3 to 7" and "from 4.5 to about 6.5," respectively. Using a pH in these ranges for the compositions of the claims would have been obvious. (*Donovan*, ¶ 182; *Schleimer*, ¶¶ 419, 424.) *Cramer* discloses that "[t]he pH of the compositions is preferably from about 4.5 to about 9, more preferably from about 6 to 7," which overlaps with the claimed ranges. (*Cramer*, 2:57; *Donovan*, ¶ 183.) *PDR 1999* discloses that Astelin® has "pH 6.8 ± 0.3," and that Flonase® "has a pH between 5 and 7," each of which overlaps with the claimed ranges. (*PDR 1999*, 1122, 3191; *Donovan*, ¶¶ 184-185.) A POSA would have been motivated to use a pH of from 4.5 to about 6.5 (or more broadly, from 3 to 7), and had a reasonable expectation of success, based on these disclosures in *Cramer* and *PDR 1999*, and for the reasons

discussed above for independent claim 1 (sections V.C.1). (*Donovan*, ¶ 186; *Schleimer*, ¶¶ 419, 424.)

i) Surfactant (Dependent Claims 15, 24)

Claim 15, which depends from claim 1, recites a surfactant "selected from the group consisting of a polysorbate surfactant, a poloxamer surfactant, and combinations thereof." Claim 24, which depends from claim 15, recites that "said surfactant comprises a polysorbate." Using a surfactant comprising a polysorbate (or more broadly, as recited) in the compositions of the claims would have been obvious. (*Donovan*, ¶ 188; *Schleimer*, ¶¶ 384, 429.) *Cramer* discloses that "[p]olysorbate 80," which is a polysorbate, is a "[t]ypical useful surfactant[] for these therapeutic compositions." (*Cramer*, 5:11-15; *Donovan*, ¶ 189.) *PDR 1999* discloses that Flonase® comprises "polysorbate 80," which is a polysorbate and acts as a surfactant. (*PDR 1999*, 1122; *Donovan*, ¶¶ 190-191.) A POSA would have been motivated to use a surfactant comprising a polysorbate (or more broadly, as recited), and had a reasonable expectation of success, based on these disclosures in *Cramer* and *PDR 1999* and this knowledge, and for the reasons discussed above for independent claim 1 (sections V.C.1). (*Donovan*, ¶ 192; *Schleimer*, ¶¶ 384, 429.)

j) Concentration of Surfactant (Dependent Claim 16)

Claim 16 depends from claim 15 and recites "from about 50 micrograms to about 1 milligram of said surfactant per ml of the formulation." Using from about 50 micrograms to about 1 milligram of surfactant per milliliter of the formulation in the compositions of the claims would have been obvious. (*Donovan*, ¶ 194; *Schleimer*, ¶ 389.) *Cramer* discloses that "[e]nhanced absorption across the nasal membrane can be accomplished employing a therapeutically acceptable surfactant," and discloses examples of "[t]ypical useful surfactants for these therapeutic compositions." (*Cramer*, 5:11-15; *Donovan*, ¶ 195.) *Cramer* discloses that "[t]he usual concentration [for the surfactant] is from 0.5% to 10% based on the total weight." (*Cramer*, 5:15; *Donovan*, ¶ 195.) The range of from 0.5% to 10% (w/w) of surfactant that is disclosed in *Cramer* equals about 5-100 mg per milliliter, from which a POSA would have arrived at the claimed about 50 μg (or 0.050 mg) to about 1 mg/mL as a matter of routine experimentation. (*Cramer*, 5:15; *Donovan*, ¶195.)

PDR 1999 discloses that Flonase® comprises polysorbate 80, which is a polysorbate that acts as a surfactant. (*PDR 1999*, 1122; *Donovan*, ¶¶ 196-197.) A POSA would have known as of the priority date, as exemplified in the prior art such as the *Handbook*, that the polysorbate 80 disclosed in *PDR 1999* could be used in a concentration ranging from 0.1 to 15% (or about 1-150 mg/mL), which

overlaps with the claimed range. (*Handbook*, 417; *PDR 1999*, 1122; *Donovan*, ¶ 197.) A POSA would have been motivated to use from about 50 micrograms to about 1 milligram of surfactant per milliliter, and had a reasonable expectation of success, based on these disclosures in *Cramer* and *PDR 1999* and this knowledge, and for the reasons discussed above for independent claim 1 (section V.C.1). (*Donovan*, ¶ 198; *Schleimer*, ¶ 389.)

k) Glycerin (Dependent Claims 17, 25)

Claim 17, which depends from claim 1, recites a tonicity adjusting agent "selected from the group consisting of sodium chloride, saccharose, glucose, glycerine, sorbitol, 1,2-propylene glycol, and combinations thereof." Claim 25, which depends from claim 17, recites that the tonicity adjusting agent "comprises glycerine." Using a tonicity adjusting agent comprising glycerin (or more broadly, as recited) in the formulations of the claims would have been obvious. (*Donovan*, ¶ 200; *Schleimer*, ¶¶ 394, 434.) *Cramer* discloses co-formulations comprising tonicity adjusting agents such as "sodium chloride" and that "examples of sodium chloride equivalents are disclosed in [*Remington*]." (*Cramer*, 4:50-55; *Donovan*, ¶ 201.) *PDR 1999* discloses that Astelin® comprises "sodium chloride," which acts as a tonicity adjusting agent. (*PDR 1999*, 3191; *Donovan*, ¶¶ 202-203.) *Remington*, in turn, discloses that glycerin may be selected instead of the sodium chloride disclosed in *Cramer* and *PDR 1999*. (*Remington*, 1467; *Cramer*, 4:50-55;

PDR 1999, 3191; *Donovan*, ¶ 202.) *Cramer*'s Example 3 discloses a co-formulation with "glycerin." (*Cramer*, 6:26-41; *Donovan*, ¶ 201.) A POSA would have been motivated to use a tonicity adjusting agent comprising glycerin (or more broadly, as recited), and had a reasonable expectation of success, based on these disclosures in *Cramer* and *PDR 1999* and this knowledge, and for the reasons discussed above for independent claim 1 (section V.C.1). (*Donovan*, ¶ 204; *Schleimer*, ¶¶ 394, 434.)

l) Preservative (Dependent Claims 20, 26)

Claim 20 depends from claim 18 and recites a preservative "selected from the group consisting of edetic acid and its alkali salts, lower alkyl p-hydroxybenzoates, chlorhexidine, phenyl mercury borate, benzoic acid or a salt thereof, a quaternary ammonium compound, sorbic acid or a salt thereof, and combinations thereof." Claim 26 depends from claim 18 and recites that the "preservative comprises edetate disodium and benzalkonium chloride." Using a preservative comprising edetate disodium and benzalkonium chloride (or more broadly, as recited) in the compositions of the claims would have been obvious. (*Donovan*, ¶ 206; *Schleimer*, ¶¶ 409, 439.)

Cramer discloses that "[a] pharmaceutically -acceptable preservative is generally employed to increase the shelf life of the compositions of the present invention," and discloses "benzalkonium chloride" and "disodium EDTA" (also

known as edetate disodium) as examples. (*Cramer*, 5:16-22; *Donovan*, ¶ 207.) *Cramer* discloses that "[m]ixtures of these preservatives may also be used." (*Cramer*, 5:21-22; *Donovan*, ¶ 207.) *PDR 1999* discloses that Astelin® comprises "benzalkonium chloride" and "edetate disodium," and that Flonase® comprises "benzalkonium chloride" and "phenylethyl alcohol." (*PDR 1999*, 1122, 3191; *Donovan*, ¶ 209.) A POSA would have been motivated to use a preservative comprising edetate disodium and benzalkonium chloride (or more broadly, as recited), and had a reasonable expectation of success, based on these disclosures in *Cramer* and *PDR 1999*, and for the reasons discussed above for independent claim 1 (section V.C.1). (*Donovan*, ¶ 210; *Schleimer*, ¶¶ 409, 439.)

m) Thickening Agent (Dependent Claims 21, 27)

Claim 21, which depends from claim 18, recites a suspending agent or thickening agent "selected from the group consisting of cellulose derivatives, gelatin, polyvinylpyrrolidone, tragacanth, ethoxose, alginic acid, polyvinyl alcohol, polyacrylic acid, pectin, and combinations thereof." Claim 27, which depends from claim 18, recites "cellulose derivatives." Using a thickening agent comprising cellulose derivatives (or more broadly, as recited) in the compositions of the claims would have been obvious. (*Donovan*, ¶ 213; *Schleimer*, ¶¶ 414, 444.) *Cramer* discloses that "[v]iscosity of the compositions may be maintained at the selected level using a pharmaceutically-acceptable thickening agent," such as

"microcrystalline cellulose" and "carboxymethyl cellulose," which are cellulose derivatives. (*Cramer*, 4:56-5:2; *Donovan*, ¶ 214.) *PDR 1999* discloses that Astelin® comprises "hydroxypropyl methyl cellulose," and that Flonase® comprises "microcrystalline cellulose" and "carboxymethylcellulose sodium," all of which are cellulose derivatives that act as thickening agents. (*PDR 1999*, 1122, 3191; *Donovan*, ¶¶ 216-217.) A POSA would have been motivated to use a thickening agent comprising cellulose derivatives (or more broadly, as recited), and had a reasonable expectation of success, based on these disclosures in *Cramer* and *PDR 1999*, and for the reasons discussed above for independent claim 1 (section V.C.1). (*Donovan*, ¶ 218; *Schleimer*, ¶¶ 414, 444.)

n) Buffer (Dependent Claim 19)

Claim 19 depends from claim 18 and recites "a citric acid-citrate buffer." Using a citric acid-citrate buffer in the compositions of the claims would have been obvious. (*Donovan*, ¶ 220; *Schleimer*, ¶ 404.) *Cramer* discloses that the formulations may contain "buffering agents." (*Cramer*, 3:47-49; *Donovan*, ¶ 221.) A POSA would have known as of the priority date, as exemplified in the prior art such as *Perrin*, that the buffering agent disclosed in *Cramer* may be a citric acid-citrate buffer. (*Perrin*, 132, Table 10.14; *Cramer*, 3:47-49; *Donovan*, ¶ 221.) *PDR 1999* discloses that Astelin® comprises "citric acid" and "dibasic sodium phosphate," which together act as a buffer. (*PDR 1999*, 3191; *Donovan*, ¶ 222.) A

POSA would have known as of the priority date, as exemplified in the prior art such as *Perrin*, that the citric acid and dibasic sodium phosphate that are disclosed in *PDR 1999* may act as a buffer across a pH range of about 2.2 to 8.0, and that a citric acid-citrate buffer may be useful across a pH range of about 3.0 to 6.2. (*Perrin*, 132, Table 10.14, 153, Table 10.45 (abbreviating dibasic sodium phosphate as Na_2HPO_4); *PDR 1999*, 3191; *Donovan*, ¶ 222.) A POSA would have used a citric acid-citrate buffer as claimed instead of the citric acid and dibasic sodium phosphate that is disclosed in *PDR 1999* as a matter of routine experimentation. (*PDR 1999*, 3191; *Donovan*, ¶ 222.) A POSA would have been motivated to use a citric acid-citrate buffer, and had a reasonable expectation of success, based on these disclosures in *Cramer* and *PDR 1999* and this knowledge, and for the reasons discussed above for independent claim 1 (section V.C.1). (*Donovan*, ¶ 223; *Schleimer*, ¶ 404.)

o) Buffer, Preservative, Suspending Agent, Thickening Agent (Dependent Claim 18)

Claim 18 depends from claim 1 and recites "at least one additional component selected from the group consisting of a buffer, a preservative, a suspending agent, a thickening agent, and combinations thereof." Using at least one of these excipients in the compositions of the claims would have been obvious

for the reasons discussed above under "preservative," "thickening agent," and/or "buffer" (sections V.C.2.l-n). (*Donovan*, ¶ 225; *Schleimer*, ¶ 399.)

p) Identified Excipients (Dependent Claim 28)

Claim 28, which depends from independent claim 1, recites "edetate disodium, glycerine, a thickening agent comprising microcrystalline cellulose and sodium carboxy methyl cellulose, polysorbate 80, benzalkonium chloride, phenyl ethyl alcohol, and purified water." Using these excipients in the compositions of the claims would have been obvious. (*Donovan*, ¶ 227; *Schleimer*, ¶ 449.)

Cramer discloses that its co-formulations may comprise "disodium EDTA" (also known as disodium edetate); a "thickening agent" comprising "microcrystalline cellulose," "carboxymethyl cellulose," and/or "pharmaceutical salts thereof"; "[p]olysorbate 80", "benzalkonium chloride"; "phenylethyl alcohol"; and "purified water." (*Cramer*, 3:45-47, 4:56-5:5, 5:11-22; *Donovan*, ¶ 228.) *Cramer*'s Examples 1 and 3 disclose co-formulations comprising, respectively, (1) "benzalkonium chloride," "microcrystalline cellulose and sodium carboxymethyl cellulose," "polysorbate 80," "phenylethyl alcohol," and "distilled water"; and (2) "ethylenediamine tetraacetic acid," "benzalkonium chloride," "polysorbate 80," "glycerin," and "distilled water." (*Cramer*, 5:38-6:4, 6:26-51; *Donovan*, ¶ 229.)

PDR 1999 discloses that Astelin® "contains benzalkonium chloride (125 μg/mL), edetate disodium, hydroxypropyl methyl cellulose, citric acid, dibasic sodium phosphate, sodium chloride, and purified water." (*PDR 1999*, 3191; *Donovan*, ¶ 230.) *PDR 1999* discloses that Flonase® "contains microcrystalline cellulose and carboxymethylcellulose sodium, dextrose, 0.02% w/w benzalkonium chloride, polysorbate 80, and 0.25% w/w phenylethyl alcohol." (*PDR 1999*, 1122; *Donovan*, ¶ 231.) A POSA would have known as of the priority date, as exemplified in the prior art such as the *Remington*, that glycerin may be selected as a tonicity adjusting agent instead of the sodium chloride disclosed in *PDR 1999*. (*Remington*, 1467; *PDR 1999*, 3191; *Donovan*, ¶ 150.)

A POSA would have been motivated to use edetate disodium, glycerin, a thickening agent comprising microcrystalline cellulose and sodium carboxy methyl cellulose, polysorbate 80, benzalkonium chloride, phenyl ethyl alcohol, and purified water, and had a reasonable expectation of success, based on these disclosures in *Cramer* and *PDR 1999* and this knowledge, and for the reasons discussed above for independent claim 1 (sections V.C.1). (*Donovan*, ¶ 232; *Schleimer*, ¶ 449.) Moreover, a POSA would have known as of the priority date, as exemplified in the prior art such as the *Handbook*, that the claimed excipients may be used in pharmaceutical formulations for the same functions that they are

used in the compositions of the claims. (*See generally Handbook*; *Donovan*, ¶ 233.)

D. No Objective Indicia Demonstrating Nonobviousness

The burden of presenting objective indicia of nonobviousness is on Cipla, and Cipla has not yet presented any such alleged evidence in this proceeding. Petitioner reserves the right to address such evidence if presented by Cipla. *See, e.g.*, *Eli Lilly & Co. v. Trs. of the Univ. of Pa.*, IPR2016-00458, Paper 7 at 21-22 (PTAB July 14, 2016); *Amneal Pharm., LLC v. Supernus Pharm., Inc.*, IPR2013-00368, Paper 8 at 12-13 (PTAB Dec. 17, 2013). Cipla presented alleged objective indicia of nonobviousness during prosecution, the Apotex litigation, and the Argentum IPR (the latter two defined below), but this alleged evidence does not demonstrate nonobviousness, for example as discussed below. (*Schleimer*, ¶ 452.)

1. No Unexpected Results over the Closest Prior Art

Cipla has not shown unexpected results supportive of nonobviousness of the claimed invention, for at least the reason that Cipla has not compared the claimed invention to the closest prior art. (*Id.*, ¶¶ 453-511.) The closest prior art is a pharmaceutical nasal formulation comprising both azelastine and fluticasone, such as those taught by *Cramer* and *Segal*. (*Id.*, ¶ 455.) Such a formulation is closer prior art to the claimed invention than (1) co-administration of an ***oral*** antihistamine that is not azelastine with an intranasal corticosteroid (even if it were

fluticasone), (2) azelastine hydrochloride nasal spray alone, and (3) fluticasone propionate nasal spray alone. (*Id.*) Co-administration of commercially available azelastine hydrochloride nasal spray and commercially available fluticasone propionate nasal spray is also closer prior art to the claimed invention than any of these. (*Id.*, ¶ 456.) Because Cipla has not presented results comparing the claimed invention to a pharmaceutical nasal formulation comprising both azelastine and fluticasone, such as those taught by *Cramer* and *Segal*, or to co-administration of commercially available azelastine hydrochloride nasal spray and fluticasone propionate nasal spray, Cipla has not shown unexpected results supportive of nonobviousness of the claimed invention. (*Id.*, ¶¶ 454, 457.)

Cipla has argued in other matters that "the formulation described in Example 3 of *Cramer* was found to be inoperable and unacceptable," relying on a declaration by inventor Geena Malhotra ("*August 2011 Malhotra Declaration*"). (*E.g.*, *'620 File History*, 156 (citing *id.*, 174-196); *Schleimer*, ¶¶ 540-541; *Donovan*, ¶¶ 241-242.) The examiner did not cite this declaration in issuing the patents. (*E.g.*, *'620 File History*, 319-342; *'723 File History*; *Schleimer*, ¶ 542; *Donovan*, ¶ 243.)

The *August 2011 Malhotra Declaration* does not support nonobviousness for at least the reason that the Ms. Malhotra does not show that her opinion on what is "unacceptable" with regard to the formulation aspects of *Cramer*'s

Example 3 equates to what a POSA would deem "inoperable." (*Donovan*, ¶ 245.) In addition, Ms. Malhotra does not address the pharmacologically recognized activity of the ingredients in *Cramer*'s Example 3 or the ability of the formulation to be administered intranasally to manage symptoms of allergic rhinitis. (*Schleimer*, ¶ 544.) She also does not refute *Cramer*'s disclosures that (1) *Cramer*'s Example 3 formulation comprising triamcinolone acetonide and azelastine hydrochloride may be administered intranasally "to provide relief from allergy or allergy-like symptoms," which a POSA would understand to include symptoms of allergic rhinitis (*Cramer*, 6:43-44); and (2) "substantially similar results are also obtained using, in whole or in part, equivalent amounts of other glucocorticoid agents such as fluticasone" (*id*., 6:44-46). (*Schleimer*, ¶ 544.) These disclosures in *Cramer* are supported by the prior art commercial availability of azelastine hydrochloride and fluticasone propionate as nasal sprays for allergic rhinitis. (*PDR 1999*; *Schleimer*, ¶ 544.) Based on these disclosures, a POSA would reasonably expect the formulations disclosed in *Cramer*'s Example 3, including formulations comprising both azelastine hydrochloride and fluticasone, would be active and operable. (*Schleimer*, ¶ 544.)

2. No Long-Felt but Unmet Need

Cipla has not shown that the claimed invention satisfied a long-felt but unmet need, for at least the reason that Cipla has not shown any such need that was

not already satisfied by co-administration of commercially available azelastine hydrochloride and fluticasone propionate nasal sprays. (*Id.*, ¶ 512-529.)

3. No Industry Praise

Cipla has not shown industry praise demonstrating nonobviousness of the claimed invention. (*Id.*, ¶¶ 530-537.)

VI. MANDATORY NOTICES

A. Real Parties-in-Interest

GlaxoSmithKline Consumer Healthcare Holdings (US) LLC is the real party-in-interest.

B. Related Matters

The following matters involved the *'723 Patent* and the related *'620 Patent*: (1) *Meda Pharmaceuticals Inc. v. Teva Pharmaceuticals USA, Inc.*, No. 1:15-cv-00785-LPS (D. Del.) (dismissed by stipulation on July 28, 2017); (2) *Meda Pharmaceuticals Inc. v. Perrigo UK FINCO Ltd.*, No. 1:16-cv-00794-LPS (D. Del.) (dismissed by stipulation on July 7, 2017); and (3) *Meda Pharmaceuticals, Inc. v. Apotex Inc.*, No. 1:14-cv-01453-LPS (D. Del.) (dismissed by stipulation on May 18, 2017) ("the Apotex litigation"). In addition, the *'620 Patent* was involved in *Argentum Pharmaceuticals LLC v. Cipla Ltd.*, IPR2017-00807 (PTAB) (terminated by joint motion on May 21, 2018) ("the Argentum IPR"). Petitioner was not a party to any of these matters.

C. Counsel and Service Information

Lead counsel is Charles E. Lipsey (Reg. No. 28,165), Finnegan, Henderson, Farabow, Garrett & Dunner, LLP ("Finnegan"), 11955 Freedom Drive, Reston, Virginia 20190-5675, charles.lipsey@finnegan.com, (571) 203-2755. Backup counsel is Trenton A. Ward (Reg. No. 59,157), Finnegan, 271 17th Street, NW, Suite 1400, Atlanta, Georgia 30363-6209, trenton.ward@finnegan.com, (404) 653-6441; Richard B. Racine (Reg. No. 30,415), Finnegan, 901 New York Avenue, NW, Washington, DC 20001-4413, rich.racine@finnegan.com, (202) 408-4038; Joann M. Neth, Ph.D. (Reg. No. 36,363), Finnegan, 901 New York Avenue, NW, Washington, DC 20001-4413, joann.neth@finnegan.com, (202) 408-4028; and Shana K. Cyr, Ph.D., (Reg. No. 77,764), Finnegan, 11955 Freedom Drive, Reston, Virginia 20190-5675, shana.cyr@finnegan.com, (571) 203-2434.

Petitioner consents to electronic service of all documents at these email addresses and Cipla-GSK-IPR@finnegan.com.

VII. THE GROUNDS ARE NOT REDUNDANT

Grounds 1 and 2 are not redundant, because the first starts with the teachings of a nasal spray formulation comprising azelastine hydrochloride and a nasal spray formulation comprising fluticasone propionate (*PDR 1999*), and the second starts with the teaching of a pharmaceutical nasal formulation comprising both azelastine and fluticasone (*Cramer*).

VIII. THE PETITION SHOULD NOT BE DENIED UNDER § 325(D)

Although *Cramer* was cited by the examiner during prosecution, the applicant overcame the rejection based solely on alleged objective indicia of nonobviousness, none of which demonstrates nonobviousness, as discussed above. Although the Argentum IPR was instituted based on the cited prior art and similar arguments, the parties settled before the Board issued a final written decision.

IX. CONCLUSION

For the reasons set forth in this Petition, the challenged claims are unpatentable. Petitioner respectfully requests that the Board grant this Petition for IPR and institute trial. The USPTO may charge any fees that are due during this proceeding to Deposit Account No. 06-0916.

Respectfully submitted,

Dated: January 31, 2020

By: */Charles E. Lipsey/*
Charles E. Lipsey, Lead Counsel
Reg. No. 28,165

CERTIFICATE OF COMPLIANCE WITH WORD COUNT

Pursuant to 37 C.F.R. § 42.24(d), the undersigned certifies that this Petition for *Inter Partes* Review of U.S. Patent No. 8,163,723 complies with the type-volume limits of 37 C.F.R. § 42.24(a)(1)(i), because it contains 11,968 words, according to the word-processing system used to prepare this Petition, excluding the words in the Table of Contents, Table of Authorities, List of Exhibits, Mandatory Notices, Certification Under § 42.24(d), and Certificate of Service, as set forth in 37 C.F.R. § 42.24(a)(1).

Respectfully submitted,

Dated: January 31, 2020

By: */Charles E. Lipsey/*
Charles E. Lipsey, Lead Counsel
Reg. No. 28,165

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105(a), the undersigned certifies that that on January 31, 2020, a copy of the foregoing **Petition for *Inter Partes* Review of U.S. Patent No. 8,163,723** and **Exhibits 1001-1015, 1017-1056, 1058, 1062, 1065-1066, 1070** were served by FedEx on the correspondence address of record indicated in the Patent Office's public PAIR system for U.S. Patent No. 8,163,723:

Rodney B. Carroll
CONLEY ROSE, P.C.
5601 Granite Parkway, Suite 500
Plano, TX 75024

Dated: January 31, 2020

By: */William Esper/*
William Esper
Litigation Legal Assistant

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, LLP