

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ARGENTUM PHARMACEUTICALS LLC

Petitioner

v.

CIPLA LIMITED

Patent Owner

Case No. IPR2017-00807

U.S. Patent No. 8,168,620

SECOND DECLARATION OF HUGH DAVID CHARLES SMYTH, PH.D.

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I, Hugh Charles David Smyth, do declare as follows:

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

I. Introduction

2. I have been retained as an expert witness by Cipla Ltd. ("Cipla") in the above *inter partes* review matter concerning U.S. Patent No. 8,168,620 ("the '620 patent") (EX1001) that was filed by Petitioner Argentum Pharmaceuticals LLC ("Argentum"). Counsel has informed me that Argentum has challenged the patentability of claims 1, 4-6, 24-26, 29, and 42-44 (collectively "the challenged claims").

3. I have been asked by Cipla to review Argentum's Petition and the declaration submitted on behalf of Argentum by Dr. Maureen Donovan, and to respond to those documents to the extent that their contents fall within my expertise.

4. I am being compensated for my time in connection with this *inter partes* review matter at a rate of \$600 per hour, and my compensation does not depend upon the ultimate outcome of this case. I will also be compensated for any reasonable expenses, including travel costs incurred in conducting activities at counsel's request.

II. Professional and educational background

5. I am presently an Associate Professor with Tenure (Hamm Endowed Faculty Fellow) in the College of Pharmacy at the University of Texas, Austin. I have held this position since 2011. I am also an Adjunct Associate Scientist at the Lovelace Respiratory Research Institute in Albuquerque, New Mexico, a position I have held since 2009. From 2009 to 2011, I served as an Assistant Professor in the College of Pharmacy at the University of Texas, Austin. From 2005 to 2009, I was an Assistant Professor in the College of Pharmacy at the University of New Mexico. And from 2004 to 2005, I was a Research Assistant Professor in the College of Pharmacy at the University of North Carolina, Chapel Hill.

6. I received a Bachelor of Pharmacy in 1995 from the University of Otago, in Dunedin, New Zealand. In 1997, I earned a Post Graduate Diploma in Pharmacy, with Distinction, from the University of Otago. In 2000, I received my Ph.D. in Pharmaceutical Sciences from the University of Otago. My thesis topic was the "Investigation of Electrically Assisted Drug Delivery in the Percutaneous Delivery of Peptides." From 2001 to 2003, I was a Post-Doctoral Fellow at the School of Pharmacy at the University of North Carolina, Chapel Hill.

7. My current research focuses on the development of novel methods for drug delivery including nasal, inhalation, transdermal, ophthalmic, and oral delivery systems for a variety of diseases.

8. My responsibilities at the University of Texas include teaching graduate courses and mentoring graduate students. I have taught courses on Advanced Manufacturing Pharmacy, Recent Advances in Pharmaceutics, and Molecular and Cellular Pharmacology, to name a few. I have supervised 18 post-doctoral fellows and visiting scientists; served on over 38 graduate student committees and the primary advisor for 12 graduate students.

9. I have published over 100 papers in peer-reviewed journals, 20 books or book chapters, and have presented over a hundred times at conferences.

10. I am currently the Editor-in-Chief of *Drug Development and Industrial Pharmacy* and serve on the Editorial Boards of the *Journal of Bioequivalence & Bioavailability* and *Drug Delivery Letters*. In the past, I served as Guest Editor on the *Journal of Nanomaterials*. I also served on the Editorial Advisory Board of *Books for the Controlled Release Society* and on the Editorial Advisory Committee for *Books for the American Association of Pharmaceutical Scientists*. My *curriculum vitae*, which includes a list of my publications, is listed as CIP2008.

11. In addition, I was previously an expert and trial witness for Cipla in the related district court litigation concerning the '620 patent against Apotex Inc. and Apotex Corp. (collectively, "Apotex").

III. Basis for my opinions

12. I have considered the following documents in coming to the opinions

I express below:

<i>Cipla's Exhibit #¹</i>	<i>Description</i>
2008	Hugh David Charles Smyth, Ph.D. <i>Curriculum Vitae</i>
2014	Dr. Maureen Donovan Deposition transcript, October 7, 2016, Meda Pharmaceuticals Inc. and Cipla Ltd., v. Apotex Inc. and Apotex Corp., Case No. 1:14-cv-01453-LPS (D. Del.)
2019	Bench Trial Transcript, Volume B, December 14, 2016, <i>Meda Pharmaceuticals Inc. and Cipla Ltd., v. Apotex Inc. and Apotex Corp.</i> , Case No. 1:14-cv-01453-LPS (D. Del.)
2021	Bench Trial Transcript, Volume D, December 16, 2016, <i>Meda Pharmaceuticals Inc. and Cipla Ltd., v. Apotex Inc. and Apotex Corp.</i> , Case No. 1:14-cv-01453-LPS (D. Del.)
2026	Gennaro, A. R. <i>Remington's Pharmaceutical Sciences</i> (17th ed., 1985), Ch. 80: 1455-1477; Ch. 82: 1478-1491; Ch. 84:1492-1517
2028	Avomeen Analytical Services Report, June 30, 2016 (PTX0129)
2029	Expert Report of Dr. Matthew J. Herpin and Corresponding Documents (PTX1663)
2030	Expert Report of Dr. Govindarajan and Corresponding Documents (PTX1664)

¹ Throughout this declaration, I will refer to these exhibits as "[Exhibit Number], [paragraph/page number(s)]."

<i>Cipla's Exhibit #¹</i>	<i>Description</i>
2031	Duonase Imitator Product Labels (PTX0026)
2038	Khan, M., <i>et al. Pharmaceutical and Clinical Calculations</i> (2nd ed., 2000), pp. 149-167 (PTX0194)
2040	British Pharmaceutical Codex (1973), "Hypromellose," pp. 232, 307-308 (PTX0193)
2044	Michael, Y., <i>et al.</i> "Characterisation of the aggregation behavior in a salmeterol and fluticasone propionate inhalation aerosol system," <i>International Journal of Pharmaceutics</i> , 221: 165-174; 2001 (PTX0179)
2051	Claritin® Approval Letter, Application Numbers 19-658/S-018, 19-670/S-018, 20-470/S-016, 20-641/S-009, and 20-704/S-008
2054	MedPointe Making Medicine Better: Astelin® Day Life CyclePlan, November 1, 2002 (PTX1005)
2056	Astelin® Nasal Spray Life Cycle Management Projects (Preliminary Plan) (PTX1006)
2058	2006.03.21 Email and attachment from Kalidas Kale to Alex D'Addio re: Astelin – Flonase Combination Product Feasibility Assessment Plan (PTX0151)
2061	MedPointe Laboratory Notebook No. 1044 - Excerpts (PTX0142)
2070	Duonase Nasal Spray – Prescribing Information (PTX0134)
2103	The United States Pharmacopeia: 24 National Formulary 19 (1999), pp. 2107-2130 (PTX0188)
2104	Lieberman, H. A., <i>et al. Pharmaceutical Dosage Forms</i> (2nd ed., 1996), Ch. 4: 149-181 (PTX0177)
2105	Shin Etsu Pharmacoat USP Hypromellose Brochure (2005) (PTX0186)
2111	Michael, Y., <i>et al.</i> "The physico-chemical properties of salmeterol and fluticasone propionate in different solvent

<i>Cipla's Exhibit #¹</i>	<i>Description</i>
	environments," <i>International Journal of Pharmaceutics</i> , 200: 279-288; 2000 (PTX0180)
2112	Allen, Jr., L.V. <i>The Art, Science, and Technology of Pharmaceutical Compounding</i> (1998), Ch. 20: 219-238 (PTX0167)
2113	Lieberman, H. A., <i>et al. Pharmaceutical Dosage Forms</i> (2nd ed., 1996), vol. 2, Ch. 5: 183-241 (PTX0192)
2114	Meda Highlights of Prescribing Information 2015 (PTX0154)
2135	Wade, A., and Weller, P. <i>Handbook of Pharmaceutical Excipients</i> (2nd ed., 1994), p. 154
2136	Talbot, Andrew, <i>et al.</i> "Mucociliary Clearance and Buffered Hyperonic Saline Solution," <i>Laryngoscope</i> , 107(4): 500-503; 1997
2141	Physicians' Desk Reference, Accolate® and Allegra-D® Prescribing Information (2002)
2144	Physicians' Desk Reference, Zyrtec-D® Prescribing Information (2002)
2148	Alexander Dominic D'Addio, Ph.D. Declaration
2151	Cipla Duonase Manufacturing Guide (PTX0153)
2152	Cipla Duonase Manufacturing Guide (PTX0135)
2153	Meda Investigation report: Dymista 6.4 g Nasal Spray Stability results (PTX0141)
2154	Meda NDA excerpt 3.2.P.3 Manufacture [Dymista (azelastine hydrochloride and fluticasone propionate) Nasal Spray, 137mcg/50 mcg] (PTX0138)
2155	Cipla Duonase Stability Testing Form
2156	Kibbe, A. H., Antimicrobial preservative Index, in <i>Handbook of Pharmaceutical Excipients</i> (3rd ed., 2000),

<i>Cipla's Exhibit #¹</i>	<i>Description</i>
	pp. 646-647

IV. Summary of my opinions

13. As I explain below, a POSA would understand the claim phrases "dosage form suitable for nasal administration" and "nasal spray" to mean "pharmaceutical formulations that are tolerable to patients, that are homogeneous, and that can be suitably deposited onto the nasal mucosa."

14. As I explain below, a POSA would not have been motivated to combine azelastine and fluticasone into the claimed combination formulation with a reasonable expectation of doing so because (1) the prior art did not provide a POSA any meaningful information in order to make such a formulation, (2) fluticasone was known to aggregate and flocculate when co-formulated with another active ingredient which would have discouraged a POSA from attempting to combine azelastine and fluticasone, and (3) following the closest prior art formulation disclosed in Example III of Cramer—an azelastine/triamcinolone formulation—did not allow a POSA to arrive at a fixed-dose combination of the challenged claims.

15. As I explain below, a POSA would not have had a motivation to select the explicitly recited excipients of claims 42-44 because the prior art would have

discouraged their use either with azelastine, fluticasone, or the other claimed excipients. And additionally, a POSA would not have had a reasonable expectation of success for these same reasons.

16. As I explain below, Meda's commercial azelastine/fluticasone product, Dymista®, Cipla's commercial azelastine/fluticasone product, Duonase, and the Duonase Imitator Products are embodiments of certain challenged claims. As I explain further below, objective indicia of non-obviousness, including skepticism of others, failure of others, copying, and unexpected results exist with respect to the challenged claims.

V. Person of ordinary skill in the art

17. Counsel has informed me that the critical date for assessing patentability of the '620 patent is June 2002. I note that Dr. Donovan uses the same date for her analysis. EX1004, ¶¶14-15.

18. Counsel also informed me that a person of ordinary skill in the art ("POSA") is a hypothetical person presumed to be aware of all pertinent art, who thinks along conventional wisdom in the art, and is a person of ordinary creativity. A POSA at that time would have the knowledge and experience of both a clinician and a formulation scientist. I believe this is the appropriate standard because the '620 patent relates to both the treatment of patients and the formulation of a therapeutically-effective nasal spray. In my opinion, the formulation aspect of this

POSA would require a B.S. in Pharmaceutical Sciences and 4-5 years of experience as a formulator, although the POSA could also be a person with a higher level of formal education and fewer years of experience. The formulator would have educational, practical training, and expertise to formulate a nasal spray. I understand from counsel that another expert will address the clinical aspect of this POSA.

VI. The '620 patent

19. In general, the '620 patent is directed to pharmaceutical formulations containing azelastine hydrochloride ("azelastine") and fluticasone propionate ("fluticasone") with various excipients in a dosage form that is "suitable for nasal administration" or that is a "nasal spray." *See* claims 1, 24, and 25.

VII. Claim construction

20. I understand from counsel that the claim terms of the '620 patent are to be given their broadest reasonable interpretation. I also understand from counsel that the patent applicant—here Cipla—can explicitly or implicitly define terms used in the claims by amending the language in those claims and/or by the patent applicant's statements to the patent examiner.

21. The challenged claims include the claim phrases "dosage form suitable for nasal administration" or "nasal spray." I have reviewed the '620 patent and the prosecution history of that patent. It is my opinion, based on my review of

the patent and the prosecution history, that the claim phrases "dosage form suitable for nasal administration" and "nasal spray" require "pharmaceutical formulations that are tolerable to patients, that are homogeneous, and that can be suitably deposited onto the nasal mucosa."

22. During prosecution, the '620 patent had been rejected as anticipated under 35 U.S.C. § 102 and/or obvious under 35 U.S.C. § 103 in view of EP 0780127 ("Cramer"), particularly the formulation of Example III. EX1002, 219-221, 507-522. In response, Cipla amended the pending claims to include the language "said pharmaceutical formulation is in a dosage form suitable for nasal administration," and likewise noted that other claims recited a "nasal spray." EX1002, 206-216, 220. A POSA would understand Cipla's statement to the patent examiner as specifying that a "nasal spray" and a dosage form "suitable for nasal administration" require these characteristics.

23. Cipla also submitted a declaration from co-inventor Geena Malhotra recreating the prior art Cramer Example III formulation and reporting that Cramer's Example III formulation exhibited (1) unacceptably high osmolality which was expected to cause irritation to patients, (2) unacceptable spray quality which adversely effects whether the intended amount of the drug is suitably deposited on

the nasal mucosa, and (3) unacceptable settling, which reduces drug homogeneity² in the formulation. EX1002, 284-287. Cipla used the declaration to tell the patent examiner that "Example 3 of Cramer (identified by the April 28, 2010 Office Action, page 16, as the closest example) is inoperable and unacceptable as *a pharmaceutical formulation in a dosage form suitable for nasal administration.*" EX1002, 220-221, 223-224 (emphasis added). Cipla also told the patent examiner that the term "suitable for nasal administration" was synonymous with the term "nasal spray," as used in the '620 patent. EX1002, 220 ("Likewise, independent claims 55 and 56 each recite a 'nasal spray'..."). Cipla additionally told the patent examiner that "the inoperability of Cramer's closest example as cited by the Office Action is a further basis for the *novelty of independent claims 1 [and] 56...*" EX1002, 221 (emphasis added). The patent examiner subsequently allowed the pending claims over Cramer. EX1002, 139-146. Because the "dosage form suitable for nasal administration" and "nasal spray" language of the pending claims were used to distinguish the prior art from Cipla's claimed invention, a POSA would understand that the formulations of the pending claims did not suffer from the

² Drug homogeneity, also known as drug uniformity, relates to the uniformity of the drug dispersion within the formulation, and is necessary to ensure safe and effective dosing for patients.

same shortcomings as Example III—i.e., they were not expected to cause irritation, suitably deposited the intended amount of the drug on the nasal mucosa, and were homogeneous. A POSA therefore would have understood the claim phrases "dosage form suitable for nasal administration" and "nasal spray" to require "pharmaceutical formulations that are tolerable to patients, that are homogeneous, and that can be suitably deposited onto the nasal mucosa."

VIII. Given the expected technical difficulties in 2002, a POSA would not have been motivated to combine azelastine and fluticasone with a reasonable expectation of success.

24. Argentum and Dr. Donovan opine that claims 1, 4-6, 24-26, and 29 would have been obvious to a POSA in 2002 in view of the combined teachings of U.S. Patent No. 5,164,194 ("Hettche") (EX1007), U.S. Patent No. 4,335,121 ("Phillipps") (EX1009), and Segal (EX1012). EX1004, ¶ 12. I disagree for the reasons below.

A. The lack of meaningful guidance in the art would have dissuaded a POSA from combining azelastine and fluticasone into a combination formulation.

25. Dr. Donovan was "asked by counsel to assume it was obvious to combine azelastine hydrochloride and fluticasone propionate into a single nasal spray." EX1004, ¶40. Therefore, Dr. Donovan does not provide any opinion on whether a *formulator* would have been motivated to combine azelastine and fluticasone into a single, fixed-dose combination formulation. But a POSA would

not have been motivated to combine Segal, Hettche, and Phillipps to arrive at a fixed-dose combination of azelastine and fluticasone because (1) there was no guidance in the prior art (e.g., working examples, textbooks, articles, or industry knowledge/experience) of how to combine a solution formulation with a suspension formulation, as encompassed by the challenged claims, and (2) the inordinate technical difficulties involved with combining two different formulations were known, as explained in more detail below.

26. First, a POSA would not have been motivated to combine azelastine and fluticasone into a combined formulation because there was no teaching, understanding, or guidance in the prior art of how a POSA would formulate such a product. Dr. Donovan's declaration is devoid of any explanation of how a POSA would have combined azelastine and fluticasone. EX1004, ¶40 ("I have been asked by counsel to *assume it was obvious to combine* azelastine hydrochloride and fluticasone propionate...") (emphasis added). She cites to no prior art teachings or prior art guidance, nor any prior art exemplary products. EX1004, ¶¶21-39. In fact, the product labels for the only FDA-approved combination allergic rhinitis drugs

by 2002—Allegra D, Claritin D, and Zyrtec D—all state that those products are solid oral dosage forms. CIP2141, 4; CIP2144, 3; CIP2051, 2.³

27. Dr. Donovan identifies two prior art references—Segal (EX1012) and Cramer (EX1011)—as disclosing antihistamine/steroid combination formulations. EX1004, ¶51. But the disclosures of Segal and Cramer would not have provided any motivation for a POSA to combine azelastine and fluticasone with any reasonable expectation of success.

28. Among Segal's disclosure of a laundry list of drugs, Segal disclosed "anti-inflammatory agents," such as corticosteroids. EX1012, 4. A POSA would understand that anti-inflammatory agents are suspension formulations, where the drug particles are dispersed in a medium. Indeed, the Flonase® label states that fluticasone "is practically insoluble in water" and that Flonase® is formulated as "an aqueous suspension." EX1010, 1. By contrast, many of Segal's other identified drug classes are solution formulations, where the active ingredient is dissolved and molecularly dispersed in a solvent. EX1012, 5. For example, Astelin®'s label states

³ The Physicians' Desk Reference is a reliable and authoritative sources of information for formulators and the public to understand what active ingredients and excipients are contained in a commercially available FDA-approved drug.

that azelastine is "sparingly soluble in water" and that Astelin® is formulated as "an aqueous solution." EX1008, 2.

29. Segal, however, contains no formulation examples from which a POSA would understand that Segal had successfully combined any of the disclosed anti-inflammatory agents like fluticasone (typically formulated as suspensions) with any of the other disclosed drugs like azelastine (typically formulated as solutions). EX1012, 3-6. Absent any explicit formulation details, such as formulation ingredients and concentrations, Segal's only mention of any guidance in the art as to how to formulate a combination product is a passing reference to the general industry text *Remington's Pharmaceutical Sciences*, 1985, 17th ed. EX1012, 6:14. A POSA would not find this disclosure meaningful because Segal does not cite to any specific passages of *Remington's*, but instead cites generally to the entire text. *Id.* Moreover, *Remington's* fails to disclose combination solution/suspension nasal formulations, instead it discusses solution formulations separately from suspension formulations. CIP2026, 13-14. If solution/suspension combination formulations were known in 2002, a POSA would have expected a general text like *Remington's* to address it—it does not.

30. Next, the lack of meaningful guidance in the art is confirmed by Cramer. Cramer contains a much more explicit disclosure of formulation information than Segal, including a lengthy discussion regarding possible

excipients and explicit formulation examples. EX1011, 4:6-6:51. Indeed, I observed Argentum's clinical expert, Dr. Robert Schleimer, testify in the related *Apotex* trial that Segal's disclosure is "less specific" than Cramer's. CIP2019, 66:17-20. But a POSA following the more explicit guidance in Cramer would not arrive at a "nasal spray" or a formulation that was "suitable for nasal administration."

31. But even with Cramer's additional information, a POSA would not have been able to arrive at a "nasal spray" or a formulation that was "suitable for nasal administration" within the scope of challenged claims. Co-inventor Geena Malhotra determined that Cramer's Example III formulation exhibits unacceptably high osmolality, poor spray quality, and unacceptable settling and caking. EX1002, 286-87. And as discussed more below, Cipla's and Apotex's experts in the related *Apotex* case confirmed that the Example III formulation was (i) unacceptably acidic; (ii) unstable, leading to significant caking of drug; and (iii) unacceptably high osmolality. *See* § VIII.C below.

32. Argentum also asserts that the '620 patent "admits" that the art teaches a POSA to formulate Segal's combination formulation because the '620 patent contains the following statement preceding its formulation examples: "*In Examples* where only the ingredients of formulations according to the present invention are listed, these formulations are prepared by techniques well known in the art." Pet.

36; EX1001, 11, col. 7, line 67 – col. 8, line 2 (emphasis added). A POSA would have viewed this sentence to be limited to the Examples listed in the '620 patent which set out the specific formulation ingredients and concentrations. EX1001, 11, col. 8, line 1 – col. 11, line 43. In that context, the fact that "these formulations are prepared by techniques well known in the art" makes sense because the examples already identify what, and how much, formulation ingredients to use. Unlike the formulation examples of the '620 patent, Segal contains no formulation examples and therefore would not be understood by a POSA to "list" "the ingredients of the formulation according to [Segal's invention]"—indeed, no formulations are listed. *See* EX1012, 4-6.

33. Argentum also cites to the fact that azelastine and fluticasone were "disclosed and claimed" in Hettche and Phillipps. Pet. 39-40. But neither Hettche nor Phillipps disclose any combination formulations, and therefore would not provide any guidance to a POSA. EX1007, Abstract ("...contains as active ingredient azelastine or a physiologically acceptable salt."); EX1009, Abstract ("Pharmaceutical compositions containing the compounds of formula I..."). That is, Hettche and Phillipps provide even less guidance than Segal and Cramer, and neither would lead a POSA to a formulation of the challenged claims.

B. The prior art taught that fluticasone would aggregate when co-formulated in liquid formulations with another active ingredient, which would have undercut any motivation a POSA may have had to combine azelastine and fluticasone into a fixed-dose

combination formulation with any reasonable expectation of success.

34. A POSA would not have been motivated to combine fluticasone with a second active ingredient—like azelastine in the challenged claims—because the prior art taught that fluticasone aggregated when co-formulated in a liquid formulation with another active drug. By 2000, a POSA would have known that researchers at GlaxoSmithKline—the developers of fluticasone—also published an investigation on a co-formulation of fluticasone and salmeterol xinafoate ("salmeterol") in a propellant-based suspension system. CIP2111, 1.

GlaxoSmithKline's publications report that the fluticasone and salmeterol undergo flocculation whereby the individual particles of the two drugs aggregate together, which can lead to substantial non-uniform drug suspensions, e.g., rapid settling or creaming, and caking of the drugs. CIP2111, 1; CIP2044, 1.⁴ GlaxoSmithKline further reported its investigation on whether the fluticasone-salmeterol flocs could be broken apart. The publication states that "the flocs persisted even at the highest

⁴ CIP2111 and CIP2044 are both peer-reviewed publications in reputable journals. Such journals, and the information contained in such publications, are considered reliable accurate and reliable sources of information upon which experts and formulators can rely. And, indeed, such journals and such publications are frequently relied upon in the formulation field.

shear rate studied, suggesting that the aggregates are not broken down to the size of the input drugs" and that the "data suggests that salmeterol xinafoate and fluticasone propionate must be inextricably bound in a hetero-flocculated state." CIP2044, 6, 9. GlaxoSmithKline concluded in the publication that "[c]ombined drug formulations are less well understood and, as a result, a significant amount of fundamental research work on the subject is being undertaken." CIP2044, 2. These teachings would have been more relevant to a POSA than those of the prior art fluticasone/salmeterol dry powder formulation for oral inhalation (Advair DISKUS) because the claimed azelastine/fluticasone formulations are liquid formulations. EX1030, 1-3; *see* claims 5 ("aqueous suspension") and 24-25, 29, and 43-44 ("nasal spray.")

35. With this knowledge in mind in 2002, a POSA would have been concerned that formulating a liquid formulation of fluticasone with another active ingredient would similarly result in the same flocculation/aggregation behavior that GlaxoSmithKline observed. This teaching would have discouraged a POSA from combining azelastine and fluticasone. First, as evidenced by widely used texts that are commonly relied upon by formulators such as the USP/NF compendium⁵ and

⁵ The USP/NF is a publication from the United States Pharmacopeia and the National Formulary of pharmacopeial standards for chemical substances, dosage forms, compounded preparations, excipients, medical devices, and the like. It is

Lieberman,⁶ acceptable suspensions administered to humans must have a uniform and homogeneous distribution of drug particles, be "redispersible into a uniform mixture upon shaking," and "must not cake." CIP2113, 5; CIP2103, 12; CIP2104, 6-7. Second, the fluticasone/salmeterol formulation would likely have administered an unintentionally high or low dose of drug in light of the flocculation/aggregation behavior. *Id.* This would have been contrary to what a formulator would have intended.

C. Cramer's Example III would have undercut any reasonable expectation of successfully combining azelastine and fluticasone into a fixed-dose combination.

36. During prosecution, the patent examiner determined that Cramer's Example III formulation, shown below, was the closest prior art to the invention of the challenged claims. EX1002, 220. I have reviewed the declaration of co-inventor Geena Malhotra (EX1002, 284-287), and the expert reports prepared in the related *Apotex* litigation: Dr. Ram Govindarajan (Apotex's testing expert) (CIP2030) and Dr. Matthew Herpin (Cipla's testing expert) (CIP2029). In the

widely regarded as a reliable and authoritative reference for experts and formulators, and is frequently relied upon.

⁶ Standard formulation texts like Lieberman are widely regarded as a reliable and authoritative references for experts and formulators, and are frequently relied upon.

related *Apotex* case, both Drs. Govindarajan and Herpin submitted declarations in which they were asked to attempt to recreate Cramer Example III as shown below and to record their observations and analysis as a POSA in 2002 would have.⁷ In my opinion the testing results shown in their declarations confirm Ms. Malhotra's findings, and demonstrate that routine modifications to Cramer Example III's formulation do not remedy its shortcomings. CIP2021, 171:8-172:15; CIP2030, 2-3.

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

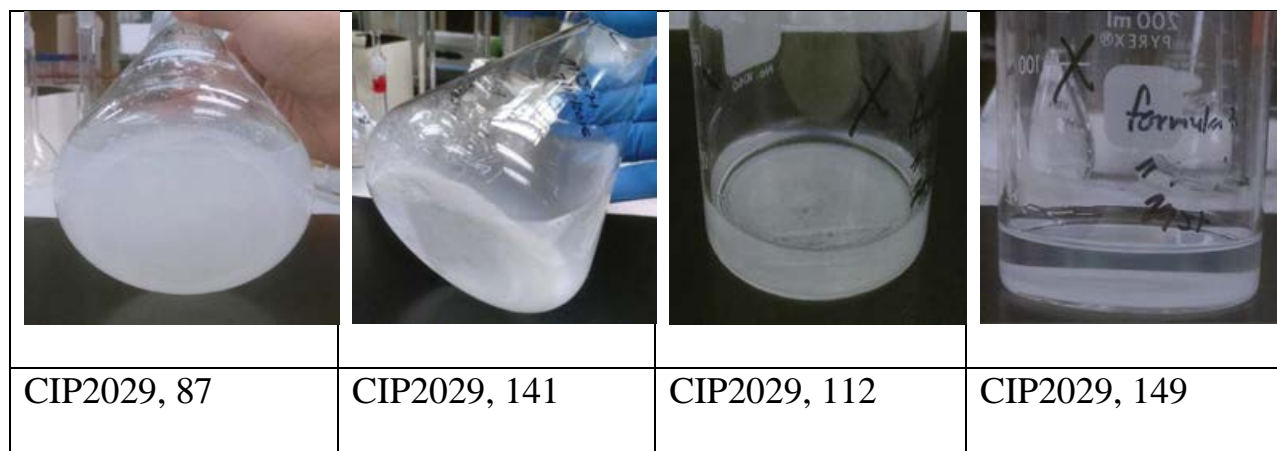
EX1011, 6:30-40.

i. Dr. Govindarajan's and Dr. Herpin's testing confirms Ms. Malhotra's findings that Example III is not “suitable for nasal administration.”

37. Dr. Govindarajan's results confirm Ms. Malhotra's determination that Cramer's Example III formulation settles quickly. Dr. Govindarajan submitted a

⁷ The information and data generated by Drs. Govindarajan and Herpin are the type of information on which formulator experts typically rely.

declaration which says that the "preparation was a cloudy dispersion" that "exhibited presence of fine settled solid upon shaking." CIP2030, 31. Similarly, Dr. Herpin's test results show that Cramer's Example III is an unstable formulation because the formulations Dr. Herpin prepared settled rapidly, continued to settle over the course of two weeks, and/or showed signs of caking. CIP2029, 42-45, 48, 53, 57. Specifically, representative photographs below show that several of Dr. Herpin's recreations resulted in significant settling and caking.



Significant settling and caking, in particular, were known in the art to be unacceptable qualities for a nasal formulation, as evidenced by Lieberman.

CIP2104, 6-7; *see also* CIP2103, 12; CIP2113, 5.

38. Second, Dr. Govindarajan's testing, as shown by his declaration, confirms Ms. Malhotra's finding that Example III had an unacceptable osmolality⁸

⁸ Osmolality is the measure of the concentration difference of a solute across a physiological membrane. As applied to physiological osmotic pressure (referred to

of 529 mOsm/kg. CIP2030, 39. This degree of osmolality is beyond the 300 mOsm/L range reported by widely used texts that formulators typically rely upon. CIP2112, 19.⁹ This also corresponds closely to the 554 mOsm/kg that Ms. Malhotra's testing showed. EX1002, 286-287. For the treatment of a chronic, long-term condition which typically requires administration of multiple doses per day for weeks at a time, a nasal formulation with such an osmolality would be unacceptable.¹⁰ Indeed, Dr. Donovan's citation to Imitrex, with an osmolality of 742 mOsm/kg, supports the point. EX1004, ¶¶74-75. Imitrex is indicated for "acute treatment of migraines" not a chronic daily treatment. EX1046, 1. The most common side effects of Imitrex are "discomfort of [a patient's] throat or nose" and a "warm, hot, burning feeling" which would be associated with Imitrex's high

as the "tonicity" of a solution)—solutions having higher osmotic pressure than bodily fluids are *hypertonic*, while solutions having lower osmotic pressure than bodily fluids are *hypotonic*. CIP2038, 4-5.

⁹ Standard formulation texts like Allen are widely regarded as a reliable and authoritative references for experts and formulators, and are frequently relied upon.

¹⁰ Although Allen identifies 200-600 mOsm/L as an acceptable isotonicity range, the osmolality of Cramer Example III is very near the upper bound. And Allen is silent on whether such a hypertonic formulation is acceptable for chronic use.

osmolality. EX1046, 19. A POSA seeking to make a medication to treat allergic rhinitis, however, would know that the formulation would be for chronic use, not acute treatment, and that any preparation with an osmolality of nearly 600 mOsm/kg is hypertonic and would be expected to irritate the nasal mucosa, particularly if used chronically. EX1002, 286-287.

39. The Rabago reference Dr. Donovan cites would not change a POSA's understanding that the osmolality of Cramer's Example III would be unacceptable for chronic, long-term use—the type of use necessary for treating allergic rhinitis. Rabago discloses the use of SinuCleanse (2% saline solution buffered with baking soda) as a nasal irrigation technique to treat the symptoms of allergic rhinitis. EX1048, 1-2. But Rabago reports that the object of nasal irrigation is to "flush[] the nasal cavity with saline solution, facilitating a wash of the structures within." EX1048, 1. And investigations into the impact of hypertonicity on mucosal clearance have reported that the buffered hypertonic saline solutions helps to

increase that clearance. CIP2136, 1.¹¹ The intent of intranasal drug delivery, however, is for the formulation to *stay* on the nasal mucosa, not for it to be cleared from the nasal mucosa, so Rabago's teachings are the antithesis of delivering a drug formulation via an intranasal administration. Even so, Rabago would tell a POSA nothing of the tolerability of an *acidic*, hypertonic formulation like Cramer Example III, as explained in more detail below.

40. And although Ms. Malhotra did not test the pH of Cramer Example III, the pH results obtained by Dr. Herpin further confirm that Example III is a formulation not suitable for nasal administration. For the multiple recreations Dr. Herpin prepared, the pH was approximately 3 or below. CIP2029, 37-45, 48, 53. A commonly used text that is widely relied upon by nasal spray formulators reports that an acceptable pH for a nasal formulation ranges from 4 to 8. CIP2112, 19. Because these pHs are well below the acceptable pH of a nasal formulation, such

¹¹ CIP2136 is a peer-reviewed publication in reputable journal. Such journals, and the information contained in such publications, are considered reliable accurate and reliable sources of information upon which experts and formulators can rely. And, indeed, such journals and such publications are frequently relied upon in the formulation field.

formulations would not be tolerable to patients and therefore would not be suitable for nasal administration.

41. It is my opinion that the results reported by Ms. Malhotra, Dr. Govindarajan, and Dr. Herpin show that Cramer's Example III is not "suitable for nasal administration" nor is it a "nasal spray" within the meaning of the challenged claims because it is (1) physically unstable, leading to settling and caking, (2) highly acidic, and (3) has an unacceptably high osmolality.

ii. Routine experimentation would not remedy the shortcomings of Example III.

42. In my opinion, fixing the deficiencies of Cramer's Example III would not be a matter of routine experimentation. I base this opinion on two grounds. First, nasal spray formulations require a fine balance of several parameters: chemical stability, physical stability, microbial stability, dose uniformity, osmolality, pH, and spray quality. Each of these parameters is interrelated, so modifying any one of them will also modify any of the other parameters in unknown ways. With that context in mind, any modification a POSA might make to remedy any of the deficiencies of Cramer's Example III would impact any of the other parameters—potentially creating more deficiencies. For example, Dr. Govindarajan's declaration states that he used HPMC to modify the formulation of Cramer's Example III. CIP2030, 27 (identifying Hypromellose, Type 2910, Pharmacoat 606). The manufacturer's product brochure for this type of HPMC

used by Dr. Govindarajan, which formulators commonly rely on for product information, states that the HPMC has a viscosity of 6 cP. CIP2105, 4-6 (identifying a viscosity of 6 cP). According to the British Pharmaceutical Codex, which is also a reference that is commonly relied upon by formulators, HPMC with a viscosity of 6 cP is a low viscosity grade. CIP2040, 4 (identify 6 cP as a low viscosity). It is my opinion that Dr. Govindarajan likely used low viscosity HPMC to obtain acceptable sprayability, but by doing so it also undermined the physical stability of the formulation, leading to unacceptable settling. Second, Ms. Malhotra and Drs. Govindarajan and Herpin's declarations show routine modifications to the formulation, but were unable to remedy Cramer's Example III shortcomings. The declarations show that the modifications attempted were:

- Dr. Govindarajan selected to use a low viscosity HPMC. CIP2030, 27; CIP2105, 4-6; CIP2040, 4.
- Dr. Herpin used a medium viscosity HPMC. CIP2029, 3.
- Ms. Malhotra applied heat to the sample preparation disclosed in her declaration. EX1002, 285-286.
- Dr. Govindarajan used high-speed mixing steps that are not shown in Cramer to prepare his formulation. CIP2030, 30-31, 33, 36, 37.

43. Despite these routine modifications, none had the effect of curing Cramer's shortcomings as seen in each of Ms. Malhotra's, and Drs. Herpin's and

Govindarajan's testing results. (¶¶37-41 above.) And because these recreations were conducted as a POSA would have done in 2002, a POSA would have arrived at the same results as Ms. Malhotra and Drs. Govindarajan and Herpin. And given that these test results lead to a formulation that is neither "suitable for nasal administration" nor a "nasal spray" even after routine modifications, a POSA would have been discouraged from pursuing an azelastine/fluticasone combination formulation.

IX. As of June 2002, a POSA would not have had a motivation to use the excipients recited in claims 42-44 in an azelastine/fluticasone combination formulation, and would not have had a reasonable expectation of success.

44. Dr. Donovan opines that based on the "FDA-approved nasal formulations for both drugs and the disclosures of the corresponding patents, Hettche and Phillipps, there were a limited number of excipients that a formulator would have turned to in order to co-formulate a combination fluticasone propionate and azelastine as a nasal spray." EX1004, ¶41. In my opinion, the excipients recited in claims 42-44 would not have been obvious because the prior art did not provide a motivation to use those excipients, nor would a POSA have had a reasonable expectation of success of doing so.

A. The prior art would have led a POSA away from using the thickening agents "microcrystalline cellulose and sodium carboxymethyl cellulose" as recited in claims 42-44.

45. Argentum and Dr. Donovan assert that a POSA would have used microcrystalline cellulose ("MCC") and sodium carboxymethyl cellulose ("CMC") as the thickening agent for an azelastine/fluticasone combination formulation. EX1004, ¶¶57-60. But in my opinion, the art would have discouraged a POSA from using MCC and CMC with azelastine.

46. By 2002, a POSA would have understood that CMC and MCC were "incompatible with cationic drugs" like azelastine. CIP2113, 24-25. Lieberman (CIP2113 and CIP2104), a widely used reference that is commonly relied upon by formulators, articulates a POSA's knowledge as of 2002 that "[c]arboxymethylcellulose solutions have poor tolerance for electrolytes . . . as they precipitate the polymer" and "CMC is compatible with other nonionic cellulose derivatives, clays, and commonly used preservatives but is incompatible with cationic drugs." CIP2113, 24-25; CIP2104, 19. And, MCC was also shown in Lieberman to be "incompatible with cationic drugs and electrolytes." CIP2113, 24-25.

47. Furthermore, in 2002 a POSA would have understood that azelastine was a cationic drug. In a pharmaceutical aqueous solution, the tertiary amine of azelastine will have a positive charge, thereby giving azelastine the behavior of a

cationic drug. Moreover, salts of azelastine will dissociate into its cationic (+) and anionic (–) portions when dissolved in solution. These anionic and cationic ions are electrolytes. That is, by 2002 a POSA would have known that azelastine salts behaved like a cationic drug and produced electrolytes in solution. Using CMC or MCC with azelastine would thus expose those thickening agents to a cationic drug and to electrolytes. In this environment, the art taught that CMC and MCC would have been expected to settle out of the formulation—undermining the stability of the formulation, especially the physical stability of the fluticasone suspension. Because the anticipated effect of using CMC and MCC with azelastine would undermine the same reason why a POSA would use CMC and MCC with fluticasone (suspending the fluticasone particles and thickening the formulation), a POSA would have been discouraged from using these thickening agents out of the many thickening agents known in the art.

48. The expected incompatibility of azelastine and MCC/CMC is consistent with Meda's observations during its efforts to formulate an azelastine/fluticasone combination formulation in 2006, discussed in more detail below. §X.C-D. At that time Meda observed that azelastine was not soluble in the Flonase® nasal spray medium containing a MCC/CMC mixture, and believed the precipitate that formed was undissolved azelastine crystals. CIP2061, 18 (finding that "a major portion of the azelastine HCl [] had not gone into solution.").

Commenting on the same experiment in the related *Apotex* case, Dr. Donovan stated that it was likely the MCC in the Flonase® nasal spray medium that was precipitating, stating "it is highly probable that the precipitate was not azelastine hydrochloride, which is sparingly soluble material but rather the MCC from the Avicel in the Flonase®." CIP2014, 240:15-21. Regardless of whether it was the azelastine crystals precipitating as Meda believed, the MCC precipitating as Dr. Donovan believes, or the CMC precipitating as the prior art teaches, a POSA would have been concerned that azelastine was incompatible with MCC or CMC, and would thus not have been motivated to use MCC or CMC in an azelastine/fluticasone combination formulation.

49. Without recognizing any of these concerns, and despite addressing this same evidence in the related *Apotex* case, Dr. Donovan opines that Hettche "discloses that an appropriate thickening agent for use in an azelastine formulation includes carboxymethyl cellulose and other cellulose derivatives." EX1004, ¶59. But Hettche discloses many other possible thickening agents that a POSA would not have overlooked—including HPMC—which a POSA would have viewed as the preferred thickening agent for azelastine because it was used in Astelin®. EX1007, 4, Example I. Also, a POSA would not have viewed Hettche's listing of CMC as a possible thickening agent for azelastine formulations to provide (1) any motivation to use CMC with azelastine formulations nor (2) a reasonable

expectation of successfully doing so for two reasons. *See* Pet. 47. First, Hettche issued in 1992 (EX1007, 1), but Lieberman published 4 years later in 1996 (CIP2113, 3). Therefore, Lieberman would have been viewed as the current understanding, not Hettche. Second, Lieberman contains the affirmative statement that MCC and CMC "[are] incompatible with cationic drugs" (CIP2113, 24) compared to Hettche's more permissive language that a thickening agent for an azelastine formulation "may, for example, be...[CMC]." EX1007, 3, col. 4, lines 54 -61.

B. The prior art provided no motivation to use a three-preservative combination of "edetate disodium" / "benzalkonium chloride" / "phenyl ethyl alcohol" as recited in claims 42-44.

50. Argentum and Dr. Donovan argue that a POSA formulating an azelastine/fluticasone combination formulation would have been motivated to use three preservatives—edetate disodium ("EDTA"), benzalkonium chloride ("BKC"), and phenyl ethyl alcohol. EX1004, ¶¶52-55. In my opinion, the use of the three-preservative edetate disodium ("EDTA") / benzalkonium chloride ("BKC") / phenyl ethyl alcohol combination was not obvious.

51. First, if a POSA was motivated to formulate azelastine and fluticasone into a single combination formulation, a POSA would have had no reason to deviate from either of the two-preservative combinations used in Astelin® and Flonase®. The product labels show that Astelin® used BKC-EDTA as its

preservatives; while Flonase® used BKC-phenyl ethyl alcohol. EX1008, 2; EX1010, 1. These preservative pairings were already used in the commercial Astelin® and Flonase® products, and so these pairings would have been viewed as preferred. Dr. Donovan identifies no shortcoming in these pairings, and even agreed that these preservative pairings in Astelin® and Flonase® were “successfully employed.” EX1004, ¶53.

52. Also, a POSA would have known that reducing the preservatives in an intranasal formulation lowers the irritability of the formulation. Indeed, Argentum and Dr. Donovan rely on Segal to argue that the claimed invention is obvious, but Segal discloses that “[p]reservative-free compositions are preferred due to reduced sensitivity and increased patient acceptance.” EX1012, 6:17-20.

53. Second, Dr. Donovan asserts that “[i]t would have been obvious to a person of ordinary skill in the art to select commonly used antimicrobial preservatives.” EX1004, ¶52. But under Dr. Donovan’s rationale, her cited art also reveals that a POSA would have been faced with many, many preservatives for use in an azelastine/fluticasone combination formulation. Hettche discloses lower alkyl p-hydroxybenzoates, chlorohexidine, phenyl mercury borate, thimerosal, quaternary ammonium compounds such as cetrимide, benzethonium chloride, and myristyl-:-picolinium chloride. EX1007, 2-3, col. 2, line 46 – col. 3, line 25. Cramer discloses benzyl alcohol, parabens, chlorobutanol, and phenylmercuric

acetate. EX1011, 5. The Handbook of Pharmaceutical Excipients also discloses at least 17 more preservatives: benzoic acid, phenolic acid, isopropyl alcohol, bronopol, chlorobutanol, chlorocresol, cresol, glycerol, imidurea, phenol, phenoxyethanol, phenylmercuric nitrate, potassium sorbate, propylene glycol, sodium benzoate, sodium propionate, and sorbic acid. CIP2156, 4-5. Furthermore, Cramer also discloses that “[m]ixtures of these preservatives may be used”—meaning that a POSA would have been faced with countless options for mixtures of preservatives for an azelastine/fluticasone combination formulation. EX1011, 5. A POSA would not have disregarded these options.

54. Third, a POSA would not have had a good reason to ignore these preservative options and to focus exclusively on EDTA, BKC, and phenyl ethyl alcohol. Dr. Donovan relies on the known synergy between (1) EDTA and BKC and (2) BKC and phenyl ethyl alcohol. EX1004, ¶54. The synergy of these pairings was well-known and was likely the reason behind their use in Astelin® and Flonase®. But Dr. Donovan provides no reason why a POSA would seek to add a third preservative to any of these pairings, and indeed, there was not such motivation. In addition, under Argentum’s and Dr. Donovan’s rationale that Cramer discloses an azelastine/fluticasone formulation, Cramer also discloses that “[t]he most preferred preservative system for use herein comprises a combination of [BKC], chlorhexidine gluconate and [EDTA].” EX1011, 5. There is no reason a

POSA would have been motivated to use a three-preservative combination and, even if they were, there was no reason for a POSA to be motivated to arrive at the claimed EDTA, BKC, and phenyl ethyl alcohol combination.

C. The prior art would not have motivated a POSA to use "glycerin"¹² as the isotonicity agent as recited in claims 42-44.

55. Dr. Donovan opines that a POSA would have used glycerin as an isotonic agent¹³ because (1) Hettche discloses that glycerin is suitable for azelastine formulations, and (2) glycerin also functions as a solvent and humectant which "add[] to the attractiveness of its use." EX1004, ¶56. In my opinion, a POSA would not have been motivated to use glycerin for at least the reasons below.

56. First, Astelin® and Flonase® each contains an isotonicity agent, and Argentum and Dr. Donovan have not provided any need to deviate from these known agents. A POSA would have known that the Astelin® label states that the Astelin® formulation includes sodium chloride as an isotonic agent, while the Flonase® label states that the Flonase® formulation includes dextrose. EX1008, 2; EX1010, 1. Dr. Donovan, however, provides no reason why a POSA would *not* use

¹² The term "glycerine" is used in the '620 patent and is synonymous with "glycerin."

¹³ Dr. Donovan uses the term "tonicity adjuster" rather than "isotonicity agent" but these terms are not inconsistent.

the pharmaceutically and commercially-acceptable isotonic agents of Astelin® and Flonase®, and instead select an isotonic agent not used in either prior art product. Sodium chloride and dextrose would have been viewed as the preferred isotonicity agents to use with azelastine and fluticasone. Beyond their use in Astelin® and Flonase®, Allen discloses a preference in the art for using dextrose and sodium chloride as isotonic agents in nasal spray formulations. CIP2112, 19 ("The preferred agents for adjusting the tonicity of nasal solutions are sodium chloride and dextrose."). A POSA would not have ignored this clear preference in the art for sodium chloride and dextrose.

57. Second, a POSA would have faced many options if they sought to use an isotonicity agent other than sodium chloride or dextrose. Hettche discloses the use of saccharose, glucose, sorbitol, and 1,2-propylene glycol. EX1007, 3, col. 4:31-35. And Cramer discloses that boric acid, citric acid, sodium tartrate, sodium phosphate, and potassium phosphate can be used. EX1011, 4. Argentum and Dr. Donovan fail to provide any reason a POSA would have disregarded these options.

58. Third, there was no reason for a POSA to pursue glycerin because it had not been used with any prior art azelastine or fluticasone formulation. But the Hettche reference relied upon by Dr. Donovan discloses that *glucose* was a "suitable" isotonic agent for azelastine formulations. EX1007, 3, col. 4, lines 31-35. A POSA would have known that glucose is also referred to as dextrose.

CIP2135, 3. Accordingly, a POSA would have known from Hettche that dextrose was a suitable isotonic agent for azelastine formulations *and* would have further known from the Flonase® label that dextrose is a suitable isotonic agent for fluticasone formulations. EX1010, 1. On the other hand, the Hettche reference would not have motivated a POSA to select glycerin for a formulation also containing fluticasone because the Hettche reference *only* relates to azelastine formulations. And, importantly Dr. Donovan makes no mention of whether glycerin would be compatible with fluticasone. *See* EX1004, ¶56.

59. Nor would a POSA have been motivated to use glycerin in light of its other functions, as Dr. Donovan suggests. In particular, the *Handbook of Pharmaceutical Excipients* teaches that glycerin can also act as a thickening agent. EX1033, 20. But, a POSA would have no reason to select glycerin based on its function as a thickening agent because the formulation already contains pharmaceutically and commercially acceptable thickening agents—MCC/CMC. Without a need for additional thickening agents—and there is no need—the multiple functions of glycerin would not have factored into a POSA's decision of whether to select glycerin as an excipient.

X. Objective indicia of non-obviousness

60. I understand from counsel that the presence of objective, real-world evidence of non-obviousness is relevant to the question of whether the challenged

claims are obvious. I further understand from counsel that the objective, real-world evidence of non-obviousness is relevant only if it has a nexus to the challenged claims.

A. Dymista® and Duonase embody the challenged claims

61. Cipla markets an azelastine/fluticasone combination nasal spray in India under the trade name Duonase. Meda Pharmaceuticals, Inc. (now part of Mylan N.V. but collectively referred to here as "Meda") markets an azelastine/fluticasone combination nasal spray in the United States under the trade name Dymista®. CIP2021, 178:4-179:20.

62. Argentum does not challenge that Dymista® and Duonase are embodiments of the challenged claims, nor did Dr. Donovan dispute that these products are embodiments during the *Apotex* trial or in her declaration here. As explained in more detail in the claim charts below, a review of the product labels for Dymista® and Duonase¹⁴ as well as data contained in Meda and Cipla technical

¹⁴ Product labels, like the Dymista® and Duonase product labels, are a reliable and authoritative source of information for formulators and the public to understand what active ingredients and excipients are contained in a commercially available FDA-approved drug.

documents¹⁵ show that: Dymista® and Duonase are combination products comprising azelastine hydrochloride and fluticasone propionate which satisfy each of the limitations of the challenged claims. Specifically, both Dymista® and Duonase: contain azelastine hydrochloride and fluticasone propionate (claims 1, 24, 25); have a particle size less than 10 µm (claim 4); are aqueous suspensions containing [REDACTED] weight/weight (w/w) azelastine and [REDACTED] w/w fluticasone (claims 5, 6, 26); and contain pharmaceutically acceptable carriers and excipients (claim 25). Furthermore, Dymista® contains the excipients EDTA, glycerin, MCC/CMC, polysorbate 80, BKC, phenyl ethyl alcohol, and water (claims 42-44).

63. Further, each of the challenged claims requires the claimed formulation to be a “dosage form suitable for nasal administration” or a “nasal spray” which, as I explained above, means that the formulations of the challenged claims are “pharmaceutical formulations that are tolerable to patients, that are homogeneous, and that can be suitably deposited onto the nasal mucosa.” *See* claims 1, 24, and 25. In my opinion, Dymista® and Duonase are pharmaceutical

¹⁵ Product data and technical documents containing such data are a reliable and authoritative source of drug information. This information is machine-generated, is the type of data commonly relied up by formulators, and is considered reliable and accurate.

formulations that are tolerable to patients, that are homogeneous, and that can be suitably deposited onto the nasal mucosa. Both Dymista® and Duonase are commercial allergy treatments that are widely-used, that are effective at relieving the symptoms of allergic rhinitis, and because of its safety and efficacy, Dymista® is FDA-approved.

64. Below is a claim chart for Meda's Dymista®:

Claim 1	Dymista®
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.	<p>Dymista® is a pharmaceutical formulation that is a nasal spray. CIP2114, 1.</p> <p>Dymista® contains █ % w/w azelastine hydrochloride and █ % w/w fluticasone propionate. CIP2154 1.</p> <p>The hydrochloride salt of azelastine is a pharmaceutically acceptable salt as it was previously used in the FDA-approved Astelin® product. EX1008, 2-3.</p> <p>The propionate ester of fluticasone is a pharmaceutically acceptable ester as it was previously used in the FDA-approved Flonase® product. EX1010, 1.</p>
Claim 4	Dymista®
The pharmaceutical formulation of claim 1, wherein said formulation has a particle size of less than 10 µm.	<p>See Claim 1 analysis, <i>supra</i>.</p> <p>Dymista® has a particle size of less than 10 µm. CIP2153, 16, 19, 22, 25, 28, and 31.</p>
Claim 5	Dymista®
The pharmaceutical formulation of claim 1, wherein said	<p>See Claim 1 analysis, <i>supra</i>.</p> <p>Dymista® is a nasal spray suspension.</p>

formulation is an aqueous suspension comprising from 0.0005% (weight/weight) to 2% (weight/weight) of said azelastine, or said pharmaceutically acceptable salt thereof, and from 0.0357% (weight/weight) to 1.5% (weight/weight) of said pharmaceutically acceptable ester of fluticasone.	CIP2114, 2. Dymista® is an aqueous-based nasal spray product. CIP2114, 12.
Claim 6	Dymista®
The pharmaceutical formulation according to claim 5, comprising from 0.001% (weight/weight) to 1% (weight/weight) of said azelastine, or said pharmaceutically acceptable salt thereof, and from 0.0357% (weight/weight) to 1.5% (weight/weight) of said pharmaceutically acceptable ester of fluticasone.	<i>See Claim 5 analysis, supra.</i>
Claim 24	Dymista®
A pharmaceutical formulation comprising azelastine hydrochloride; and, fluticasone propionate, wherein said formulation is in the dosage form of a nasal spray, and wherein said formulation is used in the treatment of conditions for which administration of one or more anti-histamine and/or one or more steroid is indicated.	Dymista® is a pharmaceutical formulation that is a nasal spray. CIP2114, 1. Dymista® contains azelastine hydrochloride and fluticasone propionate. CIP2114, 1.
Claim 25	Dymista®

<p>A nasal spray formulation comprising (i) azelastine, or a pharmaceutically acceptable salt thereof, (ii) a pharmaceutically acceptable ester of fluticasone, and (iii) a pharmaceutically acceptable carrier or excipient therefor.</p>	<p>Dymista® is a pharmaceutical formulation that is a nasal spray. CIP2114, 1.</p> <p>Dymista® contains azelastine hydrochloride and fluticasone propionate. CIP2114, 1.</p> <p>The hydrochloride salt of azelastine is a pharmaceutically acceptable salt as it was previously used in the FDA-approved Astelin® product. EX1008, 2-3.</p> <p>The propionate ester of fluticasone is a pharmaceutically acceptable ester as it was previously used in the FDA-approved Flonase® product. EX1010, 1.</p> <p>Dymista® contains edetate disodium, glycerin, microcrystalline cellulose and carboxymethylcellulose sodium (Avicel RC-611), polysorbate 80, benzalkonium chloride solution, phenylethyl alcohol, and purified water. CIP2114, 12-13; CIP2154, 1.</p> <p>Dymista®’s excipients and carrier are pharmaceutically acceptable as those excipients and carrier are compliant with the United States Pharmacopeia and the European Pharmacopeia. CIP2154, 1; CIP2153, 7.</p>
Claim 26	Dymista®
<p>The pharmaceutical formulation of claim 6, comprising 0.1% (weight/weight) of azelastine hydrochloride, and from 0.0357% to 1.5% (weight/weight) of fluticasone propionate.</p>	<p><i>See Claim 6 analysis, supra.</i></p>
Claim 29	Dymista®
<p>The pharmaceutical formulation of claim 26, wherein said dosage form suitable for nasal</p>	<p><i>See Claim 26 analysis, supra.</i></p> <p>Dymista® is a pharmaceutical formulation that is a nasal spray. CIP2114, 1.</p>

administration comprises a nasal spray.	
Claim 42	Dymista®
The pharmaceutical formulation of claim 1, further comprising edetate disodium, glycerine, a thickening agent comprising microcrystalline cellulose and sodium carboxy methyl cellulose, polysorbate 80, benzalkonium chloride, phenyl ethyl alcohol, and purified water.	See Claim 1 analysis, <i>supra</i> . Dymista® contains edetate disodium, glycerin, microcrystalline cellulose and carboxymethylcellulose sodium (Avicel RC-611), polysorbate 80, benzalkonium chloride solution, phenylethyl alcohol, and purified water. CIP2114, 12-13; CIP2154, 1.
Claim 43	Dymista®
The pharmaceutical formulation of claim 24, further comprising edetate disodium, glycerine, a thickening agent comprising microcrystalline cellulose and sodium carboxy methyl cellulose, polysorbate 80, benzalkonium chloride, phenyl ethyl alcohol, and purified water.	See Claim 24 analysis, <i>supra</i> . Dymista® contains edetate disodium, glycerin, microcrystalline cellulose and carboxymethylcellulose sodium (Avicel RC-611), polysorbate 80, benzalkonium chloride solution, phenylethyl alcohol, and purified water. CIP2114, 12-13; CIP2154, 1.
Claim 44	Dymista®
The pharmaceutical formulation of claim 25, further comprising edetate disodium, glycerine, a thickening agent comprising microcrystalline cellulose and sodium carboxy methyl cellulose, polysorbate 80, benzalkonium chloride, phenyl ethyl alcohol, and purified water.	See Claim 25 analysis, <i>supra</i> . Dymista® contains edetate disodium, glycerin, microcrystalline cellulose and carboxymethylcellulose sodium (Avicel RC-611), polysorbate 80, benzalkonium chloride solution, phenylethyl alcohol, and purified water. CIP2114, 12-13; CIP2154, 1.

65. Below is a claim chart for Cipla's Duonase:¹⁶

Claim 1	Duonase (Original and 2010 Reformulation)
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.	<p>Duonase is a pharmaceutical formulation that is a nasal spray. CIP2070, 1.</p> <p>Duonase contains [REDACTED] % w/v azelastine hydrochloride and [REDACTED] % w/v fluticasone propionate. CIP2152, 1; CIP2151, 2.</p> <p>The hydrochloride salt of azelastine is a pharmaceutically acceptable salt as it was previously used in the FDA-approved Astelin® product. EX1008, 2-3.</p> <p>The propionate ester of fluticasone is a pharmaceutically acceptable ester as it was previously used in the FDA-approved Flonase® product. EX1010, 1.</p>
Claim 4	Duonase (Original and 2010 Reformulation)
The pharmaceutical formulation of claim 1, wherein said formulation has a particle size of less than 10 µm.	<p><i>See</i> Claim 1 analysis, <i>supra</i>.</p> <p>Duonase has a particle size of less than 10 µm. CIP2152, 1.</p>
Claim 5	Duonase (Original and 2010 Reformulation)
The pharmaceutical formulation of claim 1, wherein said formulation is an aqueous suspension comprising from 0.0005% (weight/weight) to 2%	<p><i>See</i> Claim 1 analysis, <i>supra</i>.</p> <p>Duonase is a nasal spray suspension. CIP2151, 5.</p> <p>Duonase is an aqueous-based nasal spray</p>

¹⁶ Duonase is a water-based suspension with a density of essentially 1 g/mL. *See* CIP2155, 1. As a result, the w/v amounts provided may be converted to essentially equal amounts in w/w.

(weight/weight) of said azelastine, or said pharmaceutically acceptable salt thereof, and from 0.0357% (weight/weight) to 1.5% (weight/weight) of said pharmaceutically acceptable ester of fluticasone.	product. CIP2152, 1; CIP2151, 2.
Claim 6	Duonase (Original and 2010 Reformulation)
The pharmaceutical formulation according to claim 5, comprising from 0.001% (weight/weight) to 1% (weight/weight) of said azelastine, or said pharmaceutically acceptable salt thereof, and from 0.0357% (weight/weight) to 1.5% (weight/weight) of said pharmaceutically acceptable ester of fluticasone.	<i>See Claim 5 analysis, supra.</i>
Claim 24	Duonase (Original and 2010 Reformulation)
A pharmaceutical formulation comprising azelastine hydrochloride; and, fluticasone propionate, wherein said formulation is in the dosage form of a nasal spray, and wherein said formulation is used in the treatment of conditions for which administration of one or more anti-histamine and/or one or more steroid is indicated.	Duonase is a pharmaceutical formulation that is a nasal spray. CIP2070, 1. Duonase contains azelastine hydrochloride and fluticasone propionate. CIP2070, 1.
Claim 25	Duonase (Original and 2010 Reformulation)
A nasal spray formulation comprising (i) azelastine, or a	Duonase is a pharmaceutical formulation that is a nasal spray. CIP2070, 1.

pharmaceutically acceptable salt thereof, (ii) a pharmaceutically acceptable ester of fluticasone, and (iii) a pharmaceutically acceptable carrier or excipient therefor.	<p>Duonase contains azelastine hydrochloride and fluticasone propionate. CIP2070, 1.</p> <p>Duonase contains a carrier (e.g., purified water) and excipients (e.g., glycerin, microcrystalline cellulose and carboxymethylcellulose sodium, polysorbate 80, benzalkonium chloride solution, and phenylethyl alcohol). CIP2152, 1; CIP2151, 2.</p> <p>Duonase's carrier and excipients are pharmaceutically acceptable as those excipients and carrier are compliant with the United States Pharmacopeia and the European Pharmacopeia. CIP2152, 1; CIP2151, 2.</p>
Claim 26	Duonase (Original and 2010 Reformulation)
The pharmaceutical formulation of claim 6, comprising 0.1% (weight/weight) of azelastine hydrochloride, and from 0.0357% to 1.5% (weight/weight) of fluticasone propionate.	<i>See Claim 6 analysis, supra.</i>
Claim 29	Duonase (Original and 2010 Reformulation)
The pharmaceutical formulation of claim 26, wherein said dosage form suitable for nasal administration comprises a nasal spray.	<p><i>See Claim 26 analysis, supra.</i></p> <p>Duonase is administered as a nasal spray. CIP2070, 1.</p>

B. The Duonase Imitator Products¹⁷ embody the challenged claims

66. I understand from counsel that several pharmaceutical companies in India have commercially launched several azelastine/fluticasone products ("Duonase Imitator Products") in India. As part of the parallel *Apotex* case, I had counsel obtain samples of the Duonase Imitator Products from India, and six were obtained: Combinase-AQ by Zydus Cadila, Azeflo by Lupin, Nazomac-AF by Macleods, Floresp-AZ by Emcure, Ezicas-AZ by Intas, and Nasocom-AZ by Dr. Reddy's Labs. Avomeen Analytical Services tested these Duonase Imitator Products to determine their particle size and the amount of their excipients.¹⁸ CIP2028.

¹⁷ Because a very large percentage of these formulations are water, which has a density of 1 g/mL, any differences between amounts reported as weight/volume and weight/weight will be negligible. Dr. Donovan agrees with this approximation. EX1004, ¶22 n.1.

¹⁸ The laboratory data generated by Avomeen—such as data generated by high performance liquid chromatography, loss of solvent washing and drying, infrared chromatography, particle size—is machine-generated, is the type of data commonly relied up by formulators, and is considered reliable and accurate.

67. After reviewing the Avomeen report and the manufacturers' product labels for these Duonase Imitator Products¹⁹ (CIP2031), it is my opinion that each of these six Duonase Imitator Products are embodiments of the challenged claims. Specifically, the product labels of Combinase, Azeflo, Nazomac, Floresp, Ezicas, and Nasocom show that these products: contain azelastine and fluticasone (claims 1, 24, 25); have a particle size less than 10 μm (claim 4); and are aqueous suspensions containing azelastine and fluticasone (claim 5). Additionally, the product label of Combinase shows that it contains EDTA, glycerin, MCC/CMC, polysorbate 80, BKC, phenyl ethyl alcohol, and water (claims 42-44).

68. Further, each of the challenged claims requires the claimed formulation to be a "dosage form suitable for nasal administration" or a "nasal spray" which, as I explained above, means that the formulations of the challenged claims are "pharmaceutical formulations that are tolerable to patients, that are homogeneous, and that can be suitably deposited onto the nasal mucosa." As with Dymista® and Duonase, it is my opinion that Combinase, Azeflo, Nazomac,

¹⁹ Manufacturer product labels, like the Combinase, Azeflo, Nazomac, Floresp, Ezicas, and Nasocom product labels, are a reliable and authoritative sources of information for formulators and the public to understand what active ingredients and excipients are contained in a commercially available FDA-approved drug.

Floresp, Ezicas, and Nasocom are pharmaceutical formulations that are tolerable to patients, that are homogeneous, and that can be suitably deposited onto the nasal mucosa. These six Duonase Imitator Products are commercial allergy treatments that are effective at relieving the symptoms of allergic rhinitis. These six Duonase Imitator Products would not be widely-used and effective treatments if they suffered from the same shortcomings shown by Cramer's Example III formulation (i.e., significant caking and settling, difficulty resuspending, unacceptable spray quality, unacceptable osmolality, unacceptable acidity), and therefore these products are "dosage forms suitable for nasal administration" or "nasal sprays" as those terms are used in the challenged claims. I understand another expert will assess whether Combinase, Azeflo, Nazomac, Floresp, Ezicas, and Nasocom satisfy certain other limitations of the challenged claims.

69. Below is a claim chart for Zydus Cadila's Combinase-AQ product:

Claim 1	Combinase-AQ by Zydus Cadila
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.	Combinase-AQ is pharmaceutical formulation that is a nasal spray. CIP2031, 2. Combinase-AQ contains 0.14% w/v azelastine hydrochloride and 0.05% w/v fluticasone propionate. <i>Id.</i> ; CIP2028, 2-4.
Claim 4	Combinase-AQ by Zydus Cadila
The pharmaceutical formulation	<i>See Claim 1 analysis, supra.</i>

of claim 1, wherein said formulation has a particle size of less than 10 μ m.	Combinase-AQ has a particle size of less than 10 μ m. CIP2028, 2-4.
Claim 5	Combinase-AQ by Zydus Cadila
The pharmaceutical formulation of claim 1, wherein said formulation is an aqueous suspension comprising from 0.0005% (weight/weight) to 2% (weight/weight) of said azelastine, or said pharmaceutically acceptable salt thereof, and from 0.0357% (weight/weight) to 1.5% (weight/weight) of said pharmaceutically acceptable ester of fluticasone.	<p><i>See</i> Claim 1 analysis, <i>supra</i>.</p> <p>Combinase-AQ has a 0.14% w/v of azelastine hydrochloride. CIP2031, 2; CIP2028, 2-4.</p> <p>Combinase-AQ has a 0.05% w/v of fluticasone propionate. CIP2031, 2; CIP2028, 2-4.</p> <p>Based on the similarity of Combinase-AQ's formulation to Dymista® and Duonase, Combinase-AQ is an aqueous-suspension. <i>See</i> above.</p>
Claim 24	Combinase-AQ by Zydus Cadila
A pharmaceutical formulation comprising azelastine hydrochloride; and, fluticasone propionate, wherein said formulation is in the dosage form of a nasal spray, and wherein said formulation is used in the treatment of conditions for which administration of one or more anti-histamine and/or one or more steroid is indicated.	<p>Combinase-AQ is pharmaceutical formulation that is a nasal spray. CIP2031, 2.</p> <p>Combinase-AQ contains 0.14% w/v azelastine hydrochloride and 0.05% w/v fluticasone propionate. <i>Id.</i>; CIP2028, 2-4.</p>
Claim 25	Combinase-AQ by Zydus Cadila
A nasal spray formulation comprising (i) azelastine, or a pharmaceutically acceptable salt thereof, (ii) a pharmaceutically acceptable ester of fluticasone, and (iii) a pharmaceutically	<p>Combinase-AQ is administered as a nasal spray. CIP2031, 2.</p> <p>Combinase-AQ contains 0.14% w/v azelastine hydrochloride and 0.05% w/v fluticasone propionate. <i>Id.</i></p>

acceptable carrier or excipient therefor.	<p>Combinase-AQ contains excipients (e.g., glycerin, microcrystalline cellulose and carboxymethylcellulose sodium, polysorbate 80, benzalkonium chloride solution, and phenylethyl alcohol). CIP2031, 2-4; CIP2028, 2-4.</p> <p>Combinase-AQ's excipients are pharmaceutically acceptable as those excipients are compliant with the Indian Pharmacopeia. CIP2031, 2-4.</p>
Claim 42	Combinase-AQ by Zydus Cadila
The pharmaceutical formulation of claim 1, further comprising edetate disodium, glycerine, a thickening agent comprising microcrystalline cellulose and sodium carboxy methyl cellulose, polysorbate 80, benzalkonium chloride, phenyl ethyl alcohol, and purified water.	<p><i>See</i> Claim 1 analysis, <i>supra</i>.</p> <p>Combinase-AQ contains edetate disodium, glycerin, microcrystalline cellulose and carboxymethylcellulose sodium, polysorbate 80, benzalkonium chloride solution, and phenylethyl alcohol. CIP2031, 2-4; CIP2028, 2-4.</p> <p>Based on the similarity of Combinase-AQ's formulation to Dymista® and Duonase, Combinase-AQ is an aqueous-based nasal spray formulation with q.s. water. <i>See</i> above.</p>
Claim 43	Combinase-AQ by Zydus Cadila
The pharmaceutical formulation of claim 24, further comprising edetate disodium, glycerine, a thickening agent comprising microcrystalline cellulose and sodium carboxy methyl cellulose, polysorbate 80, benzalkonium chloride, phenyl ethyl alcohol, and purified water.	<p><i>See</i> Claim 24 analysis, <i>supra</i>.</p> <p>Combinase-AQ contains edetate disodium, glycerin, microcrystalline cellulose and carboxymethylcellulose sodium, polysorbate 80, benzalkonium chloride solution, and phenylethyl alcohol. CIP2031, 2-4; CIP2028, 2-4.</p> <p>Based on the similarity of Combinase-AQ's formulation to Dymista® and Duonase, Combinase-AQ is an aqueous-based nasal spray formulation with q.s. water. <i>See</i> above;</p>

	CIP2031, 2-4; CIP2028, 2-4.
Claim 44	Combinase-AQ by Zydus Cadila
The pharmaceutical formulation of claim 25, further comprising edetate disodium, glycerine, a thickening agent comprising microcrystalline cellulose and sodium carboxy methyl cellulose, polysorbate 80, benzalkonium chloride, phenyl ethyl alcohol, and purified water.	<p><i>See Claim 25 analysis, supra.</i></p> <p>Combinase-AQ contains edetate disodium, glycerin, microcrystalline cellulose and carboxymethylcellulose sodium, polysorbate 80, benzalkonium chloride solution, and phenylethyl alcohol. CIP2031, 2-4; CIP2028, 2-4.</p> <p>Based on the similarity of Combinase-AQ's formulation to Dymista® and Duonase, Combinase-AQ is an aqueous-based nasal spray formulation with q.s. water. <i>See above;</i> CIP2031, 2-4; CIP2028, 2-4.</p>

70. Below is a claim chart for Lupin's Azeflo product:

Claim 1	Azeflo by Lupin
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.	<p>Azeflo is a pharmaceutical formulation that is a nasal spray. CIP2031, 20-23.</p> <p>Azeflo contains 0.14% w/v azelastine hydrochloride and 0.05% w/v fluticasone propionate. <i>Id.</i>; CIP2028, 2-4.</p>
Claim 4	Azeflo by Lupin
The pharmaceutical formulation of claim 1, wherein said formulation has a particle size of less than 10 µm.	<p><i>See Claim 1 analysis, supra.</i></p> <p>Azeflo has a particle size of less than 10 µm. CIP2028, 2-4.</p>
Claim 5	Azeflo by Lupin

<p>The pharmaceutical formulation of claim 1, wherein said formulation is an aqueous suspension comprising from 0.0005% (weight/weight) to 2% (weight/weight) of said azelastine, or said pharmaceutically acceptable salt thereof, and from 0.0357% (weight/weight) to 1.5% (weight/weight) of said pharmaceutically acceptable ester of fluticasone.</p>	<p><i>See Claim 1 analysis, supra.</i></p> <p>Azeflo has a 0.14% w/v of azelastine hydrochloride. CIP2031, 23; CIP2028, 2-4.</p> <p>Azeflo has a 0.05% w/v of fluticasone propionate. CIP2031, 23; CIP2028, 2-4.</p> <p>Based on the similarity of Azeflo's formulation to Dymista® and Duonase, Azeflo is an aqueous-suspension. <i>See above.</i></p>
<p>Claim 24</p>	<p>Azeflo by Lupin</p>
<p>A pharmaceutical formulation comprising azelastine hydrochloride; and, fluticasone propionate, wherein said formulation is in the dosage form of a nasal spray, and wherein said formulation is used in the treatment of conditions for which administration of one or more anti-histamine and/or one or more steroid is indicated.</p>	<p>Azeflo is a pharmaceutical formulation that is a nasal spray. CIP2031, 20-23.</p> <p>Azeflo contains 0.14% w/v azelastine hydrochloride and 0.05% w/v fluticasone propionate. <i>Id.</i>; CIP2028, 2-4.</p>
<p>Claim 25</p>	<p>Azeflo by Lupin</p>
<p>A nasal spray formulation comprising (i) azelastine, or a pharmaceutically acceptable salt thereof, (ii) a pharmaceutically acceptable ester of fluticasone, and (iii) a pharmaceutically acceptable carrier or excipient therefor.</p>	<p>Azeflo is administered as a nasal spray. CIP2031, 20-23.</p> <p>Azeflo contains azelastine hydrochloride/fluticasone propionate in 140 mcg/50 mcg per spray. <i>Id.</i>; CIP2028, 2-4.</p> <p>Azeflo contains excipients (e.g., glycerin, microcrystalline cellulose and carboxymethylcellulose sodium, polysorbate 80, benzalkonium chloride solution, and phenylethyl alcohol). <i>Id.</i>; CIP2028, 2-4.</p>

	Azeflo's excipients are pharmaceutically acceptable as those excipients are compliant with the Indian Pharmacopeia. CIP2031, 20-23.
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71. Below is a claim chart for Macleods's Nazomac-AF product:

Claim 1	Nazomac-AF by Macleods
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.	Nazomac-AF is administered as a nasal spray. CIP2031, 32-34. Nazomac-AF contains 0.14% w/v azelastine hydrochloride and 0.05% w/v fluticasone propionate. <i>Id.</i> ; CIP2028, 2-4.
Claim 4	Nazomac-AF by Macleods
The pharmaceutical formulation of claim 1, wherein said formulation has a particle size of less than 10 μm .	<i>See</i> Claim 1 analysis, <i>supra</i> . Nazomac-AF has a particle size of less than 10 μm . CIP2028, 2-4.
Claim 5	Nazomac-AF by Macleods
The pharmaceutical formulation of claim 1, wherein said formulation is an aqueous suspension comprising from 0.0005% (weight/weight) to 2% (weight/weight) of said azelastine, or said pharmaceutically acceptable salt thereof, and from 0.0357% (weight/weight) to 1.5% (weight/weight) of said pharmaceutically acceptable ester of fluticasone.	<i>See</i> Claim 1 analysis, <i>supra</i> . Nazomac-AF has a 0.14% w/v of azelastine hydrochloride. CIP2031, 32-34; CIP2028, 2-4. Nazomac-AF has a 0.05% w/v of fluticasone propionate. CIP2031, 32-34; CIP2028, 2-4. Based on the similarity of Nazomac-AF's formulation to Dymista® and Duonase, Nazomac-AF is an aqueous-suspension. <i>See</i> above.

Claim 24	Nazomac-AF by Macleods
A pharmaceutical formulation comprising azelastine hydrochloride; and, fluticasone propionate, wherein said formulation is in the dosage form of a nasal spray, and wherein said formulation is used in the treatment of conditions for which administration of one or more anti-histamine and/or one or more steroid is indicated.	Nazomac-AF is administered as a nasal spray. CIP2031, 32-34. Nazomac-AF contains 0.14% w/v azelastine hydrochloride and 0.05% w/v fluticasone propionate. <i>Id.</i> ; CIP2028, 2-4.
Claim 25	Nazomac-AF by Macleods
A nasal spray formulation comprising (i) azelastine, or a pharmaceutically acceptable salt thereof, (ii) a pharmaceutically acceptable ester of fluticasone, and (iii) a pharmaceutically acceptable carrier or excipient therefor.	Nazomac-AF is administered as a nasal spray. CIP2031, 32-34. Nazomac-AF contains azelastine hydrochloride/fluticasone propionate in 140 mcg/50 mcg per spray. <i>Id.</i> ; CIP2028, 2-4. Nazomac-AF contains excipients (e.g., glycerin, microcrystalline cellulose and carboxymethylcellulose sodium, polysorbate 80, benzalkonium chloride solution, and phenylethyl alcohol). <i>Id.</i> ; CIP2028, 2-4. Nazomac's excipients are pharmaceutically acceptable as those excipients are compliant with the Indian Pharmacopeia. CIP2031, 32-34.

72. Below is a claim chart for Emcure's Floresp-AZ product:

Claim 1	Floresp-AZ by Emcure
A pharmaceutical formulation comprising: azelastine, or a pharmaceutically acceptable salt	Floresp-AZ is a pharmaceutical formulation that is a nasal spray. CIP2031, 10-11. Floresp-AZ contains 0.14% w/v azelastine

thereof, and a pharmaceutically acceptable ester of fluticasone, wherein said pharmaceutical formulation is in a dosage form suitable for nasal administration.	hydrochloride and 0.05% w/v fluticasone propionate. <i>Id.</i> ; CIP2028, 2-4.
Claim 4	Floresp-AZ by Emcure
The pharmaceutical formulation of claim 1, wherein said formulation has a particle size of less than 10 μ m.	<i>See</i> Claim 1 analysis, <i>supra</i> . Floresp-AZ has a particle size of less than 10 μ m. CIP2028, 2-4.
Claim 5	Floresp-AZ by Emcure
The pharmaceutical formulation of claim 1, wherein said formulation is an aqueous suspension comprising from 0.0005% (weight/weight) to 2% (weight/weight) of said azelastine, or said pharmaceutically acceptable salt thereof, and from 0.0357% (weight/weight) to 1.5% (weight/weight) of said pharmaceutically acceptable ester of fluticasone.	<i>See</i> Claim 1 analysis, <i>supra</i> . Floresp-AZ has a 0.14% w/v of azelastine hydrochloride. CIP2031, 10-11; CIP2028, 2-4. Floresp-AZ has a 0.05% w/v of fluticasone propionate. CIP2031, 10-11; CIP2028, 2-4. Based on the similarity of Floresp-AZ's formulation to Dymista® and Duonase, Floresp-AZ is an aqueous-suspension. <i>See</i> above.
Claim 24	Floresp-AZ by Emcure
A pharmaceutical formulation comprising azelastine hydrochloride; and, fluticasone propionate, wherein said formulation is in the dosage form of a nasal spray, and wherein said formulation is used in the treatment of conditions for which administration of one or more anti-histamine and/or one or more steroid is indicated.	Floresp-AZ is a pharmaceutical formulation that is a nasal spray. CIP2031, 10-11. Floresp-AZ contains 0.14% w/v azelastine hydrochloride and 0.05% w/v fluticasone propionate. <i>Id.</i> ; CIP2028, 2-4.

Claim 25	Floresp-AZ by Emcure
A nasal spray formulation comprising (i) azelastine, or a pharmaceutically acceptable salt thereof, (ii) a pharmaceutically acceptable ester of fluticasone, and (iii) a pharmaceutically acceptable carrier or excipient therefor.	<p>Floresp-AZ is administered as a nasal spray. CIP2031, 10-11.</p> <p>Floresp-AZ contains azelastine hydrochloride/fluticasone propionate in 140 mcg/50 mcg per spray. <i>Id.</i>; CIP2028, 2-4.</p> <p>Floresp-AZ contains excipients (e.g., glycerin, microcrystalline cellulose and carboxymethylcellulose sodium, polysorbate 80, benzalkonium chloride solution, and phenylethyl alcohol). <i>Id.</i>; CIP2028, 2-4.</p> <p>Floresp's excipients are pharmaceutically acceptable as those excipients are compliant with the Indian Pharmacopeia. CIP2031, 10-11.</p>

73. Below is a claim chart for Intas's Ezicas-AZ product:

Claim 1	Ezicas-AZ by Intas
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.	<p>Ezicas-AZ is a pharmaceutical formulation that is a nasal spray. CIP2031, 15-18.</p> <p>Ezicas-AZ contains 0.14% w/v azelastine hydrochloride and 0.05% w/v fluticasone propionate. <i>Id.</i>; CIP2028, 2-4.</p>
Claim 4	Ezicas-AZ by Intas
The pharmaceutical formulation of claim 1, wherein said formulation has a particle size of less than 10 μm .	<p><i>See</i> Claim 1 analysis, <i>supra</i>.</p> <p>Ezicas-AZ has a particle size of less than 10 μm. CIP2028, 2-4.</p>
Claim 5	Ezicas-AZ by Intas

<p>The pharmaceutical formulation of claim 1, wherein said formulation is an aqueous suspension comprising from 0.0005% (weight/weight) to 2% (weight/weight) of said azelastine, or said pharmaceutically acceptable salt thereof, and from 0.0357% (weight/weight) to 1.5% (weight/weight) of said pharmaceutically acceptable ester of fluticasone.</p>	<p><i>See</i> Claim 1 analysis, <i>supra</i>.</p> <p>Ezicas-AZ has a 0.14% w/v of azelastine hydrochloride. CIP2031, 15-18; CIP2028, 2-4.</p> <p>Ezicas-AZ has a 0.05% w/v of fluticasone propionate. CIP2031, 15-18; CIP2028, 2-4.</p> <p>Based on the similarity of Ezicas-AZ's formulation to Dymista® and Duonase, Ezicas-AZ is an aqueous-suspension. <i>See</i> above.</p>
<p style="text-align: center;">Claim 24</p>	<p style="text-align: center;">Ezicas-AZ by Intas</p>
<p>A pharmaceutical formulation comprising azelastine hydrochloride; and, fluticasone propionate, wherein said formulation is in the dosage form of a nasal spray, and wherein said formulation is used in the treatment of conditions for which administration of one or more anti-histamine and/or one or more steroid is indicated.</p>	<p>Ezicas-AZ is a pharmaceutical formulation that is a nasal spray. CIP2031, 15-18.</p> <p>Ezicas-AZ contains 0.14% w/v azelastine hydrochloride and 0.05% w/v fluticasone propionate. <i>Id.</i>; CIP2028, 2-4.</p>
<p style="text-align: center;">Claim 25</p>	<p style="text-align: center;">Ezicas-AZ by Intas</p>
<p>A nasal spray formulation comprising (i) azelastine, or a pharmaceutically acceptable salt thereof, (ii) a pharmaceutically acceptable ester of fluticasone, and (iii) a pharmaceutically acceptable carrier or excipient therefor.</p>	<p>Ezicas-AZ is administered as a nasal spray. CIP2031, 15-18.</p> <p>Ezicas-AZ contains azelastine hydrochloride/fluticasone propionate in 140 mcg/50 mcg per spray. <i>Id.</i>; CIP2028, 2-4.</p> <p>Ezicas-AZ contains excipients (e.g., glycerin, microcrystalline cellulose and carboxymethylcellulose sodium, polysorbate 80, benzalkonium chloride solution, and phenylethyl alcohol). <i>Id.</i>; CIP2028, 2-4.</p>

	Ezicas's excipients are pharmaceutically acceptable as those excipients are compliant with the Indian Pharmacopeia. CIP2031, 15-18.
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74. Below is a claim chart for Dr. Reddy's Labs' Nasocom-AZ product:

Claim 1	Nasocom-AZ by Dr. Reddy's Labs
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.	Nasocom-AZ is a pharmaceutical formulation that is a nasal spray. CIP2031, 5-9. Nasocom-AZ contains 0.14% w/v azelastine hydrochloride and 0.05% w/v fluticasone propionate. <i>Id.</i> ; CIP2028, 2-4.
Claim 4	Nasocom-AZ by Dr. Reddy's Labs
The pharmaceutical formulation of claim 1, wherein said formulation has a particle size of less than 10 μ m.	<i>See</i> Claim 1 analysis, <i>supra</i> . Nasocom-AZ has a particle size of less than 10 μ m. CIP2028, 2-4.
Claim 5	Nasocom-AZ by Dr. Reddy's Labs
The pharmaceutical formulation of claim 1, wherein said formulation is an aqueous suspension comprising from 0.0005% (weight/weight) to 2% (weight/weight) of said azelastine, or said pharmaceutically acceptable salt thereof, and from 0.0357% (weight/weight) to 1.5% (weight/weight) of said pharmaceutically acceptable ester of fluticasone.	<i>See</i> Claim 1 analysis, <i>supra</i> . Nasocom-AZ has a 0.14% w/v of azelastine hydrochloride. CIP2031, 5-9; CIP2028, 2-4. Nasocom-AZ has a 0.05% w/v of fluticasone propionate. CIP2031, 5-9; CIP2028, 2-4. Nasocom-AZ is an aqueous suspension. CIP2031, 5.

Claim 24	Nasocom-AZ by Dr. Reddy's Labs
A pharmaceutical formulation comprising azelastine hydrochloride; and, fluticasone propionate, wherein said formulation is in the dosage form of a nasal spray, and wherein said formulation is used in the treatment of conditions for which administration of one or more anti-histamine and/or one or more steroid is indicated.	Nasocom-AZ is a pharmaceutical formulation that is a nasal spray. CIP2031, 5-9. Nasocom-AZ contains 0.14% w/v azelastine hydrochloride and 0.05% w/v fluticasone propionate. <i>Id.</i> ; CIP2028, 2-4.
Claim 25	Nasocom-AZ by Dr. Reddy's Labs
A nasal spray formulation comprising (i) azelastine, or a pharmaceutically acceptable salt thereof, (ii) a pharmaceutically acceptable ester of fluticasone, and (iii) a pharmaceutically acceptable carrier or excipient therefor.	Nasocom-AZ is administered as a nasal spray. CIP2031, 5-9. Nasocom-AZ contains azelastine hydrochloride/fluticasone propionate in 140 mcg/50 mcg per spray. <i>Id.</i> ; CIP2028, 2-4. Nasocom-AZ contains excipients (e.g., glycerin, microcrystalline cellulose and carboxymethylcellulose sodium, polysorbate 80, benzalkonium chloride solution, and phenylethyl alcohol). <i>Id.</i> ; CIP2028, 2-4. Nasocom's excipients are pharmaceutically acceptable as those excipients are compliant with the Indian Pharmacopeia. CIP2031, 5.

C. Meda was skeptical that an azelastine/steroid combination formulation could be formulated and developed.

75. I understand from counsel that industry skepticism of the claimed invention can be objective evidence of non-obviousness. I have reviewed Dr. Alex D'Addio's declaration, as well as the documents it cites. Dr. D'Addio's Declaration

and the documents cited in it demonstrate that Meda was skeptical in 2002 that a combination product of azelastine and a steroid would be technically feasible.

CIP2148, ¶¶10-15. Meda identified at least two concerns with an azelastine/steroid combination: (1) Meda was concerned that the solution/suspension incompatibility may make a combination product unstable, and (2) given the dosing inconsistency between azelastine and steroids. Meda was concerned that a single formulation may not be able to administer the FDA-approved amounts of both drugs. CIP2148, ¶¶12-15; CIP2054, 11; CIP2056, 11. And in view of these concerns, Meda reported to management that the "feasibility" of an azelastine/steroid combination formulation was "low" and possessed a "high degree of technical difficulty." *Id.* Meda's concerns were so great in 2002 that they set aside their efforts to formulate and develop a combination formulation and investigated a dual-chamber device instead. CIP2148, ¶¶15-16. Dr. D'Addio and Meda also remained skeptical into 2006. When Meda learned of Cipla's Duonase product, Dr. D'Addio was surprised that a company was able to develop such a combination product. CIP2148, ¶26.

76. The skepticism expressed by Meda would have been similar to the skepticism expressed by a POSA. The Meda individuals expressing skepticism were at least POSAs under my and Dr. Donovan's definition because these individuals had technical degrees relating to pharmaceuticals and had several years of pharmaceutical formulation experience. CIP2148, ¶¶ 6-7, 18. Indeed, Meda was

the pioneer of azelastine-containing pharmaceutical formulations because Meda had successfully developed and received FDA-approval for Astelin® and was working on another azelastine formulation—Astepro®. CIP2148, ¶¶10, 21. I am not aware of another company that was as experienced with and knowledgeable about azelastine in 2002 as Meda. Yet, Meda was skeptical about the feasibility of such a formulation.

77. Additionally, Meda's skepticism in 2002 and again in 2006 has a nexus to the challenged claims. Each of the challenged claims contains azelastine and fluticasone in a single fixed-dose formulation, and Meda's skepticism goes to the core of that concept—whether a single formulation containing azelastine and a steroid (like fluticasone) would be stable or deliver the FDA-approved, safe and effective doses of both drugs.

D. Meda's failure to develop an azelastine/fluticasone combination formulation.

78. I understand from counsel that the failure of others to arrive at the claimed invention can be objective evidence of non-obviousness. I have reviewed Dr. Alex D'Addio's declaration, as well as the documents cited in it. These documents demonstrate that MedPointe—Meda's predecessor company but referred to here as "Meda"—was unsuccessful in its efforts to formulate and develop a nasal spray that contained an antihistamine and steroid in a single formulation, beginning in 2002 and continuing until 2006.

79. First, Meda's efforts did not result in an azelastine/fluticasone formulation that was suitable for nasal administration. Because the azelastine would not dissolve, or stay dissolved, in the Flonase® nasal spray vehicle, the resulting formulations were not physically stable and therefore cannot be considered to be a pharmaceutical form that is tolerable to patients, that is homogeneous, and that can be suitably deposited on the nasal mucosa. CIP2148, ¶¶22-25.

80. Second, Meda's efforts reflected the work a POSA would have undertaken because Meda employees Dr. Kalidas Kale, Mr. Gul Balwani, and Mr. John D'Aconti were at least POSAs under my and Dr. Donovan's definition. CIP2148, ¶¶18, 21-22.

81. Third, Meda's formulation failures have a nexus to the challenged claims because their work dissolving azelastine into the Flonase® nasal spray vehicle was the first step towards ultimately attempting to dissolve azelastine into Flonase®. CIP2148, ¶23; CIP2058, 2. Meda's general approach to investigating the feasibility of an azelastine/fluticasone combination formulation was to see if azelastine was soluble in the Flonase® nasal spray vehicle first, and if it was to then try to dissolve azelastine into Flonase®. CIP2148, ¶23; CIP2058, 2. Given the lack of guidance on solution/suspension combination formulations, this is a reasonable approach and is one that a POSA would try. The fact that azelastine was

not soluble in the Flonase® nasal spray vehicle simply means that there would have been little reason to move forward with subsequent efforts to dissolve azelastine directly into Flonase®. CIP2148, ¶27. This is a reasonable conclusion for Meda to draw and would have been one a POSA would draw under the same circumstances.

82. And, Meda also attempted to modify the formulation and the mixing process to enhance the dissolution of azelastine. Dr. D'Addio's declaration and the documents cited show that Meda tried to add heat to the sample to increase the dissolution of azelastine—this is a very common technique to try to enhance dissolution that I teach undergraduates so it certainly would have been known to a POSA. CIP2148, ¶25. Meda also tried to increase the stirring time to increase the amount of azelastine that dissolved. CIP2148, ¶25. This again is a very common dissolution-enhancing technique that a POSA would have been aware of. The fact that the efforts to increase the dissolution of azelastine were unsuccessful further confirms Meda's decision—and a POSA's—of not continuing-on to try to dissolve azelastine into Flonase®.

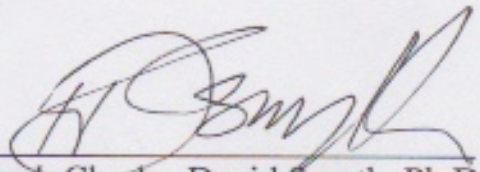
XI. Conclusion

For at least the reasons stated above, I disagree with Argentum and Dr. Donovan that the challenged claims would have been obvious to a POSA at the time of the invention.

Inter Partes Review of U.S. Patent No. 8,168,620
Second Declaration of Hugh David Charles Smyth, Ph.D. (Exhibit 2150)

I declare under penalty of perjury under the laws of the United States that
the foregoing is true and correct to the best of my knowledge.

Date: November 20, 2017



Hugh Charles David Smyth, Ph.D.