

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

MEDA PHARMACEUTICALS, INC. and)	
CIPLA LTD.)	
)	
Plaintiffs,)	Civil Action No. 14-1453 (LPS)
)	
v.)	
)	
APOTEX, INC. and APOTEX CORP.)	
)	
Defendants.)	

DEFENDANTS' PROPOSED FINDINGS OF FACT

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Dated: January 10, 2017

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Defendants Apotex Corp. and Apotex Inc. (together, “Apotex”), respectfully submit the following proposed Findings of Fact. The clear and convincing evidence at trial showed that all asserted claims from the two patents-in-suit held by Cipla Ltd. (“Cipla”) and exclusively licensed to Meda Pharmaceuticals Inc. (“Meda”), are obvious. Alternatively, they are invalid under 35 U.S.C. § 112.

I. INTRODUCTION

1. The patents-in-suit cover nasal sprays that treat allergic rhinitis (*i.e.*, “hay fever”) with two long-known active ingredients: a steroid called fluticasone propionate (“fluticasone”), and an antihistamine called azelastine hydrochloride (“azelastine”), both of which were FDA-approved before the priority date. PTX 1. The claimed co-formulation also included known excipients for known uses. Tr. (Smyth) at 652:1–654:4; Tr. (Smyth) at 670:1-6. As every single physician who testified at trial—including Plaintiffs’ experts—conceded, doctors prescribed azelastine (branded as Astelin®) with fluticasone (branded as Flonase®) to treat allergic rhinitis (“AR”) before the time of the alleged invention in June 2002. Tr. (Accetta) at 46:12-14; Tr. (Wedner) at 76:20-77:6; Tr. (Kalinier) at 433:20-434:6; Tr. (Carr) at 574:10-13. There can be no question that combining these drugs was obvious.

2. Combining fluticasone and azelastine in a single nasal spray was also expressly disclosed and taught in the prior art. Two pharmaceutical companies expressly disclosed co-formulations with these two drugs in prior art patent applications. DTX 12 (“Cramer”); DTX 21 (“Segal”). Meda itself described combination fluticasone/azelastine nasal sprays in great detail before it knew anything about the work of its co-Plaintiff, Cipla, that led to the patents-in-suit—and even described this combination as “obvious” because “Fluticasone was the then best selling steroid, and Azelastine was the best antihistamine.” Tr. (Fuge) at 137:4-8, 138:19-25; DTX 313. Even Plaintiffs’ own expert conceded (through deposition testimony when impeached) that “a

person of skill in the art” as of 2002 would have thought that they “would have improved compliance” by putting the two separate drugs “in one spray bottle.” Tr. (Kaliner) at 508:9-14. This establishes a motivation to co-formulate azelastine and fluticasone.

3. Nor was there anything inventive in co-formulating these two active ingredients with the claimed excipients. A skilled artisan before 2002 was well aware of the ingredients and manufacturing processes needed to make such a combination nasal spray work. It was obvious for an ordinarily skilled formulator to start with the excipients from the FDA-approved products and their formulation patents. Through nothing more than routine experimentation and optimization, they would have arrived at a finite number of obvious combination formulations that render all asserted claims of both patents-in-suit obvious. Tr. (Donovan) at 239:7-22. Although Plaintiffs highlighted in their opening that there would be a “solution suspension problem” because azelastine dissolves and fluticasone is suspended, the evidence showed that these ingredients behave in the patented formulation just as they did in the prior art—with azelastine dissolving and fluticasone remaining suspended. Tr. (Smyth) at 669:4-20; 670:1-6. Indeed, Plaintiffs’ formulator testified that an ordinarily skilled formulator would have been able to create the formulation of one active in solution and another in suspension using “a finite number of ways of mixing [the ingredients] together.” Tr. (Smyth) at 675:19–676:11.

II. PARTIES

4. Meda is a Delaware corporation with its principal place of business in New Jersey. Cipla is an Indian company. Meda obtained an exclusive license to the patents-in-suit from Cipla pursuant to a license agreement executed on November 13, 2006. D.I. 135 Ex. 1 at 1. Meda was recently acquired by Mylan N.V. Tr. 7:24–8:1.

5. Defendant Apotex Inc. is a Canadian corporation, and Defendant Apotex Corp. is a Delaware corporation with its principal place of business in Florida. *Id.*

III. THE PATENTS-IN-SUIT

6. On May 1, 2012, the USPTO issued U.S. Patent No. 8,168,620 B2 (“the ’620 patent”), titled “Combination of Azelastine and Steroids.” The expiration date of the ’620 patent is February 24, 2026. On February 16, 2016, the USPTO issued U.S. Patent No. 9,259,428 B2 (“the ’428 patent”), titled “Combination of Azelastine and Fluticasone for Nasal Administration.” The expiration date of the ’428 patent is June 13, 2023. The ’620 and ’428 patents have an earliest claimed priority date of June 14, 2002. D.I. 135 Ex. 1 at 1-2.

7. The named inventors of the patents-in-suit are Amar Lulla and Geena Malhotra. Mr. Lulla is deceased. Ms. Malhotra is a current employee of Plaintiff Cipla and under its control. Plaintiffs, however, did not call Ms. Malhotra to testify at trial. *Id.*

IV. THE ASSERTED CLAIMS AND PATENT SPECIFICATION.

8. Plaintiffs asserted 15 claims at trial: claims 4, 29, and 42-44 of the ’620 patent, and claims 10, 11, 13, 15, 16, 23, 24, 26, 29, and 30 of the ’428 patent (collectively, “asserted claims”). PTX 1; PTX 3; D.I. 135 Ex. 1 at 3-7. The ’620 patent claims cover pharmaceutical formulations suitable for nasal administration that contain azelastine hydrochloride and fluticasone propionate, along with various excipient ingredients and/or other characteristics such as particle size. The ’428 patent claims cover methods of using such formulations to treat allergic rhinitis. Claim 11 of the ’428 patent is illustrative of the claims. It depends from claim 1 and recites:

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

Claim 11: The method of claim 1, wherein the formulation comprises: 0.1% (weight/weight) azelastine hydrochloride; from 0.0357% (weight/weight) to 1.5%

(weight/weight) of fluticasone propionate; from 0.002% (weight/weight) to 0.05% (weight/weight) of edetate disodium; from 0.002% (weight/weight) to 0.02% (weight/weight) of benzalkonium chloride; from 0.65% (weight/weight) to 3% (weight/weight) of a combination of microcrystalline and carboxymethyl cellulose sodium; polysorbate 80; 2.3% (weight/weight) of glycerine; and 0.25% (weight/weight) of phenyl ethyl alcohol.

PTX 3.

V. THE PARTIES' WITNESSES

9. Defendants called Dr. Donald Accetta as their only live fact witness at trial. Dr. Accetta is a practicing physician at Allergy and Asthma Care in Taunton, Massachusetts. Tr. (Accetta) at 42:1-5. Notably, the Plaintiffs did not call the only living inventor of the patents, Ms. Maholtra, to testify at trial despite her being an employee of Cipla's and under its control.

10. Defendants called by deposition Dennis Fuge, Patsy Jeffery, and Jeffrey Hostler as fact witnesses. Mr. Fuge is the Vice President of Technical Operations at Meda. Tr. 131:2-3. Ms. Jeffery is an employee of Plaintiff Cipla Ltd. Tr. 753:1-2. Mr. Hostler is Chief Financial Officer of Plaintiff Meda Pharmaceuticals. Tr. 759:2-3.

11. Defendants called live Dr. H. James Wedner, Dr. Robert Schleimer, Dr. Maureen Donovan, and Mr. Jeffrey Press as expert witnesses. Dr. Wedner is professor of medicine and chief of the division of allergy and clinical immunology at Washington University of Medicine in St. Louis. Tr. (Wedner) at 72:6-10. He was offered and accepted as an expert in the treatment of patients suffering from allergic rhinitis. Tr. 75:8-13. Dr. Schleimer is the Roy and Elaine Patterson Professor, professor of medicine, and the Chief of the Division of Allergy-Immunology at Northwestern University's School of Medicine. Tr. (Schleimer) at 142:3-6. He was offered and accepted as an expert in the areas of allergy, immunology, pharmacology, and drug development. Tr. 147:13-18. Dr. Donovan is a professor at the University of Iowa's college of pharmacy. Tr. (Donovan) at 230:5-17. She was offered and accepted as an expert in the

formulation of pharmaceuticals, and specifically nasal formulations. Tr. 234:21–235:1. Mr. Press is a Director in the Forensic, Litigation & Valuation Services Group at Baker Tilly in Philadelphia. Tr. (Press) at 760:25–761:1. He was offered and accepted as an expert in the financial and economic analysis of commercial success. Tr. 764:10-15.

12. Plaintiffs called Dr. Alexander D’Addio as their only live fact witness at trial. Dr. D’Addio is a Vice President of Scientific Affairs and Medical Communications at Meda Pharmaceuticals. Tr. (D’Addio) at 352:12-16. Plaintiffs called live Dr. Michael Kaliner, Dr. Warner Carr, Dr. Hugh Smyth, and Mr. John Jarosz as experts. Plaintiffs also called by deposition Dr. Ram Govindarajan as an expert.

13. Dr. Kaliner was a practicing physician with the Institute for Asthma and Allergy. Tr. (Kaliner) at 416:7-13. He was offered and accepted as an expert in the fields of allergy and immunology and particularly in the treatment of allergic rhinitis. Tr. 419:6-11. Dr. Kaliner testified that he had a sense of loyalty to Meda, which has paid him hundreds of thousands of dollars, and that he “felt very uncomfortable and even unethical doing anything adverse to Meda.” Tr. (Kaliner) at 482:13-19; 485:4-6; 486:18–487:3. Between August 2013 and December 2015, Dr. Kaliner was the third most highly paid consultant on Meda’s Speakers’ Bureau. Tr. (Kaliner) at 482:13-19.

14. Dr. Warner Carr is a practicing physician at Allergy and Asthma Associates of Southern California. Tr. (Carr) at 516:11-18. He was offered and accepted as an expert in the treatment of allergic rhinitis and the development and conduct of clinical trials for allergic rhinitis. Tr. 517:22–5:18:2. Dr. Carr was also on Meda’s Speakers’ Bureau and was a principal investigator on the Dymista[®] trials, and estimates that he was paid by Meda approximately \$125,000 for these roles. Tr. (Carr) at 568:11-21; 570:1-4; 571:3-8.

15. Dr. Hugh Smyth is an associate professor of pharmacy at the University of Texas at Austin. Tr. (Smyth) at 601:20–602:2. He was offered and accepted as an expert in the field of drug formulation and drug delivery. Tr. 603:24–604:3. Mr. John Jarosz is a practicing economist with Analysis Group. Tr. (Jarosz) at 687:22–688:20. He was offered and accepted as an expert in the area of intellectual property protection. Tr. 689:5-7. Dr. Ramprakash Govindarajan is a Clinical Assistant Professor at the University of Iowa College of Pharmacy. PTX 1664 at 2. He testified by deposition regarding his formulation of a prior art example for Defendants in this case.

VI. PERSON OF ORDINARY SKILL IN THE ART.

16. The parties offer different definitions of a person of ordinary skill in the art from the perspective of using pharmaceutical compositions in the treatment of allergic rhinitis. Apotex's expert on this subject matter, Robert Schleimer, testified that his opinions would be the same if his understanding of a POSA or Meda's expert's understanding of a POSA were ultimately adopted. See Tr. (Schleimer) at 173:16-22; Tr. (Kaliner) at 501:21-502:1.

17. Dr. Schleimer opined that a clinical person of ordinary skill has an M.D., Ph.D. or Pharm.D. in the field of allergy/immunology and/or pharmacology (or the equivalent), and at least three additional years of experience in the treatment, or research for treatments, of allergic rhinitis, including with nasally administered steroids and antihistamines. D.I. 135 Ex. 3 at ¶ 21; Tr. (Schleimer) at 171:18-25. Meda's definition limits the POSA to only having an M.D. D.I. 135 Ex. 2 at ¶¶ 84-85; Tr. (Kaliner) at 426:11–427:1. However, Ms. Malhotra did not have an M.D., and there is no suggestion that the deceased inventor, Mr. Lulla, had an M.D. DTX 114 (Malhotra Declaration); Tr. (Kaliner) at 503:3-8.

18. Dr. Schleimer explained that he regularly supervises and teaches M.D.s and has also been intimately involved in the drug development process with M.D.s. Tr. (Schleimer) at

172:8–173:22. Dr. Kaliner also testified that Dr. Schleimer is “brilliant” and agreed that he is “qualified to offer an expert opinion in this case.” Tr. (Kaliner) at 502:2–11.

19. The parties offer different definitions of a person of ordinary skill in the art from the perspective of formulating the claimed pharmaceutical compositions. Apotex’s expert on this subject matter, Dr. Donovan, testified that her opinions would be the same if her understanding of a POSA or Meda’s expert’s understanding of a POSA were ultimately adopted. Tr. (Donovan) at 237:24–238:3.

20. Dr. Donovan opined that a person of ordinary skill in the art with respect to formulating the claimed composition would have been a pharmaceutical formulator with at least a bachelor’s degree in chemistry, biology, chemical engineering or pharmaceutical science and 3–5 years of experience in formulation development of nasal dosage forms, although the formulator could have more advanced degrees with fewer years of experience; and would have had familiarity with pharmaceutical excipients and their uses. Tr. (Donovan) at 237:5–23.

VII. IT WAS OBVIOUS TO COMBINE FLUTICASONE PROPIONATE AND AZELASTINE HYDROCHLORIDE INTO A SINGLE NASAL SPRAY FORMULATION TO TREAT ALLERGIC RHINITIS.

21. It was obvious to co-formulate fluticasone and azelastine because such a combination was actually practiced by doctors, disclosed in the prior art, and also encouraged by the prior art. Indeed, Dennis Fuge, Meda’s Vice President of Technical Operations and who was one of the first Meda representatives to visit Cipla to discuss a license for the patents-in-suit, testified that Cipla’s motive to co-formulate azelastine and fluticasone was “obvious,” because “Fluticasone was the then best selling steroid, and Azelastine was the best antihistamine.” Tr. (Fuge) at 134:3–8, 135:2–10, 138:19–25. He testified further that Meda (then called MedPointe) had also—and independently—“selected [azelastine and fluticasone] as the best two compounds

to utilize.” Tr. (Fuge) at 139:7-17. The prior art confirms Mr. Fuge’s impression that co-formulating fluticasone and azelastine was “obvious.”

A. Physicians used fluticasone propionate and azelastine hydrochloride nasal sprays together in the prior art to treat allergic rhinitis.

22. There is no dispute that physicians in the United States and elsewhere co-prescribed azelastine hydrochloride in a nasal spray formulation and fluticasone propionate in a nasal spray formulation before June 2002. Tr. (Kaliner) at 497:1-8. As described in further detail below, each testifying physician in this case, including Meda’s experts, co-prescribed the combination prior to 2002.

1. Dr. Accetta (fact witness)

23. Dr. Accetta co-prescribed Astelin[®] and Flonase[®] to treat allergic rhinitis before June 2002. Tr. (Accetta) at 46:12-14. He supported his testimony with ten patient records. *See* DTX 1-10; Tr. (Accetta) at 53:23-54:6. He co-prescribed the drugs as early as April 28, 1997. DTX 5; *see also* Tr. (Accetta) at 46:15-21. Dr. Accetta testified that he actually prescribed the combination for about a third of patients who were on combination therapy. Tr. (Accetta) at 54:20-24.

24. Azelastine was the only intranasal antihistamine that Dr. Accetta prescribed. Tr. (Accetta) at 47:10-12. He prescribed a handful of nasal steroids in the combination therapy, but referred to Flonase[®] as “one of the major ones.” Tr. (Accetta) at 46:10-21. In some cases, Dr. Accetta would prescribe the Astelin[®] on an “as needed” basis. *See, e.g.*, DTX 4 (patient record). He explained that he would prescribe the drug “as needed” for a patient with some seasonal symptoms, so the patient would supplement their steroid therapy in the months of allergen exposure. Tr. (Accetta) at 52:13-22.

25. Dr. Accetta generally used the FDA prescribed doses when co-prescribing Astelin[®] and Flonase[®] together. Tr. (Accetta) at 52:13-53:19. But he would also instruct patients to tailor their combination regimen to the lowest effective dose of the drugs. *Id.*

2. Physician expert witnesses

26. Apotex's testifying expert physician, Dr. Wedner, co-prescribed the combination as two nasal sprays for "those patients who didn't have complete relief with [Flonase[®] monotherapy]." Tr. (Wedner) at 76:20-77:6. For dosing, he would often instruct patients to modify the dose "depending on the patient's response to the therapy." Tr. (Wedner) at 77:18-22. For example, he would often start with the "conventional dose" of Astelin[®] (two sprays, twice a day), but would also instruct patients to take two sprays once a day or one spray twice a day, both of which were effective. Tr. (Wedner) at 78:24-79:12.

27. Meda's first testifying physician, Dr. Kaliner, testified that physicians, including himself, combined azelastine and fluticasone nasal sprays prior to 2002. Tr. (Kaliner) at 433:20-434:6. He further testified that his azelastine prescribing practices mirrored Dr. Accetta's and that this was the way he instructed other physicians to treat patients with AR before 2002. Tr. (Kaliner) at 454:15-17; 493:10-23; *see also* DTX 312. And similar to Drs. Wedner and Accetta, Dr. Kaliner would "try to use the lowest dose of [azelastine or fluticasone] that worked." Tr. (Kaliner) at 460:9-18.

28. Finally, Meda's other expert physician, Dr. Carr, testified that he co-prescribed the combination of azelastine and fluticasone before June 2002. Tr. (Carr) at 574:10-13.

B. The prior art discloses azelastine and fluticasone co-formulations.

29. Two prior art references, Cramer and Segal, specifically disclosed putting azelastine and fluticasone into a single nasal spray formulation and administering it to treat allergic rhinitis. *See* DTX 12; DTX 21.

30. Cramer is a European Patent application filed by the Procter & Gamble Company. It published on June 25, 1997. DTX 12. Cramer discloses a pharmaceutical composition for nasal administration comprising a glucocorticoid and a leukotriene inhibiting antihistamine. Cramer discloses fluticasone as a nasal steroid that can be used in its co-formulation. *Id.* Dr. Schleimer testified that a POSA would have been drawn to either fluticasone or mometasone because of their superior potency. Tr. (Schleimer) at 176:16-19.

31. Cramer disclosed azelastine as an acceptable leukotriene inhibiting antihistamine, which are antihistamines that, when used in the nose, can exert anti-inflammatory effects that are not found with oral versions. Tr. (Schleimer) at 175:17-24. Of the three antihistamines listed, azelastine was the only one already formulated for nasal administration and FDA approved as of the critical date. Tr. (Schleimer) at 176:20-24. Dr. Schleimer testified that a POSA viewing Cramer would have been drawn to a fluticasone/azelastine combination or a mometasone/azelastine combination for a co-formulation. Tr. (Schleimer) at 176:18–177:12.

32. Segal is an International Application filed by Warner Lambert published on November 5, 1998. DTX 21. It similarly disclosed a co-formulation of azelastine and fluticasone. *Id.* It disclosed a co-formulation containing a “topical anti-inflammatory agent” and an antihistamine. Segal lists fluticasone among its preferred anti-inflammatory steroids, and it lists azelastine among its preferred antihistamines. *Id.*; Tr. (Schleimer) at 178:1-18.

C. The prior art motivated skilled artisans to combine azelastine and fluticasone to treat allergic rhinitis.

1. Corticosteroids and antihistamines were known to have different and complementary mechanisms of action.

33. The evidence explains why physicians co-prescribed azelastine and fluticasone, and why references like Cramer and Segal disclosed co-formulations with those two drugs, prior to June 2002.

34. Prior to that date, it was well known that allergic rhinitis occurred in two phases: an early phase and a late phase. Tr. (Schleimer) at 149:8-17; Tr. (Carr) at 573:10-22; Tr. (Kaliner) at 430:13-25; *see also* PTX 333 (Drouin 1995).

35. The early phase occurs “within minutes” after an allergy sufferer is exposed to allergen. Tr. (Schleimer) at 149:8-17; *see also* DTX 34 (Galant & Wilkinson 2001); PTX 333 (Drouin 1995). Upon allergen exposure, mast cells in the nose release inflammatory mediators, including histamine. Tr. (Schleimer) at 149:23-150:5. These mediators are what cause early phase symptoms. Tr. (Schleimer) at 149:23-150:5.

36. The late phase is characterized as a “chronic inflammatory-type response.” Tr. (Schleimer) at 150:8-14. The mast cells release inflammatory mediators into the blood creating a more prolonged response. Tr. (Schleimer) at 150:8-14.

37. Corticosteroids were known to treat the late phase response and were also known to be the first-line therapy to treat allergic rhinitis. Tr. (Schleimer) at 150:17-23; PTX 326 (ARIA Guidelines 2001); DTX 34 (Galant & Wilkinson 2001). Meda’s expert, Dr. Carr, also testified that “steroids treat the late phase better than antihistamines.” Tr. (Carr) at 573:10-22. However, steroids were known to have a deficiency in that they had a slow onset of action. Tr. (Schleimer) at 151:14-18. That slow onset caused patients to stop using the drugs because they perceived them as not working well. Tr. (Schleimer) at 151:14–152:1.

38. Antihistamines, also referred to as H1 receptor antagonists, were known as the top therapy to treat the early phase response. Tr. (Schleimer) at 152:25–153:22; PTX 333 (Drouin 1995). Meda’s expert, Dr. Carr, explained that it was “medical dogma” that “antihistamines predominantly treat the early phase of allergic rhinitis more effectively than steroids.” Tr. (Carr) at 573:2-14. Unlike nasal steroids, antihistamines, and nasal antihistamines in particular, were

known to have a rapid onset of action that occurred as quickly as 15 minutes after administration. Tr. (Schleimer) at 78:3-9; Tr. (Wedner) at 84:8-19; PTX 326 (ARIA Guidelines 2001). Dr. Carr also confirmed that “antihistamines generally have a faster onset of action than steroids.” Tr. (Carr) at 573:23–574:1.

39. At the 2002 priority date, there were two formulations of antihistamines available on the market: oral and intranasal (meaning administered through the nose in a spray or solution). Intranasal antihistamines were known to have advantages over their oral counterparts. In addition to inhibiting histamine, intranasal (sometimes referred to as “topical”) antihistamines were known to have some effect on the release of inflammatory mediators, thus having some effect on the late phase in addition to the early phase. Tr. (Schleimer) at 155:3-20; DTX 26 (Berger 1999). However, these anti-inflammatory effects did not compare to a nasal steroid’s pronounced effect on the late phase. Tr. (Schleimer) at 155:21-24.

40. Intranasal antihistamines were also known to have faster onsets of action and fewer side effects than oral antihistamines because they were applied directly to the nose rather than systemically to the whole body at higher doses. Tr. (Schleimer) at 154:2-19; PTX 326 (ARIA Guidelines 2001). Dr. Kaliner agreed that “the intranasal delivery of azelastine increases global drug concentration and limits systemic distribution.” Tr. (Kaliner) at 496:5-11.

41. The prior art literature confirms that a POSA would have been motivated to treat both the early and late phases of AR to achieve the most complete treatment. For example, the Spector reference, which was published in 1999, disclosed that “[o]ptimal treatment of patients with SAR can be achieved only by managing both the [Early Phase Response] and the [Late Phase Response].” DTX 50 at 2. Spector further taught that “the ideal pharmacologic therapy would be a drug that possessed not only H1-receptor antagonist activity but also anti-

inflammatory activity.” DTX 50 at 2. Dr. Schleimer confirmed that Spector “laid . . . out” what a POSA would have known as the most complete treatment for AR. Tr. (Schleimer) at 178:23–179:14.

42. Spector also details some problems with other individual AR treatments that were available at the critical date. For example, Spector notes that decongestants only relieve nasal congestion and have “minimal effects on other symptoms of allergic rhinitis.” DTX 50 at 1. Similarly, cromolyn sodium, a mast cell stabilizer, “must be administered for several weeks before optimal relief of symptoms is realized. DTX 50 at 1; Tr. (Schleimer) at 180:2-5. Finally, it teaches that an anticholinergic, ipratropium, “is not effective for the management of symptoms of rhinitis other than rhinorrhea.” DTX 50 at 1; Tr. (Schleimer) at 180:6-10. These deficiencies reiterate Spector’s position that an “ideal drug” would be one that treats the early and late phases of AR, which would be an antihistamine and a steroid. Tr. (Schleimer) at 180:11-16.

43. Dr. Wedner echoed Spector’s criticisms of other classes of AR medication available in June 2002. He testified that mast cell stabilizers, while effective, “have to be used four times a day, and nobody uses a drug four times a day.” Tr. (Wedner) at 80:7-10. He added that leukotriene receptor antagonists “don’t add very much” and doctors “only use them largely in children.” Tr. (Wedner) at 80:11-17. He also mentioned that decongestants have “a bad side effect profile” causing hypertension, twitching, or heart problems. Tr. (Wedner) at 90:20-25.

2. Fluticasone was a preferred nasal corticosteroid because of its potency.

44. There were multiple corticosteroids available on the market as nasal sprays at the critical date. Tr. (Schleimer) at 150:17–151:4. Fluticasone was known to be the most potent. Tr. (Schleimer) at 152:11-22.

45. The 1999 Stellato reference, PTX 325, a study done in Dr. Schleimer's lab, along with the 1998 Johnson reference, DTX 39, showed that fluticasone was the most potent steroid, followed by mometasone (Nasonex®). Tr. (Schleimer) at 152:11-22.

46. Meda's expert, Dr. Kaliner, confirms "that fluticasone was the most potent of all the nasal steroids." Tr. (Kaliner) at 436:21-437:6. Dr. Kaliner also testified that "there is no controversy" that "Flonase was the leading nasal steroid." Tr. (Kaliner) at 495:6-9.

3. Azelastine was the preferred nasal antihistamine because of its efficacy.

47. There were only two FDA-approved nasal antihistamines as of June 2002: azelastine and levocabastine. Tr. (Schleimer) at 163:4-8; Tr. (Wedner) at 78:12-18. Levocabastine was rarely, if ever, used by physicians. See Tr. (Wedner) at 78:15-18; 83:5-10.

48. The 2001 Falser reference compared azelastine and levocabastine in a clinical study. PTX 66. That study found that azelastine "was statistically superior in efficacy as judged by both physicians and patients themselves." Tr. (Schleimer) at 163:4-13. This superior efficacy is further confirmed by the Kusters reference, which was published in February 2002. Tr. (Schleimer) at 163:14-15; DTX 85.

4. Oral antihistamines and nasal steroids were regularly, and successfully, combined with nasal steroids before the critical date.

49. Much like the nasal combination discussed above, physicians, including all testifying physicians here, prescribed oral antihistamines with nasal steroids to treat allergic rhinitis.

50. Dr. Schleimer testified that this "was probably the most common combination prescribed since antihistamines and intranasal steroids were both exceedingly popular drugs." Tr. (Schleimer) at 163:17-25.

51. This clinical theory behind the combination of these types of drugs was backed by pre-June 2002 research literature. For example, Drouin, a 1995 study which tested loratadine (an antihistamine marketed as Claritin®) and beclomethasone (a steroid marketed as Beconase®), found that combining them improved the treatment of patients with seasonal allergic rhinitis. Tr. (Schleimer) at 163:17-164:4; PTX 333. Brooks, which was published in 1996, further confirms the efficacy of an oral antihistamine and nasal corticosteroid combination by suggesting that the combination “should be the preferred treatment.” PTX 332; Tr. (Schleimer) at 164:5-17.

52. Dr. Kaliner also opined that he “personally used oral antihistamine as [his] primary treatment, and then [he] would add a nasal steroid . . . including fluticasone.” Tr. (Kaliner) at 435:1-5. Dr. Kaliner also opined that the “traditional approach” to treating AR was “to use oral antihistamines, and if the patients are not well controlled add a nasal steroid.” Tr. (Kaliner) at 454:21-25; *see also* Tr. (Kaliner) at 460:9-18.

53. Dr. Wedner also testified that he prescribed oral antihistamines in combination with nasal steroids. Tr. (Wedner) at 98:20-99:1. He would also add azelastine if the patient’s symptoms persisted. Tr. (Wedner) at 99:5-9.

5. The prior art recommended administration of a nasal antihistamine and a nasal steroid to treat AR.

54. The prior art, including the ARIA guidelines, the Dykewicz guidelines, the Cauwenberge reference, and the Berger reference all recommended co-administering a nasal antihistamine in combination with a nasal steroid to treat AR. This combination was also recommended by Meda’s expert, Dr. Kaliner, at a pre-June 2002 speech.

55. The ARIA guidelines are “generated by international leading experts, and they’re found to be generally very useful by practicing physicians.” Tr. (Schleimer) at 180:25–181:6. Both Apotex and Meda clinician experts rely “heavily” on the ARIA guidelines and followed

them in clinical practice before the critical date. Tr. (Kaliner) at 491:9-18; 435:10-15; Tr. (Schleimer) at 180:17-24.

56. The ARIA guidelines were published in 2001 and teach a “stepwise approach” for treating “moderate/sever persistent disease.” PTX 326 at S251. It recommends an intranasal glucocorticosteroid, like fluticasone, “as a first line treatment.” PTX 326 at S251; Tr. (Schleimer) at 181:16-23. If the steroid does not effectively manage the disease, the ARIA guidelines suggest adding an H1 antihistamine, like azelastine. PTX 326 at S251; Tr. (Schleimer) at 181:16-25.

57. Meda’s experts also “heavily” rely on the Dykewicz guidelines. Tr. (Kaliner) at 491:9-18. The Dykewicz guidelines were published in 1998 and, like the ARIA guidelines, provide practice parameters for physicians to treat AR. Tr. (Wedner) at 83:14-20; DTX 246. The Dykewicz guidelines instruct POSAs that intranasal antihistamines “are appropriate for use as a first line treatment for the symptoms of allergic rhinitis, or as part of combination therapy with nasal corticosteroids.” DTX 246 at 28. Right after giving this recommendation, the Dykewicz guidelines note that “Astelin . . . is the first intranasal antihistamine preparation approved for use in the US.” *Id.* Dr. Wedner testified that the Dykewicz guidelines were “absolutely” consistent with his prescribing practices before the critical date. Tr. (Wedner) at 88:4-6.

58. The Cauwenberge reference was published in 2000 and considered by Dr. Kaliner during expert discovery. Tr. (Kaliner) at 498:22–499:10; DTX 154. Cauwenberge’s notable authors are Bousquet, the lead author of the ARIA guidelines, and Howarth, the author of a reference relied on by Meda. Tr. (Kaliner) at 499:11-21; DTX 154. Dr. Kaliner agreed that the article “says if there is a need for therapy and there is severe symptoms, you go to nasal

corticosteroids plus oral or nasal antihistamines.” Tr. (Kaliner) at 500:5-14. And, after discussing Cauwenberge, Dr. Kaliner agreed that “the prior art . . . shows that nasal corticosteroids plus other nasal antihistamines should be used at least to treat some patients suffering from seasonal allergic rhinitis.” Tr. (Kaliner) at 500:20-24.

59. Additionally, the Berger reference, which as noted above teaches that azelastine has anti-inflammatory effects, also teaches that “[a]zelastine nasal spray can be used either in place of oral antihistamines or in combination with intranasal corticosteroids.” DTX 26 at 6; Tr. (Schleimer) at 164:23–165:1.

60. Dr. Kaliner agreed that he “told those skilled in the art in May 2002 that symptoms typical of allergic rhinitis; primarily sneezing, nasal itching and rhinorrhea; benefit most from an intranasal corticosteroid combined with an oral antihistamine to which a topical antihistamine can be added for additional symptomatic control.” Tr. (Kaliner) 490:1-8; DTX 312 at 8. Dr. Kaliner also agreed that he taught that the ARIA guidelines “suggested the combined use of an oral antihistamine with an intranasal corticosteroid” and “residual symptoms can be treated by adding the topical antihistamine azelastine to the regimen.” Tr. (Kaliner) 490:13-25. Finally, Dr. Kaliner “was quite frank” that the way to treat patients as of June 2002 was to start with “[a]n oral antihistamine, if it didn’t work we added a nasal steroid. If it didn’t work we added other agents. In this case we added a nasal antihistamine. By and large, patients improve.” Tr. (Kaliner) at 493:10-23.

61. Plaintiffs’ only response is that none of these combination therapies would have encouraged a POSA to develop a fixed-dose combination because a fixed-dose would decrease flexibility and would preclude the titration of doses to the lowest possible dose. Tr. (Kaliner) at 444:25–446:2; 512:16-21; Tr. (Carr) at 531:16-23. However, Dr. Wedner explained that a fixed-

dose combination actually increases flexibility, because a patient taking the same doses of Astelin® and Flonase® now has the flexibility to choose a more convenient fixed-dose spray; and for those patients who need a different dosing, they could always be prescribed the conjunctive use of two separate sprays. Tr. (Wedner) at 112:10-19. This is consistent with the prior art disclosure of fixed-dose combination nasal spray products for the treatment of AR—including sprays using azelastine and fluticasone. DTX 12 (Cramer); DTX 21 (Segal).

62. In sum, the prior art explicitly taught the use of intranasal antihistamines with intranasal corticosteroids. Of the only two available intranasal antihistamines on the market, the prior art taught that azelastine was superior, and it was also the most commonly used. Tr. (Schleimer) at 163:4-13; DTX 85. Of the handful of available corticosteroids, fluticasone was the most potent, Tr. (Schleimer) at 152:11; DTX 39; PTX 325, and was the “leading” steroid. Tr. (Kaliner) at 495:6-9.

6. A co-formulation of fluticasone and azelastine would have been thought to increase patient compliance.

63. The evidence also shows that the co-formulation would have been expected to improve patient compliance, because it would leverage both drugs’ mechanisms and onsets of action to provide the patient with more complete relief. Dr. Kaliner testified at deposition (used to impeach at trial) that a person of skill in the art as of 2002 would have thought that they “would have improved compliance” by putting the two separate drugs in one spray bottle. Tr. (Kaliner) at 508:5-17. This is logical because “it is more convenient to use one bottle than two bottles for patients with severe enough disease that they need both drugs.” Tr. (Schleimer) at 182:19–183:1.

64. A skilled artisan would have also known how to dose a co-formulation. As Dr. Schleimer explained, a POSA would have the initial inclination to “just use the amounts per spray that were already available in the approved products.” Tr. (Schleimer) at 183:20-25. Fluticasone

was available at 50 micrograms per spray and could be used two sprays per nostril once a day or one spray per nostril twice a day. Tr. (Schleimer) at 184:1-8; DTX 22 at 16. Azelastine was available at 137 micrograms per spray and could be used either two sprays per nostril twice a day or one spray per nostril twice a day, which is azelastine's approved dose in Europe. Tr. (Schleimer) at 184:12-23; DTX 33 at 5; PTX 326 at S226. Therefore, a skilled artisan would know that it would work to dose the co-formulation as two sprays once a day, or two sprays twice a day, with each spray containing the same amount of drug as each approved monotherapy. Tr. (Schleimer) at 184:24–185:4; *see also* DDX 4.49.

7. Fluticasone was already co-formulated with another drug to remedy compliance issues.

65. In addition to allergic rhinitis, steroids, including fluticasone, were also known as the best drugs to treat asthma. Tr. (Schleimer) at 165:9-18. Fluticasone was already known to have patient compliance issues because of its slow onset of action, which was also prevalent in the asthma field. Tr. (Schleimer) at 165:9-18. To remedy that problem, fluticasone was co-formulated with a faster acting bronchodilator, the combination of which was commercially known as Advair®. Tr. (Schleimer) at 165:9–166:6.

66. The prior art taught that Advair® increased patient compliance. The Stoloff reference taught that the “complementary mechanisms of action” of fluticasone and the bronchodilator achieved “a superior level of asthma control” and that “the availability of this combination in a single product will likely simplify and increase patient adherence to an asthma treatment plan.” DTX 77; Tr. (Schleimer) at 166:10-11.

8. Combinations studies showed a benefit to combining antihistamines and corticosteroids.

67. There were seven prior art studies discussed by the parties throughout the course of trial addressing combination therapy with a steroid and an oral (but not intranasal)

antihistamine. Five out of seven of the studies found advantages to combining a steroid with an oral antihistamine. Tr. (Schleimer) at 186:2-5. These prior art studies were published before the ARIA guidelines, which recommended by June 2002 a step-wise method for treating AR that combined a nasal steroid and antihistamines. Tr. (Schleimer) at 189:17-190:1; PTX 326. The Dykewicz guidelines also stated “at least 50% of patients need to take nasal corticosteroids and oral antihistamine to adequately control symptoms of seasonal allergic rhinitis.” DTX 246 at 29.

68. Meda argues that four of the studies (Juniper 1989; Benincasa 1994; Simpson 1994; and Ratner 1998) showed little or no benefit to a combination. However, the Simpson reference “found a statistically significant improvement compared to both monotherapies for sneezing, which is one of the hallmark symptoms of allergic rhinitis.” Tr. (Schleimer) at 187:6-11; DTX 49. And Ratner 1998 found that the “combination was considered more effective according to some patient ratings.” DTX 140 at 8; Tr. (Schleimer) at 188:24-189:1.

69. To the extent these studies can be interpreted to show little or no benefit, none actually reviewed azelastine and fluticasone or any combination of a nasal steroid and nasal antihistamine. Tr. (Schleimer) at 190:2-7. Clinical study results for a steroid antihistamine combination therapy will vary depending on the drugs being tested and the patient population. Tr. (Schleimer) at 190:8-13. Most critically, none of the studies taught a POSA to avoid, or otherwise discouraged, combining a steroid and an antihistamine, much less the specific drugs at issue here. Tr. (Schleimer) at 189:2-9. Indeed, every clinician testifying in this case used the combination of Flonase® and Astelin® for patients as of 2002. Tr. (Accetta) at 46:12-14; Tr. (Wedner) at 76:20-77:6; Tr. (Kalinier) at 433:20-434:6; Tr. (Carr) at 574:10-13.

70. Dr. Schleimer further detailed design issues that would diminish the benefit of a combination. For example, the Benincasa study did not collect data until three weeks of

treatment. Tr. (Schleimer) at 186:14-16; DTX 248. Dr. Schleimer explained that late collection ignores “the period of time when you would expect to see the real advantage of the combination,” i.e., early on before the steroid is fully effective. Tr. (Schleimer) at 186:16-20.

71. The Juniper 1989 study also used the antihistamine astemizole, which was “withdrawn from development” and not available on the market as of June 2002. Tr. (Schleimer) at 186:21-187:1; DTX 40. The same author, Juniper, later did another study combining an oral antihistamine and nasal steroid which found that “at least 50 percent of patients will need to take both types of medication in combination to control symptoms adequately.” Tr. (Schleimer) at 188:3-21; DTX 40. The oral antihistamine terfenadine, used in the Simpson study, was also not available in June 2002 because it was “withdrawn from the market due to cardiovascular side effects.” DTX 49; Tr. (Schleimer) at 187:12-16.

72. Meda additionally relied on studies that were published after June 2002 and to which a POSA would not have had access at the critical date. Tr. (Schleimer) at 191:8-15; *see also* PDX 2.15. Dr. Schleimer explained that these studies also found the combination to “be superior to the individual monotherapies in some of the symptom routes.” Tr. (Schleimer) at 191:16-23; PTX 21; PTX 12. Moreover, the ARIA guidelines have not since changed their recommendations in light of these studies. Tr. (Schleimer) at 191:24-192:3.

73. In sum, a skilled artisan in June 2002 would have been motivated to combine fluticasone and azelastine in a single formulation to treat allergic rhinitis. Tr. (Schleimer) at 182:3–183:17. It was both obvious and expressly disclosed to combine them. DTX 12; DTX 21.

VIII. IT WAS OBVIOUS HOW TO FORMULATE A NASAL SPRAY THAT COMBINES FLUTICASONE AND AZELASTINE FOR THE TREATMENT OF ALLERGIC RHINITIS.

74. A person of ordinary skill in the art at the time of the alleged invention also had a reasonable expectation of success in formulating a fluticasone propionate/azelastine

hydrochloride combination product as a nasal spray for the treatment of allergic rhinitis. Tr. (Donovan) at 279:19–280:14.

75. Dr. Maureen Donovan testified that the prior art disclosed how to formulate azelastine hydrochloride in the Astelin® product and how to formulate fluticasone propionate in the Flonase® product. These products were FDA approved, on the market, and known to be successful. Beyond standard pharmaceutical references providing textbook knowledge on pharmaceutical formulation, an ordinarily skilled formulator looking only at these two labels and to Astelin®'s corresponding formulation patent would derive a finite number of obvious formulations for putting the two active ingredients together in one nasal spray formulation. Tr. (Donovan) at 239:7-22; DTX 33; DTX 22; DTX 16. Dr. Donovan provided in summary the following chart showing the excipients in Flonase® and Astelin®, and the finite number of combinations at which a POSA would arrive:

	Flonase®	Astelin®	Obvious Combination Formulation
Active Ingredient	Fluticasone propionate (50 mcg, or 0.05 mg, or 0.05% (w/w), or 0.5 mg/mL per spray)	Azelastine HCl (0.1% (w/w or w/v), 0.137 mg per spray)	Fluticasone propionate (50 mcg, or 0.05 mg, or 0.05% (w/w), or 0.5 mg/mL per spray) Azelastine HCl (0.1% (w/w) or (w/v), 0.137 mg per spray)
Particle Size	"microfine" (< 10 microns)	Dissolved in solution	"microfine" (< 10 microns)
Vehicle	Water	Water	Water
Preservatives	(1) Benzalkonium chloride (0.02% w/w); (2) Phenyl ethyl alcohol (0.25% w/w)	(1) Benzalkonium chloride (0.0125% w/w); (2) EDTA disodium Astelin patent: other preservatives; concentrations at 0.002% to 0.05%	(1) Benzalkonium chloride (0.0125% or 0.02% w/w); (2) Phenyl ethyl alcohol (0.25% w/w) (3) EDTA disodium (0.002% – 0.05%)
Surfactants	Polysorbate 80	None needed	Polysorbate 80
Thickening Agents	MCC / CMC	HPMC Astelin patent: others, including CMC	MCC/CMC (Avicel): 1.2% HPMC
Tonicity Adjuster	Dextrose	NaCl Astelin patent: saccharose, glucose, glycerin, sorbitol, 1,2-propylene glycol	Dextrose, NaCl, saccharose, sorbitol, 1,2-propylene glycol, glucose, glycerin (<2.6%)
pH	5 to 7	6.8 +/- 0.3 (6.5 to 7.1) (buffered with citric acid and dibasic sodium phosphate)	4 to 8, adjusted as desired with pH adjusters

DDX 5.33.

A. Flonase[®] Formulation

76. The Flonase[®] label disclosed in June 2002 a dose of 50 mcg (micrograms) per 100 mL (milliliter) spray in an aqueous suspension, which is equivalent to 0.05 mg (milligrams) per spray, which is equivalent to 0.05 percent concentration weight over volume and weight over weight, which is equivalent to 0.5 milligrams per mL. Tr. (Donovan) at 241:8-21; 242:21–243:12; DTX 33.

77. The Flonase[®] label disclosed that the fluticasone propionate is “microfine,” which according to Dr. Donovan indicates that the particles are less than 10 µm (microns) in size. Tr. (Donovan) at 243:13–244:4; DTX 33; DDX 5.06.

78. The Flonase[®] label disclosed that the aqueous vehicle for the formulation is water, which is a very common and preferred vehicle for nasal formulations. Tr. (Donovan) at 244:14–17; DTX 33; DDX 5.06.

79. The Flonase[®] label disclosed the use of benzalkonium chloride in a weight/weight concentration of 0.02% and phenylethyl alcohol in a weight/weight concentration of 0.25% as antimicrobial preservatives. Such preservatives were known in the art to be necessary to prevent microbial growth in formulations, and both benzalkonium chloride and phenylethyl alcohol were known preservatives in those amounts. Tr. (Donovan) at 244:18–246:7; DTX 33; DDX 5.06. In fact, these excipients were known to be synergistic in combination. DTX 62 at 29, Handbook of Pharmaceutical Excipients (“Synergistic [antimicrobial] effects have been reported when [phenylethyl alcohol is] combined with benzalkonium chloride . . .”).

80. The Flonase[®] label disclosed the use of the surfactant polysorbate 80, which was known in the art to be used in suspensions to help the suspended particles properly disperse in the formulation. Tr. (Donovan) at 246:8–247:11; DTX 33; DDX 5.06.

81. The Flonase[®] label disclosed the use of the thickening agents microcrystalline cellulose (“MCC”) and carboxymethyl cellulose sodium (“CMC”) in combination, commonly referred to by the combination’s brand name, Avicel[®], which was known to and used in the prior art to slow down the settling of suspended particles and to thicken the formulation so it remains longer on the nasal mucosa after application. Tr. (Donovan) at 247:12–249:6; DTX 33; DDX 5.06.

82. The Flonase[®] label disclosed the use of the tonicity adjusting agent dextrose. Tonicity adjusters were and remain common in the art, and are added to formulations to balance the concentration of solutes in the formulation with the concentration of solutes in the cells in the human body that come into contact with the formulation. To adjust the tonicity of the formulation, formulators usually select molecules that are likely to have little influence on the rest of the formulation. Tr. (Donovan) at 249:7–251:13; DTX 33; DDX 5.06, 5.07. It is routine for a formulator to determine the final amount of tonicity adjustor necessary for isotonicity. Tr. (Donovan) at 276:16-25.

83. Additionally, the prior art disclosed desirable tonicities. Lloyd Allen’s “The Art, Science and Technology of Pharmaceutical Compounding” disclosed that between 200 mOsm/L and 600 mOsm/L are acceptable tonicities for nasally applied pharmaceutical products, with 300 mOsm/L being the most desirable. DTX 78 at 19; Tr. (Donovan) at 251:14–253:4; DDX 5.07.

84. Finally, the Flonase[®] label disclosed a pH of 5 to 7. Tr. (Donovan) at 253:22–254:8; DTX 33; DDX 5.06. Formulators routinely determine appropriate pH levels for formulations. Tr. (Donovan) at 255:5-8. It was routine for a formulator to determine an acceptable pH for a given formulation, Tr. (Donovan) at 278:15-23, and to buffer the system to that pH if necessary, Tr. (Donovan) at 279:2-8; *see also* DTX 78 at 19.

B. Astelin® Formulation

85. The Astelin® label discloses an aqueous solution of 0.1 percent concentration of azelastine hydrochloride weight over volume, which is approximately 0.1 percent weight over weight, and that 137 mcg of azelastine hydrochloride is delivered per spray. Tr. (Donovan) at 255:16–257:12; DTX 22; DDX 5.10.

86. Because the formulation is an aqueous solution, it does not have a particle size (and thus would meet any claim limitation for particle size). Tr. (Donovan) at 257:14-19; DDX 5.11.

87. As with Flonase®, the vehicle for the formulation of Astelin® is water. Tr. (Donovan) at 257:20-21; DTX 22; DDX 5.11.

88. The Astelin® label also disclosed the use of the known antimicrobial preservatives, benzalkonium chloride and EDTA disodium. Tr. (Donovan) at 257:22–258:14; DTX 22; DDX 5.12. Additionally, the formulation patent for the Astelin® product, U.S. Patent No. 5,164,194, disclosed a concentration of preservatives such as EDTA of 0.002 to 0.05 percent. DTX 16 at col. 2, ll. 46-68; Tr. (Donovan) at 258:15–260:3; DDX 5.13-14.

89. There is no surfactant in the Astelin® formulation because there is no need to suspend any particles, all of which are dissolved rather than suspended. Tr. (Donovan) at 260:10-19; DDX 5.15.

90. The Astelin® label disclosed the use of the thickening agent hydroxypropylmethylcellulose (“HPMC”), which, like thickening agents in other nasal sprays, is used to enable the formulation to remain longer on the nasal mucosa after application. Tr. (Donovan) at 260:24–261:13; DTX 22; DDX 5.16. The Astelin® formulation patent further disclosed other thickening agents that are acceptable for use with azelastine hydrochloride, such as CMC. DTX 16 at col. 5, ll. 51-66; Tr. (Donovan) at 261:14–262:17; DDX 5.17-18.

91. The Astelin[®] label disclosed the use of sodium chloride (NaCl) as its tonicity adjustor. Tr. (Donovan) at 262:21–263:5; DTX 22; DDX 5.19. The Astelin[®] formulation patent disclosed a number of tonicity adjustors suitable for an azelastine hydrochloride formulation including saccharose, glucose, glycerine, sorbitol, propylene glycol, and sodium chloride. DTX 16 at col. 4, ll. 31-35; Tr. (Donovan) 263:6-24; DDX 5.20-21.

92. The Astelin[®] label disclosed a pH between 6.5 and 7.1. Tr. (Donovan) 264:8-12; DTX 22; DDX 5.22.

C. It was obvious to an ordinarily skilled formulator how to co-formulate an Azelastine and Fluticasone Nasal Spray.

93. An ordinarily skilled formulator would have looked first at the finite number of possible excipients on the Flonase[®] and Astelin[®] labels and the Astelin[®] formulation patent to determine the excipients for the combination fluticasone propionate and azelastine hydrochloride product. The use of these excipients in prior successful formulations provided the POSA a reasonable expectation of success in formulating a pharmaceutical product for the treatment of allergic rhinitis. Tr. (Donovan) at 279:19–280:14.

94. An ordinarily skilled formulator making such a combination product would have found it obvious to begin with the same concentrations of the active ingredients in Flonase[®] and Astelin[®] because those amounts had been successfully formulated in those products. Tr. (Donovan) 265:6-17; DDX 5.23. And as previously explained, such amounts would have been known to be effective. *See supra* ¶ 64.

95. It would have been obvious to a formulator of ordinary skill to use microfine fluticasone propionate because that was used in the successful Flonase[®] product. Tr. (Donovan) at 265:18–266:2; DDX 5.23-24.

96. It would have been obvious to a formulator of ordinary skill to use water as the vehicle because it was the vehicle for both active ingredients in their respective formulations. Tr. (Donovan) at 266:4-7; DDX 5.25.

97. It would have been obvious to a formulator of ordinary skill to include benzalkonium chloride, phenylethyl alcohol, and EDTA disodium as antimicrobial preservatives because each had been successfully used for that purpose in one or both of the Flonase[®] and Astelin[®] formulations. Tr. (Donovan) at 266:8-25; DDX 5.26. Further, as explained above, these were known to be used together synergistically. DTX 62 at 18 (“However, when used with other antimicrobial preservatives edetic acid [EDTA] demonstrates a marked synergistic effect in its antimicrobial activity. Edetic acids and edetates are therefore frequently used in combination with such preservatives as: benzalkonium chloride”); *id.* at 29 (“Synergistic effects have been reported when [phenylethyl alcohol is] combined with benzalkonium chloride”).

98. It would have been obvious to a formulator of ordinary skill to use the concentrations for each inactive ingredient in the Flonase[®] and Astelin[®] formulations or those disclosed in Astelin[®]’s formulation patent. Such concentrations are also disclosed in prior art monographs on preservatives. Tr. (Donovan) at 267:1-14; *see, e.g.*, DTX 62, Handbook of Pharmaceutical Excipients, at 3 (0.002-0.02% benzalkonium chloride concentrations); *id.* at 20 (EDTA disodium concentrations typically 0.005-0.1% w/v); *id.* at 29 (0.25-0.5% phenylethyl alcohol concentrations).

99. Additionally, a POSA would have known how to do a preservative challenge test to determine the final concentrations of any preservative that she used. Tr. (Donovan) at 267:15–268:8. In such a test, the formulator challenges the formulation with bacteria to see

whether bacteria grows; if an unacceptable amount of growth is present, the formulator can add additional preservatives. *Id.*

100. Although EDTA disodium was not used in the Flonase[®] formulation and phenylethyl alcohol was not used in the Astelin[®] formulation, these ingredients were commonly used as antimicrobial preservatives in pharmaceutical formulations. There was nothing in the prior art that would have given the POSA any reason to believe that EDTA disodium was incompatible with fluticasone propionate or that phenylethyl alcohol was incompatible with azelastine hydrochloride. In fact, plaintiffs' formulator Dr. Smyth looked at the prior art to see if there was any art suggesting a potential incompatibility between phenylethyl alcohol and azelastine hydrochloride and found nothing. Tr. (Smyth) at 654:22–655:7. Dr. Smyth looked at the prior art to see if there was any art suggesting a potential incompatibility between EDTA disodium and fluticasone propionate and found nothing. Tr. (Smyth) at 655:8-14. The evidence thus shows that a skilled formulator would have reasonably expected success in adding either preservative to a combination formulation. Tr. (Donovan) at 268:9–269:7.

101. It would have been obvious to a formulator of ordinary skill to include the surfactant polysorbate 80 because of its role in assisting the fluticasone propionate to disperse in the formulation. Although a surfactant is not present in the Astelin[®] formulation, at the critical date polysorbate 80 was a common ingredient in pharmaceutical formulations and nothing in the literature suggested it would not work with azelastine hydrochloride. Plaintiffs' formulator Dr. Smyth attempted to find art suggesting an incompatibility between polysorbate 80 and azelastine hydrochloride and found nothing. Tr. (Smyth) at 655:20-25. A skilled formulator would have reasonably expected that polysorbate 80 in a combination formulation would assist in dispersion

of the fluticasone propionate and would have no negative effect on the azelastine hydrochloride. Tr. (Donovan) at 269:18–270:14; DDX 5.27.

102. It would have been obvious to a formulator of ordinary skill to include either MCC/CMC or HPMC as a thickening agent in a combination formulation because both had been successfully used in either the Flonase[®] or Astelin[®] formulations. Further, it would have been obvious to a formulator of ordinary skill to choose MCC/CMC over HPMC as a starting point because it successfully served both the role of thickening the formulation for retention on the nasal mucosa and the role of suspending the fluticasone propionate particles in the Flonase[®] product. Tr. (Donovan) at 270:15–271:11; DDX 5.28-29.

103. MCC/CMC was not used in the Astelin[®] formulation, but it was used in the Flonase[®] formulation and CMC was disclosed in the Astelin[®] formulation patent as an acceptable thickening agent for formulations containing azelastine hydrochloride. A skilled formulator would have a reasonable expectation of success in using CMC as a thickening agent. Further, MCC was routinely used together with CMC and was compatible with a large range of molecules. DTX 62, at 13; DDX 5.28. There was no literature suggesting it would be incompatible with azelastine hydrochloride, and a skilled formulator would have had a reasonable expectation of success in including it in a combination formulation with azelastine hydrochloride and fluticasone propionate. Tr. (Smyth) at 657:12-19; Tr. (Donovan) at 271:12-23.

104. A skilled formulator would have consulted the Handbook of Pharmaceutical Excipients, DTX 62 at 13, or other monographs to determine known concentrations of MCC/CMC suitable for its purpose as a suspending and thickening agent. Tr. (Donovan) at

271:24–273:17. For example, the Handbook discloses a 1.2% weight over volume concentration for “aqueous dispersions.” DTX 62 at 13; DDX 5.28.

105. It would have been obvious to a formulator of ordinary skill to use dextrose, NaCl, saccharose, glucose, glycerine, sorbitol, or propylene glycol as tonicity adjustors, which were disclosed as suitable in Flonase[®], Astelin[®], or Astelin[®]’s formulation patent for that purpose, although there would be no necessary reason to choose one over another. Tr. (Donovan) at 274:2–275:4. As previously explained, tonicity adjustors are common ingredients in formulations and are chosen because of their minimal impact on the rest of the formulation. Tr. (Donovan) at 249:7–251:13. Indeed, a formulator of ordinary skill chose tonicity agents through routine experimentation. Tr. (Donovan) at 274:15-18. Further, glycerin is routinely used as a tonicity adjuster in pharmaceutical formulations and is specifically suggested as a tonicity adjuster for formulations including azelastine hydrochloride. DTX 16 at col. 4, ll. 31-35. As Plaintiffs’ expert Dr. Smyth confirmed, there is nothing in the prior art suggesting any incompatibility between glycerin and fluticasone propionate. Tr. (Smyth) at 655:15-19.

106. A skilled formulator would have consulted the Handbook of Pharmaceutical Excipients or other monographs to determine the appropriate concentration of tonicity adjustor. DDX 5.30-31. For example, the Handbook discloses that a 2.6% weight/volume concentration of glycerine in water is iso-osmotic (which is essentially isotonic, i.e. the ideal tonicity for application to the nasal tissue), which tells a formulator that no more than 2.6% weight/volume of glycerin would need to be added to a formulation with other solutes already in it to make it isotonic. Tr. (Donovan) at 275:5–276:4; DTX 62 at 22. (It is uncontested by the parties that weight/volume is essentially equivalent to weight/weight for nasal sprays using water as the

vehicle. D.I. 135 at Ex. 1 ¶ 40.) In any event, it is routine for a formulator to determine the final amount of tonicity adjustor necessary for isotonicity. Tr. (Donovan) at 276:16-25.

107. Finally, a skilled formulator would know that there was a range of acceptable pH levels for drugs administered in the nose, and if a narrower range became important the formulator could subsequently narrow the range. Tr. (Donovan) at 277:1-20. The prior art described a pH range of 4 to 8 as acceptable. DTX 78 at 19; Tr. (Donovan) at 277:21–278:14. It was routine for a formulator to determine an acceptable pH for a given formulation, Tr. (Donovan) at 278:15-23, and to buffer the system to that pH if necessary, Tr. (Donovan) at 279:2-8; *see also* DTX 78 at 19.

108. In sum, using this knowledge to make a combination formulation would have resulted in a small list of obvious combinations, as illustrated in the chart above. DDX 5.33. A person of ordinary skill would have been motivated to combine these excipients as described in DDX 5.33 with a reasonable expectation of success. Tr. (Donovan) at 279:19–280:5. Any such combination formulation would have been obvious to an ordinarily skilled formulator as of 2002. Tr. (Donovan) at 280:6-14. Moreover, all limitations of the asserted claims—particle size ('620 patent claim 4); pH range ('428 patent claim 15); vehicle ('428 patent claim 16, '620 patent claim 29); categories of preservatives, surfactants, thickening agents and tonicity adjustors ('428 patent claim 30, '620 patent claims 42, 43, 44); the excipients benzalkonium chloride, EDTA disodium, phenylethyl alcohol, polysorbate 80, MCC/CMC, and glycerin ('428 patent claims 10, 11, 23, 24); the active ingredients azelastine hydrochloride and fluticasone propionate (all claims); and concentrations or ranges thereof ('428 patent claims 10, 11, 13, 23, 24, 26, 29)—encompass the finite number of obvious combination formulations about which Dr. Donovan testified. *See* DDX 5.34-48 (comparing the obvious combination formulations to each asserted

claim). All of the active ingredients and excipients function in the combination product in the same way that they do in the prior art. Tr. (Smyth) at 652:1–654:4; Tr. (Smyth) at 670:1-6.

109. Plaintiffs' formulator Dr. Smyth agreed that each of the preservatives in Dr. Donovan's set of obvious combination formulations were known in the art, were known to function as preservatives, and in fact function as preservatives in the commercial embodiment of the asserted claims (Dymista[®]) in the way a person of ordinary skill would have predicted in 2002. Tr. (Smyth) 652:1-20. He similarly agreed that polysorbate 80, MCC/CMC, and glycerin were known in the prior art to be a surfactant, suspending agent, and tonicity adjustor, respectively, and that that is how each was used in the commercial embodiment of the asserted claims in a way consistent with the prior art. Tr. (Smyth) at 652:21–654:14.

110. According to Plaintiffs' formulator Dr. Smyth, the only potential incompatibilities of which a formulator would have been aware were possible interactions between (a) CMC and azelastine hydrochloride, and (b) fluticasone propionate and another active ingredient.

111. Regarding CMC, Dr. Smyth noted that some art suggested that because CMC was negatively charged, it could interact with positively charged cations, and azelastine hydrochloride is a positively charged cation. Tr. (Smyth) at 617:19–619:24.

112. However, Dr. Smyth acknowledged that none of the prior art references on which he relied even mentioned azelastine hydrochloride. Tr. (Smyth) at 657:12-19. And, more importantly, prior art references specifically taught the use of CMC with azelastine hydrochloride. Dr. Smyth agreed that Astelin[®]'s formulation patent, which specifically deals with azelastine hydrochloride, "suggested" using CMC as a compatible thickening agent. Tr. (Smyth) at 657:12-660:3. At least one other prior art patent application disclosed the use of azelastine hydrochloride and fluticasone propionate in combination using CMC as a thickening

agent. DTX 12 (Cramer) at 5-6. Moreover, subsequent to Dr. Smyth's prior art references regarding CMC but before it had any knowledge of the patents-in-suit, Plaintiff Meda Pharmaceuticals submitted a patent application to the U.S. Patent Office again suggesting using CMC together with a formulation combining azelastine hydrochloride and a steroid, including fluticasone. Tr. (Smyth) at 660:4–662:19; DTX 313 at 41. Meda therefore independently concluded that azelastine hydrochloride and CMC could be used together based on the relevant prior art and not on their knowledge of the patents-in-suit.

113. Regarding fluticasone propionate's potential interaction with another active ingredient, Dr. Smyth cited to prior art in which fluticasone propionate was combined with the active ingredient salmeterol to support his contention that fluticasone propionate and CMC might have negative interactions if used together. Tr. (Smyth) at 621:25–624:5. However, Dr. Smyth did not refer to other statements in the reference that showed that any interaction between fluticasone propionate and salmeterol was positive: “[t]his phenomenon could be an *advantage* from a pharmaceutical point of view, i.e., the combination formulation shows a decrease in the total loss of the drugs due to deposition onto the internal surfaces of the MDI.” PTX 179 at 2 (emphasis added); Tr. (Smyth) at 663:6–664:20. A second article on fluticasone propionate combined with salmeterol by the same authors also stated that “[a] combination inhaler of Salmeterol xinafoate and fluticasone propionate in a single MDI device has been used recently to *improve* the control treatment of asthma,” and “[t]he addition of Salmeterol to the regimen is *more effective* than doubling the steroid dose.” DTX 180 (emphases added); Tr. (Smyth) at 665:7–666:16.

114. Thus, a person of ordinary skill would have been, if anything, encouraged by this prior art and further motivated to combine fluticasone propionate with another active ingredient.

115. Dr. Smyth also opined that a formulator of ordinary skill would not have been motivated to combine azelastine hydrochloride and fluticasone propionate into a single formulation, and that a skilled artisan would not have had a reasonable expectation of success, because Astelin[®] was formulated as a solution and Flonase[®] was formulated as a suspension. Tr. (Smyth) at 609:22–610:1; 610:20–612:25.

116. However, nothing in the art suggested any problem of combining one active ingredient in solution and one active ingredient suspension. Tr. (Donovan) at 301:13–302:12. Indeed, the patents-in-suit themselves make no mention at all that the prior art had indicated a problem with combining one active that goes into solution with another that remains in suspension, and certainly the patents-in-suit make no reference to having overcome such a problem if it did exist. Tr. (Smyth) at 674:18-24; *see also* Tr. (Smyth) at 674:25–676:11. The patents disclose no new techniques for formulating or manufacturing products but instead disclose that its “formulations are prepared by techniques well known in the art.” PTX 1, ’620 Patent, at col. 8, l. 67–col. 8, l. 2. Dr. Smyth testified that an ordinarily skilled formulator would have been able to create the formulation of one active in solution and another in suspension using “a finite number of ways of mixing [the ingredients] together.” Tr. (Smyth) at 675:19–676:11. The inventor of these patents did not testify at trial, and there is no evidence that the inventor believed or observed that there existed a problem reconciling active ingredients in solution with active ingredients in suspension.

117. Dr. Smyth testified that a formulator of ordinary skill would know that azelastine hydrochloride is expected to dissolve in water, as it does in Astelin[®], and that fluticasone propionate is expected to remain undissolved in water (and thus eventually to suspend), as in Flonase[®]. He agreed that “[i]t was known in 2002 that azelastine dissolved to some extent in

water” and that “[i]t was known in 2002 that fluticasone did not dissolve in water.” Tr. (Smyth) at 668:10–669:7. He further agreed that in 2002 a person of ordinary skill “would not anticipate fluticasone dissolving . . . [b]ut azelastine would have some appreciable solubility in water,” and that that is exactly what happens in Dymista[®], the commercial embodiment of the claims. Tr. (Smyth) at 669:4-20; 670:1-6.

118. Dr. Govindarajan, a formulator who testified by deposition, also stated that there are “many combination products” and because “solubilities differ, . . . there are ingredients that might dissolve and there are ingredients that might stay in suspension.” Tr. (Govindarajan) at 746:25–747:8.

119. Finally, numerous other patent applications, including the Cramer reference, the Segal reference, and Meda’s own 2005 patent application filed without the knowledge of the patents-in-suit, all suggested combining azelastine hydrochloride with fluticasone propionate, and none indicated there was any problem with combining one active ingredient that goes into solution with another that remains suspended. DTX 12; DTX 21; DTX 313.

120. Plaintiffs argue that one example—Example III—of the Cramer reference was “inoperable” and thus demonstrates the difficulty of a “solution/suspension” system. However, the only evidence that this example containing azelastine hydrochloride (but not fluticasone propionate) is inoperable came several years after the critical date of these patents through testing done by the inventor in pursuit of these patents, and at the direction of Plaintiffs’ expert Dr. Smyth who had already come to his opinions in this case before he conducted his testing. Tr. (Smyth) at 635:18-20; 676:22–673:4; 678:8-21; 678:22–679:5; 680:10-14. Although the results of the inventor’s testing was presented to the patent examiner, the examiner allowed the patents on the basis of secondary considerations after finding *prima facie* obviousness, but not on the

basis of that testing. DTX 137.0577 (Final Rejection); DTX 114 (Malhotra Declaration); DTX 137.2559 (Notice of Allowance).

121. Moreover, this testimony is contradicted by Dr. Donovan, who explained that issues with the resulting formulations in terms of tonicity and pH, for example, did not indicate a failure in the formulation. In fact, a POSA would routinely have addressed those issues through adjustments in the excipients and mixing technique. Tr. (Donovan) at 324:6–325:15. Neither the inventor nor Dr. Smyth undertook any such steps, but only attempted one formulation of Cramer III. Tr. (Donovan) at 307:5-15. Dr. Govindarajan, who did not express any opinions on obviousness in this case, was also tasked with formulating Cramer III as a person of ordinary skill in the art as of 2002. Tr. (Smyth) at 679:22–682:1. He concluded Cramer III was an acceptable pharmaceutical product. Tr. (Smyth) at 682:20–683:2; PTX 1664.

D. The patents-in-suit contain no information about how to formulate or use a combination product.

122. Consistent with the conclusion of obviousness based solely on the prior art discussed above, the patents-in-suit do not give any novel instructions to a POSA about how to make or use a combination formulation. PTX 1; PTX 3.

123. The specification contains in its examples several lists of ingredients and amounts of those ingredients that it says can be formulated into compositions suitable for use as a nasal spray or otherwise for nasal administration. Example 2 is the only example that contains manufacturing instructions, and it relates to a dosage aerosol formulation containing azelastine hydrochloride and beclomethasone dipropionate as active ingredients. PTX 1; PTX 3.

124. The specification states with respect to each of these examples that “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.” PTX 1, at 12.

125. No examples in the patents-in-suit provide any data about the disclosed composition with respect to the following parameters: pH, physical stability, chemical stability, settling characteristics, and/or dispersability characteristics. *Id.* at 12-14.

126. Additionally, the asserted claims contain no limitations about how the pharmaceutical compositions disclosed in them should be dosed to patients to treat allergic rhinitis or any other disease or how long the compositions should be dosed, nor any requirement that the compositions must be approvable by the Food and Drug Administration or suitable for commercialization; and the specifications contain no pre-clinical or clinical data showing the use of any claimed composition, or any effects of the compositions on any in vitro model or in vivo subject. PTX 1; PTX 3.

IX. THERE ARE NO SECONDARY CONSIDERATIONS THAT INDICATE THE ASSERTED CLAIMS ARE NOT OBVIOUS.

127. Plaintiffs carry the burden of production for secondary considerations, and Apotex will reply to their proposed findings on those considerations. Nevertheless, Apotex provides preliminary findings of fact as to secondary considerations below.

A. There was simultaneous independent invention that confirms it was obvious to co-formulate fluticasone and azelastine.

128. The conclusion that the claimed invention would have been obvious to a POSA in 2002 is supported by at least three simultaneous inventions. The first entity to have described a combination nasal spray product containing both azelastine and fluticasone for the treatment of allergic rhinitis was Procter & Gamble in 1997 in the form of the prior art Cramer reference. DTX 12, at 2. The second company to have described a combination nasal spray product containing both azelastine and fluticasone for the treatment of allergic rhinitis was the Warner-Lambert Company in 1998 in the form of the prior art Segal reference. DTX 21.

129. Cipla—the patentee—was the next entity to disclose a co-formulation of these two drugs, in 2002. But also in 2002, Meda’s predecessor company, MedPointe Pharmaceuticals, internally expressed the idea of combining azelastine in a nasal spray with a steroid. Tr. (D’Addio) at 382:14–383:4.

130. In 2005, Meda filed a patent application covering this subject matter. DTX 313. Although not prior art, this application recorded a formulation of azelastine hydrochloride with fluticasone that Meda represented to the USPTO would work. Tr. (D’Addio) at 401:17–402:6. That application included claims to the combination of azelastine hydrochloride and fluticasone. DTX 313, at 196 (claim 101); Tr. (D’Addio) at 404:13-16. The application also included information about appropriate excipients to use with that azelastine/fluticasone combination product. DTX 313, at 41 (can contain suspending agents like MCC and CMC; preservatives including EDTA disodium, phenyl ethyl alcohol and benzalkonium chloride; and surfactants including polysorbate 80), 42 (tonicity adjusters, including sodium chloride, dextrose and glycerin), 49 (can be formulated as suspensions or solutions with pH of 6 to 8). The document also contains an example of what the inventors believed was a working azelastine/fluticasone combination product. *Id.* at 172-73 (Example 7).

131. All of this work was done before Meda knew anything about Cipla’s patent application that resulted in the patents-in-suit, or anything contained in that application, and was thus a third disclosure of a combination azelastine/fluticasone combination product independent of the patentees. Tr. (D’Addio) at 408:25–409:10.

B. Meda has failed to produce any persuasive evidence of failure of others to make the invention.

132. Plaintiffs offered testimony that MedPointe, a Meda predecessor, conducted a confidential pre-formulation experiment in which it tried adding azelastine hydrochloride to the

existing commercial formulation of Flonase[®]. Tr. (D'Addio) at 371:11–375:17; PTX 142 at 17-19. One of MedPointe's employees involved in the pre-formulation effort explained that he was “not looking at a full development effort, just something small to confirm conceptually whether we are going to face major formulation issues or whether an existing formulation could be the starting point.” Tr. (D'Addio) at 387:23–395:16; PTX 150 at 2.

133. When MedPointe first added azelastine hydrochloride directly to the Flonase[®] formulation, it identified no problem with this combined formulation and determined that there were “no gross changes in the formulation with the addition of the azelastine.” Tr. (D'Addio) at 371:11-25; 395:7-19. This was not a failure.

134. MedPointe next attempted to remove fluticasone propionate from Flonase[®] and then add azelastine hydrochloride to the formulation. Tr. (D'Addio) at 394:21–395:2. After the fluticasone propionate was ultimately filtered, azelastine hydrochloride was added and stirred on a hotplate. The experimenters suggested that some of the azelastine had not gone into solution. They attempted additional stirring and heating but still observed some precipitate. Tr. (D'Addio) at 372:11–374:25. The experimenters concluded that it was necessary to analyze the sample they had made. But no analysis and no further testing was done. Tr. (D'Addio) at 397:9-19.

135. MedPointe developed a “Feasibility Assessment Plan” laying out a formulation strategy, which included the step: “If Azelastine Hydrochloride is not sufficiently soluble, modify the formulation or process so that Azelastine Hydrochloride is completely in solution.” PTX 151. MedPointe never undertook to complete that step. For example, notwithstanding the experimenters' belief that azelastine hydrochloride had not dissolved, the experimenters did not take the routine steps of applying solubility enhancing technologies, changing the pH of the formulation, or adding co-solvents. Tr. (D'Addio) at 397:20–398:21. MedPointe's attempted

formulation was only “a few days long” and occurred in its entirety in the last week of April 2006. Tr. (D’Addio) at 375:15-17; 393:20–394:1. It abandoned its attempt to formulate a combination product shortly thereafter, in May 2006, when it found the Cipla patent application for the present patents-in-suit and decided to license the product instead. Tr. (D’Addio) at 376:8-11; 18-22. Its only formulation actually to include both azelastine hydrochloride and fluticasone propionate revealed no formulation problems. Tr. (D’Addio) at 371:11-25; 395:7-19. Thus, MedPointe’s attempt was not a failure of others.

C. Meda has failed to produce any persuasive evidence of unexpected results.

1. Meda has not shown that Dymista®’s efficacy is unexpectedly superior to the closest prior art.

136. Meda contends that Dymista® was unexpectedly superior to azelastine monotherapy, fluticasone monotherapy, and nasal steroid/oral antihistamine combinations. *See* D.I. 135 Ex. 2 at ¶¶ 267-272. In particular, Meda argues Dymista® “exhibits a significant and clinically relevant improvement over both of its constituent active pharmaceutical ingredients.” D.I. 135 Ex. 2 at ¶ 270; Tr. (Carr) at 550:14–552:21.

137. However, the appropriate comparison is between Dymista® and the conjunctive use of Flonase® and Astelin®. Tr. (Schleimer) at 799:2-9. Meda does not point to any studies that make the appropriate comparison and undertook no such studies for purposes of this litigation. Tr. (Schleimer) at 800:3-13; *see also* PTX 227 (Carr 2012); DTX 229 (Hampel 2010).

138. Ratner 2008 compared the co-administration of Astelin® and Flonase® (the closest prior art therapy) to the individual monotherapies. Tr. (Schleimer) at 807:16-23; DTX 191. That study found that the combination was 40% superior to the monotherapies. Tr. (Schleimer) at 807:7-15. The Hampel 2010 study compared the fixed-dose combination Dymista® to the monotherapies and found a 38% improvement with Dymista®. Tr. (Schleimer) at 803:7-14;

DTX 229. These references show that Dymista®'s improvement over fluticasone monotherapy and azelastine monotherapy and the improvement over the monotherapies of the conjunctive use of Astelin® and Flonase® is about the same. Tr. (Schleimer) at 804:12-20.

139. Even if the monotherapies were the appropriate comparators, any improvement of Dymista® over the monotherapies would merely be a difference in degree because Dymista®'s efficacy is "roughly additive of the two individual components." Tr. (Schleimer) at 805:2-11; Tr. (Carr) at 586:22–587:2. And because of the complementary mechanisms of action, any improvement would also be expected. Tr. (Schleimer) at 804:21–805:1.

2. Dymista®'s onset of action was expected.

140. Meda argues that Dymista® has an unexpectedly faster onset compared to azelastine monotherapy. See D.I. 135 at Ex. 2 ¶¶ 244-248. Meda compares the Dymista® label, which shows an onset of 15-30 minutes, with the Astelin® label, which shows an onset within 3 hours. Tr. (Carr) at 558:17–559:12 *see also* DTX 22 at 8; DTX 228 at 18.

141. Azelastine was known to have a rapid onset of much less than 3 hours. For example, the ARIA guidelines instruct that "[t]opical H1-antihistamines have a rapid onset of action (less than 15 minutes) at low drug dosage." PTX 326 at 99; Tr. (Schleimer) at 809:14-25; Tr. (Wedner) at 89:8-15. The 1998 McNeely reference taught that "azelastine significantly reduced allergen-induced sneezing within 15 minutes." DTX 43 at 3; Tr. (Schleimer) at 809:12-21; Tr. (Wedner) at 129:4-21. The Greiff article, published in 1997, shows that azelastine completely inhibited histamine induced secretions within one hour of administration. DTX 99 at 7-8; Tr. (Schleimer) at 810:1–811:1. Further, in its IND application to the FDA, Meda stated "Azelastine provides rapid symptom relief compared to placebos as early as 15 minutes in an allergen chamber study." PTX 47 at 5.

142. In sum, the onset of Dymista[®] is a function of azelastine's onset. Tr. (Wedner) at 93:23–94:3. Regardless, any difference would be a matter of degree. Tr. (Carr) at 591:12-23.

3. Dymista[®]'s side effects were expected.

143. Meda argues that Dymista[®] has an unexpectedly superior side effect profile as compared to the monotherapies, particularly with respect to drowsiness and taste. D.I. 135 Ex. 2 at ¶ 266; Tr. (Carr) at 555:20–556:18. Any alleged differences in side effects is merely a difference in degree rather than in kind. Tr. (Carr) at 591:24–592:7. Further, any alleged difference in side effects would be expected given the lower dose of azelastine in a standard Dymista[®] dose as opposed to an Astelin[®] dose. Tr. (Schleimer) at 808:4-13.

D. Two blocking patents belie other secondary considerations of non-obviousness.

144. The USPTO found the patents-in-suit prima facie obvious, DTX 137.0577, but allowed the claims on the basis of secondary considerations including unmet needs and commercial success, DTX 137.2559. However, the patent examiner did not consider the existence of two blocking patents, which would have explained why a person of ordinary skill might not have made the claimed invention even if it was obvious. Tr. (Schleimer) at 813:1-19.

145. A “blocking patent” is a patent that covers a product recited in the claims of the patents in suit, but which is separate and apart from the patents in suit. Tr. (Press) at 765:16-22. A blocking patent that exists before the patents in suit were issued restricts the ability of a pharmaceutical manufacturer to launch a product covered by both the blocking patent and, later, the patents in suit. *Id.*; *see also* Tr. (Schleimer) at 813:20–814:6, 814:18-21.

146. There are two blocking patents that cover combination nasal spray products using fluticasone and azelastine. The first was U.S. Patent No. 4,335,121, which covers the fluticasone

compound. DTX 96, at 19; Tr. (Schleimer) at 813:1-8. That patent issued in 1992 and expired in May 2004. Tr. (Schleimer) at 814:7-12.

147. The second blocking patent to issue was the Astelin[®] patent, U.S. Patent No. 5,164,194. DTX 16. The Astelin[®] patent issued in 1992 and expired in May 2011. Tr. (Press) at 766:4-8; Tr. (Schleimer) 814:13-17; DDX-6.03. Dr. Donovan explained how at least Claim 1 of the Astelin[®] patent covers a product containing azelastine, including a combination product containing both azelastine and fluticasone. Tr. (Donovan) at 326:4–372:10; DDX-5.55 and 5.56; *see also* Tr. (Schleimer) at 813:9-17. Claim 1 covers combination azelastine/fluticasone products because it recites a “medicament which contains a member selected from the group consisting of azelastine and its physiologically acceptable salts.” DTX 16, at Claim 1.¹

148. The evidence showed that “patent protection of one or both of these drugs would inhibit any person of skill in the art that was in a commercial entity and considering to file a patent joining these two compounds.” Tr. (Schleimer) at 814:1-4.

E. Meda has failed to produce any evidence of commercial successes that rebuts the strong showing of obviousness.

149. Any evidence of commercial success does not indicate nonobviousness in this case because there could be circumstances under which an economically rational potential competitor might think an invention obvious but still decide not to adopt it. Tr. (Jarosz) at 712:19-23.

¹ It is “well established” that “‘containing’ is generally an open-ended term that is synonymous with ‘comprising’ or ‘including’ and does not exclude additional, unrecited elements.” *INVISTA N. Am. S.a.r.l. v. M & G USA Corp.*, 951 F. Supp. 2d 604, 615 (D. Del. 2013); *see also* MPEP § 2111.03.

1. Blocking patents make evidence of commercial success weak.

150. As explained, there are two blocking patents in this case. Even if a patent only potentially covers the combination, that is “something a rational economic actor would consider when they are deciding whether to make a product that might infringe someone else’s patents” because “there are various risks and exposure of launching a product in light of a patent.” Tr. (Press) at 765:23 – 766:3; *see also* Tr. (Schleimer) at 814:18-21. Plaintiffs’ expert, Mr. Jarosz, agreed that if selling a combination azelastine/fluticasone product before May 2011 would infringe those patents, “then it might be a rational decision not to” sell it even if it was technically obvious. Tr. (Jarosz) at 718:2-7.

2. Competitive factors make evidence of commercial success weak.

151. An economically rational pharmaceutical developer considering marketing an obvious azelastine/fluticasone combination product in 2002 would also have known that fluticasone and azelastine were both available as separate medications at that time, Tr. (Jarosz) at 722:1-10, and that a combination product would “have to differentiate itself from the availability of its own components” that are “available in generic form and sell[] at high volume.” Tr. (Press) at 766:19–767:8.

152. Indeed, Dymista had a difficult time differentiating itself from its component competitors. Tr. (Press) at 767:9-12. One of Meda’s investors concluded that “the cost benefit profile of Dymista versus cheap generic standard of care fluticasone is simply not good enough for a commercial success.” PTX 1117, at 2, 4; DDX-6.04; Tr. (Press) at 767:13-22. One of the effects of a “cost benefit profile” which is “simply not good enough for a commercial success” is that Dymista[®] has not received favorable insurance formulary placement, which means patients have to pay more for Dymista[®]. Tr. (Press) at 768:1-17. That has the effect of “hamper[ing] the use of Dymista.” PTX 1117, at 4; DDX-6.04.

153. These are “relevant factors to an economically rational decision-maker in deciding whether or not to introduce a product” and are “reasons other than nonobviousness why a competitor might not have made an azelastine/fluticasone combination product.” Tr. (Press) at 762:8-20, 769:14-23. As real world evidence of the risks these considerations presented, Meda has consistently failed to meet its internal projections for Dymista[®] sales. Tr. (Press) at 770:8-24; *see also* DDX-6.07; PTX 267, 268, 270, 1123, 1189.

3. Dymista[®]'s performance is not indicative of nonobviousness.

154. Dymista[®]'s performance in the market is also not indicative of nonobviousness. Mr. Jarosz relied for his analysis of marketplace success primarily on data about Dymista[®] prescriptions and revenues. Tr. (Jarosz) at 690:3-10. When he compared Dymista[®]'s performance to other products, he focused on branded nasal sprays. Tr. (Jarosz) at 694:3-6.

155. However, generic nasal sprays, including fluticasone and azelastine, are also competitors. Tr. (Jarosz) at 694:15-19; 734:12-19. When those competitive products and other generic nasal sprays prescribed to treat allergic rhinitis are considered, Dymista[®] has the third largest share of revenues. PTX 1189, at 4. Fluticasone has a revenue share that is 15.5% of the prescription nasal spray market, over three times larger than Dymista[®] during the same period. *Id.*

156. In terms of total prescriptions over its life, Dymista[®] was tied for fifth place for total prescriptions from 2012 to 2016, with 1.2% of the prescription nasal spray market. PTX 1189, at 1. Fluticasone accounted for 73.2% of the prescriptions written in the nasal spray market over the life of Dymista[®]. *Id.* That is roughly 61 times more prescriptions than Dymista[®] during the same period. *Id.* Generic azelastine had a prescription share of 4.3% during that time period, or about 3.5 times larger than Dymista[®]. *Id.* Dymista[®]'s 1.2% prescription share would not even be included on the demonstrative chart Mr. Jarosz showed to

the Court illustrating prescriptions between branded drugs, which excluded anything with a market share lower than 3%. *Id.*; *see also* Jarosz Demonstrative 1.

157. Dymista[®]'s share of the market is even lower when one considers over-the-counter nasal spray products that Mr. Jarosz also excluded from his analysis. Tr. (Jarosz) at 694:13-19.

158. Finally, while the number of Dymista[®] prescriptions stayed under 1,000,000 annually for each full year it has been available, the number of fluticasone prescriptions grew by roughly 4,000,000 from 2012 to 2013 and roughly 6,000,000 from 2013 to 2014. PTX 1189, at 1. The *increase* in the number of prescriptions written for the prior art fluticasone product was four to six times the *total* number of prescriptions written for Dymista[®].

4. There is no nexus between sales and the alleged invention.

159. Mr. Jarosz testified that the patented benefits of Dymista[®] are its fast acting and sustained relief, more complete symptom relief and fewer side effects than monotherapy fluticasone or azelastine, and dosing in a single spray. Tr. (Jarosz) at 702:2-17. Mr. Jarosz did not analyze what portion of Dymista[®]'s sales revenues and prescriptions are the result of its being a single formulation as opposed to its containing the prior art elements fluticasone and azelastine (and thus having a nexus only to the prior art elements). For example, a market research report generated by third-party GlobalData describes as one of Dymista[®]'s weaknesses that "[d]espite a clinically significant reduction in nasal symptoms in patients treated with Dymista compared with placebo and monotherapy...the absolute difference between the treatment arms was small, and might not be clinically relevant enough to warrant the higher price associated with the FDC [fixed-dose combination] for drug payers." PTX 397, at 133.

160. Mr. Jarosz did no analysis of what portion of Dymista[®]'s sales and revenues are attributable to any particular claim limitations other than azelastine and fluticasone as active ingredients, such as those including excipients.

161. Sales of Dymista[®]'s Indian counterpart, Duonase, were driven by factors other than the asserted claims. Tr. (Press) at 771:10-13. Cipla undertook what it referred to as a "sweet relief" campaign in 2010 that marketed the introduction of a sweetener to mask Duonase's sometimes bitter taste. Tr. (Press) at 772:18–773:5; *see also* DDX 6.11; PTX 510. This marketing campaign was unrelated to the claimed invention. Tr. (Press) at 773:3-5.

5. The Meda/Cipla License is not relevant.

162. Mr. Press also opined that the license that exists between Cipla and Meda for access to the patents-in-suit is not indicative of commercial success of Dymista[®] or the asserted claims. Tr. (Press) at 762:24-25. Cipla employee Patsy Jeffery agreed that the fees Meda paid to Cipla were low, which reflects diminished value of the licensed intellectual property (including the patents-in-suit). Tr. (Press) at 774:10-22; *see also* Tr. (Jeffery) at 754:19–756:14. Meda did not end up paying the full value that Cipla now ascribes to the patent. Tr. (Jeffery) at 774:23–775:1. Moreover, other pharmaceutical companies including Glaxo SmithKline and AstraZeneca did not offer any money at all when offered a license to the patents-in-suit. Tr. (Jeffery) at 757:18–758:25. Indeed, because Meda owned the license to the Astelin[®] patent, which was a blocking patent in the United States, only it could profit from a license to the patents-in-suit. Tr. (Jarosz) at 716:1–717:1; DTX 328.

6. Meda has failed to produce any persuasive evidence of copying.

163. There is minimal evidence of copying. Plaintiffs' commercial success expert explained that there are at least six "imitators" of Cipla's Duonase in India. Tr. (Jarosz) at 707:5-9. However, he did not present any evidence of *copying*, but merely relies on these imitator

products as evidence of “revealed preferences,” i.e., their companies believed a combination product was worth their investment. Tr. (Jarosz) at 708:2-12. Thus, these imitator products are no different than Apotex or any other generic pharmaceutical company in the United States whose business model is to imitate an already-approved drug product. Tr. (Jarosz) at 700:18–701:3.

F. Meda has failed to produce evidence that Dymista[®] satisfied a long-felt but unmet need for the alleged invention.

164. Plaintiffs also did not establish that Dymista[®] or Duonase satisfied a long-felt but unmet need. First, as noted above, the drug has no unexpected results over the prior art, *supra* ¶¶ 136-43, and the only advantage over the prior art combination of Flonase[®] and Astelin[®] is the convenience of a single nasal spray. Tr. (Wedner) at 94:23–95:4. This advantage was already disclosed by the prior art Cramer and Segal applications. DTX 12; DTX 21. Second, physicians were still prescribing both drugs to patients.

165. Regardless of what its clinical performance is, one cannot conclude that these drugs were the first marketed combination products because they were inventive. The blocking patents and other competitive factors are other reasons no company marketed this type of combination product before Cipla and Meda. *Supra* ¶¶ 144-48.

G. Meda has failed to produce any evidence of independent praise for Dymista[®].

166. The only evidence of praise presented by Plaintiffs was a summary in a journal of an article written by Dr. Carr. Tr. (Carr) at 565:21–566:21; PTX 29. The portion of the summary that Dr. Carr highlighted was the statement that Dymista[®] “can be considered the drug of choice for the treatment of allergic rhinitis.” Tr. (Carr) at 566:13-16. That conclusion parrots the conclusion Dr. Carr and his several co-authors first wrote in the underlying article, that Dymista[®] “can be considered the drug of choice for [allergic rhinitis] therapy....” PTX 227, at 7.

167. Meda funded the studies reported in the article, *id.* at 1, and four of its authors reported potential “conflicts of interest” because of their close ties to Meda. *Id.* at 1.

168. Dymista[®] is prescribed at only a fraction of the rate the prior art fluticasone and azelastine sprays are prescribed, *see supra* ¶¶ 156-58, suggesting that the medical community does not consider Dymista[®] the “drug of choice for the treatment of allergic rhinitis.”

H. Meda has failed to produce evidence that the FDA was skeptical about Dymista[®]’s safety or efficacy.

169. FDA was not skeptical about the safety or efficacy of Dymista[®]. Dr. Carr testified that FDA required Meda’s clinical development plan for Dymista[®] to “demonstrate the safety and efficacy” of the product. Tr. (Carr) at 520:18-24. However, no one at FDA ever used the word skepticism in their communications about Dymista[®], Tr. (Carr) at 593:4-8; and no one at FDA ever communicated to him in substance any skepticism that Dymista[®] would be more effective than azelastine or fluticasone given alone, Tr. (Carr) at 593:13–594:2. There was also no concern about safety, and indeed FDA told Meda it could proceed with whatever studies it wanted. Tr. (Carr) at 532:5-11.

170. What FDA discussed with Meda was its belief that the design of the clinical program Meda initially proposed was not sufficient to satisfy the FDA’s “combination rule,” which requires demonstrating that each component makes a contribution to the claimed effects. Tr. (Carr) at 520:11-24. Meda’s initial proposal—what it considered the “easy thing” to do—was to compare Dymista[®] to commercially available Flonase[®] and Astelin[®], as well as placebo. Tr. (Carr) at 520:25–521:14. FDA thought this design was inappropriate because the test Meda proposed would not rule out the possibility that any differences in efficacy were the result of differences in excipient ingredients between Flonase[®], Astelin[®], and Dymista[®], rather than differences resulting from the use of two active ingredients. Tr. (Carr) at 522:2-15. FDA instead

asked Meda to run its clinical trials comparing Dymista[®] to (a) the same formulation of Dymista[®] but without fluticasone and (b) the same formulation of Dymista[®] but without azelastine. Tr. (Carr) at 522:16–523:2.

171. The other discussion points FDA had with Meda were of a similar nature. For instance, Dr. Carr suggested that FDA questioned whether Meda had identified an appropriate patient population to study, Tr. (Carr) at 529:14-24; and questioned the ability of the proposed trial design to scientifically prove that both the azelastine and fluticasone were effective, and whether Meda had chosen appropriate clinical endpoints to prove greater efficacy. Tr. (Carr) at 529:25–530:24. These are not questions about whether Dymista[®] would be safe and work, but rather about whether Meda’s clinical program would be sufficient to satisfy the FDA’s “combination rule.” Finally, FDA suggested that the rationale for combining azelastine and fluticasone was not, by itself, sufficient to show that the product would meet the combination rule. Tr. (Carr) at 531:2-8. In sum, FDA was doing exactly what its job is—ensuring the scientific validity of a clinical development program. Tr. (Schleimer) at 811:17–812:18.

Dated: January 10, 2017

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