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I. THE PARTIES.

A. Meda.

1. Meda Pharmaceuticals Inc. (“Meda”)¹ is the exclusive licensee of the Patents-in-Suit and is a corporation organized and existing under the laws of Delaware. D.I. 135, Ex. 1 at ¶¶ 1, 20-21 (“Uncontested Facts”). On May 1, 2012, Meda received approval from the U.S. Food and Drug Administration (“FDA”) to market Dymista[®], a 137 mcg azelastine hydrochloride/50 mcg fluticasone propionate combination nasal spray, described in New Drug Application No. 202236. Uncontested Facts at ¶¶ 27-28.

B. Cipla.

2. Cipla Ltd. (“Cipla”) is a publicly held company organized and existing under the laws of India. Uncontested Facts at ¶ 2. Cipla is the owner of the Patents-in-Suit: U.S. Patent No. 8,168,620 B2 (“the ’620 patent”) and U.S. Patent No. 9,259,428 B2 (“the ’428 patent”) (collectively, “Patents-in-Suit”). Uncontested Facts at ¶ 18.

C. Apotex.

3. Apotex Inc. is a corporation organized and existing under the laws of Canada. Uncontested Facts at ¶ 3. Apotex Corp. is a corporation organized and existing under the laws of Delaware. Uncontested Facts at ¶ 4. Apotex Inc. and Apotex Corp. (collectively, “Apotex”) filed ANDA No. 207712 seeking to make and market a generic version of Dymista[®]. D.I. 93, at ¶ 1.

II. THE PATENTS-IN-SUIT.

4. On May 1, 2012, the U.S. Patent and Trademark Office (“Patent Office”) issued the ’620 patent, entitled “Combination of Azelastine and Steroids,” which expires on February 24, 2026. Uncontested Facts at ¶¶ 9, 12. The ’428 patent, entitled “Combination of Azelastine and

¹ Meda had two predecessor companies, Carter-Wallace and MedPointe, but Plaintiffs will refer to each of these companies as “Meda” for convenience.

Fluticasone for Nasal Administration,” issued on February 16, 2016 and expires on June 13, 2023. Uncontested Facts at ¶¶ 13, 16. The Patent Office issued a Certificate of Correction for the ’428 patent on May 3, 2016, which corrected typographical and other inadvertent errors made by the Patent Office. Uncontested Facts at ¶ 17. The Patents-in-Suit have an earliest filing date of June 14, 2002. Uncontested Facts at ¶ 19; Tr. 167:22-23 (Schleimer); Tr. 238:5-7 (Donovan).

5. Amar Lulla and Geena Malhotra are the named inventors of the Patents-in-Suit. Uncontested Facts at ¶¶ 10, 14, 18.

6. The Patents-in-Suit are directed to allergic rhinitis (“AR”), (Tr. 426:11-22 (Kaliner)), a common condition that afflicts millions of people in the United States that is defined as inflammation of the membranes lining the nose, characterized by nasal congestion, rhinorrhea (i.e., runny nose), sneezing, and itching of the nose. Tr. 148:18-149:7 (Schleimer); Tr. 427:22-428:1 (Kaliner); *see* PTX0022.00003-4; PTX0326.00017.

III. THE PATENTS-IN-SUIT ISSUED OVER APOTEX’S REFERENCES.

7. The ’620 patent was filed with the Patent Office as Application No. 10/518,016, which is a 35 U.S.C. § 371 national stage application of PCT/GB03/02557. PTX0001.00001. During prosecution of the ’620 patent, the patent examiner issued three Office Actions. PTX0005.09527-48; PTX0005.09850-69; PTX0005.10864-82.

8. The Patent Office considered the disclosures of Cramer (PTX0062) to be the closest prior art, (PTX0005.09866, 10050; PTX0007.09941, 09983), and therefore, every Office Action issued by the Patent Office during prosecution of the ’620 patent identified Cramer as the primary reference. PTX0005.09527-48; PTX0005.09850-69; PTX0005.10864-82. The Patent Office thrice considered the Cramer reference, and dozens of other references Apotex re-asserts

in this action despite their previous consideration by the Patent Office.² Nevertheless, the Patent Office allowed the claims to issue. PTX0005.18279-281; PTX0007.11219-226.

9. Cipla overcame these Office Actions by amending claims and providing a declaration from co-inventor Geena Malhotra setting forth evidence of unexpected results, licensing, and long-felt need. PTX0005.00288-306; PTX0005.00455-77; PTX0005.00609-29; PTX0005.00654-82. Cipla overcame the last Office Action by amending claims, providing another declaration from Ms. Malhotra explaining why the Cramer reference was inoperable, and providing three additional declarations setting forth further evidence of unexpected results, licensing, commercial success, copying, and long-felt need. PTX0005.00791-820; PTX0005.01312-33; PTX0005.01334-1433; PTX0005.01434-53; PTX0005.01454-61.

10. The same and additional art was considered during prosecution of the '428 patent. *See* PTX0003.00002-10.

IV. APOTEX ADMITS THAT IT INFRINGES THE ASSERTED CLAIMS.

11. Plaintiffs assert that Apotex infringes claims 4, 29, 42, 43, and 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"). Uncontested Facts at ¶¶ 23-24.

12. Apotex has stipulated that the filing of its ANDA No. 207712 with FDA seeking approval to market its generic 137 mcg strength azelastine hydrochloride and 50 mcg strength

² The Flonase[®] reference (PTX0059), Astelin[®] reference (PTX0011), Hettche patent (PTX0343), Phillipps patent (PTX0104), Juniper reference (PTX0336), Segal reference (PTX0088), Barnes reference (PTX0012), Di Lorenzo reference (PTX0021), Dykewicz reference (PTX0022), Nielsen references (PTX0036; PTX0085; PTX0338), Simpson reference (PTX0039), Spector reference (PTX0041), Akerlund reference (PTX0053), Falser reference (PTX0066), Galant reference (PTX0099), Hampel reference (PTX0230), Berger reference (PTX0328), Ratner references (PTX0330; PTX0331), Brooks reference (PTX0332), Drouin reference (PTX0333), Howarth reference (PTX0337), Johnson reference (DTX-039), McNeely reference (DTX-043), Shenfield reference (DTX-048), and Cauwenberge reference (DTX-154) were all considered by the Patent Office. *See* PTX0001.00002-8; PTX0003.00002-10.

fluticasone propionate combination nasal spray and the proposed generic product defined by its ANDA infringes the Asserted Claims under 35 U.S.C. § 271(a) and § 271(e)(2)(A). D.I. 104 at ¶ 1-2; D.I. 135, Joint Pretrial Order at ¶ 8. Thus, Apotex's infringement is undisputed.

V. EMBODIMENTS OF THE PATENTS-IN-SUIT.

A. Dymista®.

13. Dymista® is a nasal spray that contains the active ingredients azelastine hydrochloride ("azelastine") and fluticasone propionate ("fluticasone") and is indicated for the relief of symptoms of seasonal AR in patients six years of age and older who require treatment with both azelastine and fluticasone. Uncontested Facts at ¶¶ 29, 30. Dymista® also contains glycerin, microcrystalline cellulose and carboxymethylcellulose sodium, phenylethyl alcohol, edetate disodium, benzalkonium chloride, polysorbate 80, and purified water. Uncontested Facts at ¶ 31; PTX0138.00001. Dymista® delivers 137 mcg of azelastine and 50 mcg of fluticasone (137 mcg/50 mcg) in each 0.137 mL spray. Uncontested Facts at ¶ 32; PTX0154.00001. Dymista® is indicated for one spray per nostril twice daily. Uncontested Facts at ¶ 33; PTX0154.00001.

14. Dymista®, and its use for the treatment of AR, is covered by the Asserted Claims of the Patents-in-Suit. Tr. 470:24-471:16 (Kaliner) (citing PTX0024, PTX0134, PTX0026); Tr. 642:4-22 (Smyth) (citing PTX0138, PTX0141, PTX0154); Uncontested Facts at ¶ 35.

15. Dymista® launched in the United States in September 2012. Tr. 690:17-694:2, 695:21-698:16 (Jarosz) (citing PTX0929).

B. Duonase.

16. Cipla launched Duonase commercially in India in 2004, and a reformulated version of Duonase in 2010. Uncontested Facts at ¶ 36. Duonase is an azelastine and fluticasone combination nasal spray used for the treatment of symptoms of AR. Uncontested Facts at ¶ 37.

Duonase also contains benzalkonium chloride, glycerin, polysorbate 80, microcrystalline cellulose and carboxymethylcellulose sodium, phenylethyl alcohol, and purified water. The 2010 reformulation of Duonase includes the excipient sucralose. Uncontested Facts at ¶ 38.

17. It is undisputed that Duonase, and its use for the treatment of symptoms of AR, meets at least one Asserted Claim of each of the Patents-in-Suit. Tr. 470:24-471:16 (Kaliner) (citing PTX0024, PTX0134, PTX0026); Tr. 642:4-22 (Smyth) (citing PTX0135; PTX0153; PTX0145); Uncontested Facts at ¶ 39.

VI. APOTEX HAS FAILED TO PROVE BY CLEAR AND CONVINCING EVIDENCE THAT THE ASSERTED CLAIMS ARE INVALID AS HAVING BEEN OBVIOUS.

18. Apotex has failed to show by clear and convincing evidence that the Asserted Claims of the Patents-in-Suit would have been obvious to the POSA at the time of invention. Apotex has not shown that the POSA would have been motivated to develop a fixed-dose combination of azelastine and fluticasone. Rather, the art and practices of all testifying clinicians showed an overwhelming preference for flexibility in treatment that is inconsistent with a fixed-dose combination. Further, Apotex has not shown that the POSA would have had any expectation of successfully developing such a fixed-dose combination. Specifically, Apotex has not explained its selection of the various excipients, concentrations, and physical characteristics recited in the claims, but it admits that changing one component of the formulation would change the overall characteristics of the formulation. In short, the evidence shows that the Asserted Claims would not have been obvious to the POSA at the time of invention.

A. The Prior Art Would Not Have Motivated the POSA to Develop a Fixed-Dose Nasal Spray Formulation Comprising Azelastine and Fluticasone.

19. Apotex has failed to identify any reference or combination of references that would

have motivated the person of ordinary skill in the art at the time of invention in 2002 (“POSA”)³ to combine azelastine and fluticasone into a fixed-dose combination nasal spray.

1. The POSA would not have been motivated to select azelastine and fluticasone from among the numerous treatment options that were available in 2002.

20. By 2002, six major drug classes were used to treat AR. *See generally* PTX0022 and PTX0326. These classes included (1) decongestants, (2) mast cell stabilizers, (3) anticholinergics, (4) leukotriene receptor antagonists, (5) corticosteroids, and (6) antihistamines each of which was used at the time of invention to treat AR. *See* Tr. 434:7-13 (Kaliner); *see generally* PTX0022 and PTX0326.

21. POSAs had a broad array of choices for the treatment of AR in 2002. No fewer than 49 options from among these drug classes were known at the time of invention. PTX0022.00029-33; PTX0326.00092-138; Tr. 434:7-13 (Kaliner). They were predominantly available as oral tablets, (Tr. 606:24-607:1 (Smyth); *see also* Tr. 442:5-7 (Kaliner) (citing PTX0098)), but were also available as oral liquids, intranasal solutions, and intranasal suspensions. Tr. 607:2-5 (Smyth). Oral dosage forms were known to have systemic efficacy, such that they could treat multiple organs. *See* Tr. 46:22-47:9 (Accetta); PTX0326.00091-92. Patients overwhelmingly preferred oral dosage forms over other available modes of administration. *See* Tr. 224:6-9 (Schleimer); Tr. 444:10-15 (Kaliner); *see also* PTX00020.00005 (75.1% of patients preferred

³ Plaintiffs assert that the person of ordinary skill in the field of the invention of the Patents-in-Suit (“POSA”) would have education and experience in both (1) the treatment of patients suffering from AR and (2) the development of drug formulations. From the clinical perspective, the POSA would have the experience of a primary care physician with a medical degree and two to four years of experience. Tr. 426:13-427:1 (Kaliner). From the formulation perspective, the POSA would possess a bachelor’s of science in pharmaceutical sciences and four to five years of experience, or commensurate work experience. Tr. 426:11-427:1 (Kaliner); Tr. 605:14-21 (Smyth). Apotex’s proposed definition differs in that the POSA need not have a medical degree. Tr. 173:16-22 (Schleimer). Nevertheless, because both Plaintiffs’ and Apotex’s proposed definitions include an M.D., the opinions offered by Plaintiffs’ experts would not differ under Apotex’s proposed definition. Tr. 429:23-430:4 (Kaliner); Tr. 605:22-606:3 (Smyth).

oral dosage forms); PTX0099.00010.

22. **Decongestants** worked well on congestion. Tr. 179:21-24 (Schleimer); Tr. 433:1-6 (Kaliner); *see also* DTX-312.0005. The Dykewicz (PTX0022) and *Allergic Rhinitis and its Impact on Asthma* (“ARIA”) Guidelines (PTX0326) (collectively, “Guidelines”) were the treatment guidelines for AR in the U.S. and Europe, respectively. Tr. 83:14-23 (Wedner). They describe at least nine different oral and intranasal decongestants available for use at the time of invention. *See generally* PTX0022.00028; PTX0326.00105. Intranasal decongestants were known to work in minutes. PTX0326.00105.

23. **Mast cell stabilizers** worked well on all symptoms when used prophylactically. *See* Tr. 80:7-10 (Wedner); Tr. 180:2-5 (Schleimer); PTX0022.00030; DTX-312.0005. The Guidelines describe at least two mast cell stabilizers available for use at the time of invention. PTX0326.00104; PTX0022.00030-31.

24. **Anticholinergics** were known to treat runny nose. Tr. 180:6-10 (Schleimer); Tr. 80:1-6 (Wedner); *see* PTX0326.00107; DTX-312.0005. The Guidelines describe at least four oral and intranasal anticholinergics available for use at the time of invention. PTX0326.00106-7; PTX0022.00031-32.

25. **Leukotriene receptor antagonists**, or antileukotrienes, worked on all symptoms, but were particularly effective in treating congestion in the late phase response.⁴ *See*

⁴ In a laboratory setting, a patient’s exposure to an allergen begins a biphasic response. Tr. 149:8-17 (Schleimer); Tr. 430:22-25 (Kaliner). The immediate neurophysiological response, or “early-phase” response, occurs within minutes of exposure. Tr. 149:8-17 (Schleimer) (citing PTX0333.00002). The later inflammatory response, or “late-phase” response, may occur more than four to ten hours after allergen exposure. *Id.* This biphasic response is a useful experimental model to classify the mechanisms of an allergic reaction. Tr. 149:8-17 (Schleimer); Tr. 430:5-432:15 (Kaliner). But, in a clinical setting, outside of laboratory models, patients are continuously exposed to allergens. Tr. 431:18-24 (Kaliner). With this continuous exposure, the early- and late-phases of the allergic reaction overlap. Tr. 431:18-432:15 (Kaliner). In addition,

PTX0326.00107; PTX0022.00033. The Guidelines describe at least three oral antileukotrienes known at the time of invention. PTX0326.00107; PTX0022.00033.

26. **Corticosteroids** were known to manage all four primary symptoms of AR. Tr. 433:13-19 (Kaliner); *see* PTX0326.00100; DTX-312.0005. Corticosteroids took several days to achieve full effect. *See* PTX0059.00003; *see also* Tr. 212:14-17 (Schleimer). The Guidelines describe at least seven intranasal corticosteroids available for use at the time of invention. PTX0326.00099-103. After a few days of use, they were also known to minimize both the early- and late-phase responses. PTX0322.00015. Many patients at the time of invention refused to take corticosteroids for fear of severe side effects associated with other classes of steroid. Tr. 436:4-7, 444:16-23 (Kaliner).

27. Fluticasone propionate, an intranasal corticosteroid, was known to have an unpleasant smell that some patients did not like. Tr. 437:20-438:4, 439:6-20 (Kaliner) (citing PTX0058.00006-7). Although fluticasone was more potent than other corticosteroids in *in vitro* and asthma studies, (Tr. 152:13-22 (Schleimer) (citing PTX0325; DTX-039)), it was known in the art that the concentration of all commercially available corticosteroid products had been normalized so that each product had the same efficacy in humans. Tr. 437:3-14 (Kaliner).

28. **Antihistamines** were generally known to treat itching, sneezing, and runny nose. PTX0022.00024; *see also* Tr. 433:1-6 (Kaliner). The Guidelines described at least twenty-four antihistamines that were known at the time of invention. Tr. 434:7-10 (Kaliner); *see also* PTX0022.00024-27; PTX0326.00092-99, 00138. Antihistamines were generally divided into two

the symptoms of both early- and late-phases consist of the same symptoms—sneezing, itching, runny nose, and congestion. Tr. 430:5-432:15 (Kaliner). Due to the complexity of the condition in a clinical setting, treating clinicians focused their efforts on managing their patients' symptoms rather than basing their treatment analysis on which phase the patient presents. Tr. 430:5-433:19 (Kaliner); *see generally* PTX0022.00024-33; PTX0326.00093-107 (both describing drug efficacy in terms of symptoms managed).

classes: first-generation antihistamines, which often caused sedation, and second-generation antihistamines, which generally caused less sedation. Tr. 82:24-83:4 (Wedner); PTX0326.00092. Both classes were frequently used at the time of invention. Tr. 434:14-19 (Kaliner).

29. Antihistamines were predominantly available in oral dosage forms; only two of the twenty-four antihistamines were topical. Tr. 606:24-607:1 (Smyth); Tr. 153:2-12 (Schleimer); *see also* PTX0326; PTX0022. Patients showed a significant preference for oral dosage forms, (*see* Tr. 224:6-9 (Schleimer); Tr. 444:10-15 (Kaliner)), and the market bore out this preference. Tr. 441:14-444:15 (Kaliner) (citing PTX0098.00029). Indeed, the limited combination products that existed in the art—Allegra D[®], Claritin D[®], and Zyrtec D[®]—were *all* oral combinations of antihistamines and decongestants, (Tr. 607:10-18 (Smyth)), two drug classes that had completely complementary activity on all of the symptoms of AR. Tr. 433:1-12 (Kaliner).

30. Although azelastine was an antihistamine useful for treatment of AR, (*see* DTX-312.0005), there was no preference for azelastine at the time of invention. Tr. 224:4-23 (Schleimer); Tr. 476:16-477:5 (Kaliner). Given patient preference for oral dosage forms, the POSA would not have preferred azelastine over the numerous other oral antihistamine options at least because azelastine was no more effective than oral antihistamines, (*see* PTX0036.00007; PTX0099.00009), and it exhibited undesirable side effects including sedation and bitter taste. *See, e.g.*, Tr. 440:4-441:1 (Kaliner); PTX0011.00014; PTX0103.00004; PTX0326.00099. These issues, along with azelastine being administered in an intranasal dosage form, contributed to poor patient compliance with azelastine treatment. Tr. 440:14-20 (Kaliner). For these reasons, at the time of invention, azelastine was used extremely infrequently, particularly in comparison with the popular oral antihistamines. Tr. 441:16-443:25 (Kaliner) (citing PTX0098.00029). Based on these issues, the Guidelines recommended the use of azelastine only in one narrow circumstance:

“for mild organ-limited disease, as an ‘on-demand’ medication in conjunction with a continuous one.” PTX0326.00099.

31. Consistent with the patient preference for oral dosage forms, (*see* Tr. 224:6-9 (Schleimer); Tr. 444:10-15 (Kaliner)), and the limited use of azelastine in clinical practice, (Tr. 441:16-443:25 (Kaliner) (citing PTX0098.00029)), an assessment of the future of the antihistamine market as it stood in 2003 “hardly mentioned” azelastine at all. Tr. 443:17-21 (Kaliner) (citing PTX0098.00029).⁵ This market assessment included a breakdown of all sales of AR treatments, and it showed that oral antihistamines comprised 56% of the AR market, nasal steroids comprised 25% of the market, while at least four other intranasal anti-allergic compounds (including azelastine) *together* comprised only 2% of the total market. PTX0098.00029. Azelastine itself comprised less than 1% of the *total market*. *See* Tr. 441:16-442:19 (Kaliner) (citing PTX0098.00029).

2. *The established standard of care in 2002 would not have motivated the POSA to combine azelastine and fluticasone.*

32. Neither the published art nor clinical practices suggested any desire for a fixed-dose formulation of azelastine and fluticasone. Tr. 69:11-70:11 (Accetta); Tr. 83:11-23 (Wedner); Tr. 435:14-15 (Kaliner). Neither of Apotex’s experts, Drs. Accetta and Wedner, prescribed a fixed-dose combination of azelastine and fluticasone, nor did they prescribe azelastine and fluticasone on a consistent, conjunctive-use regimen. Tr. 68:20-70:11 (Accetta); Tr. 77:18-22; 83:11-23 (Wedner). Both, however, confirmed their desire for flexible dosing regimens, e.g. to titrate dosages up and down and to cycle through drugs to provide individualized treatment for their patients. *See, e.g.*, Tr. 69:11-70:11 (Accetta); Tr. 83:11-23 (Wedner); Tr. 435:14-15 (Kaliner).

33. By 2002, the treatment of AR was an iterative process. Tr. 100:16-18 (Wedner); *see*

⁵ 2003 was the first year that IMS carved out azelastine and other nasal anti-allergic treatments. Tr. 441:21-25 (Kaliner).

also PTX0326.00119-00120. The balance between efficacy and side effects was paramount in the treatment of AR because patients often refused to comply with the recommended treatment if the patient found the side effects unacceptable. *See, e.g.*, Tr. 458:13-18 (Kaliner); *see also* PTX0099.00010. To achieve control of a patient's symptoms with minimal side effects, clinicians at the time of invention engaged in at least three distinct practices, each of which was recommended by Apotex's cited art.

34. The first practice was known as stepwise therapy. *See* Tr. 181:16-23 (Schleimer) (citing PTX0326.00119-120). Drs. Accetta, Wedner, and Kaliner all practiced this approach. Tr. 206:25-207:2 (Schleimer) (describing Dr. Accetta's practice as stepwise); Tr. 83:11-23 (Wedner); Tr. 435:14-15 (Kaliner). Stepwise therapy involves starting a patient on one drug and increasing dosages or adding other drugs only if the initial therapy is found to be inadequate. Tr. 445:23-446:2 (Kaliner); Tr. 69:11-70:2 (Accetta); Tr. 181:16-23 (Schleimer) (citing PTX0326.00119-120). It also involves reducing the dosage or number of drugs once a patient's symptoms are under control. Tr. 69:11-70:2 (Accetta); Tr. 445:23-446:2 (Kaliner); *see* PTX0326.00120. When a patient's symptoms were generally under control, but certain triggers caused an increase in symptoms, clinicians would tell the patient to use a second drug "as needed" to control or decrease symptoms. Tr. 52:16-22 (Accetta). Again, this practice was intended to provide patients with the lowest effective dosage necessary to maintain control over their symptoms. Tr. 70:3-11 (Accetta). And, of course, the "need" for a second drug varied widely from patient to patient. Tr. 85:17-25 (Wedner).

35. The second practice was known as titration, which involved increasing or decreasing a patient's treatment dose to achieve, and then maintain, relief of symptoms while minimizing drug exposure. Tr. 205:4-7 (Schleimer); Tr. 445:7-14 (Kaliner); Tr. 69:11-70:2

(Accetta); Tr. 531:11-23 (Carr). Once a patient's symptoms are well-controlled, the patient's drug regimen is titrated down, i.e., reduced, to the lowest dose that still controls the symptoms. PTX0326.00120. According to Apotex's expert Dr. Donald Accetta, all clinicians ascribe to the practice of titration. Tr. 69:11-16 (Accetta); *see* Tr. 77:18-22 (Wedner).

36. The third practice was known as cycling. Because patients responded differently to different drugs, some might have experienced undesirable side effects where others did not, *e.g.* azelastine's prohibitively bitter taste. *See* Tr. 94:14-19 (Wedner); Tr. 440:8-441:1 (Kaliner). In order to address this patient-to-patient variability, clinicians often rotated through different drugs within the same class until they arrived at a satisfactory therapy. *See* Tr. 460:2-17 (Kaliner); Tr. 85:17-25 (Wedner); *see also* DTX-001–DTX-010 (showing years between Dr. Accetta's diagnosis of AR and arrival at concurrent azelastine and fluticasone therapy).

37. Each of these practices required flexibility, which is a "good concept for any medication," (Tr. 70:3-8 (Accetta)), and the Guidelines recommended these approaches. The Dykewicz Guidelines recommended, for example, that "[m]anagement of rhinitis *should be individualized*," including "instruction in and/or *modifications of the medication or immunotherapy program*." PTX0022.00034.

38. The ARIA Guidelines explicitly recommended a stepwise approach that incorporated the other available drug classes, including decongestants, mast cell stabilizers (chromones), and the anticholinergic ipratropium bromide. Tr. 181:16-23 (Schelimer) (citing PTX0326.00119-120). The ARIA Guidelines also recommend that, "[i]f the patient does improve, a step down [or titration] approach should be used." PTX0326.00120.

39. A fixed-dose combination is inconsistent with these flexible principles. First, it was well-known in the art that a fixed-dose combination reduces flexibility. Tr. 512:6-13 (Kaliner)

(citing DTX-048.0012). Second, use of a fixed-dose combination in accordance with these practices would still require the patient to carry a steroid monotherapy in order to titrate or cycle drugs, thus mitigating even the “modest” benefit identified by Apotex’s experts. Tr. 213:3-8 (Schleimer); Tr. 508:9-14 (Kaliner). In short, there are “very few good reasons for using combination products.” DTX-048.0014.

40. The FDA team that reviewed the Dymista[®] application were all M.D.s or Ph.D.s who fell within Dr. Schleimer’s proposed POSA. Tr. 525:22-526:15 (Carr). Years after the date of invention, these reviewers expressed concern over the lack of flexibility afforded by a fixed-dose combination, namely that “combining products eliminates flexibility with dosage titration and potentially exposes patients to unnecessary medication; and thus unnecessary risk.” Tr. 531:15-23 (Carr) (citing PTX0114).

41. While the three prescribing practices enumerated above were applicable to all drugs, they were particularly important for corticosteroids. Although generally safe, intranasal corticosteroids still presented the risk of significant adverse effects. Tr. 438:5-10 (Kaliner); PTX0099.00007. Many patients at the time of invention refused to take corticosteroids for fear of severe side effects associated with other classes of steroids. Tr. 436:4-7; 444:16-23 (Kaliner). Prior to the date of invention, Dr. Schleimer identified several significant risks associated with corticosteroid use, including bruising, skin atrophy, cataracts, moon face, buffalo hump, and hypogonadism. *See* PTX0322.00010-11. Thus, clinicians tried to minimize the dosage of corticosteroids, such as the fluticasone corticosteroid used in the claimed fixed-dose combination. Tr. 438:5-10, 444:22-23 (Kaliner); *see also* PTX0326.00120.

42. The ARIA Guidelines also provided specific recommendations for the use of azelastine. Given azelastine’s significant side effects—namely, sedation and bad taste—the

Guidelines only recommended using azelastine “for mild organ-limited disease, as an ‘on-demand’ medication in conjunction with a continuous one.” Tr. 84:15-23 (citing PTX0326.00099). ARIA’s broader stepwise recommendation is consistent with this statement, because intranasal antihistamines, like azelastine, were only identified as substitutes for oral antihistamines in mild disease situations. PTX0326.00119-120.

43. The only medical records presented in this case, those of Apotex’s witness, Dr. Accetta, do not support a fixed-dose combination. Each record reflects that Dr. Accetta diagnosed his patients with AR *years* before his happenstance arrival at the concurrent prescription of Astelin[®] and Flonase[®], which is consistent with a cycling approach and the fact that Astelin[®] was not a first-line antihistamine. Tr. 65:20-69:10 (Accetta). Dr. Accetta repeatedly told his patients to “try” Astelin[®], (*see* DTX-002; DTX-004; DTX-005; DTX-008, or use it “as needed,” (*see* DTX-001; DTX-007), both of which are consistent with the “on-demand” use recommended by ARIA. Tr. 70:3-11 (Accetta); Tr. 85:17-25 (Wedner) (citing DTX-81). Dr. Accetta instructed one patient to use Astelin[®] and, if it worked, stop taking Flonase[®]. Tr. 68:4-6 (Accetta); *see* DTX-006. This, again, is consistent with a stepwise, cycling approach and not a fixed dosing regimen. In other records, Dr. Accetta prescribed Flonase[®] to address non-allergic conditions like sinusitis and nasal polyps. *See, e.g.*, Tr. 67:7-8 (Accetta) (citing DTX-005); *see also* DTX-009. These prescriptions are unrelated to AR.

44. There is no evidence that, prior to Ratner 2008,⁶ both drugs were used sequentially or in any regimented manner. Tr. 61:25-62:13 (Accetta); Tr. 456:17-457:5 (Kaliner) (citing PTX0330); Tr. Schleimer 205:8-24; Tr. 531:17-23 (Carr) (citing PTX0114.00002).

3. *The significant drawbacks of a fixed-dose combination outweighed any modest clinical benefits.*

⁶ *See infra*. ¶ 125.

45. By 2002, Apotex's alleged benefits of a fixed-dose combination over the concurrent use of the two individual active ingredients would have been modest and transient at best. Tr. 213:3-8 (Schleimer). Indeed, Apotex's expert opined that there would be no improvement in compliance for allergy sufferers. Tr. 95:19-22 (Wedner). In addition, significant drawbacks would have outweighed these modest benefits.

46. That POSAs were not motivated to pursue a fixed-dose combination of azelastine and fluticasone is underscored by the fact that any expected benefit would have been "transient during the first few days of the use of the drug." Tr. 213:10-13 (Schleimer). This is consistent with the known clinical function of corticosteroids—and Dr. Schleimer's own work prior to 2002—that corticosteroids address all four AR symptoms and both phases of the allergic reaction after a few days of treatment. PTX0322.00015. After a few days, the antihistamine contributes nothing beyond the efficacy of the steroid alone. *See infra*. ¶¶ 55-58.

47. It was also widely accepted in clinical practice that fixed-dose combinations had several drawbacks that would have discouraged the POSA from even attempting to develop a fixed-dose combination of azelastine and fluticasone. First, a fixed-dose combination was known to decrease, if not eliminate, a clinician's ability to individualize a patient's treatment. Tr. 512:6-13 (Kaliner) (citing DTX-048.0012-0013); Tr. 531:15-23 (Carr) (citing PTX0114.00008). Every doctor testified that flexibility in treatments was paramount. Tr. 69:11-16, 70:3-8 (Accetta); Tr. 85:17-86:3 (Wedner); Tr. 454:12-455:19 (Kaliner).

48. A fixed-dose combination also cannot be titrated. *See* Tr. 531:15-23 (Carr) (citing PTX0114.00008). That is, a fixed-dose combination would be contrary to the pre-invention practices of Drs. Kaliner, Carr, Accetta, and Wedner, the testifying clinicians in this case, as well as the recommendations of the Dykewicz (PTX0022) and ARIA Guidelines (PTX0326), which

counseled individualized treatment and dose titration. *See, e.g.*, Tr. 69:11-70:11 (Accetta); Tr. 83:11-23 (Wedner); Tr. 435:14-15 (Kaliner); *see* PTX0022.00034; PTX0326.00099, 00119-00120. Shenfield specifically identifies the lack of flexibility in treatment as a drawback to fixed-dose combination products. Tr. 512:6-13 (Kaliner) (citing DTX-048.0012-13).

49. Second, at the time of invention, azelastine would not have been a preferable option for a fixed-dose combination intended to improve patient compliance and convenience. *See* Tr. 444:6-15, 446:3-7 (Kaliner); Tr. 224:4-23 (Schleimer). Even though azelastine was a topical antihistamine that would have been expected to exhibit reduced systemic side effects, (PTX0326.00091), it caused sedation in approximately 10% of patients and 19.7% of patients experienced an extremely bitter taste, both of which contributed to poor patient compliance. Tr. 440:8-20 (Kaliner); *see* PTX0011.00014. At the time of invention, the POSA would not have chosen azelastine for use in a fixed-dose combination intended to improve patient compliance and convenience. *See* Tr. 444:6-15, 446:3-7 (Kaliner); Tr. 224:4-23 (Schleimer).

50. Third, fluticasone exhibited an odor that patients found unpleasant. Tr. 439:6-14 (Kaliner) (citing PTX0058.00006-00007). This odor was not an issue with other available corticosteroid drugs, like triamcinolone (“Nasacort®”). Tr. 439:15-17 (Kaliner) (citing PTX0058.00006-00007). At the time of invention, fluticasone would not be ideal for use in a fixed-dose combination intended to improve compliance and convenience. Tr. 435:6-9 (Kaliner).

51. Moreover, by 2002, it was well-known that patients preferred oral therapies to intranasal ones. Tr. 444:9-15 (Kaliner). The POSA at the time of invention seeking to develop a combination product to improve compliance would have looked to the preferred oral dosage forms, not to intranasal therapies. *Id.*; *see also* Tr. 607:10-14 (Smyth); Tr. 433:7-12 (Kaliner).

52. And importantly, the POSA at the time of invention would have known that the use

of two active ingredients increased the risk of side effects. Tr. 457:14-17 (Kaliner); *see also* DTX-048.0012-0013. In fact, a post-invention study by Ratner in 2008 (PTX0330) examined the conjunctive use of azelastine and fluticasone and confirmed the expectation that the consistent and prolonged use of azelastine and fluticasone together exhibited a synergistic increase in bad taste and a near-additive increase in headaches, as compared to the side effects of Flonase[®] and Astelin[®] alone. Tr. 457:20-458:7 (Kaliner); *see* PTX0330. Since increased side effects were known to reduce patient compliance, (Tr. 446:3-7 (Kaliner); Tr. 556:16-18 (Carr)), the POSA would not have expected a fixed-dose combination of azelastine and fluticasone to improve compliance. Tr. 446:3-7 (Kaliner). Shenfield (DTX-048) specifically identifies the risk of increased side effects as a drawback to fixed-dose combination products. DTX-048.0012-0013.

53. The POSA would not have been motivated to combine azelastine and fluticasone based on their mechanisms of action. Both azelastine and fluticasone were known to be effective on all four AR symptoms, which suggests that they have overlapping mechanisms of action. Tr. 431:25-433:10 (Kaliner); *see also* DTX-312.0005. Indeed, Howarth (PTX0337) summarizes the understanding in 2002 that “[t]he lack of additional clinical benefit when antihistamines are used in combination with corticosteroids indicates that, *in vivo*, the anti-inflammatory effects on the airway of corticosteroids overlap those of H₁-antihistamines, making the action of the latter redundant.” PTX0337.00005. And in the context of decongestants and corticosteroids, Dr. Schleimer agreed that there is no reason to combine two drugs with overlapping efficacy. Tr. 209:7-14 (Schleimer).

4. *None of the asserted prior art references would have motivated the POSA to combine azelastine and fluticasone into a fixed-dose combination.*

54. By 2002, several studies had considered the conjunctive use of antihistamines and corticosteroids. The weight of these studies found no benefit from the addition of an

antihistamine to a corticosteroid monotherapy. Experts in the field reviewed these studies and confirmed this finding. And nothing in the remaining identified prior art references would have motivated the POSA to combine azelastine and fluticasone in a fixed-dose combination.

55. Several studies considered the conjunctive use of oral antihistamines and intranasal corticosteroids and found no clinically meaningful benefit beyond use of the steroid alone. Juniper 1989 (PTX0336), Simpson (PTX0039), Benincasa (PTX0013), and Ratner 1998 (PTX0331) studied the conjunctive use of (1) beclomethasone dipropionate and astemizole; (2) budesonide and terfenadine; (3) **fluticasone** and cetirizine; and (4) **fluticasone** and loratadine, respectively. Neither Juniper 1989, Simpson, Benincasa, nor Ratner 1998 studied the conjunctive use of azelastine and fluticasone, nor did any of the references study a fixed-dose combination of the two active ingredients. *See generally* PTX0336; PTX0039; PTX0013; PTX0331. Juniper 1989, Simpson, Benincasa, and Ratner 1998 concluded that the conjunctive use of an oral antihistamine with an intranasal corticosteroid did not result in any additional benefit of clinical significance beyond the use of the corticosteroid alone. PTX0336.00003; PTX0039.00006; PTX0013.00001; PTX0331.00003; *see also* Tr. 449:9-451:24 (Kaliner) (citing PTX0036.00014; PTX0053.00017). The only potential clinically meaningful benefit identified in these studies—an improvement in ocular symptoms identified in Juniper 1989 (PTX0336.00003)—would have been recognized by the POSA as resulting from use of an oral (i.e., systemic), not intranasal, antihistamine. PTX0326.00091; *see also* Tr. 46:25-47:5 (Accetta).

56. Drouin (PTX0333) and Brooks (PTX0332) both studied the efficacy of the oral antihistamine loratadine and the corticosteroid beclomethasone dipropionate. PTX0333.00002; PTX0332.00001. Neither fluticasone nor azelastine were considered in either study. *See generally* PTX0333; PTX0332. Neither study showed a clinically meaningful benefit to

conjunctive use. Drouin showed extremely marginal benefit, (*see* Tr. 452:13-453:15 (Kaliner) (citing PTX0333.00005)), while Brooks aberrantly showed that beclomethasone alone was no more effective than loratadine alone. PTX0332.00005.

57. Juniper 1997 (DTX-107) studied the difference in using fluticasone and adding terfenadine as needed or using terfenadine and adding fluticasone as needed. *See* DTX-107.0001. Juniper 1997 did not study the conjunctive use of azelastine and fluticasone, nor did it study a fixed-dose combination of two active ingredients. *See generally* DTX-107. Juniper 1997 does not report an improvement in efficacy from the addition of an oral antihistamine to the use of an intranasal corticosteroid. *Id.* In fact, nothing in Juniper 1997 suggests the need for, or utility of, a fixed-dose combination because the second drug for each treatment arm was used only on an as-needed basis. *See* DTX-107.0005. The disclosed practice of only using a second drug when absolutely needed is inconsistent with a fixed-dose combination, and likewise mitigates even the modest benefit identified by Dr. Schleimer. *See supra* ¶ 39.

58. By 2002, many researchers looked at the body of clinical evidence concerning the conjunctive use of an oral antihistamine with an intranasal corticosteroid and likewise concluded that there was no additional benefit. Tr. 447:16-20, 449:9-450:4 (Kaliner). In 2000, Howarth (PTX0337) concluded that the available studies “do not support a superior effect with long-term regular therapy with the combination [of antihistamines and corticosteroids] compared with topical corticosteroid alone.” PTX0337.00004-5. In 2001, Nielsen (PTX0036) concluded that “[t]he common clinical practice of combining [intranasal corticosteroids] and oral antihistamines in the treatment of AR has no support in clinical evidence, as the combination has not provided effects beyond [intranasal corticosteroids] alone and so it cannot be considered cost effective.” Tr. 449:3-450:4 (Kaliner) (citing PTX036.00014). In reaching this conclusion, the Nielsen

authors considered Juniper 1989 (PTX0336), Ratner 1998 (PTX0331), Simpson (PTX0039), Brooks (PTX0332), and Juniper 1997 (DTX-107). *See* PTX036.00013.

59. In 2003, the Nielsen team reiterated their findings by again stating that the available studies showed no benefit to the addition of an oral antihistamine to an intranasal corticosteroid. *See* PTX0085.00010. In addition to the Nielsen team, Akerlund concluded in 2005 that several studies “failed to show any significant difference on nasal symptoms between intranasal corticosteroid with and without oral antihistamine.” Tr. 450:10-13 (Kaliner) (quoting PTX0053.00017). Akerlund explicitly considered Juniper 1989 (PTX0336), Benincasa (PTX0013), Simpson (PTX0039), and Ratner 1998 (PTX0331). *See* Tr. 450:5-451:6 (Kaliner) (citing PTX0053.00023). Dr. Schleimer’s opinions on the art are contrary to the stated views in the art before and after the invention date. Tr. 185:8-191:1 (Schleimer).

60. While no study considered the benefit of adding azelastine to a corticosteroid prior to 2008, (*see* Tr. 455:20-25 (Kaliner) (citing PTX0330)), fluticasone was repeatedly shown to obtain no benefit from the addition of an antihistamine. *See* PTX0013; PTX0331.

61. The remaining identified prior art would not have motivated the POSA to combine azelastine and fluticasone into a fixed-dose combination. Spector (PTX0041) did not suggest a fixed-dose combination of azelastine and fluticasone. Tr. 477:14-478:16 (Kaliner). And despite recognizing oral and topical forms of other drugs, Spector did not recognize the existence of topical antihistamines. Tr. 477:21-478:16 (Kaliner) (citing PTX0041.00001-00002). Spector disclosed that the current stable of antihistamines and corticosteroids were inadequate and that what was needed was an antihistamine with anti-inflammatory activity. Tr. 477:21-478:16 (Kaliner). Dr. Schleimer followed this recognize by patenting the use of oral antihistamines for anti-inflammatory effect. Tr. 201:8-202:2 (Schleimer).

62. Berger (PTX0328) studied the use of azelastine alone compared to the use of loratadine and beclomethasone, the same pair of drugs considered in Drouin (PTX0333) and Brooks (PTX0332). Berger concluded that azelastine could be used alone, with a steroid, or as a substitute for intranasal steroids. Tr. 476:11-477:9 (Kaliner) (citing PTX0328.00006). Berger did not study the conjunctive use of azelastine and fluticasone, nor did it study a fixed-dose combination of the two active ingredients. *Id.*

63. Segal (PTX0088), an abandoned patent application, broadly discloses “nasal compositions comprising a therapeutically effective amount of a topical anti-inflammatory agent and a therapeutically effective amount of *at least one* agent suitable for topical nasal administration and selected from the group consisting of a vasoconstrictor, a neuramidinase inhibitor, an anticholinergic agent, a leukotriene inhibitor, an antihistamine, an antiallergic agent, and anesthetic, and a mucolytic agent” including fluticasone and azelastine. PTX0088.00004. Segal identifies (1) six steroids; (2) four vasoconstrictors (decongestants); (3) three antileukotrienes; (4) one neuromidinase inhibitor; (5) nine antihistamines; (6) three antiallergic agents; (7) one anticholinergic agent; (8) three topical anesthetics; and (9) three mucolytic agents. Segal identifies no exemplary formulations from among the hundreds of possible combinations disclosed, (PTX0088.00004-7), and it does not specifically identify azelastine and fluticasone from among hundreds of possible combinations. *See generally* PTX0088.

64. Advair DISKUS[®] (DTX-077; DTX-068), a metered-dose inhalation powder product containing fluticasone and a second active ingredient, salmeterol xinafoate, for the treatment of asthma, would have been of limited relevance to the POSA. AR and asthma are different in clinical practice. Tr. 431:3-432:3 (Kaliner). Salmeterol is not an antihistamine, so the mere fact that it worked with fluticasone for treating asthma does not show that another drug class for a

different condition might confer a similar improvement for AR.⁷ See Tr. 190:8-11, 209:7-14.(Schleimer). While a fixed-dose combination might be appropriate for asthma treatment, all of the testifying clinicians agreed that flexibility was more important in the treatment of AR. Tr. 69:11-16, 70:3-8 (Accetta); Tr. 85:17-86:3 (Wedner); Tr. 454:12-455:19 (Kaliner).

B. The POSA would have had no reasonable expectation of successfully formulating an azelastine and fluticasone fixed-dose combination intranasal spray.

65. As discussed above, POSAs in 2002 lacked any motivation to combine azelastine and fluticasone into a fixed-dose combination nasal spray. Assuming such a motivation existed, the POSA would not have a reasonable expectation of successfully formulating azelastine and fluticasone into a combination nasal spray formulation. Azelastine and fluticasone had competing solubility concerns which would have counseled against a fixed-dose combination. In addition, the formulator would have encountered a number of formulation challenges. And even assuming the POSA would develop an azelastine/fluticasone formulation, nasal sprays have a number of narrow, interconnected parameters which the POSA would need to balance.

1. Solubility concerns would have counseled against combining azelastine and fluticasone into a fixed-dose combination nasal spray.

66. The active ingredient and dosage forms are central concerns for POSAs and the starting point for the formulator's design. Tr. 606:7-21, 615:5-16 (Smyth).

67. In 2002, AR products would have been available in oral, nasal solution, and nasal suspension forms. Tr. 607:2-5 (Smyth). At that time, it was understood that the development of a combination product is a challenging and complex task, but that tablets for oral administration

⁷ In addition, the formulator POSA would look to the dosage form at the start of developing a product. Tr. 606:7-607:14 (Smyth). A formulator looking to develop a nasal spray would not find an inhalation powder instructive. Tr. 622:2-13 (Smyth). However, the POSA would consider the published formulation difficulties experienced by Glaxo related to its *suspension* Advair[®] product. See ¶ 76, *infra*. That would be relevant to the POSA's expectation of success in developing a fixed-dose formulation containing fluticasone in suspension.

may be relatively less complex to develop than a combination of solutions and suspensions. Tr. 607:10-14 (Smyth). In fact, the existing AR combination products were all oral forms. Tr. 607:10-18 (Smyth).

68. Although the POSA would not have been motivated to select a nasal spray formulation over oral dosage forms, assuming the POSA went forward with a nasal spray formulation, the POSA would consider the active ingredients. The physical and chemical properties of the active ingredients would be paramount and the formulation excipients would be selected to accommodate the stability and performance of the active ingredient. *Id.*

69. By 2002, azelastine was known to be a *sparingly soluble* compound marketed as Astelin[®], a solution nasal spray. Tr. 609:22-610:1, 611:7-10 (Smyth). Further, fluticasone was known to be a practically *insoluble* compound and commercially available as Flonase[®], a suspension nasal spray. Tr. 607:23-608:15, 609:22-610:1, 611:7-10 (Smyth).

70. A solution system is one where the active ingredient is dissolved into a medium. Tr. 610:20-25 (Smyth). The goal of a solution system—like Astelin[®]—is to keep the active ingredient, here azelastine, fully dissolved in the solution medium. *Id.* If a solution is formulated incorrectly, the active ingredient may precipitate out of solution or form crystals. Tr. 611:14-20 (Smyth). A formulator POSA in 2002 would understand that precipitation of the active ingredient would decrease the uniformity of the active ingredient dispersion in the solution, which would make the solution pharmaceutically unacceptable because the formulation would not administer an accurate dose as intended. Tr. 611:14-612:6 (Smyth).

71. A suspension system—like Flonase[®]—is one where the active ingredient is not dissolved, but rather is in its particle or crystal form. Tr. 611:1-6 (Smyth). The goal of a suspension system is to ensure that the active ingredient, here fluticasone, remains undissolved

and uniformly dispersed in the suspension medium. Tr. 612:10-16 (Smyth). Because the active ingredient is not dissolved in a suspension system, the active ingredient particles naturally want to separate out from the dispersion medium. *Id.* By 2002, the POSA would have understood that rapid sedimentation, particle aggregation, and caking of the active ingredient must be avoided because these phenomena result in the loss of dose uniformity, which renders the formulation pharmaceutically unacceptable. Tr. 612:10-25 (Smyth). Lieberman's *Pharmaceutical Dosage Forms: Disperse Systems* (1996) conveys this understanding as of 2002 when it explains that "the suspended material should not settle readily at the bottom of the container" and "must not cake." Tr. 613:1-17 (Smyth) (citing PTX0192.00005). Both of Apotex's formulation experts, Dr. Donovan and Dr. Ramprakash Govindarajan, admitted that dose uniformity was an important consideration in product development. Tr. 339:13-340:10 (Donovan); Tr. 742:24-743:1 (Govindarajan Deposition Designation).

72. Given the competing environments required for solution and suspension systems, the POSA would have had no motivation to combine azelastine and fluticasone into one intranasal formulation nor have had a reasonable expectation of success in doing so. Tr. 609:4-610:1 (Smyth). Indeed, Meda had these same concerns in 2002 when it considered developing an azelastine/steroid combination. *See infra.* § VII.A.

73. Dr. Donovan contends that Allen's *The Art, Science, and Technology of Pharmaceutical Compounding* (PTX0167) teaches how to formulate a solution/suspension combination formulation, (Tr. 299:17-300:22 (Donovan)), but the specific instruction she identifies—to "dissolve and mix" the preparation—is little more than an instruction to weigh out ingredients and mix them in water. Tr. 614:13-20 (Smyth) (citing PTX0167.00018). Allen is a general guidance text that separately discusses solution systems and suspension systems, and

does not reference combination solution/suspension formulations. Tr. 614:5-12 (Smyth) (citing PTX0167.00017). Furthermore, Allen is directed to and used by compounding pharmacists, not formulators. Tr. 614:21-615:4 (Smyth) (citing PTX0167); PTX0167.00008, 00016, 00020 (referencing the “compounding pharmacist” and offering guidance on “Patient Counseling.”).

2. *The POSA attempting to combine Astelin[®] and Flonase[®] faced formidable challenges in selecting the ingredients and other properties.*

74. Apotex’s formulation expert, Dr. Donovan, started her analysis with the assumption that Dymista[®] could be formulated, selected the commercially marketed products for its two active ingredients, Astelin[®] and Flonase[®], (Tr. 239:3-22 (Donovan)), selected only certain of their excipients and properties, (Tr. 242:2-16 (Donovan)), and then scoured the art to identify what was missing from the claimed formulations, located those in the art and then using that hindsight, selected amongst those limited options to then opine that the formulation of Dymista[®] was obvious. Tr. 341:6-348:12 (Donovan). Dr. Donovan’s obviousness opinion is only based on hindsight and, as such, lacks credibility.

75. Apotex ignores that the POSA would have faced a variety of significant difficulties when combining Astelin[®] and Flonase[®]. Tr. 628:16-19 (Smyth). No guidance was available in 2002 to teach the POSA how to make a combination solution-suspension intranasal formulation and, before Duonase and Dymista[®], no combination intranasal product for the treatment of AR existed. Tr. 199:5-200:2 (Schleimer); Tr. 613:25-614:12 (Smyth).

76. No one knew whether the separate active ingredients, azelastine and fluticasone, would negatively interact in a fixed-dose formulation. Tr. 621:21-622:1 (Smyth); *see* DTX-048.0012-0013. By 2002, it was publicly known that the pharmaceutical company Glaxo encountered formulation difficulties when developing a metered-dose inhaled Advair[®] product (as distinguished from the Advair DISKUS[®] noted above). Tr. 621:21-625:11 (Smyth). Glaxo

discovered that combining fluticasone propionate with a second active ingredient, salmeterol xinafoate, resulted in flocculation, or aggregation, of the drugs in the *suspension* system. Tr. 622:14-624:5 (Smyth) (citing PTX0179.00010); *see* PTX0180. The Glaxo researchers stated that “[c]ombined drug formulations are less well understood and, as a result, a significant amount of fundamental scientific research work on the subject is being undertaken.” Tr. 624:6-625:11 (Smyth) (citing PTX0179.00002). This work would have been relevant to the POSA because it concerned a suspension dosage form containing fluticasone and a second active ingredient. *Id.*

77. In addition to the difficulties associated with the active ingredients, in selecting excipients, the POSA would have also been aware of potential excipient interactions, which would influence the POSA’s choices. For example, a potential incompatibility existed between azelastine in Astelin[®] and carboxymethylcellulose (CMC) in Flonase[®]. Tr. 617:19-618:17 (Smyth) (citing PTX0192.00024). Lieberman (PTX0192) discloses that CMC has poor tolerance for electrolytes and is incompatible with cationic drugs. *Id.* Azelastine is a cationic drug in solution. Tr. 618:18-19 (Smyth). Hettche (PTX0343) discloses CMC as a thickening agent that may be used in a composition with azelastine, but Hettche only discloses CMC as one in a list of 12 possible thickening agents and fails to disclose any examples or claims that use CMC. Tr. 619:5-24 (Smyth). And Astelin[®]—the commercial embodiment of the Hettche patent—does not use CMC. PTX0011.00006. The POSA formulator would have relied upon more authoritative texts—like Lieberman—that were published after Hettche. Tr. 618:4-619:24 (Smyth) (citing PTX0192.00024).

78. The POSA seeking to combine Astelin[®] and Flonase[®] would also have had to reconcile the dosing inconsistencies between the two products. Tr. 609:4-610:10 (Smyth). In 2002, Astelin[®] was dosed at two sprays twice a day to give a total therapeutic dose of 1,096

micrograms. Tr. 627:1-4 (Smyth) (citing PTX0011.00002). Flonase[®] was dosed at either two sprays once a day or one spray twice a day, with a total therapeutic dose of 200 micrograms. Tr. 627:5-8 (Smyth) (citing PTX0059.00005). To reconcile these incompatibilities, the formulator could have chosen to follow Astelin[®]'s dosing, delivering two sprays twice a day which would result in a total daily dose of 400 micrograms of fluticasone, or twice the amount known to be safe per the FDA label, or follow Flonase[®]'s dosing which would result in underdosing azelastine by half. Tr. 627:9-19; 627:20-25 (Smyth). A formulator could alter the quantities of the active ingredients to address these issues, but it would have been a difficult approach. Tr. 628:1-4 (Smyth). For example, the POSA could follow the Flonase[®] label's dosing regimen and double the amount of azelastine in the formulation, but with azelastine already being sparingly soluble, such an approach would be a significant challenge. Tr. 628:5-13 (Smyth). In fact, contemporaneous art identified incompatible pharmacokinetics as a potential drawback to fixed-dose combinations. DTX-048.0012-13.

79. Dr. Donovan relies upon only the labels for Astelin[®] and Flonase[®] to allegedly reconcile the dosing of azelastine and fluticasone. Tr. 242:24-243:13, 257:1-12, 265:1-14 (Donovan) (citing PTX0011.00002 and PTX0059.00005). Dr. Donovan fails to address, much less account for, the significant difficulties inherent to the drugs' dosing inconsistencies. These dosing inconsistencies are compounded by the fact that the spray volume of Astelin[®] and Flonase[®] are different, meaning that altering the spray volume will alter the concentration of the active ingredients administered. Tr. 343:6-344:9 (Donovan). Dr. Donovan failed to acknowledge any these inconsistencies and concomitant challenges. *Id.*

3. *Even assuming the POSA could have successfully addressed the formulation challenges, nasal spray formulations require a narrow set of interrelated parameters.*

80. A pharmaceutically acceptable nasal spray formulation must meet certain

interrelated formulation parameters. Tr. 628:20-630:1 (Smyth). First, the formulation must be chemically stable, which means the active ingredient must not degrade or have unexpected chemical interactions with other ingredients. Tr. 629:1-6 (Smyth). Second, it must have microbiological stability or be free from contamination at the time of use. Tr. 629:7-8 (Smyth). Third, the formulation must have dose uniformity, which ensures that each time the patient uses the nasal spray, he or she gets the accurate, intended dose. Tr. 629:9-13 (Smyth). This is a particularly important consideration for nasal sprays, where the dose delivered is a very small volume of potent active ingredients. *Id.* Fourth and fifth, the formulation must have appropriate osmolality and pH to make sure it is not irritating to the nasal mucosa. Tr. 629:14-19 (Smyth). Sixth, the nasal spray formulation must be able to be dispensed as a spray, not a jet, so the nasal mucosa can be targeted. Tr. 629:20-23 (Smyth). Lastly, the formulation must be physically stable, so the particles in suspension do not separate out. Tr. 629:24-630:1 (Smyth). Particle size can affect physical stability. Tr. 632:6-11 (Smyth). The Asserted Claims specifically cover these formulation parameters by requiring a “pharmaceutically acceptable” formulation that is “suitable for nasal administration.” Tr. 630:2-14 (Smyth). The claims also disclose specific limitations like pH and the amounts of excipients to ensure specific parameters are met. *Id.*

81. In 2002, the POSA would have been aware of these formulation parameters, and would also have been aware of specific tools and approaches to modify each parameter individually. Tr. 309:25-313:15 (Donovan); 630:15-19 (Smyth). However, modifications to each parameter cannot be made in isolation from the other parameters, because a change to one parameter would affect others. Tr. 630:15-631:1 (Smyth). Altering the pH, for example, may change the chemical stability or solubility of a formulation. Tr. 631:2-17 (Smyth). Alternatively, changing the spray quality to avoid a jet spray may influence the physical stability and dose

uniformity of the formulation. Tr. 631:18-632:5 (Smyth). Apotex's Dr. Donovan failed to acknowledge the interconnection of these parameters. Tr. 338:7-340:10 (Donovan).

82. The only prior art Dr. Donovan identified as disclosing a combination of azelastine and fluticasone is the abandoned patent application Cramer (PTX0062), which discloses Example III, a combination of azelastine and triamcinolone. Tr. 302:13-304:7 (Donovan) (citing DTX-012.00007; PTX0062.00007). Rejections based on Cramer's Example III were overcome during prosecution of the Patents-in-Suit. *See supra* ¶¶ 8-10. Apotex's expert Dr. Govindarajan and Plaintiffs' expert Dr. Matthew Herpin each followed the guidance of Cramer and recreated the formulation of Cramer Example III. Tr. 635:8-636:15 (Smyth) (citing PTX1663; PTX1664); Tr. 745:24-751:25 (Govindarajan Deposition Designation).

83. Each of the formulations prepared according to Dr. Govindarajan's protocols or Dr. Herpin's protocols resulted in pharmaceutically unacceptable formulations, and were thus inoperable. Tr. 637:10-24 (Smyth). The only acceptable formulation parameter achieved by the Example III preparation was spray quality with the use of low-viscosity grade HPMC (hydroxypropyl methylcellulose). Tr. 639:12-13 (Smyth). But Example III failed to achieve any of the other basic requirements that were tested and the POSA would have recognized these cumulative formulation issues as evidence that Cramer Example III was far from being a pharmaceutically acceptable formulation. Tr. 638:3-641:17 (Smyth). Specifically, each of the Cramer Example III formulations prepared by Drs. Govindarajan and Herpin 1) were unacceptably acidic, 2) were unstable even after a short period of time, 3) gave inconsistent dose delivery, and 4) were unable to produce a spray when the medium viscosity grade of the ingredient HPMC (hydroxypropyl methylcellulose) was used. Tr. 634:18-23 (Smyth). Many of these same issues were found by co-inventor Geena Malhotra when she recreated the Cramer

Example III formulation during prosecution of the Patents-in-Suit. Tr. 635:1-637:24 (Smyth).

84. In addition, the POSA would understand that nasal spray formulations for the treatment of AR need to be stable at least over a period of weeks because that is the duration of time for which the patient would require treatment. Tr. 204:9-18 (Schleimer); Tr. 244:21-245:7, 266:8-16 (Donovan); Tr. 540:9-12, 547:13-15 (Carr); Tr. 632:22-633:6 (Smyth). The Example III formulation prepared by Dr. Govindarajan, and recreated by Dr. Herpin, however, showed a complete separation between the particles and medium after 14 days. Tr. 639:15-21 (Smyth) (citing PTX1663.00151). Even after remixing, it was evident that “caking is occurring, agglomeration is occurring, changes in particle size is occurring, which would be pharmaceutically unacceptable due to poor dose uniformity.” Tr. 639:21-640:1 (Smyth) (citing PTX1663.00152). The unacceptability of these solubility issues would have been well-known to the POSA in 2002 and such expected formulation hurdles would have dissuaded the POSA from attempting a combination solution-suspension formulation. Tr. 609:13-611:10 (Smyth). Even Dr. Donovan admitted that particle lumping or aggregation in a suspension would be an issue that a formulator would seek to avoid. Tr. 246:11-247:3 (Donovan).

85. Apotex’s formulation expert Dr. Donovan, in reaching her conclusion that Example III was operable, considered only that the composition could be made and characterized—not whether any formulation parameters of the resulting composition were acceptable to the POSA. Tr. 338:7-340:10 (Donovan). Similarly, Dr. Govindarajan stated that even if Example III resulted in a “goop,” it would by definition still be a pharmaceutical composition. Tr. 739:5-23 (Govindarajan Deposition Designation). Drs. Donovan and Govindarajan failed to consider that a nasal spray formulation must also meet several requirements before it can be considered pharmaceutically acceptable as required by the Asserted Claims. Dr. Donovan also described

Example III as an initial step that the POSA could later modify, but nowhere does Cramer describe Example III as an initial step. Tr. 340:1-56 (Donovan).

86. Furthermore, even if the POSA could have made Example III operable, he or she would *still* not have a reasonable expectation of successfully making a pharmaceutically acceptable fluticasone/azelastine combination nasal spray because, as the POSA would have understood the active ingredient in a formulation cannot be switched in and out and expected to work. Tr. 641:5-17 (Smyth). Moreover, Apotex's formulation expert agrees that formulators would have understood that variation in specific ingredient choices would result in an entirely different formulation. Tr. 751:3-20 (Govindarajan Deposition Designation) (citing PTX0062.00006) (stating that Cramer Example I (beclomethasone/loratadine formulation) is "altogether [a] different composition" to Example III).

C. The Asserted Claims of the Patents-in-Suit Are Not Obvious in View of Apotex's Asserted Prior Art.

87. Dr. Donovan uses combinations of Flonase[®], Astelin[®], Hettche, Allen, and the *Handbook*, to form an "Obvious Combination Formulation." Tr. 347:11-348:12 (Donovan).⁸ In so doing, Dr. Donovan cherry-picked among the prior art to identify those five references without reason as to why the POSA would ignore other prior art references, and then continues to cherry-pick among the disclosures of each reference without reason as to why the POSA would ignore the complete teaching of those references.

88. Dr. Schleimer identified Cramer (PTX0062), an abandoned patent application, as a known combination corticosteroid/antihistamine nasal spray because it generically discloses

⁸ Apotex asserts that the combination of Flonase[®], Astelin[®], Hettche, Allen, and the *Handbook* renders obvious claims 15, 29, and 30 of the '428 patent. Apotex also asserts that the combination of Flonase[®], Astelin[®], Hettche, and the *Handbook* renders obvious claims 10, 11, 13, 16, 23, 24, and 26 of the '428 patent and claims 4, 29, 42-44 of the '620 patent. Tr. 281:1-296:11, 327:11-20 (Donovan).

intranasal formulations containing a glucocorticoid and a leukotriene inhibiting antihistamine, including azelastine and fluticasone, among a laundry-list of many active ingredients. Tr. 175:12-177:3 (Schleimer) (citing PTX0062). Cramer discloses Example III, which is a formulation containing azelastine, in solution, and another active ingredient, triamcinolone acetonide, in suspension. Tr. 302:13-304:7 (Donovan) (citing PTX0062.00007). Highlighting Dr. Donovan's hindsight analysis, she cites Cramer Example III as an example of a combination solution/suspension, but then ignores Cramer when developing her "Obviousness Combination Formulation." Tr. 280:6-296:15 (Donovan). Cramer's disclosures in fact undermine Dr. Donovan's motivations to select the claimed excipients and, as discussed above, *see supra* ¶¶ 82-86, recreations of Example III would undermine the POSA's reasonable expectation of successfully formulating azelastine and fluticasone into a single formulation.

89. As above, if the POSA were motivated to combine Astelin[®] and Flonase[®], the POSA would recognize that those product have only two excipients in common—benzalkonium chloride and water—and would be left with no reasonable expectation of success because the POSA would need to determine almost all of the excipients to use for an azelastine/fluticasone combination product. Tr. 340:19-341:5 (Donovan); Tr. 617:8-18 (Smyth) (citing PTX0011.00006; PTX0059.00002). Dr. Donovan provides no reasons to select the claimed excipients in their concentrations.

90. Dr. Donovan considered each ingredient in Astelin[®] and Flonase[®] by its "general or most likely purpose" to allegedly simplify the ingredient selection process. Tr. 242:3-17 (Donovan). But, Dr. Donovan ignored the fact that each excipient may have one or more of several different functions and provided no reason to focus on any one specific function for categorization. Tr. 242:3-264:23 (Donovan); Tr. 650:9-654:14 (Smyth). Indeed, that approach is

inappropriate in the context of combining a solution and a suspension because the function of an excipient, even if in the same category, may be very different between the two systems. Tr. 650:9-20 (Smyth). For example, HPMC in Astelin[®] and microcrystalline cellulose and carboxymethylcellulose sodium (MCC/CMC) in Flonase[®] are both categorized as thickening agents. But each ingredient performs different functions in a solution versus a suspension system and MCC/CMC used in a suspension is more accurately considered a suspending agent, not a thickening agent. Tr. 650:9-20, 653:13-19 (Smyth).

91. In fact, the *Handbook of Pharmaceutical Excipients* (PTX0189), which is an encyclopedia-like reference that lists hundreds of excipients that formulators have used before in various products, (Tr. 616:4-617:1 (Smyth)), and further discloses that each excipient has multiple functions and that multiple options exist for each functional category, with no guidance on which specific excipient to use. Tr. 616:20-617:1 (Smyth). This is because the *Handbook* is typically used by formulators to learn more detailed properties once an excipient has been identified. *Id.* For example, the *Handbook* discloses benzalkonium chloride as not only a preservative but also a “solubilizing agent” and “wetting agent” or surfactant. PTX0189.00003.

92. Setting aside Dr. Donovan’s failure to consider multi-function excipients, the POSA would need a reason to select from the many excipients disclosed in the art and to select specific excipient amounts. *See supra* ¶¶ 74-75. But Dr. Donovan fails to provide any reason for the specific excipients and concentrations. Tr. 341:6-348:12 (Donovan). In fact, Dr. Donovan admitted that her analysis “did not directly explain why a [POSA] might select any one of those agents over any other.” Tr. 346:14-22 (Donovan).

93. **Isotonization agent:** Astelin[®] used sodium chloride as an isotonization agent to control the formulation’s isotonicity, i.e., the number of solids in a liquid. Tr. 620:13-621:13

(Smyth) (citing PTX0011.00006). However, Flonase[®] used dextrose as an isotonization agent. *Id.*; Tr. 346:10-11 (Donovan). Furthermore, glycerin, the isotonization agent recited in the Asserted Claims, was not present in either Astelin[®] or Flonase[®]. Tr. 620:13-621:13 (Smyth) (citing PTX0059.00002). Dr. Donovan provides no reason why the POSA would look beyond the teachings of Astelin[®] and Flonase[®], would not select the isotonization agent in either Astelin[®] or Flonase[®], nor would have reason to select glycerin over the five other isotonization agents disclosed in Hettche. Tr. 346:9-22 (Donovan); PTX0343.00003. Nor does Apotex provide a reason why the POSA would not have considered the teachings in numerous other isotonization agents identified in Cramer. PTX0062.00007. Dr. Donovan's selection is based on hindsight.

94. **Thickening/suspending agents:** Flonase[®] discloses the use of MCC/CMC as a thickening or suspending agent, but Astelin[®] discloses the use of hydroxypropyl methylcellulose (HPMC) as the thickening agent. PTX0011.00006; PTX0059.00002. Dr. Donovan did not explain why the POSA would not select HPMC as disclosed in Astelin[®] but instead select the claimed MCC/CMC. Tr. 345:17-346:8 (Donovan). Further, Apotex does not provide any reason why the POSA would not look beyond Astelin[®] and Flonase[®]—like above—to consider the teachings of Hettche which discloses hundreds of thickening agents that may be used with azelastine (PTX0343.00003), or Cramer which further discloses that methyl cellulose is the preferred thickening agent but discloses that six other thickening agents may be used with azelastine (PTX0062.00005-6). Dr. Donovan's selection is based on hindsight.

95. **Preservatives:** Flonase[®] discloses benzalkonium chloride and phenyl ethyl alcohol, and Astelin[®] discloses benzalkonium chloride and edetate disodium. Tr. 245:7-9 (Donovan) (citing PTX0059.00002), 257:22-258:6 (Donovan) (citing PTX0011.00006). Dr. Donovan did not explain why she chose to combine all three preservatives found individually in Astelin[®] and

Flonase[®] into her “Obvious Combination Formulation” rather than using the exact preservatives from Astelin[®] or Flonase[®]. Tr. 266:8-25 (Donovan). Moreover, Dr. Donovan did not explain why the POSA would look to the Hettche patent to arrive at the concentrations of benzalkonium chloride and edetate disodium, but disregard Hettche’s teachings on the concentration of edetate disodium. Tr. 341:6-343:4 (Donovan). Dr. Donovan’s selection is based on hindsight.

96. **pH:** Astelin[®] contained a buffer system of citric acid and dibasic sodium phosphate, intended to control the pH of the formulation. Tr. 620:2-12 (citing PTX0011.00006). Thus, the POSA would understand that azelastine was very sensitive to pH changes in that formulation. *Id.* Flonase[®] did not contain a buffer system. Tr. 621:14-17 (Smyth) (citing PTX0059.00002). Further, Flonase[®] and Astelin[®] used different pH ranges—Flonase[®] taught a pH range of 5 to 7 while Astelin[®] taught a pH range of 6.5 to 7.1. PTX0011.00006; PTX0059.00002. But Dr. Donovan does not explain why the POSA would not have selected the pH of Flonase[®] or the pH of Astelin[®] alone, or even their overlapping range, and instead looked to a different pH range of 4 to 8, as disclosed in Allen. Tr. 278:3-14 and 344:11-345:10 (Donovan).

97. **Particle Size:** Flonase[®] contained micronized fluticasone, which has a particle size of less than 10 μm . Tr. 243:10-244:4 (Donovan). Astelin[®] had no particles because the azelastine was dissolved in solution. Tr. 257:14-19 (Donovan). However, in 2002, suspensions were available that used both nonmicronized and micronized active ingredients, (Tr. 632:12-16 (Smyth)), but Dr. Donovan provides no reason why the POSA would have selected a micronized active ingredient to use in a combination solution/suspension product.

98. Apotex has not provided any reason why the POSA would have looked to each individual reference to select the claimed excipients in the claimed concentrations. The only reasonable inference is that such selections are improperly based on hindsight. Even in

combination, Dr. Donovan has not explained why the POSA would have ignored the disclosures of other potentially suitable excipients to arrive at her “Obvious Combination Formulation.”

VII. OBJECTIVE INDICIA SHOW THAT THE ASSERTED CLAIMS ARE NOT OBVIOUS.

99. Plaintiffs’ real-world objective evidence further supports the conclusion that the Patents-in-Suit are nonobvious. Tr. 352:10-378:15 (D’Addio); Tr. 424:17-425:10 (Kaliner); Tr. 518:23-519:9 (Carr); Tr. 689:9-690:22 (Jarosz).

A. Meda’s Skepticism in 2002 and Failure to Formulate an Azelastine and Fluticasone Combination Product in 2006 Supports Nonobviousness.

100. Dr. Alexander Dominic D’Addio, Vice President of Scientific Affairs and Medical Communications at Meda, testified that in 2002 Meda was skeptical that an azelastine and steroid combination product could be successfully formulated and developed, and that Meda tried and failed to develop an azelastine and fluticasone combination product in 2006. Tr. 352:10-376:22 (D’Addio). By 2002, Dr. D’Addio and Meda had more than twenty years of experience with the development and formulation of drugs containing azelastine, including the formulation and development of Astelin®. Tr. 353:18-354:25 (D’Addio); *see* PTX0011.

101. In 2002, Meda evaluated the feasibility of formulating an azelastine and corticosteroid combination nasal spray. Tr. 355:1-7 (D’Addio); *see* PTX1006; PTX1005. At the time, Meda found no guidance in the literature on how to develop an azelastine and corticosteroid combination nasal spray. Tr. 355:8-20 (D’Addio).

102. Meda recognized several significant technical formulation problems associated with developing a combination product containing azelastine and a corticosteroid. Tr. 358:15-359:10 (D’Addio) (citing PTX1006.00011); *see* PTX1005.00011. Meda recognized that there was a significant formulation issue in combining azelastine, a solution, with a corticosteroid, that is typically a suspension. Tr. 358:1-363:3 (D’Addio) (citing PTX1006.00011); *see*

PTX1005.00011. Meda was also concerned about reconciling the dosing differences between Astelin and Flonase. Tr. 359:24-361:7 (D’Addio) (citing PTX1006.00011). Meda further determined there was a low likelihood that a combination of azelastine and a corticosteroid would be more efficacious than either of the single monotherapies alone. Tr. 362:6-362:21 (D’Addio) (citing PTX1006.00011).

103. In light of these recognized problems, Meda determined that the feasibility of successfully combining azelastine and a corticosteroid into a single formulation was “low.” Tr. 361:22-362:5, 364:14-23 (D’Addio) (citing PTX1006.00011). Meda then attempted to design around the technical combination formulation issues by searching for, and failing to find, a dual-chamber nasal spray device that would separately store an azelastine formulation and a corticosteroid formulation. Tr. 365:4-21 (D’Addio); *see* PTX0149; PTX0150.

104. Meda filed U.S. Non-Provisional Application No. 11/284,109 (“109 Application”) in 2005 listing hundreds of possible combinations comprising azelastine and other active pharmaceutical ingredients, including steroids. DTX-313.0187-190; DTX-313.0195-208.

105. In 2006, Meda turned its attention back to formulating an azelastine and steroid combination product. Tr. 365:22-370:11 (D’Addio). Meda and Dr. D’Addio still believed that such a combination product would be difficult to formulate. Tr. 365:22-370:11 (D’Addio). Thus, Meda drafted plans to assess the feasibility of creating a single combination nasal spray formulation of azelastine and a corticosteroid to confirm whether there would be major formulation issues. Tr. 366:5-370:16, 390:1-16 (D’Addio) (citing PTX0150; PTX0151). The plans were drafted by Dr. Kalidas Kale and Gul Balwani, who each had 15-20 years of formulation experience with nasal suspensions and azelastine. Tr. 366:18-367:21 (D’Addio).

106. John D’Aconti, a formulation scientist at Meda who had experience working with

the azelastine molecule, began work on combining azelastine and fluticasone under the direction of Mr. Balwani. Tr. 370:24-371:8, 373:21-374:3 (D'Addio) (citing PTX0142.00002). Meda first conducted screening experiments to confirm that there were no obvious, visible incompatibilities when combining azelastine and fluticasone. Tr. 371:11-25 (D'Addio) (citing PTX0142.00017).

107. As part of the screening experiments, Meda isolated the Flonase[®] medium (i.e., removing fluticasone solids) and added an aliquot of azelastine crystals to dissolve in the solution. Tr. 373:3-374:3 (D'Addio) (citing PTX0142.00018). Numerous attempts to dissolve the azelastine failed. Tr. 374:7-25 (D'Addio) (citing PTX0142.00019).

108. Despite the '109 Application's prophetic example combining azelastine and a steroid in a nasal preparation, it issued with claims covering only azelastine as the active ingredient after several days of experiments confirmed Meda's concern that major formulation issues existed with solution-suspension combination nasal sprays. Tr. 375:4-17; 390:1-16 (D'Addio); *see* PTX0150; PTX1005.00011; PTX1006.00011. The predicted solubility issues with azelastine rendered the test sample unsuitable for nasal administration as a homogenous nasal spray. Tr. 370:11-375:23 (D'Addio); *see* PTX0142.00017-00019.

B. Licensing of Cipla's Patent Applications Leading to the Patents-in-Suit Supports Nonobviousness.

109. Shortly after Meda's failure, Meda discovered Cipla's pending U.S. Patent Application No. 10/518,016, the patent application from which all the Patents-in-Suit are derived. Tr. 375:24-376:11 (D'Addio); *see* PTX0001.00001; PTX0003.00001. Meda entered into a licensing agreement with Cipla on November 13, 2006, enabling access to Cipla's intellectual property relating to azelastine/fluticasone combination formulations. PTX1016.

110. Meda considered Cipla's intellectual property to be an important component to the licensing agreement because Meda wanted to ensure that it had patent protection before

embarking on a significant pharmaceutical development program. Tr. 378:1-5 (D’Addio). Had Meda believed that Cipla’s patent applications were invalid or unpatentable, Meda would not have licensed them. Tr. 377:22-25 (D’Addio).

111. Under the Meda-Cipla license agreement (PTX1016), Meda paid Cipla a one-time fee of \$750,000 and three milestone payments totaling \$750,000. PTX1016.00007. Although isolated individuals at Cipla may have believed that the license undervalued its intellectual property, others at Cipla believed that completing the deal at a low value would “initiate a very good business relationship [and] initiate a level of trust and respect” with Meda. Tr. 755:10-757:13 (Jeffery). The Meda-Cipla licensing agreement was amended on November 7, 2011 to include a 15% royalty. PTX0282.00003.

C. FDA Was Skeptical of the Claimed Invention.

112. FDA was skeptical that an azelastine/fluticasone fixed-dose combination product would be sufficiently clinically meaningful for the treatment of AR to justify approval. Tr. 518:23-519:9 (Carr). The FDA division assigned to review Dymista[®] was the Division of Pulmonary and Allergy Products. *See e.g.*, Tr. 515:12-20 (Carr); *see* PTX0114.00002. It is undisputed that the Division of Pulmonary and Allergy Products reviewers who evaluated Dymista[®] included individuals who met the description of the POSA. *See e.g.*, Tr. 525:17-526:15 (Carr); *see* PTX0114.00002. Dymista[®] was the first approved combination nasal spray for AR, and a new drug necessitated new rules and review at the FDA. Tr. 527:16-21, 529:7-531:25 (Carr) (citing PTX0114). During the Division’s review—even before Meda had conducted any clinical trials on Dymista[®]—FDA raised four particularized concerns regarding Dymista[®]. Tr. 528:19-531:25 (Carr) (citing PTX0114).

113. FDA rejected rationales for a fixed-dose combination of azelastine and fluticasone based on “pharmacodynamics reasoning, such as mechanism of action, onset of symptom relief,

etc., are [] not sufficient to justify” Dymista[®]. Tr. 530:25-531:8 (Carr) (citing PTX0114.00005).

114. FDA was concerned that a fixed-dose combination of azelastine and fluticasone “eliminates flexibility with dosage titration and potentially exposes patients to unnecessary medication, and thus unnecessary risk.” Tr. 531:15-23 (Carr) (citing PTX0114.00005).

115. FDA “expressed concerns that [Meda] ha[d] not provided evidence that a population for this combination product exists.” Tr. 529:14-19 (Carr) (citing PTX0114.00004). FDA required Meda to submit a justification that an appropriate patient population existed for Dymista[®]. PTX0047.00004. Meda’s proposed clinical studies targeted a patient population with moderate-to-severe symptoms, measured as a minimum Total Nasal Symptom Scores of 8 out of 12 on three separate evaluations and a congestion score of 2 or 3. PTX0047.00005.

116. Further, FDA did not believe that Dymista[®] could satisfy the combination rule—requiring that each component of a combination product make a contribution to the efficacy of the combination. Tr. 529:25-530:15 (Carr) (citing PTX0114.00004); *see* PTX0110.00002. Meda had proposed using commercial Flonase[®] and commercial Astelin[®] as clinical comparators for Dymista[®]. Tr. 519:24-523:2 (Carr) (citing PTX0110.00002). Because FDA was concerned that formulation differences between Dymista[®] and commercial Flonase[®] and Astelin[®] could “significantly impact efficacy and safety,” Meda had to develop monotherapy comparators that were “essentially the combination product minus one of the active ingredients.” Tr. 519:24-523:2, 535:5-537:21 (Carr) (citing PTX0110.00002).

117. In view of FDA’s concerns, Meda informed FDA that Meda considered the regulatory pathway for Dymista[®] to be “halted.” Tr. 533:6-19 (Carr) (citing PTX0114.00009). To continue forward, FDA recommended that Meda “formally dispute the Division” to the Office Director. Tr. 534:8-535:4 (Carr) (citing PTX0114.00009).

118. The Office Director ultimately allowed Meda to conduct clinical studies, including three pivotal studies: MP4002, MP4004, and MP4006. Each pivotal study was a double-blind, randomized, placebo-controlled study designed with a Dymista[®] treatment arm, a treatment arm of Dymista[®] containing only azelastine, another treatment arm of Dymista[®] containing only fluticasone, and a placebo treatment arm. Tr. 535:12-536:25 (Carr) (citing PTX0114.00009).

119. FDA approved Dymista[®] after it was shown to be superior to the placebo, Dymista[®] containing only azelastine, and Dymista[®] containing only fluticasone arms. PTX0227.

D. Dymista[®] Fulfills a Long-Felt Need and Is Unexpectedly More Effective with a Faster Onset of Action and Fewer Side Effects than Astelin[®] and Flonase[®].

120. Although there were numerous treatment options available at the time of invention, there remained a need for better AR treatment. *See generally* Tr. 434:1-25 (Kaliner); *see* PTX0326; PTX0022. Although 74% of patients were using two or more medicines and 23% of patients were using three or more medicines to treat AR, 80% and 92% of patients surveyed still considered themselves impaired in work and daily life. Tr. 435:19-436:7 (Kaliner); *see* PTX0020; PTX0042. The available treatment options in 2002 also exhibited significant side effects that left 65% of patients concerned about the drugs they were using to treat their AR. Tr. 436:4-7 (Kaliner); *see* PTX0042.00003. Taken as a whole, a need for faster, more effective, and safer treatments for AR was evident. *See* Tr. 475:15-17 (Kaliner).

121. As of 2002, the POSA would also have expected that a combination of azelastine and fluticasone would have an onset equal to azelastine's established three-hour onset. Tr. 473:9-13 (Kaliner) (citing PTX0024; PTX0011.00008; PTX0059; PTX0230.00003). Although azelastine exhibits a positive effect on sneezing in 15-30 minutes, (Tr. 89:10-15 (Wedner) (citing DTX-081)), and azelastine takes effect in non-allergic patients in *in vivo* laboratory histamine challenges within minutes, (Tr. 810:1-811:3 (Schleimer) (citing DTX-207, PTX0326, DTX-

099)), reliance on that data alone is misplaced because it does not measure azelastine's onset for *all* symptoms, and is not congruent with a real-world clinical setting with patients suffering from AR. Tr. 560:5-561:18 (Carr) (citing DTX-043). Azelastine's onset of action of "within three hours" as stated on the FDA-approved label for Astelin[®] is a much more reliable and real-world indicator of azelastine's onset of action for all AR symptoms. Tr. 560:1-561:18 (Carr).

122. Finally, by 2002, the POSA would have expected a fixed-dose combination of azelastine and fluticasone to exhibit increased side effects. Tr. 457:14-458:18, 475:4-7 (Kaliner) (citing PTX0330.00005; DTX-048.0012-13).

123. To the contrary, Dymista[®] fulfills the need for faster and more effective symptom relief and is safer than azelastine and fluticasone. Tr. 475:16-21 (Kaliner). Dymista[®] has onset of 30 minutes, (Tr. 473:14-18 (Kaliner) (citing PTX0024; PTX0011; PTX0059; PTX0230.00003); Tr. 559:4-12 (Carr) (citing PTX0024.00018)), which is faster than azelastine's three-hour onset or fluticasone's 12-hour onset. *See* Tr. 473:9-13 (Kaliner) (citing PTX0024; PTX0011; PTX0059; PTX0230.00003); Tr. 558:19-560:4, 561:13-18 (Carr) (citing DTX-043.0004); *see* PTX0022.00028. Dymista[®] is 296% more effective than azelastine and 190% more effective than fluticasone accounting for placebo. (Tr. 458:23-459:2, 472:2-475:24 (Kaliner); Tr. 541:17-25, 542:14-548:12 (Carr) (citing PTX0227.0005-7)); PTX0024; PTX0011; PTX0059; PTX0230.00003. Dymista[®]'s clinical side effects are also reduced by approximately 80% as compared to the Astelin[®] or Flonase[®] monotherapies. Tr. 475:11-14 (Kaliner) (citing PTX0024; PTX0011; PTX0059; PTX0230.00003); Tr. 553:18-556:23 (Carr) (citing PTX0024); *compare* PTX0024.00006 *with* PTX0011.00014 *and* PTX0059.00009.

124. Prior to this litigation, Apotex's expert Dr. Wedner presented a slide deck on behalf of Meda praising the benefits of Dymista[®] to the Missouri Coalition of Nurses in Advanced

Practice. PTX1668. The slide deck showed that patients were dissatisfied with available treatment options even when using multiple therapies. PTX1668.00005. Dr. Wedner's presentation touted Dymista[®]'s improvement over those monotherapies, thus suggesting that Dymista[®] satisfied these needs. *See generally* PTX1668.

125. Although Ratner 2008 (PTX0330) is not prior art, Apotex erroneously relies on Ratner 2008 (PTX0330) to justify its claim that Dymista[®] exhibits no unexpected results. Ratner 2008 does not demonstrate or suggest the properties of Dymista[®]—faster, more effective, and safer treatment of AR. Tr. 456:6-458:7 (Kaliner). Ratner 2008 is not prior art, and it also does not describe prior art prescribing practices. Tr. 456:17-22 (Kaliner). Ratner 2008 examined the long-term, consistent conjunctive use of azelastine and fluticasone in patients. *See generally* PTX0330. Neither Dr. Accetta's records, (DTX-001-DTX-010), nor any testimony regarding the pre-invention concurrent use of azelastine and fluticasone suggest a similar, consistent regimen. *See generally* Tr. 69:11-70:11 (Accetta); Tr. 83:11-23 (Wedner) (citing DTX-81; DTX-246); Tr. 435:14-15 (Kaliner) (citing DTX-81; DTX-246). Apotex presented no evidence that patients were ever instructed to administer azelastine and fluticasone in a consistent manner on a specific dosing schedule. Apotex also presented no evidence of follow-up by Drs. Accetta and Wedner to assess their patients' compliance with prescriptions for concurrent use of azelastine and fluticasone. Tr. 64:23-65:3 (Accetta). In contrast, Ratner 2008 had a 98% compliance rate. Tr. 456:17-22 (Kaliner) (citing PTX0330.00005-00006).

126. Ratner 2008 also does not have a placebo group. Tr. 537:1-13 (Carr); *see* PTX0330. As Dr. Schleimer testified, to understand a treatment's actual efficacy and remove false positives associated with placebo, it is important to account for placebo. Tr. 825:23-826:5 (Schleimer); *see also* Tr. 537:1-21 (Carr). This is particularly important in AR, where placebo (saline) itself is

often an effective treatment option. Tr. 469:2-21 (Kaliner); Tr. 98:10-17 (Wedner).

127. Ratner 2008 does not offer any evidence of improved onset. *See generally* PTX0330. It does show that the sequential use of azelastine and fluticasone offers improvement over either monotherapy, but that improvement takes days longer than Dymista[®]—despite the fact that the daily dose of Dymista[®] is only half the daily dose of the azelastine used in Ratner 2008. Tr. 543:23-547:18 (Carr) (citing PTX227.00005); *compare* PTX0330.00005 with PTX0227.00005. Finally, Ratner 2008 confirms the expectation that using two drugs together would engender increased side effects, showing a synergistic increase in bad taste and a near-additive increase in headaches. PTX0330.00005. As set forth above, (*see supra* ¶ 123), Dymista[®] reduces these side effects by approximately 80% and 87%, respectively, over the monotherapies.

E. Dymista[®] Received Industry Praise.

128. On the eve of Dymista[®]'s FDA-approval in May 2012, the editors of the *Journal of Allergy and Clinical Immunology* ("JACI"), despite its high rejection rate, accepted Dr. Warner Carr's manuscript regarding Dymista[®]'s clinical trials for publication. Tr. 565:21-566:5 (Carr) (citing PTX0029). The JACI editors selected the Carr manuscript for inclusion in "The Editors' Choice." Tr. 565:21-566:5 (Carr) (citing PTX0029.00001).

129. It is undisputed that JACI is considered to be "essentially the top allergy journal in the world." Tr. 565:11-16 (Carr). Drs. Schleimer and Wedner sat on the JACI editorial board and Dr. Schleimer was an associate editor from 1993-1998. Tr. 145:2-5 (Schleimer); Tr. 73:12-21 (Wedner). The editors, Drs. Donald Y.M. Leung and Stanley J. Szeffler, are considered to be "premier allergy physicians" and are "very, very highly esteemed." Tr. 565:8-10 (Carr).

130. The JACI editors reviewed the clinical data from Dymista[®]'s three pivotal clinical studies, as well as the meta-analysis included in the Carr manuscript, and concluded that: "Given these findings, MP29-02 [Dymista[®]] can be considered the drug of choice for the treatment of

AR.” Tr. 566:8-21 (Carr) (citing PTX0029.00001). The JACI editors reported that Dymista[®] possessed superior efficacy to fluticasone and azelastine monotherapies, Dymista[®]’s improved onset of action compared to fluticasone and azelastine, and Dymista[®]’s improved symptom relief. Tr. 566:8-21 (Carr) (citing PTX0029.00001).

131. Dr. Carr provided undisputed testimony that he did not know how materials were selected as The Editors’ Choice, and that he did not ask to have his manuscript highlighted in The Editors’ Choice section of the journal, nor did he tell the JACI editors what language to use in that section. Tr. 565:17-20, 598:19-23 (Carr).

132. JACI has never identified the sequential or conjunctive administration of azelastine and fluticasone as the treatment of choice for AR. Tr. 566:22-567:1 (Carr). The ARIA guidelines also did not identify the sequential or conjunctive administration of azelastine and fluticasone as the treatment of choice, or even the first line treatment for AR. PTX0326. Jean Bousquet—lead author of the ARIA Guidelines—was also a senior author on the Carr manuscript. Tr. 548:13-16 (Carr). As a co-author of the Carr manuscript, Jean Bousquet agreed with the overall conclusion of the manuscript that Dymista[®] was the “drug of choice” for treating AR. Tr. 548:17-549:2 (Carr) (citing PTX0029.00001).

133. Other publications also praised Dymista[®], calling it a “breakthrough in AR management.” PTX0015.00001; *see also* PTX0038.

F. Dymista[®] Is A Commercial Success in the United States.

134. Dymista[®] is a commercial success. Tr. 689:20-690:22, 711:2-7 (Jarosz). Immediately upon launch, Dymista[®] amassed approximately 2,897,540 in total prescriptions from September 2012 to April 2016 and generated approximately \$447,619,441 in total gross revenue in that time. Tr. 690:17-694:2, 695:21-698:16 (Jarosz) (citing PDX5.02-03).

135. Dymista[®]’s direct competitors are other branded prescription nasal sprays. Indirect

competitors, such as oral AR treatments and over-the-counter (“OTC”) treatments are not direct competitors to Dymista[®] because those treatments 1) are not directed to treat moderate-to-severe AR like Dymista[®], and 2) are typically used by patients as a self-medication before consulting a clinician, whereas Dymista[®] is typically prescribed by a clinician after OTC treatments are found to be ineffective. Tr. 444:6-23, 454:22-24 (Kaliner); Tr. 694:3-695:20 (Jarosz).

136. By April 2016, Dymista[®]’s prescription market share was 19.3% and its revenue share 15.6% among branded prescription nasal sprays. Even considering generic nasal sprays, Dymista[®] is a success in terms of total prescriptions and gross revenue. Tr. 690:23-692:14, 695:21-697:16 (Jarosz) (citing PTX0929; PDX5.04-05). By 2014, Dymista[®] was the second most prescribed branded nasal spray. Tr. 695:21-698:8 (Jarosz) (citing PDX5.04-05).

137. Dymista[®]’s marketplace performance has a nexus to the Patents-in-Suit. Tr. 706:22-707:2 (Jarosz). Dymista[®] was marketed on its benefits which include fast acting and sustained relief for patients suffering from AR, more complete symptom relief, and fewer side effects than monotherapy treatments. Tr. 701:14-707:4 (Jarosz) (citing PTX0271; PTX0397; PTX1118).

138. Apotex’s effort to enter the marketplace with a generic version of Dymista[®], despite already offering generic azelastine and fluticasone monotherapy nasal sprays, suggests that Apotex believes that Dymista[®] offers competitive advantages beyond azelastine and fluticasone alone. Tr. 700:18-701:13 (Jarosz).

139. Dymista[®] did not have favorable pricing or insurance coverage compared to other AR treatments. Tr. 723:18-729:9 (Jarosz); Tr. 768:13-769:6 (Press). In addition, Meda’s sales force had limited reach and marketing potential. Tr. 723:18-727:16, 728:17-729:9 (Jarosz); Tr. 768:21-769:6 (Press); *see* PTX1118.0009; PTX0271.00035; PTX0397.00126-133.

1. No Patents Blocked the Commercialization of a Fixed-Dose Combination Fluticasone-Azelastine Nasal Spray.

140. Plaintiffs' objective evidence of nonobviousness is not attributable to the existence of the so-called "blocking patents" U.S. Patent No. 5,164,194 ("Hettche") (PTX0343) and U.S. Patent No. 4,335,121 ("Phillipps") (PTX0104). Tr. 645:1-14 (Smyth); Tr. 717:9-20 (Jarosz). Hettche and Phillipps do not cover Dymista[®]. Tr. 645:1-14 (Smyth). And in any event, a reasonable competitor could have commercially launched a product containing azelastine or fluticasone after May 1, 2011—the expiration of the later expiring patent—but before Dymista[®] was FDA-approved or commercially marketed. Tr. 717:9-20 (Jarosz). There is no evidence that the Hettche or Phillipps patents actually foreclosed or dissuaded a reasonable competitor from pursuing pharmaceutical compositions containing either azelastine or fluticasone before Dymista[®] was commercially launched. Tr. 779:5-17 (Press).

141. ***Phillipps is not a "blocking patent"***: Phillipps expired on May 14, 2004. PTX0104.00001. Representative of Phillipps, claim 1 covers a genus of compounds that includes fluticasone. PTX0104.00019. Phillipps does not mention azelastine or the use of any active ingredient other than the disclosed corticosteroids. *See generally* PTX0104.

142. ***Hettche is not a "blocking patent"***: Hettche expired on May 1, 2011, including pediatric exclusivity. PTX0343.00001. Representative of Hettche, claim 1 covers: "A method for the treatment of irritation or disorders of the nose and eye which comprises applying directly to the nasal tissues or to the conjunctival sac of the eyes a medicament which contains a member selected from the group consisting of azelastine and its physiologically acceptable salts." Tr. 326:4-12 (Donovan) (citing PTX0343.00005). The Hettche patent does not describe any other active ingredient, or any combination products. Tr. 645:1-10 (Smyth), Tr. 328:6-14 (Donovan).

143. ***Other pharmaceutical companies pursued fixed dose products***: Prior to June 2002, at least three companies were not dissuaded from seeking patent protection on a pharmaceutical

composition containing azelastine or fluticasone. Tr. 786:1-10, 793:2-14 (Press). Cipla filed international patent application no. PCT/GB03/02557 on June 13, 2003, which designated the United States and eventually led to the Patents-in-Suit. PTX0001.00001. In addition, Apotex argued that Segal (PTX0088) and Cramer (PTX0062)—two abandoned patent applications—allegedly showed pharmaceutical companies’ interest in developing combination nasal sprays containing azelastine and fluticasone. *See* PTX0062; PTX0088. As such neither Cipla, Warner-Lambert, nor Procter & Gamble were dissuaded from seeking to develop pharmaceutical compositions containing azelastine or fluticasone. Tr. 786:1-10, 793:2-14 (Press).

144. Moreover, the POSA would understand that public announcements of Meda’s Phase III clinical trials for Dymista[®] guarantee neither FDA-approval nor patentability of the underlying pharmaceutical product. Tr. 721:11-17 (Jarosz); *see e.g.*, DTX-326.0027.

145. The publicly available patent applications leading to the Patents-in-suit are not “separate and apart from the patents in suit” and had not been allowed by the Patent Office, and are therefore not “blocking patents” Tr. 765:16-22 (Press).

2. *Duonase and Its Imitators Are a Commercial Success in India.*

146. Since the commercial launch of Duonase in 2004, eleven companies copied Duonase and launched their own azelastine and fluticasone fixed-dose combination products in India. Tr. 425:7-18, 470:18-471:16 (Kaliner) (citing PTX0024; PTX0134; PTX0026); Tr. 605:6-7, 643:1-20 (Smyth) (citing PTX0129; DTX-265; PTX0026); Tr. 707:5-709:17 (Jarosz); *see* PTX0204.

147. Combinase AQ, Azeflo, Nazomac-AF, Floresp-AZ, Ezicas-AZ, and Nasocom-AZ are copies of Cipla’s Duonase. Each of these products is an azelastine/fluticasone fixed-dose combination product used for the treatment of AR in India and each is therefore an embodiment of at least one of the Asserted Claims of each of the Patents-in-Suit. Tr. 425:7-18, 470:18-471:16

(Kaliner) (citing PTX0024; PTX0134; PTX0026); Tr. 605:6-7, 643:1-20 (Smyth) (citing PTX0129; DTX-265; PTX0026); Tr. 707:5-709:17 (Jarosz); *see* PTX0204.

148. The units shipped of Duonase have steadily grown every year since it was first launched in India in 2004. Tr. 708:13-22 (Jarosz) (citing PTX0204). Starting in 2006, Duonase-imitators launched and the units shipped of the Duonase-imitators have grown every year. Tr. 707:5-708:1, 708:23-709:17 (Jarosz) (citing PTX0204). Collectively, the Duonase and Duonase-imitators comprise 21% of all nasal sprays in the Indian market. Individually, Duonase has the largest market share of all the azelastine and fluticasone combination nasal sprays in India. Tr. 707:5-709:17 (Jarosz) (citing PTX0204).

149. There is a nexus between the marketplace success of Duonase and the Duonase-imitators and the patented inventions. Duonase and its imitators provide the same benefits as the patented inventions and are primarily marketed based on those benefits. Tr. 709:18-711:1 (Jarosz) (citing PTX0412). Cipla's "Sweet Relief" marketing campaign in 2010 and Cipla's brand equity did not affect the steady unit growth of Duonase and do not account for the market growth of Duonase-imitators. Tr. 772:14-774:7 (Press); *see* PTX0204.

VIII. APOTEX HAS FAILED TO PROVE BY CLEAR AND CONVINCING EVIDENCE THAT THE ASSERTED CLAIMS ARE INVALID FOR LACK OF ENABLEMENT.

150. The Asserted Claims of the Patents-in-Suit are enabled by their specifications. PTX0001; PTX0003. The Asserted Claims of the Patents-in-Suit are not invalid for lack of an enabling disclosure of how to make the claimed azelastine/fluticasone combination. The specifications of the Patents-in-Suit disclose exemplary azelastine/fluticasone combination formulations. PTX0001.00012-14; PTX0003.00014-16. In particular, Example 3, which appears in both specifications, discloses a nasal spray containing azelastine and fluticasone. PTX0001.00012. In addition, the claims of the '428 patent recite additional formulation

information. *See, e.g.*, PTX0003.00017 (claim 24).

151. Armed with the exemplary formulations disclosed in the Patents-in-Suit and the claims, the POSA would be able to prepare the formulations by standard techniques. PTX0003.00014 (“these formulations are prepared by techniques well known in the art.”).

152. There is no record evidence that the POSA could *not* make any of the Asserted Claims of the Patents-in-Suit. Indeed, Apotex’s formulation expert Dr. Donovan testified that simply preparing a formulation, regardless of its parameters, means that the POSA can make it. Tr. 313:16-314:1; 338:16-339:12 (Donovan).

153. The Asserted Claims of the Patents-in-Suit are not invalid for lack of an enabling disclosure of how to use the claimed azelastine/fluticasone combination. *See* PTX0001.00009 (“it is known to use the antihistamine azelastine...as a nasal spray against seasonal and perennial allergic rhinitis” and “among, the corticosteroids known for nasal use are...fluticasone”). The claimed active ingredients—azelastine and fluticasone—were FDA-approved drugs for the treatment of AR. Tr. 168:7-17 (Schleimer) (citing DTX-253); *see* PTX0011; PTX0059.

154. The Examples disclosed in the Patents-in-Suit state that “[e]ach spray delivers Azelastine Hydrochloride (140 mcg) and Fluticasone propionate (50 mcg).” *See* PTX0001.00012. The amounts delivered per spray of the claimed azelastine/fluticasone nasal spray formulations deliver the same amount per spray as Astelin[®] (140 mcg/spray) and Flonase[®] (50 mcg/spray). PTX0011.00006; PTX0059.00002.

155. The POSA in 2002 would have known of the FDA-approved dosage of fluticasone and azelastine, and based on those dosages, would have been able to ascertain the effective dosage of the claimed formulations without undue experimentation. Tr. 52:13-53:19 (Accetta); Tr. 77:18-22, 78:24-79:12, 88:23-89:3 (Wedner); Tr. 460:18-461:19 (Kaliner); *see* PTX0059.

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Dated: January 10, 2017

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