

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

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

DEFENDANTS' OPENING POST-TRIAL BRIEF

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Dated: January 24, 2017

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INTRODUCTION

The trial record presents clear and convincing evidence that the asserted claims of U.S. Patent No. 8,168,620 (“the ’620 patent”) and U.S. Patent No. 9,259,428 (“the ’428 patent”) are invalid as obvious. Before the priority date, each and every testifying physician had personally used Flonase® (fluticasone propionate) in combination with Astelin® (azelastine hydrochloride) to treat seasonal allergic rhinitis (“AR”). The patents-in-suit merely claim the co-formulation of these two known, FDA-approved drugs for this known use—with known excipients. All asserted claims are thus obvious because they represent nothing more than the “predictable use of prior art elements according to their established functions.” *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 417 (2007). There is, in short, nothing inventive about them.

The trial focused on two questions: (1) was it obvious to treat AR using a nasal spray with both fluticasone and azelastine as active ingredients; and, if so, (2) was it obvious how to co-formulate those drugs with pharmaceutical excipients? Defendants presented clear and convincing evidence that the answer to both questions is yes.

First, using fluticasone and azelastine together to treat AR was the epitome of an obvious clinical practice as of the June 2002 priority date—indeed, it was part of clinical practice. Both ingredients were marketed in the prior art as FDA-approved nasal sprays branded as Flonase® (fluticasone) and Astelin® (azelastine). D.I. 156 ¶ 1. Every physician who testified at trial—including Plaintiffs’ two clinician experts—prescribed Flonase® together with Astelin® to treat AR before June 2002. *Id.*; Tr. (Accetta) at 46:12-14; Tr. (Wedner) at 76:20-77:6; Tr. (Kaliner) at 433:20-434:6; Tr. (Carr) at 574:10-13. The rationale for such combination therapy was straightforward: the drugs had complementary mechanisms of action and, therefore, using two drugs was more effective than using either one alone. D.I. 156 ¶¶ 35-38.

The next logical and obvious step in this therapy was to combine the active ingredients from these FDA-approved drugs into a single nasal spray. Again, the rationale for doing so was so obvious that Plaintiffs' own expert conceded (through impeachment testimony) that "a person of skill in the art" as of 2002 would have thought that they "would have improved compliance" by putting the two separate drugs "in one spray bottle." D.I. 156 ¶ 2; Tr. (Kaliner) at 508:9-14.

But the Court need not rely only on the Plaintiffs' expert—because two pharmaceutical companies expressly disclosed using the two drugs in a single combination nasal spray, just like the one claimed in the patents-in-suit. *Id.* ¶ 2, DTX 12 ("Cramer"); DTX 21 ("Segal"). The first, referred to at trial as "Cramer," is a European Patent application published on June 25, 1997, five years before the priority date in this case. D.I. 156 ¶ 30. It discloses an AR treatment for nasal administration comprising a steroid and an antihistamine, and it discloses fluticasone as a useful steroid and azelastine as a useful antihistamine. DTX 12. The second reference, "Segal," published in 1998, likewise discloses a combination nasal spray containing a "topical anti-inflammatory agent" such as fluticasone, with an antihistamine such azelastine, to treat AR. D.I. 156 ¶ 32.

Driving this point home, Meda—which marketed Astelin and is *not* the patentee but, instead, took a license to Cipla's patent later in time—found it obvious to co-formulate its drug, azelastine, with fluticasone. As Meda employee Dennis Fuge aptly put it in his testimony, combining the two drugs was "obvious" at the time, because "Fluticasone was the then best selling steroid, and Azelastine was the best antihistamine." D.I. 156 ¶ 2. Plaintiffs' efforts to distort the prior art teachings—including teachings by their own clinical expert, Dr. Kaliner—are not credible.

Second, the only question left is whether it was obvious to use the excipients claimed in the patents-in-suit. Indeed it was. All claimed excipients and their functions were all known in the art—and even disclosed as potential excipients for fluticasone, azelastine, or both. Indeed, Meda itself filed a U.S. patent application in 2005, before it had knowledge of the patents-in-suit, that claimed a combination of azelastine and fluticasone and disclosed as suitable each of the excipients in the claims asserted here. D.I. 156 ¶¶ 128-30.

The person of ordinary skill in the art (“POSA”) in 2002 was well aware of how to make a combination fluticasone/azelastine nasal spray, and the patents-in-suit merely claim some of the most obvious formulations. The prior art Flonase® and Astelin® labels, along with their associated public patents and basic formulation texts, disclosed all the ingredients that made these prior art drugs work in nasal sprays. This included detailed information about suitable thickening agents, preservatives, surfactants, and tonicity adjustors for fluticasone and azelastine formulations, just like the claims cover. D.I. 156 ¶¶ 76-84; D.I. 156 ¶¶ 85-92. By consulting nothing more than the most basic formulation information, a POSA would have arrived at a finite number of obvious combination formulations.

Because a formulator would have had a “reasonable probability of success” using those known excipients for known purposes, that renders all asserted claims of both patents-in-suit obvious. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007); *see also KSR*, 550 U.S. at 417, 421. That conclusion is consistent with the patents’ specification, which confirms that the product can be “prepared by techniques well known in the art,” and gives no new information showing that the claimed combination safely and effectively treats AR. D.I. 156 ¶ 116; PTX 1 at col. 8, l. 67–col. 9, l. 2.

Time and again, the Federal Circuit has held similar types of patent claims obvious. For example, in *Allergan, Inc. v. Sandoz Inc.*, the Federal Circuit found claims covering a co-formulation of two eye drop drugs to treat glaucoma obvious, because key prior art taught “fixed combinations” of similar drugs “for the treatment of glaucoma,” and such a co-formulation could improve “patient compliance,” which was a “clear motivation to combine.” 726 F.3d 1286, 1289-90, 1293 (Fed. Cir. 2013). And in *Richardson-Vicks, Inc. v. Upjohn Co.*, the Federal Circuit affirmed the district court’s decision to overturn a jury verdict that a combination pain relief/decongestant tablet was valid, because “[t]he only difference between the prescribed combination [of ibuprofen and pseudoephedrine] and the patented invention is that the prescription was not contained in a single tablet”—and “[s]uch a combination was clearly suggested by the prior art.” 122 F.3d 1476, 1483-84 (Fed. Cir. 1997).

The asserted claims here are no different. They cover the obvious combination of two known drugs for a known use with known pharmaceutical excipients. Plaintiffs’ efforts to rely on purported formulation difficulties and multiple formulation options all conflict with controlling precedent. The mere “general unpredictability of the formulation arts” cannot support a showing of non-obviousness. *Allergan*, 726 F.3d at 1292-93. Nor does the existence of more than one obvious formulation make any of those particular formulations non-obvious, because “mere disclosure of more than one alternative does not amount to teaching away from” the invention. *SightSound Techs., LLC v. Apple Inc.*, 809 F.3d 1307, 1320 (Fed. Cir. 2015) (internal quote marks omitted). And, of course, obviousness does not require an “absolute predictability of success.” *In re O’Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988). Try as they might, Plaintiffs cannot posit a viable theory of non-obviousness in light of these and other relevant legal standards.

The record thus provides clear and convincing evidence that Plaintiffs' are not entitled to a monopoly on combining azelastine and fluticasone into a single nasal spray. The claimed invention is nothing more than the obvious formulation of a drug combination that had been taught years before the work of the inventors. The asserted secondary considerations of non-obviousness all fail for both legal and factual reasons.

Therefore, the Court should enter a judgment of obviousness under 35 U.S.C. § 103 in favor of Apotex. Alternatively, if the Court were to credit Plaintiffs' arguments, the patent disclosure is inadequate to satisfy the enablement requirement of 35 U.S.C. § 112.

ARGUMENT

I. LEGAL FRAMEWORK

The asserted claims in this case are invalid as obvious because one cannot patent a combination pharmaceutical product when all of the claimed elements were known in the prior art, combined in ways the prior art suggested, and then resulted in an expected form of treatment.

A patent claim is invalid for obviousness under 35 U.S.C. § 103(a) if the differences between the subject matter of the claim and the prior art are "such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the pertinent art." *In re Kahn*, 441 F.3d 977, 985 (Fed. Cir. 2006) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 13-14 (1966)). To determine if a patent claim is obvious, "the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level or ordinary skill in the pertinent art are resolved." *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). And "[s]uch secondary considerations as commercial success, long felt by unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented." *Id.* at 17-18.

Obviousness does not require an “absolute predictability of success,” only a “reasonable expectation” that the combination will succeed. *See In re O’Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988). The mere existence of unpredictability is insufficient for a finding of nonobviousness. The Federal Circuit has even reversed a district court finding “that there was no reasonable expectation of success in view of the general unpredictability of the formulation arts and particularized, yet irrelevant, difficulties associated with the development of [the drug product].” *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1292-93 (Fed. Cir. 2013). Similarly, the mere existence of alternatives is also insufficient for a finding of nonobviousness. “[M]ere disclosure of more than one alternative’ does not amount to teaching away from one of the alternatives where the reference does not ‘criticize, discredit, or otherwise discourage the solution claimed.’” *SightSound Techs., LLC v. Apple Inc.*, 809 F.3d 1307, 1320 (Fed. Cir. 2015) (quoting *In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004)).

Even if “a combination was” merely “obvious to try,” that “might show that it was obvious under § 103.” *KSR Int’l Co. v. Teleflex, Inc.*, 550 U.S. 398, 421 (2007). For example, in the context of claims to pharmaceutical products that include excipients, courts in this district have held that “within the finite range of excipients disclosed to be suitable . . . , it would be obvious to try one such excipient characterized by the prior art” as having the desired property. *Senju Pharm. Co. Ltd. v. Apotex, Inc.*, 717 F. Supp. 2d 404, 422-23 (D. Del. 2010) (Robinson, J.), *aff’d*, 485 F. App’x 433 (Fed. Cir. 2012).

In light of these standards, the asserted claims are obvious over the Flonase® label, the Astelin® label and Astelin®’s formulation patent, in combination with standard formulation references such as the Handbook of Pharmaceutical Excipients.

II. IT WAS OBVIOUS TO COMBINE FLUTICASONE PROPIONATE AND AZELASTINE HYDROCHLORIDE IN A SINGLE NASAL SPRAY TO TREAT ALLERGIC RHINITIS.

The concept of using azelastine and fluticasone together to treat AR was undisputedly recommended and, in fact, practiced in the prior art. That alone is enough to make their co-formulation obvious. Beyond the prescribing habits of physicians and the teachings of the guidelines they followed, however, the prior art also provided significant motivations to make that combination.

A. Persons of ordinary skill in the art

The parties offer different definitions of a person of ordinary skill in the art from the perspective of using pharmaceutical compositions in the treatment of allergic rhinitis. Dr. Schleimer opined that a clinical person of ordinary skill has an M.D., Ph.D. or Pharm.D. in the field of allergy/immunology and/or pharmacology (or the equivalent), and at least three additional years of experience in the treatment, or research for treatments, of allergic rhinitis, including with nasally administered steroids and antihistamines. D.I. 135 Ex. 3 ¶ 21; Tr. (Schleimer) at 171:18-25. Meda's definition limits the POSA to only having an M.D. D.I. 135 Ex. 2 ¶¶ 84-85; Tr. (Kaliner) at 426:11–427:1. Regardless of which of these definitions the Court adopts, the claimed invention is obvious.

B. It was obvious to combine fluticasone with azelastine to treat AR.

1. Doctors prescribed fluticasone (Flonase®) with azelastine (Astelin®) in clinical practice.

There is no dispute that physicians in the United States and elsewhere co-prescribed azelastine in a nasal spray formulation and fluticasone in a nasal spray formulation before June 2002, for AR patients inadequately controlled by either drug alone. Each testifying clinician in this case, including Meda's own experts, did so. D.I. 156 ¶¶ 22-28. This practice was thus part of

the knowledge of a POSA. *See In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006) (“the understandings and knowledge of persons having ordinary skill in the art at the time of the invention” are relevant to obviousness); *Cross Med. Prods., Inc. v. Medtronic Sofamor Danek, Inc.*, 424 F.3d 1293, 1322 (Fed. Cir. 2005) (“It has long been the law that the motivation to combine need not be found in prior art references, but equally can be found in the knowledge generally available to one of ordinary skill in the art.”) (citations and quote marks omitted).

This practice was not surprising given that it was recommended by prior art references and AR treatment guidelines. The 2001 ARIA Guidelines recommended a “stepwise approach” for treating “moderate/severe persistent disease.” D.I. 156 ¶ 56; PTX 326 at S251. It recommended an intranasal glucocorticosteroid like fluticasone “as a first line treatment” and to “add” an “H₁ antihistamine” like azelastine if the symptoms were inadequately controlled. D.I. 156 ¶ 56. The 1998 Dykewicz Guidelines taught that intranasal antihistamines “are appropriate for use as a first line treatment for the symptoms of allergic rhinitis, or as part of combination therapy with nasal corticosteroids.” D.I. 156 ¶ 57; DTX 246 at 28. Right after giving this recommendation, the Dykewicz guidelines noted that “Astelin . . . is the first intranasal antihistamine preparation approved for use in the US.” D.I. 156 ¶ 57.

The 2000 Cauwenberge “consensus statement on the treatment of allergic rhinitis” taught that “[i]f that patient presents with severe symptoms or if the treatment with nasal steroids in the case of moderate disease does not have an adequate effect, a combination of nasal steroids and antihistamines (oral and/or topical [*i.e.*, nasal]) is recommended.” D.I. 156 ¶ 58; DTX 154 at 10. The 1999 Berger reference similarly taught that “[a]zelastine nasal spray can be used either in place of oral antihistamines or in combination with intranasal corticosteroids.” D.I. 156 ¶ 59; DTX 26 at 6.

Plaintiffs' own expert, Dr. Kaliner, agreed that he made a presentation before the June 2002 priority to allergists where he "told those skilled in the art in May 2002 that symptoms typical of allergic rhinitis; primarily sneezing, nasal itching and rhinorrhea; benefit most from an intranasal corticosteroid combined with an oral antihistamine to which a topical antihistamine can be added for additional symptomatic control." D.I. 156 ¶ 60; Tr. (Kaliner) 490:1-8; DTX 312 at 8. Dr. Kaliner also agreed that he taught that the ARIA guidelines "suggested the combined use of an oral antihistamine with an intranasal corticosteroid" and "residual symptoms can be treated by adding the topical antihistamine azelastine to the regimen." D.I. 156 ¶ 60.

2. The prior art explains the clinical practice of combining fluticasone and azelastine to treat AR.

There were at least two significant motivations to use fluticasone and azelastine together. *First*, the benefits of using fluticasone and azelastine together were known in the prior art to be attributable in part to the complementary mechanisms of action of the two drugs. AR was generally thought of as being split into two phases of symptoms: an early phase response and a late phase response. As explained in the 1999 Spector reference, "The symptoms observed in [the early phase response] are most effectively managed by an [antihistamine], whereas the effects of [the late phase response] are best managed with a corticosteroid." DTX 50 at 2; *see also* PTX 333 (Drouin 1995) at 347.

Meda's own expert, Dr. Carr, testified that it was "medical dogma" in 2002 that "antihistamines predominantly treat the early phase of allergic rhinitis more effectively than steroids" and that "steroids predominantly treat the late phase reactions more effectively than antihistamines." D.I. 156 ¶ 38; Tr. (Carr) at 573:2-22. Corticosteroids like fluticasone, together with antihistamines like azelastine, were therefore the treatment of choice for treating AR. DTX 85 (Kusters 2002), at 98 ("Histamine H₁-receptor antagonists together with topical steroids are the

treatment of choice in allergic rhinitis.”); *see also* DTX 12 at 2 ll. 25-27 (Cramer) (“The present inventor has found that by combining a nasal corticosteroid with a leukotriene inhibiting antihistamine, improved intranasal compositions result, providing improved relief of symptoms generally associated with either seasonal or perennial allergic rhinoconjunctivitis.”).

The clinical benefit of capitalizing on the complementary mechanisms of actions of steroids and antihistamines was reported in the literature. Several prior art studies involving combinations of oral antihistamines with intranasal steroids showed benefits to a combination over either monotherapy with respect to at least itching and sneezing, two hallmark symptoms of allergic rhinitis. D.I. 156 ¶¶ 67-73.

Complementary mechanisms of action are a well known and “clear motivation to combine” two drugs. *Allergan*, 726 F.3d at 1292-93 (the prior art “showed that alpha₂-agonists and beta blockers are complementary and should be used together”). For instance, the Federal Circuit held in one recent case that it was “well-known in the art that two drugs having different mechanisms for attacking diabetes may be more effective than one, and so drugs were often tested in combination therapy after demonstrating effectiveness in monotherapy.” *Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd.*, 719 F.3d 1346, 1351 (Fed. Cir. 2013). The district court there found *prima facie* obviousness because it was at least “obvious to try” the particular combination of insulin secretagogue and insulin sensitizer at issue, and the parties did not even dispute on appeal that that was sufficient for a finding of *prima facie* obviousness. *Id.* Likewise, here “it was obvious to try” a combination of azelastine and fluticasone because it was “well-known in the art that [antihistamines and corticosteroids] having different mechanisms for [relieving allergic rhinitis] may be more effective than one, and so [antihistamines and corticosteroids] were often tested in combination therapy after demonstrating effectiveness in monotherapy.” *Id.*

Second, the fact that antihistamines worked faster than steroids was another reason physicians used them together. The POSA knew that steroids like fluticasone had delayed onsets of action, taking days to reach full effect. D.I. 156 ¶ 37; DTX 33, Flonase® Label at 2 (“A decrease in nasal symptoms has been noted in some patients 12 hours after initial treatment with FLONASE Nasal Spray. Maximum benefit may not be reached for several days.”). Antihistamines—and especially topical antihistamines—were known to have much faster onsets of action. D.I. 156 ¶ 38; DTX 22, Astelin® label (relief within three hours); PTX 326 at S230 (“Topical H1-antihistamines have a rapid onset of action (less than 15 minutes) at low drug dosage”); PTX 99, Galant & Wilkinson 2001 at 456 (relief within an hour); DTX 43, McNeely 1998 at 92 (“Symptom improvements are evident as early as 30 minutes after intranasal administration of azelastine . . . and are apparent for up to 12 hours”); *id.* at 102 (mean onset of 17 minutes.); DTX 99, Greiff 1997 at 442 (antihistamine response within an hour). Meda’s expert agreed that “antihistamines generally have a faster onset of action than steroids.” Tr. (Carr) at 573:23–574:1. Physicians thus used antihistamines with steroids so that patients could get relief quickly from the antihistamine, and later from the more potent steroids. Tr. (Wedner) at 78:4-9, 19-23; Tr. (Schleimer) at 182:12-13.

C. It was obvious to make the clinical practice of combining fluticasone and azelastine more convenient for patients by co-formulating these drugs in a single nasal spray.

1. Other pharmaceutical companies expressly disclosed co-formulating fluticasone and azelastine in a single nasal spray.

Fixed-dose combination nasal sprays—i.e., putting two drugs in one bottle rather than having to separately administer them with two prescriptions—were also expressly taught by the Cramer and Segal references. DTX 12; DTX 21. Cramer disclosed a pharmaceutical composition for nasal administration comprising a glucocorticoid and an antihistamine. It disclosed fluticasone

as one among six suitable nasal steroids and azelastine as one of three acceptable leukotriene inhibiting antihistamines. DTX 12; D.I. 156 ¶¶ 30-31. The Segal reference similarly disclosed a fixed-dose combination of a “topical anti-inflammatory agent” and an antihistamine. Segal lists fluticasone among its preferred anti-inflammatory steroids, and lists azelastine among its preferred antihistamines. DTX 21; D.I. 156 ¶ 32.

Although there were a handful of corticosteroids available on the market in 2002 and referenced in Cramer and Segal—any one of which would have been obvious to try in a combination nasal spray—fluticasone was the top corticosteroid to combine with azelastine. The 1999 Stellato reference and the 1998 Johnson reference taught that fluticasone was the most potent of the corticosteroids. D.I. 156 ¶ 45; PTX 325; DTX 39. Meda’s own expert testified that “there is no controversy” that its commercial embodiment, Flonase®, “was the leading nasal steroid.” D.I. 156 ¶ 46; Tr. (Kaliner) at 495:6-9.

Azelastine was also the best choice for an intranasal antihistamine. Topical antihistamines in general were known to have anti-inflammatory effects unknown to oral antihistamines, and to work faster and more effectively than oral antihistamines because of their local delivery to the nose. D.I. 156 ¶¶ 39-40. Meda’s expert agreed that “the intranasal delivery of azelastine increases global drug concentration and limits systemic distribution.” D.I. 156 ¶ 40; Tr. (Kaliner) at 496:5-11. And, as of 2002, there were only two antihistamines available in intranasal form—azelastine and levocabastine. D.I. 156 ¶ 47; D.I. 155 ¶ 29. The 2001 Falser reference taught that azelastine was statistically superior in efficacy as judged by both physicians and patients. D.I. 156 ¶ 48; PTX 66. The clinicians at trial testified that levocabastine was very rarely used to treat patients. D.I. 156 ¶ 47.

Dennis Fuge, Meda's Vice President of Technical Operations who was one of the first Meda representatives to visit Cipla to discuss a license for the patents-in-suit, confirmed that the use of azelastine and fluticasone in particular was obvious:

Q. You stated that it is your interpretation of why [Cipla] selected those two, meaning Azelastine and Fluticasone, because it was obvious. What did you mean by that?

A. My interpretation was that Fluticasone was the then best selling steroid, and Azelastine was the best antihistamine.

D.I. 156 ¶ 21; Tr. (Fuge) at 134:3-8, 135:2-10, 138:19-25. He testified further that Meda (then called MedPointe) had independently "selected [azelastine and fluticasone] as the best two compounds to utilize." D.I. 156 ¶ 21; Tr. (Fuge) at 139:7-17. This testimony, alone, establishes a simultaneous invention, which is supportive of obviousness. *Ecolochem, Inc. v. S. Cal. Edison Co.*, 227 F.3d 1361, 1379 (Fed. Cir. 2000).

2. There were several motivations to co-formulate fluticasone and azelastine in a single nasal spray.

There was a clear reason why pharmaceutical companies disclosed the co-formulation of fluticasone and azelastine in a single nasal spray: a POSA would have expected such a product to be *more convenient* for patients, which would then lead to *improved patient compliance* and better treatment outcomes.

The above art unambiguously explains the benefits of using fluticasone and azelastine together for the treatment of AR. But co-administration of two drugs in two separate spray bottles required patients to take many sprays per day, resulting in a relatively large volume of liquid in the nose. Segal explained that "[t]he volume of liquid that can effectively be applied nasally is limited by the surface area of the nostril and the bioadhesiveness of the liquid," and further that "[p]atient compliance may be compromised by the inconvenience of applying multiple spray

products or nose drops. Patients complain when excess spray drains into their throats where it can be tasted, resulting in a need for flavor masking of bitter medicaments.” DTX 21 at 1-2.

The solution to these problems was well known and disclosed by 2002: a fixed-dose combination product would decrease the number of sprays per day, decrease the volume per spray, and thus increase patient compliance. In fact, the 1986 Shenfield reference taught that “[t]he most frequently quoted reason for using fixed combination products is improved compliance.” DTX 48 at 16; *see also* DTX 246 at 512 (Dykeiwicz guidelines) (“Compliance is enhanced when: (1) a fewer number of daily doses is required”); DTX 50 at 1 (Spector) (“To ensure patient compliance, the drug should only have to be taken when the patient has symptoms with a dosing schedule of once or twice daily.”). Plaintiffs’ own expert conceded (through deposition testimony when impeached) that “a person of skill in the art” as of 2002 would have thought that they “would have improved compliance” by putting the two separate drugs “in one spray bottle.” D.I. 156 ¶ 2; Tr. (Kaliner) at 508:9-14.

The evidence also shows that fluticasone had previously been used in a fixed-dose combination product to improve patient compliance when two drugs are recommended. Fluticasone was combined with the β_2 -agonist salmeterol for the treatment of asthma in a drug product called Advair®. D.I. 156 ¶¶ 65-66; DTX 77 at 6. The 2002 Stoloff reference taught that the “complementary mechanisms of action” of fluticasone and the salmeterol achieved “a superior level of asthma control” and that “the availability of this combination in a single product will likely simplify and increase patient adherence to an asthma treatment plan.” DTX 77 at 1, 13.

Combining fluticasone with the β_2 -agonist salmeterol was also thought to improve compliance because of the complementary onsets of action of the two drugs, just as here. The 2002 Stoloff reference taught, “This early onset of effect [of the fixed dose combination with

salmeterol] would diminish the risk of suboptimal adherence to a treatment plan and would ensure that patients taking a long-acting β_2 -agonist always would use an antiinflammatory corticosteroid concurrently and would not selectively discontinue an inhaled corticosteroid [which takes longer to take effect than the β_2 -agonist].” DTX 77 at 11. The Stoloff reference, in view of the similarly different onsets of action for antihistamines and steroids, also expresses a “clear motivation to combine” fluticasone and azelastine. *Allergan*, 726 F.3d at 1293.

D. Federal Circuit authorities compel a finding that it was obvious to co-formulate fluticasone and azelastine into a single nasal spray to treat AR.

The Federal Circuit found claims to a fixed-dose combination drug product invalid as obvious under similar circumstances in *Allergan v. Sandoz*. The key prior art reference in *Allergan* taught “fixed combinations of α_2 -agonists and beta-blockers for the treatment of glaucoma,” a disease of the eye that can cause blindness. 726 F.3d at 1289. The prior art “explain[ed] that a significant number of glaucoma patients require *more than one drug* to achieve therapeutic reduction of intraocular pressure,” and “[taught] that then-existing treatment regimens requiring administration of two or more medications in separate, spaced dosages, several times a day often resulted in poor patient compliance, particularly in elderly patients.” 726 F.3d at 1289-90 (emphasis added). The Federal Circuit held that this provided a “clear motivation to combine.” *Id.* at 1293. In fact, the Federal Circuit found that, because “it was common at the time of the invention to provide brimonidine and timolol [*i.e.*, the later claimed drugs] to a patient in serial fashion and [a prior art reference] taught that by combining drugs in a fixed-combination formulation, patient compliance could be increased,” there was “clear error in the district court’s finding that there was no motivation to develop a fixed combination brimonide/timolol product.” *Id.* at 1292.

Indeed, the Federal Circuit found the claims obvious even though the prior art reference that suggested combination of the relevant categories of drugs did not list the particular alpha₂-agonist claimed in the invention. *Id.* Here, by contrast, there were at least two prior art references teaching a fixed combination and calling out both azelastine and fluticasone for use in the combination. That alone is also sufficient to find a clear motivation to combine. Because “it was common at the time of the invention to provide [fluticasone] and [azelastine] to a patient in serial fashion and [prior art references] taught that by combining drugs in a fixed-combination formulation, patient compliance could be increased,” it would be “clear error” to find “that there was no motivation to develop a fixed combination [fluticasone]/[azelastine] product.” *Id.*

Similarly, in *Richardson-Vicks, Inc. v. Upjohn Co.*, the Federal Circuit noted that “[t]he only difference between the prescribed combination [of ibuprofen and pseudoephedrine] and the patented invention is that the prescription was not contained in a single tablet.” 122 F.3d 1476, 1483-84 (Fed. Cir. 1997). The court noted that “[s]uch a combination was clearly suggested by the prior art” where similar medications had been combined into single tablets. *Id.* at 1484. Here, similarly, “[t]he only difference between the prescribed combination [of azelastine and fluticasone] and the patented invention is that the prescription was not contained in a single [spray].” *Id.* at 1483-84. But “[s]uch a combination was clearly suggested by the prior art,” which had combined fluticasone with another ingredient in a single formulation for the treatment of a related condition. *Id.* at 1484; D.I. 156 ¶¶ 65-66. The law compels a finding of motivation here.

E. Plaintiffs’ contrary arguments misstate the facts and otherwise fail as a matter of law.

Plaintiffs’ contrary arguments fail on the present record under controlling law.

First, Plaintiffs argue that by 2002 there were at least 49 “options” for monotherapy treatment of AR; that there was a general preference for oral AR treatments over nasal AR

treatments; and that there were certain undesirable aspects of fluticasone and azelastine such as unpleasant tastes, smells, and other side effects. D.I. 155 ¶¶ 20-21, 27-28, 30. The point is apparently that a POSA may not have looked to fluticasone and azelastine as the *most obvious* drugs to combine.

That argument fails as a matter of law. Apotex does not need to prove that a combination of azelastine and fluticasone was the *only* obvious choice, or even that it was the best or most obvious choice. The mere existence of alternatives does not render one particular combination non-obvious. As the Federal Circuit held, “‘mere disclosure of more than one alternative’ does not amount to teaching away from one of the alternatives where the [prior art] does not ‘criticize, discredit, or otherwise discourage the solution claimed.’” *SightSound Techs.*, 809 F.3d at 1320 (citation omitted). In *SightSound* the patentee argued that it would not have been obvious to use a “hard disk” to store digital signals because although the prior art disclosed the availability of hard disks for this purpose, the relevant available consumer devices used only the more widely available floppy disks. *Id.* at 1319-20. The Federal Circuit rejected the argument that the commercial prominence of floppy disks criticized, discredited, or otherwise discouraged the use of otherwise obvious hard disks. In short, as long as the claimed combination is among obvious choices, the patent is invalid. *See In re Mouttet*, 686 F.3d 1322, 1334 (Fed. Cir. 2012) (“This court has further explained that just because better alternatives exist in the prior art does not mean that an inferior combination is inapt for obviousness purposes.”)

Here, similarly, even if other medications like oral AR treatments were more widely used, that in no way criticizes, discredits, or discourages use of the most effective intranasal steroid and the most effective intranasal antihistamine. The fact that the commercially available Flonase® and Astelin® products may have had bad tastes or other side effects is likewise irrelevant. That would

not have discouraged the development of a combination product for those patients whose allergic rhinitis improved when they took those drugs individually or as co-prescribed in the prior art—and in fact it did not discourage at least three simultaneous inventors.

Apotex must simply show that it was at least *obvious to try* a combination of fluticasone and azelastine. As in *Caraco Pharmaceutical Laboratories*, here “it was obvious to try” such a combination because it was “well-known in the art that [antihistamines and corticosteroids] having different mechanisms for [relieving allergic rhinitis] may be more effective than one, and so [antihistamines and corticosteroids] were often tested in combination therapy after demonstrating effectiveness in monotherapy.” 719 F.3d at 1351; *see also KSR*, 550 U.S. at 421 (even if “a combination was” merely “obvious to try,” that “might show that it was obvious under § 103”).

Plaintiffs’ argument also fails because they misstate the factual record. Intranasal steroids and antihistamines were undisputedly the leading available therapies. *See, e.g.*, DTX 85 (Kusters 2002), at 98 (“Histamine H₁-receptor antagonists together with topical steroids are the treatment of choice in allergic rhinitis.”). Although Dr. Kaliner stated that fluticasone was not his preferred nasal steroid because of its smell, he agreed that he was *not* “suggesting that a skilled artisan in 2002 wouldn’t have looked at fluticasone as an intranasal steroid to treat allergic rhinitis.” Tr. (Kaliner) at 494:10-15. Nor could he credibly have said that: at the time of the invention fluticasone was a billion-dollar drug, whereas Dr. Kaliner’s preferred nasal steroid Nasacort (triamcinolone) sold only half as well. Tr. (Kaliner) at 494:19–494:6; PTX 98. Dr. Kaliner succinctly testified that “Flonase was the leading nasal steroid. I think there is no controversy about that.” Tr. (Kaliner) at 494:7-8. It defies reason to suggest that fluticasone was not an obvious choice for a combination product given that it was the leading nasal steroid, and nasal steroids were understood to be the most effective treatment for allergic rhinitis. DTX 246, Dykewicz 1998

at 506 (“Nasally inhaled corticosteroids are the most effective medication class in controlling symptoms of allergic rhinitis.”).

Similarly, that some patients preferred oral dosage forms would not have discouraged the selection of azelastine in a combination product that already included the nasal spray fluticasone. Indeed, azelastine was the *most* logical antihistamine for a combination nasal spray. Plaintiffs admit there were only two intranasal antihistamines available. D.I. 155 ¶ 29. Of these, azelastine was known to be more effective and it was far more commonly used than levocabastine. D.I. 156 ¶¶ 47-48. That is why Meda’s own employee testified that Cipla’s motive to co-formulate azelastine and fluticasone was “obvious” because “Fluticasone was the then best selling steroid, and Azelastine was the best antihistamine.” D.I. 156 ¶ 21.

Second, Plaintiffs argue that physicians desired flexibility in their prescribing options, and “[a] fixed-dose combination is inconsistent with these flexible principles” because “it was well-known in the art that a fixed-dose combination reduces flexibility.” D.I. 155 ¶¶ 32-44, 45, 47-48. Plaintiffs again misrepresent the facts. A doctor and patient always have the option to use a fixed-dose combination product when that is called for, or to prescribe drugs separately when that is called for. In fact, Dr. Wedner testified that a fixed-dose combination *increases* flexibility, because it gives patients the convenience of a single spray if and when their treatment calls for the particular amounts of azelastine and fluticasone in the combination product. D.I. 156 ¶ 61.

That indisputable fact applies across most of medicine, and it is precisely why the Federal Circuit has already rejected just such an argument about flexibility. In *Richardson-Vicks*, the patentee argued that “[a]lthough both [testifying physicians] prescribed ibuprofen and pseudoephedrine together, neither had combined them into a single unit dosage” as claimed because “their practices require flexibility in treating patients, which requires them to prescribe

the two drugs in varying ratios.” 122 F.3d at 1482. The Federal Circuit rejected this argument, holding: “The fact that doctors wanted greater flexibility in prescribing this combination does not teach away from the claimed combination. It merely recognizes that doctors must treat a variety of differently situated patients including children and adults.” *Id.* at 1484. It thus found combining ibuprofen and pseudoephedrine into a fixed-dose combination obvious despite a flexibility argument identical to the ones Plaintiffs make here. *Id.*

Third, Plaintiffs argue in a similar vein that a POSA would not have known how to dose a co-formulation, and thus would not have made the combination. The argument rests on the notion that the maximum recommended dosing of Astelin® (*two* sprays twice a day) was twice as much as the maximum recommended dosing for Flonase® (*one* spray twice a day). D.I. 155 ¶ 78. This argument also fails as a matter of both fact and law. On the facts, Plaintiffs’ dosing argument mischaracterizes the maximum recommended dosing of Astelin® as the *necessary* dose to treat AR. That is wrong. A POSA would have known that azelastine could be dosed exactly as fluticasone was dosed in Flonase®—one spray twice a day—and still be effective. That dose of Astelin® was the well-known dose in Europe. D.I. 156 ¶ 64; DTX 33 at 5; PTX 326 at S226. It was also how patients in the U.S. dosed Astelin® before 2002 when they did not need the maximum recommended daily dose. Tr. (Wedner) at 78:24–79:12. Therefore, a skilled artisan would have known that a fixed-dose combination product would meet the minimal efficacy requirements of the asserted claims if dosed just like Flonase® at one spray twice a day. D.I. 156 ¶ 64; *see also* DDX 4.49.

Like Plaintiffs’ arguments about other available treatment options and allegedly reduced flexibility, the Federal Circuit also previously rejected the argument that different dosing regimens of two prior art products can save an otherwise obvious patent that combines them in a fixed-dose

combination. In *Allergan*, the district court had rejected an obviousness challenge in part because it “found that certain aspects of the prior art taught away from the claimed invention including the potential side effects, the different dosing regimens in commercially available forms of brimonidine and timolol, and the disparate half-lives of brimonidine and timolol.” 726 F.3d at 1293. The Federal Circuit “accept[ed] the district court’s factual findings on these matters,” but it refused to “conclude that they render the invention nonobvious” in light of the “clear motivation to combine” expressed by the prior art teaching that compliance would be increased. *Id.* Thus, not only does Plaintiffs’ dosing argument fail, so does their argument as to side effects. *See* D.I. 155 ¶ 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.”).

Fourth, although Plaintiffs did not make a teaching away argument at trial, they have pointed to a handful of prior art studies that they say showed no benefit to a combination intranasal steroid and oral antihistamine. D.I. 155 ¶¶ 54-64. These references are legally irrelevant because they do not teach away from the claimed invention. That is, none of the seven studies actually criticized, discredited, or discouraged either azelastine or fluticasone. D.I. 156 ¶ 69; *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 739 (Fed. Cir. 2013) (“A reference does not teach away if it does not ‘criticize, discredit, or otherwise discourage’ investigation into the invention claimed.”) (citation and alteration omitted). None of the studies involved azelastine at all—and hence cannot be taken to discourage the use of azelastine. Only two of the studies involved fluticasone, and *these* did not criticize, discredit, or discourage the use of fluticasone in combination. D.I. 155 ¶ 55; D.I. 156 ¶ 46.

Regardless, as already explained (*see supra*, p. 9), five of the seven prior art studies of this kind *did* show a benefit, and that was the enduring conclusion of these studies. By 2002, and after

all of these studies were published, the practice guidelines were *still* recommending this combination, and every doctor who testified in this case was *still* prescribing the combination of steroids and antihistamines. D.I. 156 ¶¶ 22-28, 56. Indeed, the lead author of one of the studies on which Plaintiffs rely to argue the prior art “discouraged” antihistamine/steroid combinations conducted another study of an antihistamine/steroid combination *eight years later* and concluded that “at least 50% of patients will *need* to take both types of medication in combination to control symptoms adequately.” DTX 107 at 1 (emphasis added). Thus, the prior art *as a whole* taught the benefits of the claimed combination. *In re Kahn*, 441 F.3d at 985 (patent claim is invalid for obviousness if the differences between the subject matter of the claim and the prior art are “such that the subject matter *as a whole* would have been obvious at the time the invention was made to a person having ordinary skill in the pertinent art.”) (emphasis added) (citing *Graham*, 383 U.S. at 13-14).

In summary, just as in *Allergan* and *Richardson-Vicks*, it is indisputable that there was a clear motivation to combine azelastine and fluticasone into a single nasal spray. The only difference between the prior art and the claimed invention is the use of these two drugs in a single spray rather than serially, just as in *Allergan*; further, the prior art taught that a fixed-dose combination would, at minimum, increase compliance, just as it also did in *Allergan*. And just as in *Richardson-Vicks*, where it was obvious to combine two drugs into a single tablet, dosing differences, flexibility concerns, and side effect concerns cannot overcome the clear suggestion by the prior art to combine. The motivation here was even stronger than in either *Allergan* or *Richardson-Vicks* because the prior art explicitly *disclosed* combining these two active ingredients into a single spray. Meda cannot credibly argue that it was inventive to think of combining fluticasone and azelastine in June 2002.

III. IT WAS OBVIOUS HOW TO FORMULATE A NASAL SPRAY THAT COMBINES FLUTICASONE AND AZELASTINE.

Faced with the several prior art motivations to combine fluticasone and azelastine for the treatment of AR, the physician practice of doing so, and two prior art references that expressly taught to put those drugs together in one nasal spray, Plaintiffs offered contrived arguments that the particular claimed excipients somehow can save their patents from an obviousness judgment. Try as they might to make routine formulation activities seem inventive, the claimed ingredients are all known excipients used for their known functions—as amply disclosed in the prior art. That evidence establishes that a POSA had every reasonable expectation of success in formulating the claimed combination product.

A. Person of ordinary skill in the art.

The parties offer different definitions of a person of ordinary skill in the art from the perspective of formulating the claimed pharmaceutical compositions. Dr. Donovan, Apotex’s formulation expert, opined that the relevant person of ordinary skill in the art would have been a pharmaceutical formulator with at least a bachelor’s degree in chemistry, biology, chemical engineering or pharmaceutical science and 3-5 years of experience in formulation development of nasal dosage forms, although the formulator could have more advanced degrees with fewer years of experience; and would have had familiarity with pharmaceutical excipients and their uses. Tr. (Donovan) at 237:6-24. Dr. Smyth, Meda’s formulation expert, opined that a POSA formulator would not necessarily have experience with a particular dosage form. Tr. (Smyth) at 605:16-19. Regardless of which definition the Court adopts, the claimed formulations are obvious.

B. The prior art disclosed a finite number of obvious possible combination formulations.

“When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue

the known options within his or her technical grasp.” *KSR*, 550 U.S. at 421. Here, the record shows that in 2002 there was a “finite number of identified, predictable solutions” for co-formulating azelastine and fluticasone in a single pharmaceutical formulation. The prior art disclosed how to formulate azelastine in the Astelin[®] product and fluticasone in the Flonase[®] product. In addition to standard references providing textbook knowledge on pharmaceutical formulation, an ordinarily skilled formulator looking only at these two labels and to Astelin[®]’s corresponding formulation patent would have derived those predictable solutions for putting the two active ingredients together in one nasal spray formulation. D.I. 156 ¶ 75; DTX 33 (Flonase[®] Label); DTX 22 (Astelin[®] Label); DTX 16 (Astelin[®] formulation patent); *KSR*, 550 U.S. at 421. Those solutions match up with the claims, and the claims are thus invalid as obvious.

1. Flonase[®] label

The Flonase[®] label disclosed before June 2002 a dose of 50 mcg (micrograms) per 100 mL (milliliter) spray in an aqueous suspension, which can also be expressed as 0.05 mg (milligrams) per spray, 0.5 mg/mL, or 0.05% concentration weight over volume and weight over weight. D.I. 156 ¶ 76. It also disclosed that the fluticasone particles are “microfine,” which all agree means less than 10 µm (microns) in size. D.I. 156 ¶ 77; D.I. 155 ¶ 97. The Flonase[®] label further disclosed water as the aqueous vehicle, which was common. D.I. 156 ¶ 78.

The Flonase[®] label also disclosed various inactive ingredients. It listed benzalkonium chloride in a weight/weight concentration of 0.02% and phenylethyl alcohol in a weight/weight concentration of 0.25%. These were known as antimicrobial preservatives and known to be synergistic in combination. D.I. 156 ¶ 79. The Flonase[®] label disclosed the use of the surfactant polysorbate 80, which was known to be used in suspensions to help the suspended particles properly disperse in the formulation. D.I. 156 ¶ 80. The Flonase[®] label further disclosed the use of thickening agents called microcrystalline cellulose (“MCC”) and carboxymethyl cellulose

sodium (“CMC”) in combination, commonly referred to as Avicel®. This was known in the prior art to slow down the settling of suspended particles and to thicken the formulation so it remains longer on the nasal mucosa after application. D.I. 156 ¶ 81.

The Flonase® label also disclosed the use of dextrose as a tonicity adjuster. It was routine for a formulator to determine the final amount of tonicity adjuster necessary for isotonicity, which the prior art disclosed as the ideal tonicity. D.I. 156 ¶¶ 82-83. Finally, the Flonase® label disclosed a pH of 5 to 7. Formulators routinely determined appropriate pH levels for formulations and it was routine to buffer the system to that pH if necessary. D.I. 156 ¶ 84.

2. Astelin® label and formulation patent

As for the Astelin® label, it disclosed an aqueous solution of 0.1% concentration of azelastine hydrochloride weight/volume, which Plaintiffs agree is substantively identical to 0.1% concentration weight/weight, and that 137 mcg of azelastine hydrochloride is delivered per spray. D.I. 156 ¶ 85; DTX 22. Because the formulation is an aqueous solution, it does not have a particle size. D.I. 156 ¶ 86. As with Flonase®, water is the vehicle. D.I. 156 ¶ 87.

The Astelin® label also disclosed the use of the known antimicrobial preservatives benzalkonium chloride (0.0125%) and EDTA disodium. D.I. 156 ¶ 88. The formulation patent for the Astelin® product, U.S. Patent No. 5,164,194, disclosed a concentration of preservatives such as EDTA disodium of 0.002 to 0.05 percent. *Id.*; DTX 16 at col. 2, ll. 46-68. The Astelin® label disclosed the use of the thickening agent hydroxypropylmethylcellulose (“HPMC”), which, like the thickening agents in Flonase® was used to help the formulation remain longer on the nasal mucosa after application. D.I. 156 ¶ 90. The Astelin® formulation patent disclosed other thickening agents suitable for use with azelastine, such as CMC. *Id.*; DTX 16 at col. 5, ll. 51-66.

The Astelin® label disclosed the use of sodium chloride (NaCl) as its tonicity adjuster, and the Astelin® formulation patent disclosed, in addition to NaCl, other tonicity adjusters suitable for

an azelastine hydrochloride formulation, namely saccharose, glucose, glycerine, sorbitol, and propylene glycol. D.I. 156 ¶ 91; DTX 16 at col. 4, ll. 31-35. The Astelin® label disclosed a pH between 6.5 and 7.1. D.I. 156 ¶ 92.

3. A POSA would have arrived at a finite number of obvious possible combination formulations.

An ordinarily skilled formulator would have looked first at the excipients in the Flonase® and Astelin® labels, and those disclosed as suitable in the Astelin® formulation patent, to arrive at a finite number of possible excipients for a combination fluticasone propionate and azelastine hydrochloride product. Such a formulator would have looked to the same concentrations of active ingredients, which were known to be effective for treating AR and which had been successfully formulated in those amounts. A POSA formulator would have also looked to some combination of the preservatives benzalkonium chloride, EDTA disodium, and phenylethyl alcohol, which had been used successfully in Flonase®, Astelin®, or both; would have looked to polysorbate 80, which was used in Flonase® to support the dispersability of fluticasone; would have looked to MCC/CMC or to HPMC, which had been successfully used as thickeners in Flonase® and Astelin®, respectively; and to any of the seven tonicity adjustors used in Flonase® or Astelin® or disclosed as suitable in the Astelin® patent. D.I. 156 ¶¶ 94-106. A skilled formulator would have consulted the labels, the Handbook of Pharmaceutical Excipients, or other monographs to determine known concentrations of the various excipients suitable for their purposes. *Id.* Finally, a skilled formulator would have known that nothing in the prior art suggested any incompatibilities among these excipients. *Id.*

In sum, using the prior art knowledge of the two prior formulations would have resulted in a small list of obvious possible combination formulations, as illustrated in D.I. 156 ¶ 75:

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

A POSA would have been motivated to combine these excipients as described in these possible combination formulations with a reasonable expectation of success. *KSR*, 550 U.S. at 421 (“When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp.”). Any such combination formulation would have been obvious to an ordinarily skilled formulator as of 2002.

Furthermore, Plaintiffs’ own formulator agreed that all of the active ingredients and excipients function in the invention in the same way that they do in the prior art. D.I. 156 ¶¶ 108-09. Thus, the formulation claims are obvious for this reason, too. The Supreme Court has long since held that “[t]he mere aggregation of a number of old parts or elements which, in the aggregation, perform or produce no new or different function or operation than that theretofore performed or produced by them, is not patentable invention.” *Great Atl. & Pac. Tea Co. v. Supermarket Equip. Corp.*, 340 U.S. 147, 151 (1950) (quoting *Lincoln Eng’g Co. of Illinois v.*

Stewart-Warner Corp., 303 U.S. 545, 549 (1938)). “A patent for a combination which only unites old elements with no change in their respective functions, such as is presented here, obviously withdraws what already is known into the field of its monopoly” *Id.* at 152-53. Similarly, “one skilled in the art concerned with [obtaining a certain result] would reasonably expect to achieve this goal by adding a known compatible . . . excipient . . . in the amounts taught by the[] prior art references” *Senju Pharm. Co.*, 717 F. Supp. 2d at 424. Here, each excipient disclosed in the claims functions as it did in the prior art, and was known to be compatible either with fluticasone propionate, azelastine hydrochloride, or both. “[A] court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions.” *KSR*, 550 U.S. at 417. The answer to that question here is clear: all of the excipients combine for a “predictable use” “according to their established functions.” *Id.*

C. The obvious possible combination formulations render all asserted claims obvious.

In light of the obvious combination formulations in the trial record, any difference between the asserted claims and the prior art would have been obvious to a POSA in June 2002.

1. '428 Claim 11

Claim 11 of the '428 patent is the narrowest of the claims. It relies on claim 1, which claims “[a] method for the treatment of seasonal allergic rhinitis, comprising administration of a therapeutically effective amount of nasal spray formulation comprising: from 0.001% (weight/weight) to 1% (weight/weight) of azelastine hydrochloride; from 0.0357% (weight/weight) to 1.5% (weight/weight) of fluticasone propionate; one or more preservatives; one or more thickening agents; one or more surfactants; and one or more isotonization agents.” Each limitation of Claim 1 is obvious. The prior art Flonase® and Astelin® formulations contained amounts of azelastine hydrochloride (0.1%) and fluticasone propionate (0.05%) within the claimed

ranges. “When a claim recites a limitation that captures a range of values, it is anticipated if a specific example falling within that range is disclosed in the prior art.” *In re Haase*, 542 F. App’x 962, 965 (Fed. Cir. 2013). These ranges of these drugs were also known to treat allergic rhinitis.

Additionally, both prior art Flonase® and Astelin® formulations contained preservatives, thickening agents, and isotonization agents, and the Flonase® formulation contained a surfactant. Plaintiffs’ formulation expert agreed that it was known that pharmaceutical formulations had to be free of antimicrobial activity, should have proper uniformity, and should have a proper tonicity. D.I. 155 ¶ 80. Indeed, he testified that “these are basic requirements of pharmaceutical formulations.” Tr. (Smyth) at 632:19-20.

Claim 11 narrows the range of azelastine hydrochloride to 0.1%, but this was the exact concentration in Astelin® and is thus obvious. *In re Haase*, 542 F. App’x at 965. It then claims a range of benzalkonium chloride in a concentration from 0.002% to 0.02%, MCC/CMC in a concentration from 0.65% to 3%, 0.25% phenylethyl alcohol, and 2.3% glycerin. Flonase® and Astelin® had benzalkonium chloride concentrations of 0.02% and 0.0125%, respectively, and thus fall squarely within the claimed range, which is thus obvious. *Id.* MCC/CMC is disclosed to create aqueous dispersions at 1.2% concentration, which is squarely within the 0.65% to 3% range claimed. D.I. 156 ¶ 104; DTX 62 at 12. That limitation is thus obvious. *In re Haase*, 542 F. App’x at 965. Flonase® had 0.25% phenylethyl alcohol, which is the concentration claimed and which is thus obvious. *Id.*

Finally, the prior art disclosed 2.6% glycerin to be isotonic in water. D.I. 156 ¶ 106. Dr. Donovan explained, however, that in the presence of other solutes less than 2.6% would be needed, and that it was within the ability of ordinarily skilled formulators to determine the final amounts of tonicity adjuster necessary for isotonicity. *Id.* Thus, the 2.3% concentration of glycerin, if it is

a difference from the prior art at all, is a difference that “would have been obvious at the time the invention was made to a person having ordinary skill in the pertinent art.” *In re Kahn*, 441 F.3d at 985; *see generally* DDX 5.34.

Plaintiffs make two arguments that this claim is not obvious. First, they argue that Defendants have not provided a reason why glycerin would have been chosen over the other tonicity adjustors listed in Astelin®’s formulation patent. D.I. 155 ¶ 93. Defendants need not make such a showing, however: “[M]ere disclosure of more than one alternative’ does not amount to teaching away from one of the alternatives where the reference does not ‘criticize, discredit, or otherwise discourage the solution claimed.’” *SightSound Techs.*, 809 F.3d at 1320 (citation omitted). In *Senju Pharmaceutical Co. v. Apotex Inc.*, the district court found EDTA disodium to be an obvious excipient to use even though it was “listed among eight ‘conventional ingredients’” in two prior patents. 717 F. Supp. 2d at 420. The court emphatically rejected plaintiff’s argument that EDTA was listed “among a ‘laundry list’ of excipients.” *Id.* Here, glycerin was disclosed along with only five other tonicity adjustors as suitable for a formulation including azelastine hydrochloride, and its use is thus similarly (if not more) obvious.

Moreover, the Federal Circuit has noted that where “the difference between the claimed invention and the prior art is some range or other variable within the claims[,] . . . the applicant must show that the particular range [or other variable] is *critical*, generally by showing that the claimed range [or other variable] achieves unexpected results relative to the prior art range.” *In re Woodruff*, 919 F.2d at 1578 (emphasis in original) (citations omitted). Plaintiffs have not even tried arguing that the selection of glycerin over any other tonicity adjustor was critical.

Second, they argue that “Dr. Donovan did not explain why the POSA would not select HPMC as disclosed in Astelin® but instead select the claimed MCC/CMC.” D.I. 155 ¶ 94. That

is incorrect as a matter of fact, but also irrelevant as a matter of law. Dr. Donovan *did* explain why MCC/CMC would be the more obvious choice—because it would serve the thickening function of HPMC *but also* the suspending function it served in Flonase®. D.I. 156 ¶ 102. Regardless, *either* would have been obvious to try with a reasonable expectation of success because both were known thickening agents and each had been successfully used in one of the two prior art formulations. *Senju Pharm. Co.*, 717 F. Supp. at 422-23; *KSR*, 550 U.S. at 421.

2. '428 Claim 10

Claim 10 depends on Claim 9, which depends on Claim 1. The only new limitations in these claims are that polysorbate 80 and edetate disodium are included. The claimed range for edetate disodium is 0.002% to 0.05%. The claimed range of benzalkonium chloride is slightly expanded to 0.002% to 0.05%, and the claimed range of glycerin is slightly expanded to 2.3 to 2.6%. The prior art disclosed examples within these ranges (0.0125% and 0.02% for benzalkonium chloride, 2.6% for glycerin), and thus these expanded ranges are similarly obvious to the more narrow ranges in Claim 11. *In re Haase*, 542 F. App'x at 965. Polysorbate 80 was included in Flonase® as a surfactant and it is included in the invention as a surfactant for the same purpose. Its inclusion is thus obvious. Edetate disodium was included in Astelin® as a preservative, and it serves as a preservative in the claimed invention and is thus obvious. *See generally* DDX 5.35.

Finally, the concentration range given for EDTA disodium is the exact range disclosed in Astelin®'s formulation patent (0.002% to 0.05%) for preservatives such as EDTA. D.I. 156 ¶ 88; DTX 16 at col. 2, ll. 65-68. Indeed, example 1 of that patent provides a concentration of EDTA

disodium of 0.05%.¹ Thus, the EDTA disodium concentration limitation is anticipated because “a specific example falling within that range is disclosed in the prior art.” *Haase*, 542 F. App’x at 965. Although Meda appears to be arguing that the disclosed range for EDTA specifically was higher than the range claimed in the invention here, D.I. 155 ¶ 95, they have made no showing that any such difference in range (if indeed different) was critical to their invention. *Cf. In re Woodruff*, 919 F.2d at 1578 (“In the absence of adequate evidence showing that ranges of [EDTA disodium] concentration recited in claims . . . are critical,” the claims should be “reject[ed] . . . under 35 U.S.C. § 103.”).

Plaintiffs appear to argue that this claim is not obvious because there was no suggestion in the prior art to include all *three* preservatives used in Flonase® and Astelin® as opposed to any combination of the two as used in those products. D.I. 155 ¶ 95. That is irrelevant as a matter of law. Apotex does not need to show that the excipients Meda chose for its formulation were *more* obvious than a benzalkonium chloride/EDTA or benzalkonium chloride/phenylethyl alcohol combination would have been. “[M]ere disclosure of more than one alternative’ does not amount to teaching away from one of the alternatives where the reference does not ‘criticize, discredit, or otherwise discourage the solution claimed.’” *SightSound Techs.*, 809 F.3d at 1320 (citation omitted). The possibilities of a combination of benzalkonium chloride/EDTA, of benzalkonium chloride/phenylethyl alcohol, or of all three together create a “finite number of identified, predictable solutions” that a POSA has “good reason to pursue.” *KSR*, 550 U.S. at 421.

¹ That example discloses 5 grams of EDTA disodium, which is half the mass of azelastine (10 g) in that example. The formulation is then diluted so that the azelastine is at 0.1% concentration, which means 5 g of EDTA is half that concentration, or 0.05%. DTX 16 at col. 6, ll. 6-20.

3. '428 Claim 13

The only new limitation in Claim 13 is that it claims that 0.02 mg to 3 mg of azelastine hydrochloride and from 0.05 mg to 0.15 mg of fluticasone propionate is released per individual actuation of the nasal spray product. Astelin® contained 0.137 mg of azelastine hydrochloride per spray and is squarely within the claimed range. Flonase® released 0.05 mg of fluticasone per spray, within the claimed range. These are therefore obvious. *In re Haase*, 542 F. App'x at 965; *see generally* DDX 5.36.

4. '428 Claim 15

The only new limitation in Claim 15 is that it claims a pH of 4.5 to about 6.5. Plaintiffs argue that Defendants have given no reason why a 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.” D.I. 155 ¶ 96. But Apotex need not make such a showing. Because there are no pH buffers required in the asserted claims, the pH limitation is merely an inherent property of the composition, which is not patentable. When a “claimed limitation [is] an ‘inherent property’ of a formulation that ‘adds nothing of patentable consequence,’” it is “inherently disclosed by the prior art formulation.” *PAR Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1195 (Fed. Cir. 2014) (quoting *In re Kao*, 639 F.3d 1057, 1070 (Fed. Cir. 2011)). If a claim limitation is “the natural result of the combination of elements explicitly disclosed by the prior art,” then it is obvious. *Id.* at 1196; *see generally* DDX 5.37.

Regardless, the prior art taught that a pH range of 4 to 8 was acceptable. Thus, for this narrower range in the claim to be a patentable difference, Plaintiffs must have adduced evidence at trial that this narrower range is critical to their invention. They have not done so. *In re Woodruff*, 919 F.2d at 1578 (“[C]ases have consistently held that in such a situation, the applicant must show

that the particular range is *critical*, generally by showing that the claimed range achieves unexpected results relative to the prior art range.”).

Additionally, Claim 14, on which Claim 15 depends, claims a method for “minimizing symptoms of seasonal allergic rhinitis.” This limitation is equally obvious over the prior claims claiming a method for “treating” allergic rhinitis.

5. '428 Claim 16

The only new limitation of Claim 16 is that the formulation is an aqueous suspension. Flonase® is an aqueous suspension because fluticasone propionate remains suspended, as it would remain in any combination formulation. This claim is thus obvious over Flonase® and in any event is merely “the natural result of the combination of elements explicitly disclosed by the prior art.” *PAR Pharm.*, 773 F.3d at 1196; *see generally* DDX 5.38.

6. '428 Claim 29

Claim 29 contains no new limitations, except that Claim 28 on which Claim 29 depends claims a weight/volume range of fluticasone propionate from about 50 µg/mL to about 5 mg/mL. Flonase® contains 0.5 mg/mL of fluticasone propionate, which is squarely within the claimed range. The claimed range is thus obvious. *In re Haase*, 542 F. App'x at 965; *see generally* DDX 5.42.

7. '428 Claims 23, 24, 26, and 30

Claims 23, 24, 26, and 30 contain no new limitations and are thus obvious for the reasons discussed above. *See* DDX 5.39-43.

8. '620 Claim 43

Claim 43 of the '620 patent contains no new limitations and is thus obvious. Claim 24 on which Claim 43 depends claims a dosage form that is a “nasal spray.” Both Astelin® and Flonase® were nasal sprays and thus this limitation is obvious. *See* DDX 5.45.

9. '620 Claim 44

Claim 44 of the '620 patent contains no new limitation and is thus obvious, except that Claim 25 on which it depends claims a “pharmaceutically acceptable carrier.” Both Flonase® and Astelin® were pharmaceutically acceptable carriers, and nasal sprays were known to be such carriers. This claim is also obvious. *See* DDX 5.46.

10. '620 Claim 4

Claim 4 of the '620 patent claims no new limitation except for a particle size of less than 10 µm. Because azelastine dissolves in the formulation, only fluticasone propionate has a particle size. Plaintiffs concede that the fluticasone propionate in Flonase® is under 10 µm, and thus it is obvious to include in a combination formulation. *See* DDX 5.47.

11. '620 Claim 29 and 42

Claims 29 and 42 of the '620 patent contain no new limitations and are thus obvious for the reasons stated above. *See* DDX 5.44, 5.48.

D. Plaintiffs' theories about potential incompatibilities would not have deterred a POSA from formulating the claimed combination product.

Plaintiffs nevertheless argue that a POSA would have had no motivation to try combining the claimed excipients with a reasonable expectation of success because of three *potential* incompatibilities—none of which finds support in any of the prior art. First, Plaintiffs argue that “[n]o one knew whether the separate active ingredients, azelastine and fluticasone, would negatively interact in a fixed-dose formulation.” D.I. 155 ¶ 76. Second, Plaintiffs say a “POSA would have also been aware of potential excipient interactions, which would influence the POSA’s choices,” and suggest as an example that “a potential incompatibility existed between azelastine in Astelin® and [CMC] in Flonase®.” *Id.* ¶ 77. Finally, they argue that “[a] pharmaceutically acceptable nasal spray formulation must meet certain interrelated formulation parameters” and that

“modifications to each parameter cannot be made in isolation from the other parameters, because a change to one parameter would affect others.” *Id.* ¶¶ 80-81.

All of these arguments fail as a matter of law. The mere existence of general unpredictability is insufficient for a finding of nonobviousness. In *Allergan v. Sandoz*, the district court rejected an obviousness defense based in part “on general statements regarding the unpredictability associated with developing drug formulations” and on specific challenges in the plaintiff’s internal development program. *Allergan*, 726 F.3d at 1292. The Federal Circuit agreed “that formulation science carries with it a degree of unpredictability,” but held that “obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success.” *Id.* (quoting *Pfizer*, 480 F.3d at 1364). Thus, the Federal Circuit reversed the district court’s “finding that there was no reasonable expectation of success in view of the general unpredictability of the formulation arts and particularized, yet irrelevant, difficulties associated with the development of [the drug product].” *Id.* at 1292-93.

All three of Plaintiffs’ arguments fail under this Federal Circuit holding. The notion that no one knew whether there would be incompatibilities when combining azelastine with fluticasone or azelastine with CMC is at most “general unpredictability.” As already explained, the POSA had “good reason” to use these known excipients for their known purposes, and nothing in the art suggested they would create incompatibilities. To the contrary, Cramer and Segal taught to use them together. DTX 12; DTX 21. And Meda’s last claim—that its formulation is nonobvious “because a change to one parameter” when making a formulation can affect the others—is nothing but a statement of the general “degree of unpredictability” in the “formulation science” recognized by the Federal Circuit but rejected as a basis for finding nonobviousness.

Even if these potential incompatibilities were legally relevant (they are not), Meda is also wrong on the facts. The only reference Meda cites for the argument that fluticasone might interact with another active ingredient explained that this interaction was a *benefit* to the combination. D.I. 156 ¶ 113. The only reference Meda cites for the argument that azelastine might be incompatible with CMC is a general reference that said CMC might be incompatible with cations, without mentioning azelastine. Yet Meda ignored Astelin®'s formulation patent that *specifically* mentioned CMC as compatible in an azelastine formulation. D.I. 156 ¶ 112. In fact, subsequent to the prior art reference Meda invokes regarding CMC, but before it had any knowledge of the patents-in-suit, Meda itself submitted a patent application again suggesting using CMC together with a formulation combining azelastine hydrochloride and a steroid, including fluticasone. *Id.*

The only other reason Meda argues a POSA would not have had a reasonable expectation of success is because “azelastine was known to be a *sparingly soluble*,” “fluticasone was known to be a practically insoluble compound,” and that, “[g]iven 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.” D.I. 155 ¶¶ 69, 72 (emphasis in original). However, the testimony from Plaintiffs’ own expert, Dr. Smyth, was that “[i]t was known in 2002 that azelastine dissolved to some extent in water,” “[i]t was known in 2002 that fluticasone did not dissolve in water,” and thus a person of ordinary skill in 2002 would anticipate that azelastine would dissolve in water while fluticasone would not. D.I. 156 ¶ 117; Tr. (Smyth) at 668:10–669:20. That is exactly what happens in Dymista®, the commercial embodiment of the claims. D.I. 156 ¶ 117; Tr. (Smyth) at 670:1-6.

Thus, fluticasone and azelastine behave in the commercial embodiment of the claims exactly as they would have been expected to behave by a POSA. The claimed invention is nothing more than an “aggregation of a number of old parts or elements which, in the aggregation, perform or produce no new or different function or operation than that theretofore performed or produced by them.” *Great Atl. & Pac. Tea Co.*, 340 U.S. at 151 (citation omitted). Where prior art elements have “expected traits” that the patentee merely “ha[s] to verify through routine testing,” the invention is obvious. *Pfizer*, 480 F.3d at 1367.

Indeed, nothing in the art suggested any problem combining two active ingredients of different solubilities. D.I. 156 ¶¶ 116, 119. “In considering motivation in the obviousness analysis, the problem examined is not the specific problem solved by the invention but the general problem that confronted the inventor before the invention was made.” *In re Kahn*, 441 F.3d at 988. Here, however, there is no evidence that “the general problem that confronted the inventor” was that of combining two active ingredients of different solubilities. The patents-in-suit make no mention at all that the prior art had indicated a problem with combining one active that goes into solution with another that remains in suspension, and certainly the patents-in-suit make no reference to having overcome such a problem if it did exist. D.I. 156 ¶ 116. Further, the inventor was not even called to testify at trial. *Id.* There is no evidence that combining two active ingredient of different solubilities was “the general problem that confronted the inventor,” or was a problem at all. *Kahn*, 441 F.3d at 988.

Plaintiffs’ only remaining argument is that Cramer’s Example III, which disclosed a formulation of azelastine with a different steroid, triamcinolone, would have discouraged a POSA from making a combination formulation. Meda’s argument is that experiments performed starting in 2011 show that Example III is “inoperable” because it is “unacceptably acidic,” “unstable,” and

gave “inconsistent dose delivery.” D.I. 155 ¶ 83. This is a perfect example of Meda’s inappropriate hindsight approach to reading the prior art: when a reference like Cramer expressly says in 1998 to combine fluticasone and azelastine and gives no indication that such a combination would be problematic, Meda developed tests in 2011 and even later in an effort to cast doubt on the prior art’s unambiguous teachings.

But Meda’s factual conclusions about Example III are also untrue. A POSA would have known how to optimize such a formulation to resolve any alleged issues before commercialization, if commercialization was its goal. D.I. 156 ¶¶ 120-21. Plaintiffs’ argument is also irrelevant as a matter of law. Whether a POSA could make Cramer’s Example III perfectly on the first try has no bearing on this case because “[a] reference . . . is prior art for all that it discloses, and there is no requirement that a teaching in the prior art be scientifically tested, or even guarantee success, before providing a reason to combine. Rather, it is sufficient that one of ordinary skill in the art would perceive from the prior art a reasonable likelihood of success.” *Duramed Pharm., Inc. v. Watson Labs., Inc.*, 413 F. App’x 289, 294 (Fed. Cir. 2011) (citations omitted). There is no requirement in the law that Cramer’s Example III “be scientifically tested, or even guarantee success”—“it is sufficient that one of ordinary skill in the art would perceive from [Cramer, and other references] a reasonable likelihood of success.” *Id.*

IV. THERE ARE NO SECONDARY CONSIDERATIONS SUFFICIENT TO REBUT THE STRONG *PRIMA FACIE* SHOWING OF OBVIOUSNESS.

Plaintiffs will likely argue that the Patent Office already considered references like the Flonase® and Astelin® labels, and Cramer, when it issued the patents. Critically, the examiner found the asserted claims *prima facie obvious* in light of that art. He nevertheless allowed the claims only on the basis of secondary considerations including satisfaction of unmet needs and commercial success. D.I. 156 ¶ 144.

That decision cannot be confirmed in this Court because “objective evidence of nonobviousness simply cannot overcome . . . a strong prima facie case of obviousness.” *Agrizap, Inc. v. Woodstream Corp.*, 520 F.3d 1337, 1344 (Fed. Cir. 2008); *see also Sundance, Inc. v. Demonte Fabricating Ltd.*, 550 F.3d 1356, 1368 (Fed. Cir. 2008) (same). For example, in *Richardson-Vicks*, the Federal Circuit held the claims obvious because “[t]he only difference between the prescribed combination [of ibuprofen and pseudoephedrine] and the patented invention is that the prescription was not contained in a single tablet” and “[s]uch a combination was clearly suggested by the prior art.” 122 F.3d at 1483-84. There, although “[t]he unexpected results and commercial success of the claimed invention” were “supported by substantial evidence,” they “[did] not overcome the clear and convincing evidence that the subject matter sought to be patented is obvious.” *Id.* at 1484.

But Plaintiffs’ secondary considerations also fail for other reasons, many of which were never analyzed by the Patent Office but are part of the record here.

A. Three simultaneous inventions indicate that co-formulating azelastine and fluticasone was within the level of ordinary skill in the art.

First, the Examiner never appreciated that the obviousness of combining fluticasone and azelastine together in one bottle was supported by at least three simultaneous inventions. “The fact of near-simultaneous invention, though not determinative of statutory obviousness, is strong evidence of what constitutes the level of ordinary skill in the art.” *Ecolochem, Inc. v. S. California Edison Co.*, 227 F.3d 1361, 1379 (Fed. Cir. 2000) (citation omitted). And when three companies independently report the combination of azelastine and fluticasone independently of the patentee here, that is evidence that the asserted claims were well within the level or ordinary skill in the art as of 2002.

Procter & Gamble's 1997 Cramer application and Warner-Lambert's 1998 Segal application are the first two simultaneous inventions (indeed, they are prior art) that disclose co-formulating azelastine and fluticasone. (DTX 12; DTX 21.)

In 2002, Meda's predecessor company, MedPointe Pharmaceuticals, also independently decided it would be useful to combine azelastine in a nasal spray with a steroid. D.I. 156 ¶¶ 128-29. In 2005, before it knew anything about the work of the inventors in this case, Meda filed a patent application covering this subject matter—thus representing to the Patent Office that such a co-formulation was enabled to a POSA. D.I. 156 ¶ 130. That application included claims to the combination of azelastine and fluticasone and the appropriate excipients to use in such a product. The disclosed excipients included MCC, CMC, EDTA disodium, phenylethyl alcohol, benzalkonium chloride, polysorbate 80, and glycerin, and noted that such combinations could be formulated as either solutions or suspensions with a pH from about 6 to 8. The application also contained an example of what the inventors believed was a working azelastine/fluticasone combination product. *Id.*

That three other companies in the pharmaceutical space were making the same combination in the years before and immediately following the alleged invention here strongly suggests that the patentees work was not inventive at all. *Ecolochem*, 227 F.3d at 1379; *see also, e.g., Insight Tech. Inc. v. SureFire, LLC*, 447 F. Supp. 2d 120, 135 (D.N.H. 2006) (finding “persuasive” that “three companies working independently on a problem [were] simultaneously developing similar solutions”).

B. Two blocking patents render remaining secondary considerations weak at best.

The patent examiner granted the patents-in-suit on the basis of secondary considerations, but the examiner was not made aware of two blocking patents—patents that would have prevented

a POSA from making the claimed invention and that therefore render evidence of secondary considerations irrelevant, or weak at best. Evidence of unmet need and commercial success are relevant to the obviousness analysis because if such a medical or financial incentive to practice the claimed invention existed as of the priority date, the fact that a person of ordinary skill in the art did not do so may tend to show the claimed invention is not obvious. *E.g., Merck & Co. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1376 (Fed. Cir. 2005) (“Commercial success is relevant because the law presumes an idea would successfully have been brought to market sooner, in response to market forces, had the idea been obvious to persons skilled in the art.”). Therefore, where at the time of invention a patent existed that would have “blocked” others from making the invention, evidence of unmet need and commercial success are of limited probative value. *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 740 (Fed. Cir. 2013) (“Where ‘market entry by others was precluded [due to blocking patents], the inference of non-obviousness of [the asserted claims], from evidence of commercial success, is weak.’” (quoting *Merck*, 395 F.3d at 1377) (brackets in original))). This Court applied this principle in *Warner Chilcott Co, LLC v. Teva Pharm. USA, Inc.*, holding that “Plaintiffs’ evidence of the commercial success . . . fails to raise a genuine issue of material fact” because “P&G’s U.S. Patent No. 5,583,122, claiming the risedronate compound, would have discouraged development of risedronate products.” 37 F. Supp. 3d 731, 739 (D. Del. 2014), *aff’d*, 594 F. App’x 630 (Fed. Cir. 2014).

Here, there were two blocking patents—one covering the fluticasone compound and the other covering formulations including azelastine. D.I. 156 ¶¶ 144-48. Although Plaintiffs argue that these are not blocking patents because they don’t describe *combinations* of the two, D.I. 155 ¶¶ 141-42, as a matter of claim construction both patents are blocking. A compound patent would discourage the development of any product containing fluticasone. *See Warner Chilcott*, 37 F.

Supp. 3d at 739 (“P&G’s [patent], claiming the risedronate compound, would have discouraged development of risedronate products.”).

And the azelastine patent covers, “A method for the treatment of irritation or disorders of the nose and eye which comprises applying directly to nasal tissues or to the conjunctival sac of the eyes *a medicament which contains* a member selected from the group consisting of *azelastine* and its physiologically acceptable salts.” D.I. 156 ¶ 147; DTX 16 at Claim 1. It is “well established” that “‘containing’ is generally an open-ended term that is synonymous with ‘comprising’ or ‘including’ and does not exclude additional, unrecited elements.” *INVISTA N. Am. S.a.r.l. v. M & G USA Corp.*, 951 F. Supp. 2d 604, 615 (D. Del. 2013); *see also* MPEP § 2111.03. Thus, as a matter of law, any skilled artisan who combined azelastine hydrochloride and fluticasone propionate into a single nasal spray for the treatment of allergic rhinitis before the priority date of the patents-in-suit would have infringed the ’194 patent. Such a product would have been “a medicament which contains a member selected from the group consisting of azelastine and its physiologically acceptable salts” “for the treatment of irritation or disorders of the nose and eye.” Thus, evidence of commercial success or unmet need is legally irrelevant, or weak at best.

C. Meda has failed to produce any evidence of commercial success or unmet need that rebuts the strong showing of obviousness.

Even putting aside the blocking patents, which explain why a POSA would not have pursued this invention even though it was obvious, Plaintiffs have not put on any serious evidence of commercial success or that Dymista satisfied a long-felt but unmet need. D.I. 156 ¶¶ 149-65. Crucially, Plaintiffs focus on Dymista®’s absolute numbers in sales and prescriptions. D.I. 155 ¶ 134. But “[t]he most probative evidence of commercial success is not overall sales, but whether those sales represent ‘a substantial quantity in th[e] market.’” *Caraco Pharm. Labs.*, 719 F.3d at 1356 n.5 (citing *In re Applied Materials, Inc.*, 692 F.3d 1289, 1300 (Fed. Cir. 2012)). Thus,

Plaintiffs have no choice but to turn to Dymista®’s competition—and they exclude any product that is not a *branded* nasal spray. D.I. 155 ¶ 135. They exclude “indirect competitors” like over-the-counter (“OTC”) treatments because these are not “directed to treat moderate-to-severe AR like Dymista®.” *Id.* By this reasoning, Flonase® *now* is not a direct competitor because it is OTC, even though it *was* a direct competitor a few years ago before it was OTC. That is absurd, because Flonase® is used to treat the same patient population regardless of whether it is OTC or not. Regardless, even just including *generic* Flonase® and Astelin®, Dymista®’s market share is vanishingly small—only 1.2% of total prescriptions. D.I. 156 ¶ 156. This market share is hardly sufficient to overcome the “strong prima facie case of obviousness.” *Agrizap*, 520 F.3d at 1344.

As for the sales of the commercial embodiment in India, Plaintiff Cipla undertook a “sweet relief” campaign in 2010 that marketed the introduction of a sweetener to mask the product’s sometimes bitter taste. D.I. 156 ¶ 161. But where “the commercial success is due to an unclaimed feature of the device, the commercial success is irrelevant.” *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1312 (Fed. Cir. 2006). That is particularly true here because Plaintiffs’ data on *relative* performance in India date from no earlier than 2010. Tr. (Jarosz) 709:12-17.

Plaintiffs also rely heavily on the fact that Meda wanted to license the patents-in-suit from Cipla. D.I. 155 ¶¶ 109-11. However, this license is not relevant. Not only was its value low, but Meda owned the license to the Astelin® patent—which was a blocking patent in the United States—so only it could profit from a license to the patents-in-suit. D.I. 156 ¶ 162. Indeed, no other companies expressed interest in a license. *Id.*

As discussed below, moreover, there are no superior results to Dymista® compared to the closest prior art, and thus Plaintiffs have also not shown that Dymista® met a long-felt but unmet need. The evidence demonstrates that the only need was for a more convenient fixed-dose

combination likely to increase compliance. In light of the prior art, it was obvious that a fixed-dose combination would fill such a need; the only reason it was not previously filled was blocking patents would have discouraged a POSA from making the combination. D.I. 156 ¶¶ 164-65.

D. There is no evidence of copying.

Although it is unclear whether Meda intends to argue that there is evidence of copying, it did not present any evidence of copying at trial; their experts merely relied on the existence of Indian imitator products as evidence of “revealed preferences,” i.e., their companies believed a combination product was worth their investment. Tr. (Jarosz) at 708:2-12. Thus, these imitator products are no different than Apotex or any other generic pharmaceutical company in the United States whose business model is to imitate an already-approved drug product. That is not evidence of copying. “The mere fact that generic pharmaceutical companies seek approval to market a generic version of a drug, without more, is not evidence of commercial success that speaks to the non-obviousness of patent claims.” *Galderma*, 737 F.3d at 740.

E. There are no superior results over the closest prior art, and any improvement over individual monotherapies was expected.

Meda also argues that Dymista® was unexpectedly superior to fluticasone and azelastine taken alone in terms of efficacies and onset of action, and that it had fewer side effects than would be expected from a combination therapy. D.I. 155 ¶¶ 121-23. However, the only appropriate comparison to assess whether there were unexpected results is between Dymista® (the alleged invention) and the conjunctive use of Flonase® and Astelin® as the closest prior art. D.I. 156 ¶ 137. *Abbott Labs. v. Andrx Pharms., Inc.*, 452 F.3d 1331, 1345 (Fed. Cir. 2006) (any superior results “must be shown to be unexpected compared with the closest prior art”) (citing *In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991)). Meda does not point to any studies that make that comparison and undertook no such studies for purposes of this litigation. D.I. 156 ¶ 137.

In the absence of the legally required comparison, the best evidence in the record comes from a comparison of Ratner 2008 and Hampel 2010. The former compared the co-administration of Astelin® and Flonase® to the individual monotherapies, and the latter compared the fixed-dose combination Dymista® to the monotherapies. These studies showed an approximately equal improvement of Dymista *and* the co-administration of Astelin® and Flonase® over the monotherapies, D.I. 156 ¶ 138, suggesting Dymista® is not superior to the closest prior art.²

Even if the monotherapies were appropriate comparators, then the superior results were entirely expected by 2002. Doctors were already prescribing both drugs together for patients inadequately controlled by either alone, which the guidelines recommended. Nor is Dymista®'s onset of action unexpectedly superior to the prior art, as Meda has claimed. The record thoroughly demonstrates that the quick onset of Dymista® is entirely a function of azelastine, and the prior art, as already discussed, was replete with references to a 15-to-30 minute onset of action for azelastine. D.I. 156 ¶ 141. Any alleged difference in side effects can be attributed to the lower dose of azelastine that a patient gets on a standard Dymista® dose as opposed to an Astelin® dose.³

Finally, Meda's witnesses agreed that any superiority was merely a difference in "degree." D.I. 156 ¶ 139, 142, 143. Unexpected results, however, must be a difference "in kind and not merely in degree." *Galderma Labs.*, 737 F.3d at 739 (citations omitted).

F. There was no industry skepticism.

Plaintiffs argue that "in 2002 Meda was skeptical that an azelastine and steroid combination product could be successfully formulated and developed." D.I. 155 ¶ 100. This was not genuine

² Apotex does not rely on Ratner 2008 as prior art. Rather, it demonstrates the efficacy of the prior art (the conjunctive use of Astelin® and Flonase®) for purposes of secondary considerations.

³ This dose was the European dose of only one spray per nostril twice a day. The ARIA guidelines reported: "[A]zelastine does not induce sedation at doses used in Europe (0.56 mg). However, it has a reported incidence of sedation (slightly greater than placebo) at doses used in the US (1.12 mg)." PTX 326 at S226. Thus, the lower dose was fully expected to result in fewer side effects.

skepticism, however, because shortly thereafter—and before knowing anything of the patents-in-suit—Dr. D’Addio and Meda filed a patent application claiming the invention of a combination product of azelastine and a steroid. D.I. 156 ¶ 130. Dr. D’Addio testified that he signed and submitted the patent application under oath, and his signature represented to the U.S. Patent Office that they believed the invention would work. *Id.* Regardless, Meda’s purported skepticism in 2002 was disclosed solely in internal and confidential documents and not made public. Tr. (D’Addio) at 386:7-11. Thus, it is entitled to particularly little weight because “skepticism expressed in a private communication is likely less considered and less self-scrutinized than statements of skepticism intended to be published to the scientific community.” *ViiV Healthcare UK Ltd. v. Lupin Ltd.*, 6 F. Supp. 3d 461, 497 (D. Del. 2013), *aff’d*, 594 F. App’x 686 (Fed. Cir. 2015).

Plaintiffs also argue that FDA was skeptical of the claimed invention for four reasons: (i) FDA wrote that “pharmacodynamics reasoning, such as mechanism of action, onset of symptom relief, etc., are [] not sufficient to justify” Dymista®; (ii) FDA was concerned about the lack of flexibility; (iii) Meda had “not provided evidence” that a population with sufficiently severe AR for this product existed; and (iv), FDA thought Meda could not satisfy FDA’s combination rule, i.e., show the contribution of each monotherapy component. D.I. 155 ¶¶ 112-16.

As to the first two concerns cited by Meda, these are particularly lacking in value because in *Caraco Pharm. Labs* the district court, the Federal Circuit, and even both the parties agreed that complementarity in mechanisms of action provided a motivation to combine. 719 F.3d at 1351. And in *Richardson-Vicks* the Federal Circuit rejected the argument that lack of flexibility suggests nonobviousness. 122 F.3d at 1484. Indeed, FDA’s stray comments in confidential communications with Meda reveal the wisdom in holding that “skepticism expressed in a private

communication is likely less considered and less self-scrutinized than statements of skepticism intended to be published to the scientific community” and is thus entitled to little weight. *ViiV Healthcare*, 6 F. Supp. 3d at 497. Finally, FDA’s other two concerns regarded the parameters of Meda’s clinical trials—they did not reflect skepticism that a combination product would work. D.I. 156 ¶¶ 169-71.

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

The only evidence of praise presented by Plaintiffs was a summary in a journal of an article written by Dr. Carr. D.I. 155 ¶¶ 128-32; D.I. 156 ¶¶ 166-68. The journal’s summary stated that Dymista® “can be considered the drug of choice for the treatment of allergic rhinitis.” D.I. ¶ 166. That conclusion, however, parrots the conclusion Dr. Carr and his several co-authors first wrote in the underlying article, that Dymista® “can be considered the drug of choice for [allergic rhinitis] therapy....” *Id.* Indeed, Meda funded the studies reported in the article and four of its authors reported potential “conflicts of interest” because of their ties to Meda. *Id.* ¶ 167.

Industry praise must be objective and not self-serving statements by the patentee or related entities. *Geo. M. Martin Co. v. All. Mach. Sys. Int’l LLC*, 618 F.3d 1294, 1305 (Fed. Cir. 2010). Similarly, the Federal Circuit in *Bayer Healthcare Pharms., Inc. v. Watson Pharms, Inc.*, found the industry praise “legally insufficient” where the patentee proffered journal citations that referenced information from the patentee’s own publications and cited an article authored by the first-named inventor of the patent that described the claimed method as an “innovative strategy.” 713 F.3d 1369, 1377 (Fed. Cir. 2013). The court found that these “bare journal citations and self-referential commendation” fell well short of demonstrating true industry praise. *Id.*

H. MedPointe’s single experiment does not constitute failure of others.

Lastly, Plaintiffs argue that MedPointe’s pre-formulation experiment in which it tried adding azelastine hydrochloride to the existing commercial formulation of Flonase® was a failure

of others. D.I. 155 ¶¶ 100-08. MedPointe’s attempted formulation was only “a few days long” and occurred in its entirety in the last week of April 2006. D.I. 156 ¶ 135. In this short experiment, MedPointe’s experimenters believed azelastine had not dissolved. However, MedPointe had developed a “Feasibility Assessment Plan” in which it laid out a formulation strategy, which included the step: “If Azelastine Hydrochloride is not sufficiently soluble, modify the formulation or process so that Azelastine Hydrochloride is completely in solution.” *Id.* MedPointe never undertook to complete that step using techniques known in the art. *Id.*

Courts have rejected these kinds of experiments as evidence of failure. In *AstraZeneca LP v. Breath Ltd.*, the court rejected a finding of failure of others where defendant attempted “to make a sterilized budesonide suspension” but had “introduced an internal decision tree” describing steps to be taken yet “there was no competent evidence that” the company had “considered or even performed each of the listed steps.” 88 F. Supp. 3d 326, 391 (D.N.J.), *aff’d*, 603 F. App’x 999 (Fed. Cir. 2015). Here, similarly, MedPointe had not “considered or even performed each of the listed steps” in its “internal decision tree.” That is not a failure of others—it is a failure even to try. Indeed, the only reason MedPointe abandoned its attempt to formulate a combination product was because it discovered the Cipla patent application for the present patents-in-suit shortly thereafter. D.I. 156 ¶ 135.

What’s more, Plaintiffs’ characterization of this 2006 experiment as a failure is disingenuous in light of the patent application filed by MedPointe in 2005 claiming a combination product. Plaintiffs even describe the azelastine/fluticasone example in that application as a “prophetic example.” D.I. 155 ¶ 108. Indeed it was. A prophetic example “describes an embodiment of the invention based on *predicted* results rather than work actually conducted or results actually achieved.” MPEP § 2164.02 (emphasis added). If the result of co-formulating its

azelastine/fluticasone example was predicted to be successful, then a person of ordinary skill in the art would have a reasonable expectation of success in making such a combination. Thus, Meda and Apotex agree: a POSA had both motivation to combine fluticasone and azelastine into a combination product and had a reasonable expectation of success in doing so.

V. ALTERNATIVELY, THE CLAIMS ARE NOT ENABLED.

Consistent with the conclusion of obviousness based solely on the prior art discussed above, the patents-in-suit do not give any novel instructions about how to make or use a combination formulation. D.I. 156 ¶¶ 122-26. Thus, if Plaintiffs are correct that the patents-in-suit are nonobvious because the prior art does not teach how to make the claimed combination, then the claims are invalid for failing to satisfy the enablement requirement of 35 U.S.C. § 112. The Federal Circuit “has stated that an applicant’s failure to disclose how to use an invention may support a rejection under ... section 112, paragraph 1 for lack of enablement ... ‘when there is a complete absence of data supporting the statements which set forth the desired results of the claimed invention.’” *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1323 (Fed. Cir. 2005) (citing cases). Here, the specification contains no pre-clinical or clinical data showing the use of any claimed composition, or any effects of the compositions on any in vitro model or in vivo subject, and confirms that its compositions can be “prepared by techniques well known in the art.” D.I. 156 ¶¶ 116, 126. Thus, if Plaintiffs are correct that things like inconsistent dosing, concerns about side effects, or potential incompatibilities would have discouraged a POSA from making the combination, then their patents are not enabled because they teach a POSA nothing about these matters. If Plaintiffs’ theory of nonobviousness is correct, then “there is a complete absence of data supporting the statements which set forth the desired results of the claimed invention,” and the claimed invention is invalid as not enabled. *Rasmusson*, 413 F.3d at 1323.

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Dated: January 24, 2017