

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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ARGENTUM PHARMACEUTICALS LLC  
Petitioner

v.

CIPLA LTD.  
Patent Owner

Patent No. 8,168,620  
Issue Date: May 1, 2012  
Title: COMBINATION OF AZELASTINE AND STEROIDS

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*Inter Partes* Review No. IPR2017-00807

**PETITIONER REPLY TO PATENT OWNER RESPONSE**

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## I. INTRODUCTION

The prior art teachings in this case are remarkably clear. The two drugs required by the claims, azelastine and fluticasone, were already commercialized nasal sprays as of the filing date, with doctors regularly prescribing the two together to treat severe AR. The Segal reference provides clear motivational teachings for combining these two drugs into a single spray—which would have satisfied even the more rigid TSM test pre-*KSR*. Nor does the '620 Patent describe any critical formulation requirements, using only well-known excipients in standard concentrations to arrive at the claimed formulation, thus disproving any litigation-inspired allegations regarding reasonable expectation of success.

Hemmed in by these indisputable prior art teachings, Cipla offers selective-but-misleading excerpts from the record to create an impression of uncertainty in the art, and a superficial appearance of secondary considerations. None of Cipla's arguments withstand scrutiny, nor do they overcome the overwhelming obviousness of the challenged claims. *Richardson-Vicks Inc. v. Upjohn Co.*, 122 F.3d 1476, 1484 (Fed. Cir. 1997) (finding “combination” drug obvious over secondary considerations).

## II. CLAIM CONSTRUCTION

Cipla advances a claim construction of “pharmaceutical formulations that are tolerable to patients, that are homogeneous, and that be suitably deposited onto

the nasal mucosa” for the claim terms “nasal spray” and “suitable for nasal administration.” POR, 8-9. This construction should not be adopted for several reasons.

First, the Board should only construe claim terms as needed to resolve the parties’ controversy. *Vivid Techs., Inc. v. Am. Sci. & Eng’g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999). Here, all of the §103 prior art references are expressly directed to nasal sprays suitable for nasal administration. *E.g.*, EX1007, 2:12-17; EX1009, 32:57-60; EX1010, 1; EX1012, Abstract, 4-6. Hettche and Phillipps disclose Astelin® and Flonase®, respectively, and Segal discloses aqueous compositions formulated as nasal drops or sprays that are both isotonic and pH-adjusted, making construction of these claim terms unnecessary. EX1012, 6; EX1004, ¶¶24, 32.

Second, any special definitions for claim terms must be set forth with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994). Entirely skipping the claims and specification, Cipla argues that its proposed construction was used during prosecution to distinguish the prior art (*i.e.*, Cramer). POR, 9. However, during prosecution, Cipla at most distinguished Cramer based on settling/caking over time, its alleged difficulty in being sprayed, and its osmolality. EX1002, 223. Cipla’s construction should not be adopted because: it is not commensurate with its remarks regarding Cramer; the

Examiner did not rely on Cipla's remarks in allowing the claims (*see* EX1002, 143-146); and the proposed construction is hopelessly vague (EX1145, ¶¶7-11).

Third, Cipla's real motive is to use its proposed construction to improperly import even more limitations into the claims, such as Dr. Smyth's attempt to import a pH limitation of 4 to 8 into the claims in order to distinguish Cramer (CIP2150, ¶40), despite claim 45's call for a pH of 3 to 7. Similarly, Dr. Smyth argues that the terms "nasal spray" and "suitable for nasal administration" are equivalents (EX2150, ¶23; EX1143, 60:9-19; 62:20-22, 85:9-11), effectively importing the limitation of "nasal spray" into the claims via this alleged equivalency. This argument ignores claims 13 and 14, which expressly cover nasal drops—which are markedly distinct from nasal sprays (EX1143, 51:7–53:9), creating an inconsistency Dr. Smyth was unable to reconcile (*Id.*, 60:9–65:5).

### **III. AMPLE MOTIVATION TO COMBINE EXISTED IN THE ART**

Before June 2002, a POSA would have been motivated to combine azelastine hydrochloride ("azelastine") and fluticasone propionate ("fluticasone") in a single nasal formulation in view of any of Segal, Cramer, or the clinical art. Contrary to Cipla's assertions (POR, 10-27), it is not hindsight for a POSA to do what the prior art expressly recommends.

**A. Segal expressly suggests combining azelastine and fluticasone in a nasal spray**

Cipla's endless hindsight arguments flatly ignore the motivations found in Segal, a reference included in both instituted obviousness grounds. Petitioner cited Segal as motivation for its express teaching to combine azelastine and fluticasone into a single nasal product for treating allergic rhinitis (AR). Pet., 22, 25-33, 35; EX1003, ¶80. Cipla does not dispute this teaching in its Response, and Cipla's expert, Dr. Carr, does not even mention Segal in his 71-page declaration. EX1142 249:18–250:20; EX1144, ¶¶11-12.

Segal's motivation to combine is akin to that in *Merck v. Biocraft* (874 F.2d 804, 806 (Fed. Cir. 1989)), where a prior art reference disclosed a multitude of combinations for a known use, rendering a two-drug pharmaceutical obvious. *Id.*, 807. Because “all disclosures of the prior art, including unpreferred embodiments, must be considered,” (*Id.*) Cipla's anticipation arguments, absent from its Response, do not apply to obviousness. As a matter of law, the Board should find motivation to combine azelastine and fluticasone in a nasal spray as expressly taught by Segal.

**B. The clinical art also motivated a POSA to combine azelastine and fluticasone**

The clinical art before June 2002 provides overwhelming motivation for a POSA to combine azelastine and fluticasone in a single nasal formulation. Pet.,

35-39. The treatment Guidelines (collectively EX1019, EX1022, and EX1024)—which reflect clinical practice of the time—recommend combination therapy using antihistamines and intranasal steroids (INS). Pet., 35-36; EX1144, ¶13. Dykewicz expressly recommends the use of INS with intranasal antihistamines and discusses only azelastine. EX1019, 505; Pet., 35. Clearly, the physicians behind the Guidelines found such combinations beneficial.

The wide-spread practice of using antihistamines combined with INS to treat AR is reflected in the numerous references and studies of record. EX1144, ¶¶13, 28-29, 42. Berger, Juniper '97, and Nielsen (“[a] combination of antihistamine and INCS is often used in clinical practice”) are just a few of the references acknowledging this practice. *Id.* The Dymista<sup>®</sup> authors even note, “reports of the use of these agents [azelastine and fluticasone] in combination are common.” EX1045, 74; *see also* CIP2165 at 7 (same).

Consistent with this practice, all four of the physicians who testified at the *Cipla v. Apotex* trial had co-prescribed azelastine and fluticasone prior to 2002. EX1144 ¶41. Copies of Dr. Acetta’s patient notes established exactly this.<sup>1</sup> *Id.*

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<sup>1</sup> Waiting until the evening before this Reply was due, Cipla refused Petitioner’s request for these records and would not allow Apotex to provide them either. EX1158.

Cipla's experts, including Dr. Carr, also admitted to co-prescribing the combination. *Id.* ; EX1142, 6:8–11:15. Cipla's other expert, Dr. Kaliner, admitted that before June 2002, "the combination of a nasal steroid and an antihistamine was the best treatment I can give," and recommended the combination to other allergists. CIP2021, 498:4-7, 488:12–490:7; EX1144, ¶39.

In discussions with the FDA, Cipla's licensee acknowledged that the rationale for its combination product came from allergists who treated many of their SAR patients with both azelastine and fluticasone nasal sprays (EX2165, 7), which is essentially an admission that a motivation to combine existed before Cipla's filing date. Cipla cannot credibly claim hindsight bias.

Cipla's assertion that the art showed no clinical benefit to co-administration of steroids and antihistamines (POR, 12-16) is wrong. At a minimum, beneficial effects were seen in all shorter studies of 1-3 weeks and in the early weeks of the 6-week Juniper'89 study. EX1003, ¶¶83-91; EX1144, ¶¶15-27. The outcome of the 8-week study by Benincasa is explained by the complementarity of antihistamines and steroids in treating, respectively, early phase reaction (EPR) and late phase reaction (LPR) symptoms. Pet., 35-36; EX1144, ¶¶27-31, 58. Antihistamines were known to mitigate initial EPR symptoms such as sneezing and itching, while steroids address LPR symptoms that develop hours later, *e.g.*, congestion. While steroids exert their full effect on all AR symptoms over days or

weeks, the effects of the antihistamine on EPR symptoms were readily observed in the shorter studies. EX1144, ¶¶7-9. Expectedly, as the studies progressed, the effect of the steroid eventually dominated, meaning that studies looking only at endpoints or mean TNSS scores missed the antihistamine effects. *Id.*, ¶14.

Rather than addressing these well-known phenomena, Dr. Carr simply disparages or ignores data that does not support his view. His analyses of Drouin and Brooks are illustrative. Dr. Carr asserts that the improvement observed for the antihistamine/INS combination over the steroid alone in Drouin is “less than that shown by the typical placebo group” and without clinical benefit. POR, 14; CIP2147, ¶59. Yet the difference between the two groups in Drouin is at least as large, if not larger, than that observed for Dymista<sup>®</sup> versus fluticasone, as evidenced by Dr. Carr’s own paper. EX1144, ¶¶15-18. Adjusting for the difference in TNSS scales, the advantage of the combination over steroid in Drouin is 1 point while that of Dymista<sup>®</sup> is 0.8—indicating that Drouin’s results are at least as clinically relevant as Dymista<sup>®</sup>’s. *Id.* Cipla’s criticism of Brooks (POR, 14) is equally flawed. Dr. Carr cherry-picks a single statement from Brooks and ignores all other data to the contrary. EX1144, ¶¶19-23.

Consistent with Segal and the clinical art, a POSA would also have wanted to combine azelastine and fluticasone to take advantage of known complementarity. Pet., 36-38. First, like other antihistamine/steroid pairs,

azelastine and fluticasone address EPR and LPR symptoms to provide faster and more complete relief of severe AR symptoms. *Id.*; EX1003, ¶¶53-54. Cipla does not contest this other than to incorrectly assert that EPR and LPR symptoms cannot be clinically distinguished. EX1144, ¶¶7-9. Second, azelastine was known to have a fast onset of action that complemented the slower-developing effects of fluticasone, just as salmeterol did in Advair. *Id.*, 46; *infra* VI.C. Third, azelastine's anti-inflammatory properties were known to act on LPR symptoms as well as EPR symptoms. EX1003, ¶¶62-67.

Cipla's allegation that the *in vivo* action of antihistamines was thought to be redundant with steroids (POR, 18) is a mischaracterization. Howarth focused solely on whether antihistamines could be used in long-term prophylactic treatment of AR. EX1144, ¶¶32-36. Howarth's conclusion was based on undisclosed "limited studies" that did not involve azelastine or address EPR/LPR short-term complementarity. *Id.* Cipla's other reviews did not address complementarity and ignored data that contradicted their conclusions. *Id.* ¶¶37-38. On this record, a POSA would hardly conclude that antihistamines and steroids have redundant *in vivo* mechanisms of action. *Id.*

A POSA would also have expected improved compliance for a combined azelastine/fluticasone nasal spray to avoid the inconvenience of multiple spray products and assure adequate dosing. Pet., 38; EX1012, 2:2-3, 1:15-20. Cipla's

argument that the art had disproven this premise (POR, 20-22) overreaches. Cipla provides no evidence that tablet-number studies—cited in Shenfield—are relevant to nasal-spray dosing. EX1144, ¶45. Certainly, its licensee didn’t think so, as Meda expressly represented to the FDA that “compliance is an issue” and Dymista® “would be better than the individual ingredients because **patients would not have to take four sprays** of medication at one time.” CIP2165, 7; EX1144 ¶45.

Cipla’s argument that azelastine’s side effects would dissuade a POSA from selecting it rather than an oral antihistamine (POR, 21-23) has no basis in fact. Cipla’s quotation of a pediatric review does not show compliance is improved in adults by selecting an oral medication that tastes good. EX1041, 462. While azelastine may show a temporary bad taste if it runs down the back of the throat, this is temporary and not noticed by the majority of patients. EX1144, ¶51. Cipla cites no evidence suggesting lack of compliance because of bad taste. *Id.* Cipla’s Figure 1 (POR, 22) is scientifically invalid. *Id.* ¶¶49-51; *infra* §VI.C.

Cipla’s characterization of the “on-demand” nature of the Guidelines’ instructions to combine antihistamines and INS (POR, 20) fails to support its hindsight allegations. As shown above, the art as whole demonstrates that conjunctive use of antihistamines and INS—including azelastine/fluticasone—for treatment of severe AR was wide-spread before 2002, and that the combination showed clinical

efficacy. Nothing in the Guidelines mandates that a fixed-dose regimen for combined therapy should never be used. While the Guidelines discourage certain practices, no such warnings are attached to the use of antihistamines and INS. EX1144 ¶40.

#### **IV. A POSA'S REASONABLE EXPECTATION IS WELL-EVIDENCED**

By 2002, fluticasone and azelastine were already available in FDA-approved aqueous nasal-spray formulations (Flonase® and Astelin®). EX1008; EX1010. Segal and Cramer both taught aqueous nasal-spray solution-suspensions using well-known excipients. EX1145, ¶8. In addition, Dr. Smyth admits that (i) adjusting pH, osmolality, and viscosity using suitable agents was known; (ii) both Astelin and Flonase included viscosity and tonicity-adjusting agents; and (iii) the prior known tonicity-adjuster glycerin acted as expected when included in Dymista. EX2021, 640:16-19; 651:17-19; 654:2-19; EX1143, 59:1-10, 70:2-72:20. With such knowledge, a POSA would have reasonably expected success in formulating a nasal spray with both drugs, especially given the numerous suspension-solution drugs already in the art. EX1004, ¶¶35,59-61; EX1145, ¶¶18-40, 50-55.

Cipla conceives of “significant problems” to impugn this reasonable expectation (POR, 28-29), but as discussed below, no such problems existed (EX1145, ¶¶12-29). Further, Cipla attempts a distraction by narrowly obsessing on

Cramer's Example III, while blatantly avoiding verifying Dr. Govindarajan's successful Example III formulations. EX1145, ¶¶30-55.

**A. Monovalent cationic drugs, like azelastine, were routinely included with MCC and CMC**

Well before the '620 patent, mixtures of MCC and CMC (*e.g.*, Avicel® RC591) were known to provide stable aqueous pharmaceutical suspensions with monovalent cationic drugs ("MCDs") like azelastine. EX1145, ¶¶21-29. When dissolved, azelastine is a MCD. EX1145, ¶¶28. Ignoring product guides and prior art specifically discussing Avicel® RC591 suspensions, Cipla cites selectively to Lieberman to allege incompatibility of azelastine with Avicel® RC591. CIP2150, ¶¶45-47; EX1145, ¶¶18-29. Indeed, Dr. Smyth admits he didn't consult Lieberman's citations or any art describing MCDs with Avicel® RC591. EX1143, 40:9-21.

A POSA would not be so willfully ignorant of the pertinent art, but instead would be well-versed on up-to-date source material. EX1145, ¶¶20. Notably, Lieberman's statement on Avicel RC® 591 cites to FMC Corp. (CIP2113, 24, 61 n.51), which itself teaches that CMC is incompatible with di- and trivalent salts. EX1146, 8. Critically, monovalent salts, like azelastine, are not called out as problematic. EX1145, ¶¶20.

A POSA would also be aware of multiple successfully-formulated aqueous solution-suspension formulations reported in the art that include one or more MCDs with Avicel® RC591, including a 1997 patent describing stable aqueous suspensions of multiple MCDs together with Avicel® RC 591. EX1154, Examples 1-4; EX1145, ¶¶21-25. In fact, even suspensions including both a MCD and Avicel® RC591 formulated as a nasal spray were already known. EX1155, 3:54-56; Examples 1-3; EX1145, ¶26.

**B. CIPLA's criticisms contradict its positions in obtaining other patents in this family**

Cipla asserts that a POSA's understanding in preparing the claimed nasal sprays could only come from the specific examples in the patent showing particular ingredients and concentrations. EX2150, ¶32; EX1143, 113:15-21. Cipla thereby contends that Hettche, Phillipps, Segal, and Cramer all lack "meaningful guidance" enabling a POSA to make the claimed combination. POR, 33, 39. Yet Cipla only asserts this view when convenient.

Two continuations of the '620 patent (EX1166, EX1167) claim compositions "suitable for nasal administration" that include azelastine and ciclesonide—a steroid essentially insoluble in water (EX1151). However, neither the '620 patent nor the child applications contain any working examples with azelastine and ciclesonide, yet Cipla obtained claims covering this combination,

thus showing that Cipla was perfectly willing to rely on the general understanding of a POSA in formulating solution-suspensions when convenient. EX1145, ¶¶56-58. *Lampi Corp. v. Am. Power Prods., Inc.*, 228 F.3d 1365, 1377 (Fed. Cir. 2000) (applying judicial estoppel where party sought to repudiate arguments relied upon to obtain a favorable result in earlier administrative proceedings).

**C. Cipla misleadingly cites GlaxoSmithKline's research**

Cipla claims that a POSA knew fluticasone would cake when co-formulated in a “liquid formulation” with a second active ingredient. POR, 29 (citing CIP2111 and CIP2044). However, this “liquid” is a non-aqueous chlorofluorocarbon—a far different solvent than water. EX1145, ¶¶12-13. CIP2044 itself highlights that different solvents provide different behavior (in one of the chlorofluorocarbons the particles could be easily resuspended), and that aqueous formulations yielded even better suspension properties. CIP2044, Abstract, 5-10; CIP2111, 9-10; EX1145, ¶¶13-16. Cipla's own references thus encourage a POSA to combine fluticasone with another active using an aqueous system. EX1145, ¶¶15-17.

**D. Dr. Govindarajan successfully recreated a suitable nasal spray from Cramer's Example**

Dr. Govindarajan was an expert for Apotex in its litigation against Cipla tasked with recreating and testing Cramer's Example III. EX2030, 2-3. Using the

same criteria as Cipla for assessing whether a nasal suspension is acceptable (EX2150, ¶35; EX2113, 5; EX2103, 12; EX2104, 6-7; *cf.* POR, 35 (equating settling with caking)), he concluded that Cramer's suspensions were physically stable, and yielded pharmaceutically-acceptable products that "could be delivered as a fine spray using a nasal spray pump." EX2030, 4, 39; EX1145, ¶¶35-40. Contrary to Cipla's misstatements, Dr. Govindarajan had no formulation problems nor did his recreations "fail." EX1145, ¶¶31-49; *cf.* POR, 34-35. Nor does Cramer, Segal, or even the '620 patent refer to any formulation difficulties, refuting Cipla's argument that formulation was key to the invention. *In re Epstein*, 32 F.3d 1559, 1658 (Fed. Cir. 1994) (refusing to accept after-the-fact arguments in favor of patentability where the specification lacked such detail).

Tellingly, Cipla's experts never made or tested any of Dr. Govindarajan's recreations; instead, they used a different HPMC and avoided generating Dr. Govindarajan's spray-tested batch.<sup>2</sup> EX2030, 27; EX2029, 2-3; EX1145, ¶¶41-45.

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<sup>2</sup> During prosecution, Cipla submitted a declaration by one of the co-inventors, Dr. Malhotra, allegedly testing Cramer's Example III formulation. EX1002, 284-87. However, Cipla refused to make Dr. Malhotra available for deposition in this proceeding, and therefore Dr. Malhotra's declaration should not be considered for its truth. Further, Dr. Malhotra's formulation did not reproduce those created and

Cipla's experts also ignored early indications of erroneous reproduction, apparently having predetermined failure. EX1145, ¶43.

Yet even Cipla's flawed attempt at Dr. Govindarajan's example produced a pH within the range the '620 patent states is "suitable for nasal administration." EX1001, claim 45; EX1143, 79:9-16; EX1145, ¶46. Further, the osmolality of all the recreations fall within art-accepted osmolality values for nasal sprays. EX1145, ¶¶47-49. There is no basis in the art for Cipla's conclusory position that these examples show unacceptable osmolality. EX2150, ¶38; EX1145, ¶¶47-48. Thus, Cramer's Example III supports rather than undercuts a POSA's reasonable expectation of success. EX1145, ¶¶30-33.

**V. CLAIMS 42-44 ARE OBVIOUS OVER SEGAL, HETTICHE, PHILLIPPS, AND THE FLONASE® LABEL**

A POSA would have been motivated to look to and employ the excipients described in Hettche (EX1007) and Phillipps (EX1009) and listed in Flonase® (EX1010). EX1004, ¶¶21-39, 52-64. The excipients were well known in the art and used for the exact same functions as in the individual nasal formulations. *Id.* Thus, a POSA would have had a reasonable expectation of success in co-

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tested by Dr. Govindarajan, and therefore suffer from the same shortcomings as Dr. Herpin's alleged tests. EX1002, 285; EX2029, 3, 20; Ex. 1145, ¶¶42-45.

formulating azelastine and fluticasone into a single nasal spray. *Id.*, ¶¶65-67; EX1145, ¶12-58.

While Cipla concocts an “obvious-to-try” argument in an attempt to circumvent the obviousness of claims 42-44 (POR, 38-40), even in this fictitious scenario Cipla’s assertions are still wrong. As evidenced by the Table below, Flonase® and Hettche (Example I) include the same active ingredients, same vehicle, and all of the same excipients listed in claims 42-44 except glycerin(e). EX1145, ¶60; EX1007, 6:6-18; EX1010, 1:3.

	<b>Flonase®</b>	<b>Hettche</b>	<b>'620 Patent Claims 42-44</b>
<b>Active Ingredient(s)</b>	<b>Fluticasone propionate</b>	<b>Azelastine HCl</b>	<b>Fluticasone Propionate</b> <b>Azelastine HCL</b>
<b>Vehicle</b>	<b>Water</b>	<b>Water</b>	<b>Water</b>
<b>Preservatives</b>	<b>(1) BKC; (2) Phenyl ethyl alcohol</b>	<b>(1) BKC; (2) EDTA</b>	<b>(1)BKC (2) Phenyl ethyl alcohol (3)EDTA</b>
<b>Surfactants</b>	<b>Polysorbate80</b>	<b>None needed</b>	<b>Polysorbate80</b>
<b>Thickening Agents</b>	<b>MCC/CMC</b>	<b>HPMC</b>	<b>MCC/CMC</b>
<b>Tonicity Adj.</b>	<b>Dextrose</b>	<b>Sodium chloride</b>	<b>Glycerin(e)</b>

A POSA would have reasonably expected successful combination of azelastine and fluticasone with MCC and CMC in a suspension suitable for nasal administration. *Supra*, §V. All components would be regarded as compatible and adjustment of parameters was well within a POSA's skill. EX1145, ¶¶12-29, 50-55, 67-72.

In another attempt to misstate a reference's teachings, Cipla asserts "Segal teaches minimizing the use and amount of preservatives." POR, 42. However, the passage of Segal cited is directed to *unit-dose* formulations and special systems—not typical *multi-dose* formulations. POR, 42; EX1012, 6:15-20; EX1045 ¶66.

It is well known that multi-dose nasal spray formulations must be preserved against microbial contamination. EX1145, ¶59. It was obvious to preserve a co-formulation of azelastine and fluticasone using the preservatives taught by Hettche and Flonase®—edetate disodium ("EDTA"), benzalkonium chloride ("BKC"), and phenylethyl alcohol. EX1145, ¶¶60-65; EX1010, 1:3; EX1007, 6:6-18. A POSA would reasonably expect using all three preservatives together with azelastine and fluticasone would result in passing a preservative challenge test, because the preservatives were already successfully used in the individual formulas. *Id.* A POSA would understand a combination of preservatives with multiple synergies

means a greater chance of passing a preservative challenge test (synergy 1: phenylethyl alcohol/BKC; synergy 2: BKC/EDTA). *Id.*, ¶¶64; EX1033, 5 and 27.

The substitution of glycerin as a tonicity adjustor was nothing more than routine optimization and an obvious substitution among known interchangeable components, because:

- it was listed by Hettche for such purposes;
- it is known for its useful functions as a solvent and humectant;
- a POSA would *avoid* using sodium chloride with MCC/CMC;
- a POSA would *avoid* using dextrose because it aids bacterial growth;
- at low concentration its viscosity is similar to water;
- there was no reason to believe it is incompatible with fluticasone.

EX1007, 4:31-34; EX1145, ¶¶67-72.

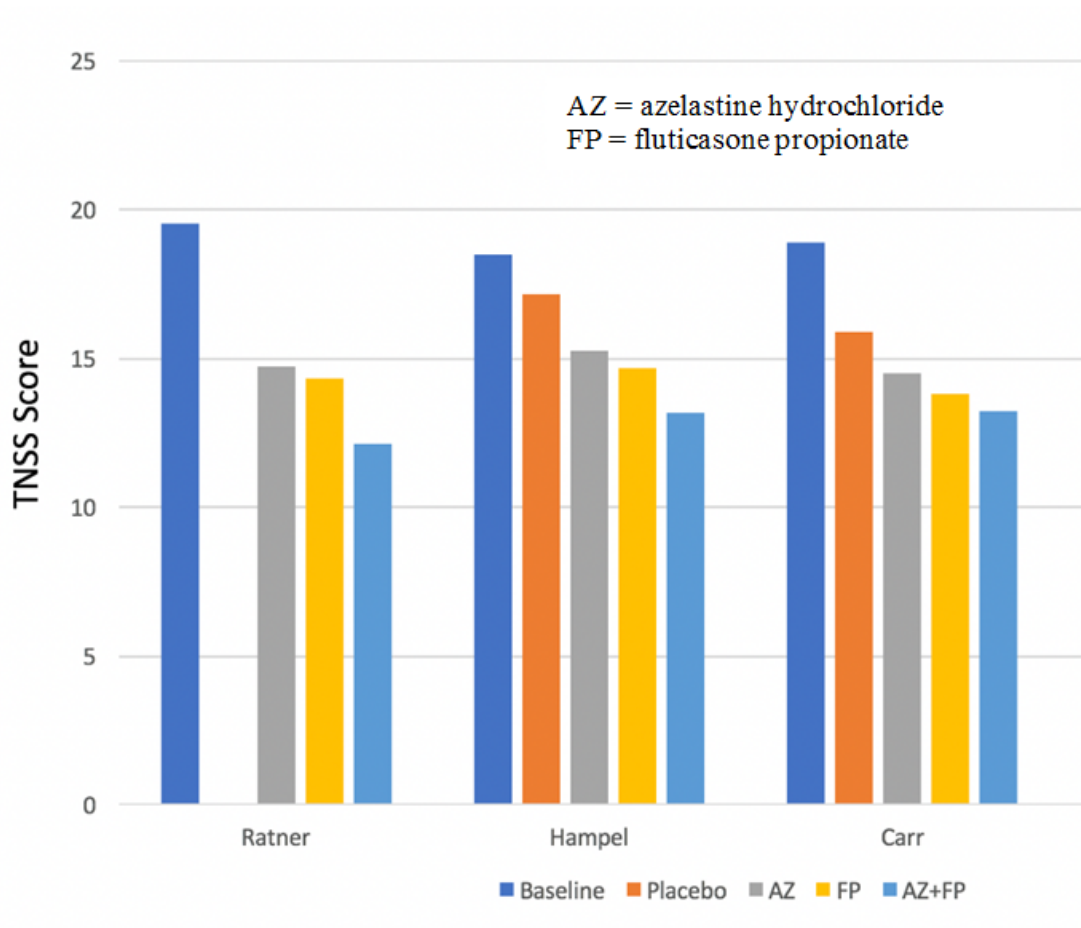
## **VI. DYMISTA® SHOWS NO UNEXPECTED EFFICACY OR SIDE-EFFECTS**

Evidence of unexpected results must stem from a comparison to the closest prior art. *Bristol-Myers Squibb v. Teva Pharm. USA*, 752 F.3d 967, 977 (Fed. Cir. 2014). Here, the closest prior art is Segal, Cramer, and the clinical art of co-administering Astelin® and Flonase®. *Supra*, §III. Thus, to establish unexpected results, the proper comparison is not to the individual monotherapies, but to the co-administration of azelastine and fluticasone (“conjunctive-use”).

Cipla is silent as to this closest prior art, and instead only considers the combination of INS with oral antihistamines (not azelastine), or azelastine and fluticasone as monotherapies. POR, 46-53; CIP2147 ¶¶101-106; EX1144 ¶¶52-60. While Cipla claims that there was no meaningful clinical benefit to co-administering an antihistamine with a steroid (POR, 50) (which is not true), it ignores the clinical practice of Cipla's own expert and many others co-prescribing azelastine and fluticasone for conjunctive-use before 2002. EX1144, ¶¶53-54.

**A. Dymista®'s efficacy is the same as conjunctive-use**

Ratner2008 (EX1045) provides the necessary data for comparing the conjunctive-use of the monotherapies to Dymista® (Hampel (CIP2045) and Carr (EX1037)). EX1144, ¶61. The correct comparison conclusively demonstrates that Dymista® is no better than conjunctive-use, as illustrated in Dr. Schleimer's Figure A:

**Figure A: Comparison of raw TNSS in Ratner 2008, Hampel, and Carr**

*Id.*, ¶62. The data shows the net effect of the monotherapies, conjunctive-use with separate sprays (Ratner2008), and Dymista®’s co-formulation (Hampel/Carr). *Id.*, ¶¶61-62. Hampel and Carr differ in that Hampel compared Flonase® and Astelin® to Dymista®, whereas Carr used azelastine and fluticasone formulated with Dymista®’s excipient package. *Id.*, ¶61. All three studies had similar (1) baseline (raw)total nasal symptom score (“TNSS”), (2) (raw)TNSS in response to each of the monotherapies, and (3) (raw)TNSS in response to the combination of

azelastine/fluticasone—whether administered as two separate sprays (Ratner2008) or a single spray (Hampel/Carr). *Id.*, ¶62.

Dr. Schleimer's Figure B (not reproduced) demonstrates that, if anything, conjunctive-use had slightly better efficacy compared to Dymista®. *Id.*, ¶63. Accordingly, these studies demonstrate that the combination of azelastine/fluticasone worked equally-well whether administered from the same or separate containers, proving that Dymista® exhibits no surprising or unexpected results. *Id.*, ¶¶65-66.

Furthermore, even if the closest prior art were the monotherapies of azelastine and fluticasone (which it is not), these studies show that Dymista® simply exhibits the expected additive effects of Astelin® and Flonase®. *Id.*, ¶¶64,67. This is at best a difference in degree, *not* a difference in kind as asserted by Cipla. *Id.*; POR, 52-53

**B. Dymista®'s onset of action is expected, and the same as azelastine**

Dymista®'s onset of action is no better than the quicker-acting ingredient in the formulation, azelastine. EX1144, ¶73. In asserting Dymista® has a faster onset, Cipla again fails to compare the closest prior art. *Id.*, ¶68. Instead, Cipla cites: three co-administration studies (none including azelastine); Ratner2008 (did not study the onset); and Astelin®'s label. *Id.*, ¶¶68-69; POR, 47-48.

However, POSA would have been aware that azelastine was reported to have roughly the same onset time as Dymista®—much less than 3 hours. EX1144, ¶¶69-73. For example, Greiff (EX1147) found azelastine had an impact within minutes, and inhibited sneezing and vascular leak profoundly within one hour. EX1144, ¶¶70-71. Other studies have confirmed an azelastine onset in as little as 15 minutes after initial administration. *Id.*, ¶¶72-73. Thus, as expected, azelastine and Dymista® have the same onset of action. *Id.*, ¶73.

**C. Dymista®’s side effects are worse than azelastine or fluticasone**

Cipla’s selective citation of side-effect data is scientifically unsound, and ignores the comparative data in Dymista®’s own prescribing label. *Id.*, ¶¶74-75. Cipla completely disregards Dymista®’s own label, which expressly teaches that clinical trials from different studies should not be compared. *Id.*, ¶75; CIP2066, 5. Instead, Cipla does just that, cherry-picking data from the separate studies reported on the Astelin® and Flonase® labels to arrive at its flawed analysis—all-the-while failing to inform the Board about Dymista®’s own prescribing label data that directly compares Dymista® to the monotherapies and shows its side effects to be slightly worse than the monotherapies. EX1144, ¶¶75-86; CIP2066, 5-7; CIP2147 ¶¶123-128. Cipla’s assertions to the contrary (POR, 48-50) are scientifically unsound and highly misleading to the Board. EX1144, ¶81.

## **VII. SECONDARY CONSIDERATIONS DO NOT OVERCOME THE STRONG CASE OF OBVIOUSNESS**

Cipla claims other secondary considerations support non-obviousness of the challenged claims. POR, 53-66. However, “where a claimed invention represents no more than the predictable use of prior art elements according to established functions, as here, evidence of secondary indicia are frequently deemed inadequate to establish nonobviousness.” *Ohio Willow Wood Co. v. Alps S., LLC*, 735 F.3d 1333, 1344 (Fed. Cir. 2013).

### **A. Lack of Nexus to the Challenged Claims**

Cipla incorrectly claims a nexus between Dymista<sup>®</sup> and Duonase and the claims. POR, 55. Cipla acknowledges that Duonase does not meet the limitations of claims 42-44 (POR, 55-56), so Mr. Jarosz’ conclusions about the success of Duonase are not relevant to them. EX1140, ¶86.

Other factors that undercut nexus include the fact that Dymista<sup>®</sup> has minimal benefit over conjunctive-use of the monotherapies. *Id.*, ¶¶109-117. In addition, Mr. Jarosz incorrectly eliminated non-patented features in his analysis (*e.g.*, heavy discounts and rebates) driving Dymista<sup>®</sup>’s sales. *Id.*, ¶¶118-135.

With respect to Duonase sales in India, Mr. Staines reports: Duonase is a “branded generic” with sales driven by price; its sales reflect demand for azelastine alone; non-imitator products indicate sales are not driven by features of the ’620

patent; and marketing of Duonase does not claim superiority over separate use. *Id.*, ¶¶136-147. Thus, the evidence relating to Duonase lacks nexus to the claims.

**B. Dymista® did not satisfy long-felt unmet needs**

Contrary to Cipla's claim Dymista® satisfied "a need for a more effective, faster, and safer treatment of AR" (POR, 56), Mr. Staines notes that the alleged "need" artificially resulted from a lifecycle management strategy leveraging the "unique nature of pharmaceutical economics." *Id.*, ¶113. Further, any "need" was already met by doctors—including Dr. Carr—who regularly co-prescribed fluticasone and azelastine for conjunctive-use before 2002. EX1144, ¶87.

**C. FDA skepticism was directed only to Cipla's proposed experiments**

While Cipla argues the FDA was "skeptical" (POR, 57-58), in reality the FDA was only skeptical that Meda created appropriate clinical studies. *Id.*, ¶¶88-89. This is apparent from the FDA's statements to Meda, for example:

**FDA Letter to Meda (Sept. 7, 2007)**

In addition, according to 21CFR300.50, the combination should be safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug. Therefore, you need to identify a patient population that requires such a combination product. Your clinical development program should evaluate the proposed combination product in the proposed patient population that requires concurrent therapy with both azelastine and fluticasone propionate. Identification of such a patient population may be a challenge for your development program.

CIP2164, 3; CIP2165, 7-8. Likewise, any reduced flexibility or dosage titration concerns were tied to Meda creating appropriate experimental parameters.

EX1144, ¶89. This is not skepticism of the alleged invention, just skepticism that the proposed clinical trials were appropriate.

**D. Dymista®’s “Industry Praise” is not reflective of its results**

Cipla cites only two instances of industry praise. POR, 59-60. The first does not amount to independent praise of Dymista®, but rather a direct quotation from Dr. Carr’s own paper in the same volume of the journal. EX1144, ¶¶90-91; CIP2052; EX1037. The second results from Cipla misstating the reference, which says INCS (intranasal corticosteroids) “are currently the gold-standard treatment for AR therapy.” EX1144, ¶92; CIP2053, 133. Cipla also altogether ignores the laundry list of Dymista®’s weakness recited on the same page. *Id.* Indeed, Dymista® is not considered the drug of choice for most doctors and patients. EX1144, ¶93; CIP2018, 54:20-56:17, 91:2-93:13.

Furthermore, Mr. Jarosz notes that even Meda’s offer to cut Dymista®’s price by more than half (58%) could not persuade one of the largest insurers to provide reimbursement. EX1140, ¶114.

**E. Meda did not try to co-formulate Azelastine and Fluticasone**

While Cipla treats decisions by Cramer, Segal, and Meda to not pursue FDA approval to market combination products as evidence of unobviousness (POR, 60), such decisions might simply have resulted from the blocking patents (section VII.I., *infra*) or economic factors. EX1140, ¶¶47-55.

Further, Cipla fails to show that Meda failed to formulate an azelastine-fluticasone combination formulation in 2006. In *AstraZeneca LP v. Breath Ltd.*, the Court rejected a finding of “failure-by-others” where the defendant had not yet performed steps of a development plan. 88 F. Supp. 3d 326, 391 (D.N.J.), *aff’d*, 603 F. App’x 999 (Fed. Cir. 2015). Here, Meda completed only a single step of its “Plan A.” EX2148, ¶23; EX1141, 66:6-9. Indeed, Meda’s attempted development lasted all of three days, in which Meda made no serious attempt to resolve any alleged difficulties in solubilizing the solid precipitate, and ended its efforts as soon as Cipla’s published patent application was discovered. EX1145, ¶73-84.

Cipla also argues that Meda’s failure resulted from “significant settling” (POR, 2), yet Cipla has not shown that Dymista®/Duonase do not exhibit the same settling issues. EX1145, ¶83. Notably, the Dymista® drug label under “Important Administration Instructions” recommends that the user “shake the bottle gently before each use.” EX2066, 2. In sum, Cipla has not shown that Meda “failed,” as opposed to intentionally abandoning its efforts in favor of partnering with Cipla.

**F. The Meda-Cipla license does not demonstrate a nexus**

Cipla presents the Meda-Cipla license as evidence of unobviousness (POR, 62), but the small license fee appears to only cover a tiny fraction of sunk costs in the development up to that point. EX1140, ¶¶148-150. Furthermore, the pre-launch agreement to Cipla royalties may have reflected faulty sales predictions,

which Dymista® grossly underperformed which have no nexus to actual commercial success. *Id.*

**G. Cipla's copying evidence lacks nexus**

Cipla suggests that evidence of Duonase imitators in India shows unobviousness (POR, 63), but factors unique to the Indian pharmaceutical market undercut nexus. Duonase is a branded generic product. EX1140, ¶137. Indian suppliers develop variations of existing drugs that require little investment to be recouped, with the most popular variation being fixed-dose combinations of existing drugs like Duonase. *Id.* These unique India marketplace factors account for the widespread copying rather than any special demand associated with the features of the '620 patent.

**H. Cipla's commercial-success arguments fail to rebut the strong case of obviousness**

Cipla's commercial success arguments (POR, 63-65) are flawed. Average growth rates alone do not demonstrate success. *Id.*, ¶¶21-25. Furthermore, the actual net revenue levels and growth are lower than reported by the Jarosz Declaration. *Id.*, ¶¶26-55.

In addition, comparisons to generic-eroded sales of other brands is not probative, nor are the sales reported by Mr. Jarosz meaningful given their failure to address OTC competition and concurrent use of the individual drugs in generic

form. *Id.*, ¶¶47-55. While Cipla suggests that OTC treatments are not direct competitors because they do not require a prescription and are used before a patient seeks a prescription (POR, 64), Mr. Jarosz's cited document indicates that doctors do recommend concurrent administration of an INCS in addition to an "OTC" or Xyzal (an oral prescription antihistamine). *Id.*, ¶49. Lastly, the sales reported by Mr. Jarosz are not significant compared to pre-launch forecasts. *Id.*, ¶¶66-74. For all of these reasons, the alleged commercial success is insufficient to establish nonobviousness.

#### **I. Blocking patents undercut nexus**

Cipla incorrectly attempts to redefine "blocking patents" as having to be owned by the same owner of the patent-at-issue. POR, 65-66. No precedent supports this novel theory. Regardless, the Hettche patent covering azelastine was owned by Cipla's US licensee (Meda's predecessor, MedPoint) since August 2002 (EX1157), which explains why Cipla and Meda had to partner in 2006 to market the proposed drug combination.

Cipla also argues that blocking did not occur because both Hettche and Phillipps expired before Dymista® launched. POR, 66. But it was Meda who both owned Hettche (the last-expiring blocking patent) and launched Dymista® under an exclusive license from Cipla. EX2049. Moreover, the safe harbor of §271(e) which Cipla cites (POR, 66), applies only to pre-regulatory approval activity; it

does not allow third parties to bring a product “to market”—the focus of the Federal Circuit’s timing inquiry regarding blocking. *Galderma Labs. L.P. v., Tolmar Inc.*, 737 F.3d 731, 740 (Fed. Cir. 2013) (“[M]arket entry by others was precluded.”).

While Cipla argues that there is no evidence of actual blocking (POR, 66-67), the relevant question is only whether a POSA would have been dissuaded by the existence of the patents. *Galderma*, 737 F.3d at 740 (finding blocking/obviousness as a matter-of-law without actual instances of blocking). The fact that Segal and Cramer abandoned their applications (POR, 61) only evidences the blocking effect of Meda’s patent. EX2021, 829:4–830:23.

## CONCLUSION

For the foregoing reasons, Petitioner respectfully requests that the instituted claims be canceled as obvious.

Respectfully submitted,

Dated: March 6, 2018

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**CERTIFICATE OF COMPLIANCE WITH 37 C.F.R. § 42.24(C)(1)**

The undersigned certifies that the foregoing petition complies with the requirements of 37 C.F.R. § 42.24(c)(1). Excluding the portions exempted by 37 C.F.R. § 42.24(c) (table of contents, table of authorities, listing of facts which are admitted, denied, or cannot be admitted or denied, a certificate of service or word count, or appendix of exhibits), this reply brief contains **5,575** words as counted by the word-processing system used to prepare it. This reply brief has been prepared in a double-spaced typeface in 14 point Times New Roman font, in compliance with PTAB rules and regulations.

Dated: March 6, 2018

By: s/Michael R. Houston/  
Michael R. Houston  
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Counsel for Petitioner

**CERTIFICATE OF SERVICE**

The undersigned hereby certifies that a copy of the **foregoing Petitioner's Reply to Patent Owner's Response** and all Exhibits and other documents filed together with it were served on March 6, 2018, by email directed to the attorneys of record for the Patent Owner at the following addresses:

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