

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 LIMITED

Patent Owner

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Case No. IPR2017-00807

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

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**PATENT OWNER RESPONSE**

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## I. INTRODUCTION

The challenged claims cover a combination nasal spray formulation with two active ingredients: azelastine hydrochloride (“azelastine”) and fluticasone propionate (“fluticasone”). Cipla’s successful combination formulation of these two ingredients was a breakthrough: the world’s first combination of an intranasal antihistamine (azelastine) with an intranasal corticosteroid (fluticasone). Indeed, Cipla’s invention was the first time *any* of the myriad available allergic rhinitis (“AR”) treatments were ever combined into a nasal spray formulation, by *anyone*, *anywhere*. As a result, Dymista<sup>®</sup>, the U.S. commercial embodiment of Cipla’s invention remains, more than fifteen years later, the only fixed-dose nasal spray combination approved by the Food and Drug Administration (“FDA”) for the treatment of AR. Faced with the groundbreaking nature of Cipla’s invention, Petitioner resorts to hindsight, relying either on art that was already considered—and overcome—during prosecution to build its case, or art that contradicts Petitioner’s obviousness theories.

Petitioner has failed to prove that Hettche, Phillipps, and Segal render claims 1, 4-6, 24-26, and 29 obviousness. First, Petitioner’s evidence falls far short of demonstrating that a person of ordinary skill in the art (“POSA”) would have been motivated by the prior art to select azelastine, or to combine azelastine and fluticasone into a combination formulation. Instead, Petitioner and its clinical

expert—Dr. Robert Schleimer—rely on stray statements in the art to claim a motivation to combine these drugs, yet these same references provide teachings that are squarely at odds with a combination formulation as claimed in the '620 patent, and in particular with the use of azelastine.

Petitioner's hindsight-driven analysis also fails to demonstrate that a POSA in 2002, looking forward, would have had a reasonable expectation of success in combining azelastine and fluticasone into a combination “nasal spray” that was “suitable for nasal administration.” Petitioner and its formulation expert—Dr. Maureen Donovan—fail to address the incompatibilities between (i) fluticasone and other active ingredients in liquid formulations and (ii) azelastine and the claimed thickening agents carboxymethyl cellulose (“CMC”) and microcrystalline cellulose (“MCC”). Petitioner side-steps the inconvenient fact that multiple attempts to recreate the closest prior art formulation resulted in a formulation that was not suitable for nasal administration because it was: (i) unacceptably acidic; (ii) unacceptably unstable with significant settling and caking; and (iii) unacceptably hypertonic.

Petitioner next stitches together four prior art references—Hettche, Phillipps, Segal, and the Flonase® label—to argue that the specific excipients recited in claims 42-44 would have been obvious. Petitioner continues its hindsight approach by cherry-picking from the disclosures of those references. Petitioner, however,

provides no justification for why a POSA would have deviated from the successfully employed excipients in either the prior art commercial azelastine product (Astelin<sup>®</sup>) or the prior art commercial fluticasone product (Flonase<sup>®</sup>), or why a POSA would have ignored the known incompatibilities with the claimed excipients. Indeed, hundreds of possibilities are identified for the claimed excipients. Further exposing its hindsight, Petitioner then argues that a POSA would have selected glycerine as an excipient, but ignores that many other isotonicity agents are known, and that Astelin<sup>®</sup> and Flonase<sup>®</sup> already successfully employed isotonicity agents different than glycerine. Using the claims as a blueprint, as Petitioner does here, is hindsight pure and simple.

Additionally, Petitioner and its declarants failed to address the publicly-available objective indicia of nonobviousness of which they were aware before the Petition was filed. Petitioner's representative attended trial on the '620 patent in a related district court proceeding less than seven weeks before this Petition was filed. And both of Petitioner's declarants addressed objective indicia of nonobviousness applicable to the '620 patent at that trial, but failed to acknowledge, much less, address it here. These compelling objective indicia of nonobviousness further confirm the non-obviousness of the challenged claims.

**Unexpected results.** Dymista<sup>®</sup>—the U.S. commercial embodiment—exhibits surprising improvements in efficacy, onset, and safety as compared to the

closest prior art.

**Long-felt need.** Because Dymista<sup>®</sup> exhibits improved efficacy, onset, and safety, Dymista<sup>®</sup> satisfies a long-felt but unmet need for a safer, more effective treatment of AR.

**Industry skepticism.** Meda (the exclusive licensee of the '620 patent) considered developing an azelastine/steroid combination formulation in 2002 but, before licensing the '620 patent, abandoned the project because of the expected difficulties. FDA was also skeptical. Years after the invention date, FDA did not have any approval pathway in place for combination products like the one claimed, and its concerns mirrored many of the problems a POSA would have seen in 2002.

**Industry praise.** Dymista<sup>®</sup> was hailed as the “drug of choice” for the treatment of AR.

**Failure by others.** When Meda ultimately attempted to make an azelastine/fluticasone combination formulation in 2006, Meda confirmed its initial skepticism, finding that significant precipitation occurred when azelastine was added to the Flonase<sup>®</sup> excipients. And, other companies investigated antihistamine/steroid combination formulations but failed to bring a product to market. Only with the '620 patent was Meda able to succeed.

**Licensing.** Unable to develop its own azelastine/fluticasone formulation, Meda licensed the '620 patent from Cipla.



**Copying.** Duonase—the commercial embodiment in India—was subject to widespread copying within two years of market entry.

**Commercial success.** Since its introduction into the market, Dymista<sup>®</sup> has consistently gained market share and is currently the most prescribed branded nasal spray for the treatment of AR.

The Board should affirm the patentability of the challenged claims.

## **II. BACKGROUND**

### **A. The '620 patent and its commercial embodiments**

The '620 patent is directed to intranasal pharmaceutical formulations containing azelastine and fluticasone, along with specific pharmaceutical excipients. CIP2150, ¶19. The application that matured into the '620 patent was filed on June 13, 2003 as PCT/GB03/02557 and claims priority to GB 0213739.6, filed June 14, 2002, under 35 U.S.C. § 119. Cipla is the assignee of the '620 patent. EX1001, 1. Duonase was not only the first-ever nasal spray combination of an antihistamine and a steroid, but it was also the first-ever nasal spray combination of any type, anywhere in the world. As a result, soon after its introduction into the market, several azelastine/fluticasone copycat products (“Duonase copycats”) also entered the market.

Meda Pharmaceuticals, Inc. (“Meda”, now part of Mylan Pharmaceuticals, Inc.) licensed the '620 patent from Cipla, and developed and received FDA

approval to market Dymista<sup>®</sup>—a commercial embodiment in the U.S. and the first and still *only* FDA-approved fixed-dose nasal spray combination formulation.

**B. Background of related litigation**

The '620 patent is listed in the FDA Orange Book in connection with Dymista<sup>®</sup>, which is approved for the treatment of seasonal AR. Apotex Inc. and Apotex Corp. (“Apotex”) filed an Abbreviated New Drug Application (“ANDA”) seeking approval to introduce a generic copy of Dymista<sup>®</sup>. In response, Cipla (along with its exclusive licensee, Meda) sued Apotex in the District of Delaware in December 2014 asserting infringement of the '620 patent. *Meda Pharm., Inc. v. Apotex, Inc.*, Civ. No. 14-1453 (D. Del.). There was a bench trial December 13-16, 2016, with closing arguments in March 2017.<sup>1</sup> All trial and hearing transcripts, and all post-trial submissions were publicly available to Petitioner from the Court’s docket. Petitioner’s declarants in this IPR—Drs. Robert Schleimer and Maureen Donovan—served as testifying experts on Apotex’s behalf at trial on the issue of the '620 patent’s validity. Finally, Petitioner admitted that “[it] attended the public portions of the trial.” CIP2127, 1. No part of trial was closed to the public.

**C. Person of ordinary skill in the art**

The hypothetical POSA in the field of the '620 patent would have education and experience in both (1) the treatment of patients suffering from AR and (2) the

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<sup>1</sup> The parties settled the district court dispute in May 2017.

development of drug formulations. From the clinical perspective, a POSA would have the experience of a primary care physician with a medical degree and 2-4 years of experience. CIP2147, ¶18. From the formulation perspective, a POSA would possess a bachelor of science degree in pharmaceutical sciences and 4-5 years of experience as a formulator, although the POSA could also be a person with a higher level of formal education and fewer years of experience. CIP2150, ¶¶17-18.

Petitioner's proposed definition differs in that it incorrectly renders optional clinical experience in treating patients. Pet. 11.<sup>2</sup> By omitting the critical clinical experience of a POSA, Petitioner's arguments seek to rely only on laboratory models. But the challenged claims are directed to *pharmaceutical* formulations, which indicates use in patients. CIP2147, ¶19. Petitioner's limited view is problematic because it overlooks the significant body of clinical literature in 2002, discussed below, showing that (1) the addition of an antihistamine to a steroid treatment regimen conferred no meaningful benefit, and (2) antihistamines and steroids had redundant activity.

### **III. PETITIONER FAILS TO CONSIDER THE "SUITABLE FOR NASAL ADMINISTRATION" AND "NASAL SPRAY" CLAIM LIMITATIONS.**

Petitioner's obviousness grounds fail because they do not address every

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<sup>2</sup> As used herein, "Pet." refers to Petitioner's Petition, Paper 1.

limitation of the claims. Namely, Petitioner has not demonstrated that the asserted prior art teaches the **“nasal spray”** or **“suitable for nasal administration”** elements required by each and every challenged claim. These terms, properly construed, mean **“pharmaceutical formulations that are tolerable to patients, that are homogeneous, and that can be suitably deposited onto the nasal mucosa.”** CIP2150, ¶¶20-21. But Petitioner’s references do not teach such azelastine and fluticasone combined pharmaceutical formulations.

The Board construes claim terms under a “broadest reasonable interpretation” standard. 37 C.F.R. § 42.1000(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144-46 (2016). And, the Board “must consult the patent’s prosecution history in proceedings in which the patent has been brought back to the agency for a second review.” *Hospira, Inc. v. Genentech, Inc.*, IPR2017-00731, Paper 29, 8 (Oct. 26, 2017) (Yang, APJ) (quoting *Microsoft Corp. v. Proxyconn, Inc.*, 789 F.3d 1292, 1298 (Fed. Cir. 2015)). *See also Hulu, LLC v. Intertainer, Inc.*, CBM2014-00052, Paper 35, 8 (June 12, 2015) (Murphy, APJ) (citing *Tempo Lighting, Inc. v. Tivoli, LLC*, 742 F.3d 973, 977-78 (Fed. Cir. 2014)).

During prosecution, the terms “nasal spray” or “suitable for nasal administration” were construed to have a special meaning. The Examiner believed that the initial pending claims were broad enough to encompass formulations that would *not* have been tolerable, homogeneous, or suitable for deposition on the

nasal mucosa, but the inventors explicitly disclaimed those formulations. For example, the Examiner rejected the pending claims over Cramer's Example III, which disclosed a combination of azelastine hydrochloride and triamcinolone acetonide, as the closest prior art. CIP2147, ¶27; CIP2150, ¶22; EX1002, 507-522. However, attempts to recreate, and testing of, Cramer Example III revealed that the formulation exhibited: (1) unacceptable osmolality, which would have caused irritation to patients; (2) unacceptable spray quality, which would not have suitably deposited onto the nasal mucosa; and (3) unacceptable settling, which would have adversely affected homogeneity of the formulation. CIP2150, ¶23; EX1002, 284-87, 220-21. These problems rendered Cramer Example III unsuitable for use as either a "nasal spray" or a "pharmaceutical formulation in a dosage form suitable for nasal administration." CIP2147, ¶28; CIP2150, ¶23; EX1002, 220-24, 286-87.

Accordingly, Cipla amended several claims to include the "suitable for nasal administration" limitation and explained that a "nasal spray," within the meaning of its claims, must meet the same suitability requirements, which ultimately led to allowance. CIP2150, ¶¶22-23; EX1002, 203-231. These amendments and arguments demonstrate that the term "nasal spray," as used in the challenged claims, is specific and materially different from the meaning of that term in Cramer and Segal. CIP2150, ¶23; EX1011, 1; EX1012, 1. Indeed, neither teaches how to make two-drug "pharmaceutical formulations that are tolerable to patients, that are

homogeneous, and that can be suitably deposited onto the nasal mucosa.”

Based on the arguments and amendments made during prosecution, a POSA would have understood “nasal spray” or “suitable for nasal administration” to mean “pharmaceutical formulations that are tolerable to patients, that are homogeneous, and that can be suitably deposited onto the nasal mucosa.”

CIP2150, ¶¶21-23. This construction is the broadest reasonable construction in light of the intrinsic record, and should apply here.

Petitioner has not even attempted to show that the art taught the “suitable for nasal administration” and “nasal spray” limitations. In fact, Petitioner’s formulation expert, Dr. Maureen Donovan, actually wrote the limitation out of the claims: according to her claim 1 of the ’620 patent recites azelastine, fluticasone, “and not much more.” EX1004, ¶42. This mistake underscores Petitioner’s overall failure to consider and address all claim limitations in the art.

#### **IV. PETITIONER’S MOTIVATION-TO-COMBINE ARGUMENTS REFLECT PURE HINDSIGHT.**

Petitioner’s obviousness grounds are built on the faulty premise that a POSA would have been motivated to select azelastine and fluticasone for use in a combined formulation. But each of Petitioner’s alleged reasons for selecting azelastine and fluticasone for use in a combination formulation are all either absent in the prior art or are squarely contradicted by it.

**A. The prior clinical use of antihistamines and steroids would not have been a motivation to pursue a combination formulation.**

Petitioner's reliance on the clinical co-administration of antihistamines and steroids prior to 2002 is both legally incorrect and factually misguided. Pet. 35-36. At most, all Petitioner has shown is that both azelastine and fluticasone were *known* in the art, and that those drugs might have been co-prescribed to some patients at some times. But the mere possibility that azelastine and fluticasone could be co-administered is not enough. The Federal Circuit has repeatedly found non-obvious combined formulations even in cases where the record showed that individual constituent drugs were regularly prescribed together. *See, e.g., Leo Pharm. Prods. Ltd. v. Rea*, 726 F.3d 1346, 1358 (Fed. Cir. 2013); *In re Brimonidine Patent Lit.*, 643 F.3d 1366, 1374 (Fed. Cir. 2011) (the fact that two drugs “were routinely prescribed together ... does not establish that it would have been obvious to combine the two in a single formulation.”).

Accordingly, Petitioner was required to demonstrate that a POSA would have had reason, looking at the art as of 2002, to proactively combine azelastine and fluticasone in a combination formulation. Petitioner has not met its burden. In fact, Petitioner has not demonstrated that the two agents were even used *routinely* or in any *fixed regimen*, as in the *Leo Pharma* and *Brimonidine* cases that nevertheless fell short of obviousness. Thus, Petitioner's “clinical use” motivation is insufficient as a matter of law, and reveals a textbook case of improper

hindsight.

Next, Petitioner's argument that the AR treatment guidelines recommend the use of azelastine and fluticasone is equally unpersuasive. Pet. 35-36 (citing Dykewicz (EX1019); Berger (EX1021); Cauwenberge (EX1022) (collectively, "AR treatment guidelines"); and Kusters (EX1016)). Those guidelines actually demonstrate that: (i) there was no clinical benefit to co-administration of steroids and antihistamines compared to steroids alone; and (ii) physicians treating AR required a flexible approach to treating patients that allowed for dose titration and combination of different therapies. Nothing in the guidelines suggest, even remotely, that azelastine and fluticasone should be administered in a combined formulation.

In contrast, the art as of 2002 showed that there was no clinical benefit to co-administration of steroids and antihistamines compared to steroids alone. Indeed, the guidelines and prevailing clinical practice all taught a flexible approach, where an antihistamine could be added to a steroid in an "as needed" or "intermittent" basis. CIP2147, ¶¶66-71, 84. Second, a POSA would have read the AR treatment guidelines in view of other teachings in the art that the fixed co-administration of steroids and antihistamines were no more effective than steroids alone, further negating any alleged "motivation" to pursue a combination formulation. CIP2147, ¶85.



No less than six studies had published by 2002 to evaluate whether the co-administration of antihistamines and steroids would yield any additive benefit. Several included data that showed increased side effects, and none showed a reduction in side effects from the co-administration of two agents. CIP2147, ¶¶ 52, 55-56, 59; EX1039, 6; EX1036, 6; EX1040, 6; EX1035, 8. Of those, four concluded that:

- Beclomethasone (a steroid) when used with astemizole (an antihistamine) “***provided no better control of rhinitis than beclomethasone alone.***” EX1039, 627 (emphasis added).
- Fluticasone when used with cetirizine (an antihistamine) showed “***no significant difference in efficacy***” compared to fluticasone. EX1040, 225 (emphasis added).
- Budesonide (a steroid) when used with terfenadine (an antihistamine) “***produced a similar effect to treatment with budesonide alone.***” EX1036, 497 (emphasis added).
- Adding loratadine (an antihistamine) to fluticasone “***does not confer meaningful additional benefit.***” EX1034, 118 (emphasis added).

A POSA would have understood these studies to teach no additional benefit to co-administration of antihistamines and steroids than steroids alone. CIP2147, ¶¶ 52, 55-57.

Petitioner relies on the remaining two studies, but they too do not establish any meaningful clinical benefit. For example, Drouin (EX1035) reported data across the four primary AR symptoms—itching, sneezing, runny nose, and congestion (individually and collectively)—showing purported clinical improvements from co-administering beclomethasone (a steroid) and loratadine (an antihistamine) ranging from 2% to 13%. EX1035, 5; CIP2147, ¶59. But, these “improvements” are less than that shown by the typical placebo group—a standard control group used to eliminate bias in clinical studies. CIP2147, ¶59, n.3. This result would not have motivated a POSA to pursue a combination formulation of azelastine and fluticasone.

Brooks (EX1038) fares no better. In fact, a POSA, as Dr. Carr explains, would have viewed Brooks’ results to be unreliable. For example, Petitioner repeatedly asserts that steroids were well-known to be substantially more effective than antihistamines in treating AR. EX1003, ¶¶52, 54. Yet Brooks reports the opposite—that beclomethasone (a steroid) was no more effective than loratadine (an antihistamine) alone. EX1038, 195. That outcome is contrary to clinical knowledge as of 2002, as even Petitioner concedes. CIP2147, ¶60; EX1003, ¶52. These findings come nowhere close to motivating a POSA to pursue a steroid/antihistamine combination. CIP2147, ¶85.

After Drouin and Brooks, researchers in 2000-2002 reviewed the available

literature in retrospective analyses. CIP2147, ¶¶61-63; CIP2041; CIP2042). The unanimously concluded that using a steroid with an antihistamine conferred no meaningful benefit. In 2000, Howarth taught that the available co-administration studies “do not support a superior effect” with co-administration versus the steroid alone. CIP2041, 10. And then, in 2001, Nielsen stated that “[c]ombining antihistamines and steroids in the treatment of [AR] does not provide any additional effect to intranasal corticosteroids alone.” CIP2042, 1564. In 2002, Andy stated that “[c]ombination nasal steroids and nonsedating antihistamines yields no additional benefits,” and further assigned the grade of “A” to the strength of the evidence supporting this conclusion. CIP2147, ¶63; CIP2162, 1.

Nielsen and Andy explicitly considered several of the references that Petitioner and Dr. Schleimer now use to argue that a clinical benefit existed: Juniper 1989 (EX1039); Ratner (EX1034); Benincasa (EX1040); Simpson (EX1036); Brooks (EX1038); and Juniper 1997 (EX1031). *See* CIP2042, 1572. Howarth, Nielsen, and Andy reflect the total weight of clinical evidence in 2002 and confirm what a POSA would have understood—that there was no reason to combine an antihistamine and a steroid in the same formulation for treating AR. CIP2147, ¶64. Further, this knowledge, in conjunction with Shenfield’s teaching that “[i]n some circumstances patients may be exposed to additional ingredients with little therapeutic benefit and major potential side effects,” would have

dissuaded a POSA from pursuing a combination of an antihistamine and a steroid. CIP2147, ¶85; CIP2043, 13.

In addition, based on these teachings, a POSA would have recognized that the statements in the art regarding co-administration were guided by benefits other than clinical efficacy—things like patient compliance and reduced side-effects—that inure specifically from the selection of an *oral* antihistamine (not an intranasal antihistamine like azelastine). CIP2147, ¶¶74-79, 86-87. Thus, the statements identified in the Petition would have guided a POSA to one of several oral antihistamines, which dominated the AR market, and away from the claimed invention that uses intranasal azelastine.

Next, Petitioner's assertions of motivation are further belied by the realities of clinical practice, where physicians treating AR required a flexible approach to treating patients. CIP2147, ¶¶65-72, 84. The treatment guidelines recommended a stepwise approach starting with intranasal steroids and, if that did not work, attempting any of the following: (1) adding oral steroids, (2) adding nasal decongestants, (3) doubling the dose of intranasal steroid, (4) adding an antihistamine, (5) adding an anticholinergic, and (6) adding an oral antihistamine/decongestant. EX1024, 110-111. Once symptoms were controlled, these treatments were to be reduced in stepwise fashion. EX1024, 111. And other guidelines recommended a flexible approach of titrating drug doses or cycling

through therapies, which is further consistent with the clinical trial-and-error treatment approach. CIP2147, ¶¶66-67.

A combined formulation would cause physicians to act against the AR guidelines and prevailing clinical practice, and relinquish the long-practiced flexible approach to treating patients with AR. Indeed, Shenfield taught “[o]ne of the major problems [with fixed dose combination] is that the prescribing doctor loses flexibility in patent management.” EX2043, 12. Consequently, a POSA would not have been motivated to combine a steroid with an antihistamine in a dosage form for treating AR. On its face, these reasons demonstrate why, before Cipla’s invention, no one else had previously brought to market a combined steroid/antihistamine nasal spray formulation despite these drugs being *known* for decades. CIP2167, 1 (antihistamines known since 1950s); EX1024, 90 (nasal steroids introduced in 1973). Indeed, the motivation was to have them separate so as to preserve clinical flexibility to titrate as needed. CIP2147, ¶¶69.

In sum, the weight of clinical evidence by 2002 confirmed that no meaningful clinical benefit resulted from using an antihistamine with a steroid, the treatment guidelines recommended a trial-and-error approach, and physicians needed flexibility in dose titration and choice of therapy. The prevailing knowledge and clinical practice in 2002 gave a POSA no motivation to combine azelastine and fluticasone into a combination formulation; it did just the opposite.

**B. A POSA would have understood that azelastine and fluticasone had redundant mechanisms of action *in vivo*, further negating any motivation to combine into a single formulation.**

Petitioner's assertion that alleged "complementary mechanisms of action" of azelastine and fluticasone would have motivated a POSA to pursue a combined formulation is not supported. Pet. 36-38. As of 2002, the art had rejected the idea that antihistamines and steroids had complementary mechanisms of action because it was discovered that their mechanisms of action were redundant *in vivo*. CIP2147, ¶¶ 16, 19, 37, 61-62, 71, 88; CIP2041, 5.

For example, Howarth's retrospective study discussed above explicitly rejected Petitioner's "complementary mechanisms of action" theory. Howarth explained that, "although antihistamines and corticosteroids *might appear to have complementary mechanisms of action*," nonetheless "the lack of additional clinical benefit when antihistamines are used in combination with corticosteroids indicates that, *in vivo*, the anti-inflammatory effects on the airway of corticosteroids *overlap* those of the H<sub>1</sub>-antihistamines, making the action of the latter *redundant*." CIP2041, 6, 10. Accordingly, by 2002, a POSA would not have expected complementary mechanisms of action between azelastine and fluticasone and therefore would have had no reason to combine based on any expectation of complementarity.

Petitioner also relies on Advair DISKUS to support its complementary

mechanisms of action theory. Pet. 42. But Petitioner is reaching, as Advair DISKUS is for the treatment of asthma, and irrelevant to the treatment of AR. CIP2147, ¶72, n.6; EX1030, 16; EX1033, 2-3. It also is a powder dosage form for oral inhalation, not a steroid suspended in an antihistamine solution for nasal administration. CIP2150, ¶34; EX1033, 2-3. Similarly, the drug components of Advair DISKUS—a steroid and a long-acting bronchodilator—were established undisputedly to have complementary mechanisms of action, whereas the opposite was shown for steroids and antihistamines. CIP2147, ¶72, n.6; CIP2161, 1. Accordingly, a POSA would not have been motivated by Advair DISKUS.

Petitioner also relies on Spector to suggest motivation to combine. Pet. 36. This also is wrong. A POSA would not have viewed Spector as calling for a combination formulation. First, Spector provided a laundry list of available drugs, but does not even acknowledge the existence of intranasal antihistamines, like azelastine. *See generally* EX1023. Second, Spector states that the “ideal pharmacologic therapy” for AR should have a “favorable safety profile” but then explicitly identifies steroids in general, and fluticasone in particular, as causing a “safety” “concern.” CIP2147, ¶72; EX1023, 2. Third, a POSA would have viewed Spector’s call for an “ideal pharmacologic therapy” to be seeking a new chemical entity, not a combination of available drugs. CIP2147, ¶¶72-73.

**C. There is no factual support for Petitioner's assertion that combining azelastine and fluticasone would increase treatment compliance.**

Petitioner claims that improved patient compliance would have motivated a POSA to arrive at a combined formulation. Pet., 38-39. Several facts undermine Petitioner's assertion. First, Petitioner has not come forward with any evidence that compliance was a problem for this patient population, or that physicians were faced with any difficulty in ensuring that patients were taking steroids with intermittent antihistamines. To the contrary, Juniper 1997 shows that compliance was *not* a problem for the "on demand" therapy recommended for azelastine. CIP2147, ¶¶ 68-69. Next, the art had disproven Petitioner's premise that a fixed-dose combination would have greater compliance than the use of two drugs separately administered. A POSA in 2002 would have known that "combining 2 drugs in a single tablet had no effect on compliance." CIP2147, ¶86; CIP2043, 16.

The AR treatment guidelines specifically recommended that when azelastine is used with another drug, it should be used as an "on demand" treatment. CIP2147, ¶70; EX1024, 90; EX1022, 5. Juniper 1997, which Petitioner relies upon, provides an example of this recommendation in practice. There, patients were instructed to take a steroid consistently and, "when needed," use an antihistamine. Juniper showed that patients "needed" the antihistamine only once every seven days. EX1031, 5. As this data showed, when patients felt that they "needed" a

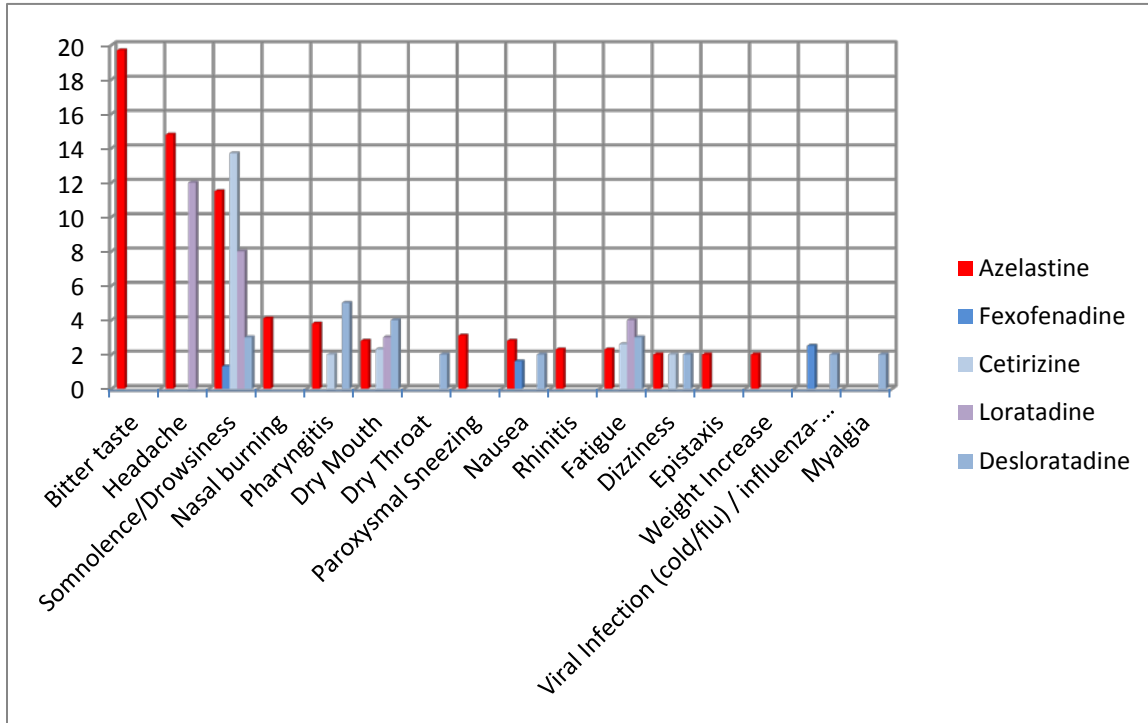


second drug in accordance with the recommendations for use of azelastine, they took it. CIP2147, ¶¶69; CIP2043, 18 (suggesting compliance is not a concern when, as in AR, treatment is symptomatic). There was no compliance issue.

The art would have further dissuaded a POSA from using azelastine to address compliance concerns. First, azelastine was administered intranasally. EX1008, 2. But Galant taught that “[t]he clinician can improve adherence by selecting *oral medications* that taste good, require once daily administration, and have an obvious beneficial effect with minimal adverse effects,” all of which were problems with azelastine at the time. EX1041, 10 (emphasis added). A POSA seeking to improve patient compliance would thus have turned to the more preferred oral antihistamines to supplement the steroid treatment, not intranasal azelastine, because they did not have bad taste, generally required only once-daily administration, and otherwise had fewer (and less frequent) side effects than azelastine. CIP2147, ¶¶88-90. These problems with azelastine, however, would actually decrease compliance. CIP2147, ¶¶87-91; CIP2043, 6.

As shown in Figure 1, azelastine had substantially more side effects as compared to oral antihistamines like Allegra<sup>®</sup> (fexofenadine), Zyrtec<sup>®</sup> (cetirizine), Claritin<sup>®</sup> (loratadine), and Clarinex<sup>®</sup> (desloratadine).

Figure 1



CIP2147, ¶¶75-78; EX1008, 3; CIP2034, 4, 6, 9; CIP2169, 2.

Notably, the only drug with a bad taste—a specific side effect known to reduce compliance—was azelastine. CIP2147, ¶88; EX1024, 90; EX1022, 5 (both identifying bad taste as “specific” to azelastine). Moreover, as Shenfield explains: “the use of 2 drugs will always increase the risk of adverse drug reactions both idiosyncratic and pharmacological.” EX2043, 13. Indeed, “[i]n some circumstances patients may be exposed to additional ingredients with little therapeutic benefit and major potential side effects.” *Id.* Since a POSA would have not expected any meaningful treatment benefit from a fixed antihistamine-and-steroid regimen, and would have expected increase in side effects, a POSA actually

would have had concerns that patient compliance would drop with a intranasal azelastine/fluticasone combined dosage form. CIP2147, ¶¶ 88-90.

**D. Petitioner's "anti-inflammatory properties" justification for selecting azelastine is based on improper hindsight.**

Petitioner wrongly asserts that a POSA would have been motivated to select azelastine for use in a combination formulation because of its anti-inflammatory (*i.e.*, decongestant) effect. Pet. 35; EX1003, ¶¶62, 66-67. Exercising hindsight, Petitioner and its expert, Dr. Schleimer, admittedly only considered intranasal antihistamines, but ignored the vastly larger and more widely used class of available oral antihistamines that had the same properties. CIP2158, 36:9-37:2 (testifying, in response to a question about oral antihistamines, that "this line of questioning is taking us away from the relevant area. I think what's relevant in the context of this litigation is the antihistamines that could be administered locally in a nasal formulation, and there are only two of them."). Contrary to Dr. Schleimer's assertion, potential anti-inflammatory effects are not unique to azelastine, so this property would not have motivated a POSA in 2002 to select the lesser-desired intranasal azelastine over a more-desired oral antihistamine.

Petitioner cites Kusters as its sole support contending that azelastine was "unique" due to its anti-inflammatory properties. Pet. 35 (citing EX1016).

Petitioner's reliance is misguided given that Kusters tested the effect on various inflammatory mediators of several antihistamines, and the data shows that oral

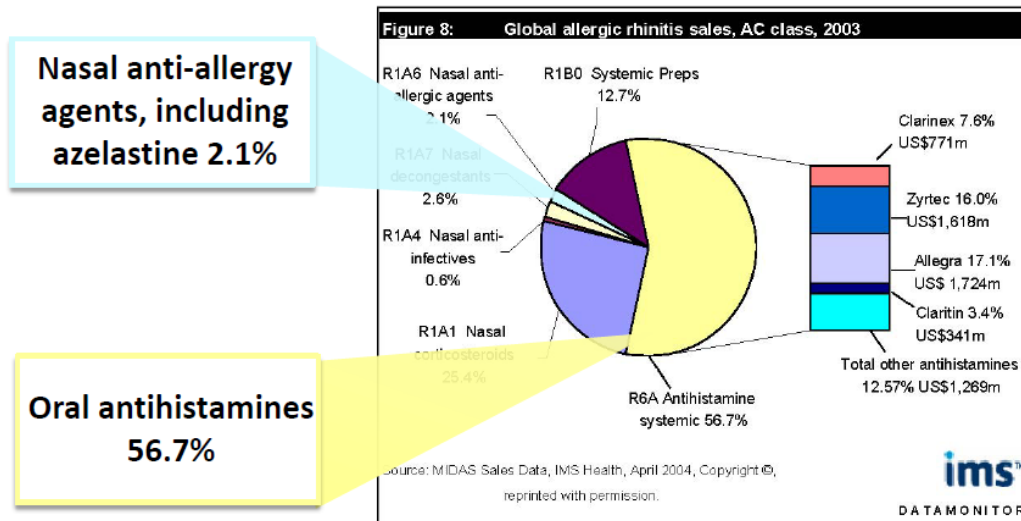
terfenadine was “equally effective as azelastine” in inhibiting inflammatory mediators. CIP2147, ¶93; EX1016, 3-4. Kusters also states that at least loratadine, desloratadine, and mizolastine have similar promise in inhibiting inflammatory mediators. EX1016, 3-4. But Kusters was not the only resource on this topic: Dr. Schleimer’s own patent (filed in 2001) is replete with reference to desloratadine’s anti-inflammatory activity in an oral dosage form. CIP2147, ¶94; CIP2145. Hayashi, cited in the Schleimer patent, adds cetirizine and ketotifen to the list of oral antihistamines with anti-inflammatory activity. CIP2147, ¶¶73, 94; CIP2157, 1-2.

Moreover, all of Petitioner’s alleged motivations to select azelastine and to combine azelastine and fluticasone into a combination formulation are directly undermined by the dominance of oral antihistamine use by 2002. Specifically, the oral antihistamines in 2002 had no compliance issues that azelastine had, were at least as effective as azelastine (CIP2147, ¶102; CIP2042, 4), had better side effect profiles than azelastine (CIP2147, ¶¶75-78; CIP2034, 4, 6, 9; CIP2169, 2), and had anti-inflammatory effects similar to azelastine. CIP2147, ¶¶92-94; EX1016, 3-4; CIP2145; CIP2157, 1-2). But rather than consider the art as a whole, as they must, Petitioner and Dr. Schleimer admittedly ignored oral antihistamines completely in their analysis. CIP2158, 36:9-37:2.

The preference for oral antihistamines and the dislike for azelastine is

reflected in drug sales data around 2002. Figure 2 shows that nearly 60% of AR drug sales were for oral antihistamines, and only about 2% for all intranasal agents, which included azelastine. CIP2147, ¶¶79; CIP2138, 29.

Figure 2

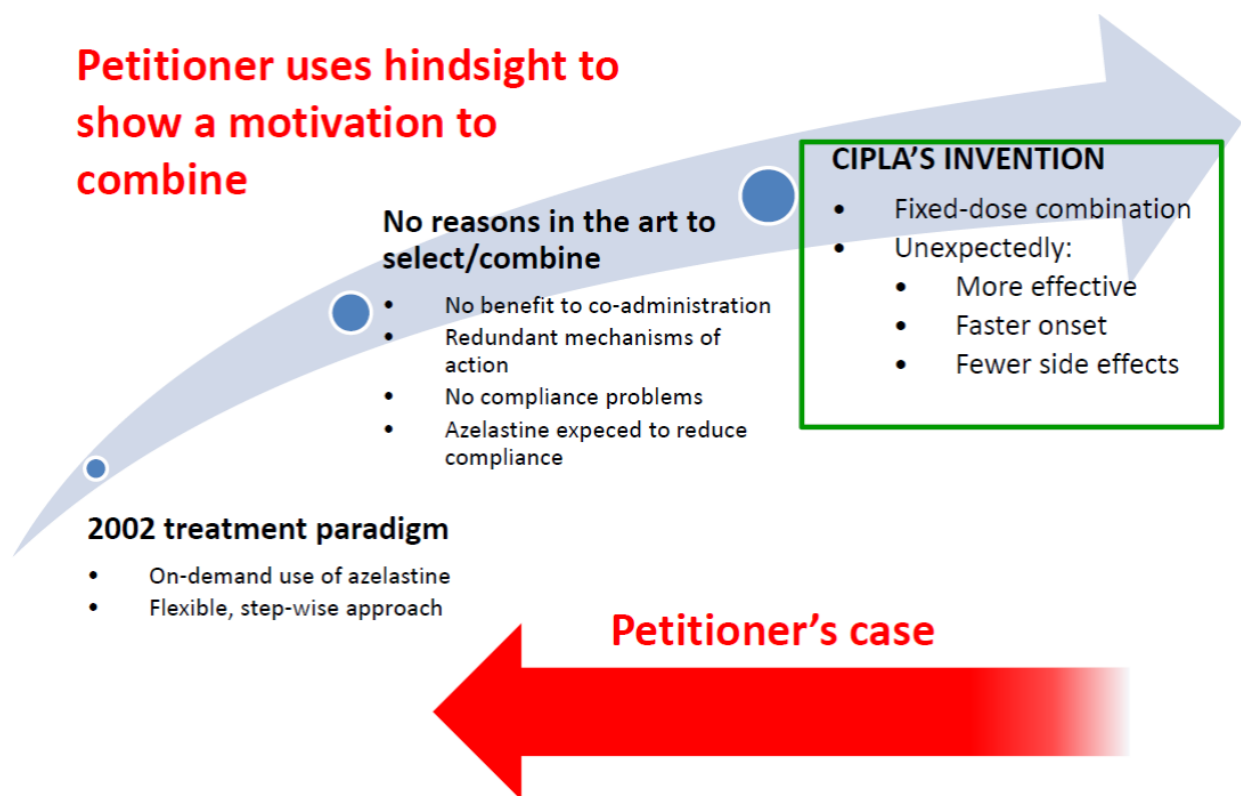


Petitioner's failure to even address oral antihistamines underscores the hindsight plaguing its obviousness theories. Indeed, when asked about the efficacy of oral antihistamines at his deposition, Dr. Schleimer admitted that his analysis, where he summarily asserted that "azelastine was the most effective antihistamine on the market," actually only considered one other *intranasal* antihistamine, and that oral antihistamines were not "relevant" to this case because the challenged claims relate to azelastine—an intranasal antihistamine. CIP2158, 36:9-37:2. He essentially admitted that he began his analysis with the claims and worked backward. But "defining the problem in terms of its solution," as Petitioner and Dr.

Schleimer have done here, “reveals improper hindsight in the selection of the prior art relevant to obviousness.” *Insite Vision Inc. v. Sandoz, Inc.*, 783 F.3d 853, 859 (Fed. Cir. 2015).

Figure 3 illustrates how Cipla proceeded, contrary to the prior art and prevailing practice, to arrive at its pioneering formulation. Ignoring the art as a whole, Petitioner and its declarants selectively “cherry-pick” through the prior art, relying on references it views as favorable and ignoring the rest. Petitioner’s “cherry-picking” is symptomatic of hindsight. *See Azko N.V. v. U.S. Int’l Trade Comm’n*, 808 F.2d 1471, 1481 (Fed. Cir. 1986) (explaining it is improper to “pick and choose among individual parts of assorted prior art references as a mosaic to recreate a facsimile of the claimed invention.”).

Figure 3



**V. A POSA WOULD NOT HAVE HAD A REASONABLE EXPECTATION OF SUCCESSFULLY COMBINING AZELASTINE AND FLUTICASONE INTO A SINGLE DOSAGE FORM THAT WAS “SUITABLE FOR NASAL ADMINISTRATION.”**

Every challenged claim requires that the azelastine/fluticasone combination formulation be “suitable for nasal administration” or a “nasal spray.”<sup>3</sup> See § III. Petitioner has not established that a POSA in 2002 would have had a reasonable

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<sup>3</sup> And as above in §III, the meaning of the claim term “nasal spray” of claims 24 and 25 would be synonymous with the meaning of the term “suitable for nasal administration.” CIP2150, ¶¶21-23.

expectation of successfully combining Segal, Hettche, Phillipps, and the Flonase<sup>®</sup> label to arrive at the claimed azelastine/fluticasone combination formulation that is “suitable for nasal administration.” *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016) (“The reasonable expectation of success requirement refers to the likelihood of success in combining references to meet the limitations of the claimed invention.”).

As with its motivation arguments, Petitioner’s allegations concerning any reasonable expectation of success are based on hindsight. Petitioner presumes, incorrectly, that a POSA would begin formulating by simply selecting Astelin<sup>®</sup> and Flonase<sup>®</sup>, the branded azelastine and fluticasone products commercially available in 2002. Pet., 39-41, 44-50. But Petitioner ignores the significant problems with that approach: (1) fluticasone was known to aggregate and settle when co-formulated in liquid formulations with a second active ingredient; (2) the thickening agents used in Flonase<sup>®</sup> and recited in the challenged claims—MCC and CMC—were incompatible with cationic drugs and electrolytes like azelastine salts; and (3) a POSA following the prior art guidance of Cramer and Segal would not have arrived at a formulation that was “suitable for nasal administration.” Multiple formulators, acting as a POSA in 2002, all failed to formulate Cramer’s Example III to arrive at a formulation that was “suitable for nasal administration” because it was: (i) unacceptably acidic; (ii) unacceptably unstable with significant



settling and caking; and (iii) unacceptably hypertonic. Each of these issues is addressed in turn below and demonstrate no reasonable expectation of success.

**A. A POSA would have been dissuaded by fluticasone's propensity to aggregate when co-formulated with other drugs in liquid formulations.**

Aware that the prior art taught that fluticasone would aggregate, cake, and settle when co-formulated in a liquid formulation with a second active ingredient, a POSA would not have had a reasonable expectation of successfully arriving at liquid formulations claimed in the '620 patent. CIP2150, ¶34. Prior to 2002, GlaxoSmithKline—the developer of fluticasone—reported that fluticasone particles aggregated and settled when co-formulated in a liquid formulation with a second active ingredient (salmeterol xinafoate). CIP2150, ¶34; CIP2111,1; CIP2044, 1. A POSA would have been concerned that such known problems would result in loss of dose uniformity and physical stability of the formulation, negating any reasonable expectation of successfully arriving at an azelastine/fluticasone combination formulation that was “suitable for nasal administration.” CIP2150, ¶¶34-35.

The problems involving co-formulating with fluticasone reported by GlaxoSmithKline—aggregation, settling, and caking—are the very shortcomings in the prior art that distinguished the claimed “suitable for nasal administration” azelastine/fluticasone formulation. *See* § III. GlaxoSmithKline recognized that

“[c]ombined drug formulations are less well understood and, as a result, a significant amount of fundamental scientific research work on the subject [would need to be] undertaken.” CIP2044, 2. A POSA, thus, would have understood the risks in combining fluticasone with a second active ingredient in liquid formulations and that “a significant amount of fundamental scientific research work” would be needed, so these concerns would have caused a POSA to doubt whether fluticasone could be successfully combined with azelastine. CIP2150, ¶¶34-35.

**B. Azelastine was known to be incompatible with MCC and CMC, the thickening agents used in Flonase<sup>®</sup>.**

Petitioner’s overly simple assertion that a POSA would merely have arrived at the claimed invention by cherry-picking from the excipients in Astelin<sup>®</sup> (the commercial embodiment of Hettche) and Flonase<sup>®</sup> ignores known incompatibilities between ingredients in these products. Before 2002, the art taught that azelastine and the thickening agents CMC and MCC would be incompatible, further undercutting any reasonable expectation of successfully combining the two formulations. CIP2150, ¶45.

For example, Lieberman teaches that “[CMC] solutions have poor tolerance for electrolytes ... as they precipitate the polymer.” CIP2150, ¶¶46-47; CIP2113, 24. Lieberman further discloses that “CMC . . . is incompatible with cationic drugs,” and concludes that MCC was also known to be “incompatible with cationic

drugs and electrolytes.” *Id.* And it was known by 2002 that azelastine was formulated as a salt. CIP2150, ¶47; EX1007, 3:48-56; EX1008, 1. An azelastine salt—like the claimed azelastine hydrochloride—would dissociate into electrolytes, with azelastine being a cation and the chloride ion being an anion. CIP2150, ¶47. And in solution, azelastine behaves as a cationic drug. *Id.* Accordingly, CMC and MCC would be in the presence of both electrolytes and a cationic drug if formulated with the claimed azelastine salts as Petitioner advances, which would be contrary to Lieberman’s warning.

Rather than addressing this known incompatibility facing a POSA, Petitioner turns to yet another reference, Hettche, relying on its identification of CMC as one of many possible thickening agents for azelastine formulations. Pet. 44-45, 47; EX1004 ¶59. In so doing, Petitioner assumes that no incompatibilities existed, without providing any scientific support or rationale. But Hettche’s broad disclosure does not overcome the known compatibility problems. Hettche does not disclose any example formulations using CMC with azelastine but does disclose azelastine formulations using HPMC—the thickening agent used in Astelin<sup>®</sup>. CIP2150, ¶49; EX1007, 4:54-61. And because Lieberman’s disclosure is later in time and explicit, Lieberman would trump the earlier and non-specific list in Hettche. CIP2150, ¶49; CIP2113, 24; EX1007, 1.

Azelastine’s incompatibility with MCC and CMC was confirmed by Meda’s

(developer of Astelin<sup>®</sup>) work with azelastine formulations. CIP2150, ¶48. As explained in detail in §VIII.E, Meda continually observed a precipitant, which it believed was azelastine, when it tried to dissolve azelastine into the Flonase<sup>®</sup> excipients that contained CMC/MCC. And Dr. Donovan's admissions in the related *Apotex* case are consistent with the expected incompatibility between MCC/CMC and azelastine salts. There, Dr. Donovan tried to rebut evidence of Meda's failure (*see* §VIII.E) by stating: "it is highly probable that the precipitate was not azelastine hydrochloride, which is a sparingly soluble material but rather the MCC from the Avicel in the Flonase<sup>®</sup>." CIP2014, 240:15-21.

Regardless of whether it was the azelastine crystals precipitating as Meda believed, the MCC precipitating as Dr. Donovan contends, or the CMC precipitating as the prior art teaches, there is no dispute that unacceptable precipitation occurs when azelastine is formulated with MCC or CMC; an important incompatibility that Petitioner has neither reconciled nor even addressed. Hence, a POSA would have had no reasonable expectation that one could simply combine Astelin<sup>®</sup> and Flonase<sup>®</sup> and arrive at an azelastine/fluticasone combination formulation that is suitable for nasal administration. CIP2150, ¶45.

**C. Cramer and Segal underscore the lack of reasonable expectation of success.**

Petitioner relies on two abandoned patent applications—Segal and Cramer—for its unsupported mantra that it would have been "routine" to combine azelastine

and fluticasone into a combination formulation. Pet. 39-40; EX1004, ¶¶51, 67. But Segal and Cramer provide *no* meaningful guidance as to the critical formulation information, for example, what excipients and concentrations of excipients to use to successfully formulate an azelastine/fluticasone combination. And besides Cramer and Segal, the art generally did not provide this guidance. CIP2150, ¶¶24-26.

Starting with Cramer, Petitioner artfully tries to avoid the inconvenient fact that Example III of Cramer, identified by the PTO as the closest prior art, was shown not to be “suitable for nasal administration” both during original prosecution and again in litigation. CIP2150, ¶36; EX1002, 220, 286. A POSA would not have reasonably expected any success in co-formulating azelastine/fluticasone into a formulation “suitable for nasal administration” when the only other example in the prior art was not suitable. *See Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.*, 320 F.3d 1339, 1354 (Fed. Cir. 2004) (“[T]here can be little better evidence negating an expectation of success than actual reports of failure.”).

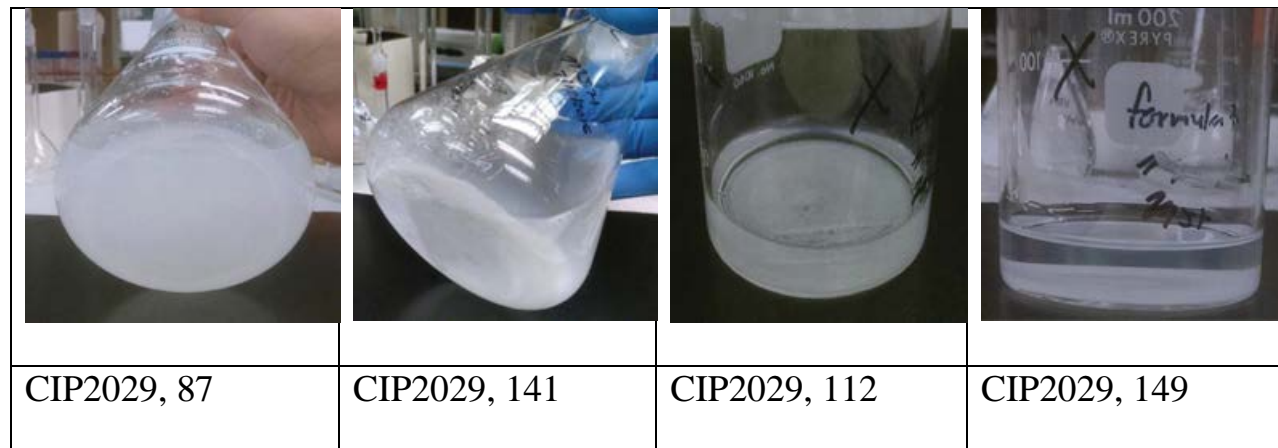
Cramer’s Example III (azelastine hydrochloride/triamcinolone acetonide) formulation—which the Patent Office determined to be the closest prior art—was repeatedly found to not be suitable for nasal administration. First, co-inventor Geena Malhotra found that Cramer Example III exhibited (1) unacceptable settling

and difficulty resuspending, which would undermine the drug homogeneity of the formulation, (2) unacceptable jet spray, which would undermine the ability of the drug to be deposited on the nasal mucosa, and (3) unacceptably high osmolality, which would be expected to cause irritation. EX1001, 284-287.

Next, during the *Apotex* case, Dr. Donovan's colleague, Dr. Ram Govindarajan, also attempted to recreate Example III, and failed. CIP2150, ¶¶37-41. Notably, although Dr. Donovan relied on Dr. Govindarajan's testing in the *Apotex* case, Dr. Donovan now retreats from that testing in this proceeding, failing to even mention it or explain Dr. Govindarajan's findings. CIP2150, ¶¶68-75; CIP2030, 31, 39; CIP2015, 63-64. And for good reason, Dr. Govindarajan's attempted formulations were: (i) unacceptably acidic; (ii) unstable, leading to significant caking of azelastine; and (iii) unable to consistently deliver proper doses. CIP2150, ¶¶37-41; EX1002, 286-287; CIP2030, 31, 39; CIP2029, 37-45, 48-49, 53, 57.

Further, Cipla's testing expert in the *Apotex* case, Dr. Herpin, also confirmed that Example III possessed a non-uniform formulation, exhibited significant settling and caking, had an unacceptably high osmolality, and was unacceptably acidic. *Id.* In sum, three different formulators have attempted to recreate Example III and each time the results proved that Example III rapidly settles, exhibits an unacceptably high osmolality, and is unacceptably acidic—all reasons why Cramer

Example III was not suitable for nasal administration. CIP2150, ¶¶37, 38, 40; CIP2104, 6-7; CIP2103, 12; CIP2113, 5; CIP2112, 19. Representative images from Dr. Herpin's testing, which show the considerable degree to which Example III settles and cakes, are shown below.



Petitioner baldy asserts that “excipients may be adjusted for a desired effect and/or substituted with different excipients to obtain the desired effect.” Pet. 49; EX1004, ¶ 65-71. Not so. Dr. Govindarajan applied routine deviations and still could not overcome the formulation problems. CIP2150, ¶¶42-43. Dr. Govindarajan's recreations used a low-viscosity grade HPMC thickening agent and high-speed mixing steps not shown in Cramer, but was unable to keep the formulation from settling. CIP2150, ¶¶42-43; CIP2030, 27, 30-31, 33, 36, 37; CIP2105, 4-6; CIP2040, 4. Likewise, Dr. Herpin tried various modifications to Cramer's teachings, also to no avail. Dr. Herpin used a medium-viscosity grade HPMC, but also experienced significant settling. CIP2150, ¶¶42-43; CIP2029, 3; CIP2029, 3. These modifications to Example III that still failed belies Petitioner's

overly simplistic assertion that “routine modifications” could be made to arrive at Cipla’s invention, and confirms that a POSA would not have had a reasonable expectation of successfully arriving at the claimed “suitable for nasal administration” formulation. CIP2150, ¶¶42-43.

Next, Segal is worse than Cramer, lacking any meaningful formulation details such as suitable excipients or suitable concentrations of excipients, and contains no formulation examples that might guide a POSA. CIP2150, ¶¶27-29; EX1012, 4-6. And although Segal cites to *Remington’s*, *Remington’s* does not contain a discussion of how to suspend an active ingredient in a solution of another active ingredient, like Cipla’s invention. CIP2150, ¶29; EX1012, 6; CIP2026, 13-14. Indeed, the Board has already found that Segal “literally discloses more than 800 million compositions.” Paper 11, p. 13. Unlike Segal, Cramer, which Cipla already overcame during prosecution, contains exemplary formulations and discussion of possible excipients. CIP2150, ¶¶30-31; EX1011, 4:6-6:51. And even with Cramer’s disclosure, it was still insufficient to arrive at an azelastine/fluticasone combination formulation that was suitable for nasal administration. CIP2150, ¶¶30-31.

**D. Petitioner’s remaining assertions of reasonable expectation of success equally fail.**

Petitioner asserts that the ’620 patent “admits” that a POSA can formulate an azelastine/fluticasone combination formulation. Pet. 39. The ’620 patent contains



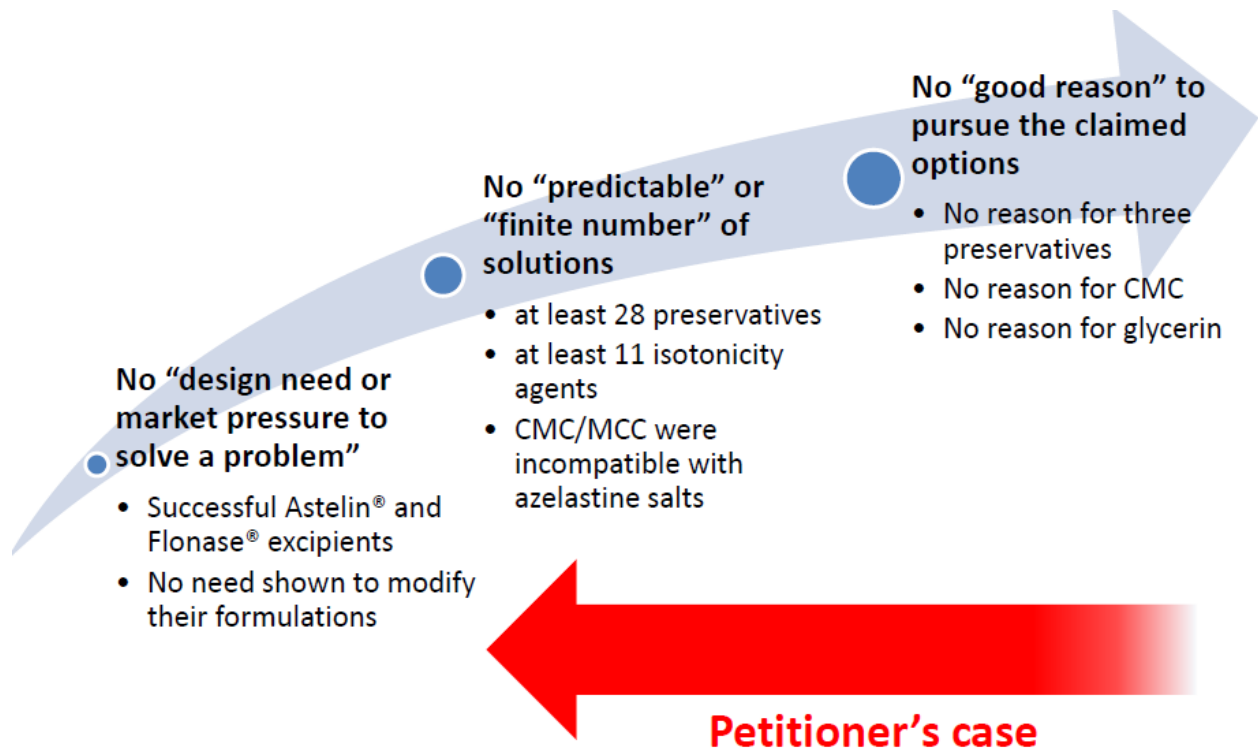
no such “admission.” Here’s the passage Petitioner cherry picks: “*In Examples* where only the ingredients of formulations according to *the present invention are listed*, these formulations are prepared by techniques well known in the art.” EX1001, 7:67-8:2 (emphasis added). This language refers to the subsequent Examples disclosed in the ’620 patent, and mentions prior art formulation techniques only in that context. CIP2150, ¶32. A POSA would have understood that known techniques could be used to formulate the invention of the ’620 patent after viewing its teachings. *Id.* “That the inventors were ultimately successful is irrelevant to whether one of ordinary skill in the art, at the time the invention was made, would have reasonably expected success.” *Life Techs., Inc. v. Clontech Labs., Inc.*, 224 F.3d 1320, 1326 (Fed. Cir. 2000); *Lupin Ltd. v. Pozen Inc.*, IPR2015-01773, Paper 36, at 35 (Sawert, J.) (rejecting use of the specification of the challenged patent in an obviousness analysis). Petitioner’s attempt to use disclosures in the very ’620 patent that they challenge serves only to further highlight the hindsight prevalent throughout its arguments.

Equally unsupported is Petitioner’s assertion that “a POSA was presumptively enabled to make a formulation” of azelastine and fluticasone because those drugs were patented in Hettche and Phillips. CIP2150, ¶33. Neither Hettche nor Phillips disclose any combination formulation, nor does Dr. Donovan so contend. *See* EX1004 ¶51.

**VI. CLAIMS 42-44 WOULD NOT HAVE BEEN OBVIOUS IN VIEW OF SEGAL, HETTCHÉ, PHILLIPPS, AND THE FLONASE<sup>®</sup> LABEL.**

Perhaps Petitioner's most egregious use of hindsight occurs in theorizing how a POSA would have selected the specific excipients recited in claims 42-44. Petitioner relies on an "obvious to try" theory, but to succeed, Petitioner must show that a POSA would have been aware of: (i) a "design need or market pressure to solve a problem;" (ii) "a finite number of identified, predictable solutions;" and (iii) a "good reason to pursue the known options within his or her technical grasp." *KSR Intern. Co. v. Teleflex Inc.*, 550 U.S. 398, 402 (2007). These requirements safeguard against improper hindsight, and aim to prevent using an inventor's patent as a blueprint for obviousness. *Id.* As summarized in Figure 4 and as explained in more detail below, Petitioner fails on all three prongs.

Figure 4



To render claims 42-44 obvious-to-try, Petitioner must prove there was a "problem" with the excipients successfully employed in Astelin® (the commercial embodiment of Hettche) and Flonase® (the commercial embodiment of Phillipps) for which "a finite number of identified, predictable solutions [i.e., excipients]" existed and that a POSA had "good reason" to pursue. *KSR*, 550 U.S. at 418. Petitioner's argument fails at each stage.

Instead, of identifying a prior-art-recognized design need or market pressure, Petitioner identifies the alleged problem by starting with claims 42-44 themselves, and then improperly tracing steps backwards by cobbling together four different prior art references—Hettche, Phillips, Segal and the Flonase® label—to support its

theory. Pet., 44-48. But even assuming a POSA would have been motivated to combine azelastine and fluticasone and to consider these references, as Petitioner posits,<sup>4</sup> Petitioner provides no evidence to support why a POSA would then cherry pick excipients from between the four combined references rather than selecting the successfully employed excipients used individually in Astelin<sup>®</sup> and Flonase<sup>®</sup>. Further, Petitioner provides no motivation for a POSA to ignore the successfully used isotonicity agents in Astelin<sup>®</sup> and Flonase<sup>®</sup> and instead use glycerine.

**A. MCC and CMC were incompatible with cationic drugs and electrolytes like azelastine salts.**

Claims 42-44 each require MCC and CMC. Flonase<sup>®</sup> uses MCC/CMC, whereas Astelin<sup>®</sup> uses HPMC as the thickening agent. EX1008, 2; EX1010, 1. Petitioner claims that a POSA would use MCC/CMC because it was used in Flonase<sup>®</sup> and disclosed in Hettche. Pet. 44-45. But, here too, Petitioner ignores the important known incompatibility with these excipients and azelastine salts in solution that would have dissuaded a POSA, as explained in § V.B. Neither Petitioner nor Dr. Donovan provide any rationale to overcome this incompatibility to justify its argument that a POSA would ignore this concern, and still forge ahead with MCC/CMC. This is again hindsight. Rather, a POSA would have looked to any of the other known thickening agents, including HPMC—the thickening agent that was already known to be compatible with azelastine. CIP2150, ¶49.

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<sup>4</sup> See §§ IV-V above as to why they would not.

MCC/CMC would not have been an obvious thickening agent to try given its potential incompatibility with azelastine, and given the myriad other acceptable options. CIP2150, ¶¶44-49.

Given the expected incompatibility, there would have been no motivation to use either MCC or CMC with azelastine because at least one of the following would have been expected to occur: (1) azelastine would precipitate out of the formulation, (2) CMC or MCC would precipitate out of the formulation, or (3) fluticasone would precipitate out of its suspended state due to the compromised thickening agents. CIP2150, ¶¶47-48. And for the same reason, a POSA would have had no reasonable expectation of success. *Id.*

**B. There was no design need or market pressure to use the claimed three preservative combination.**

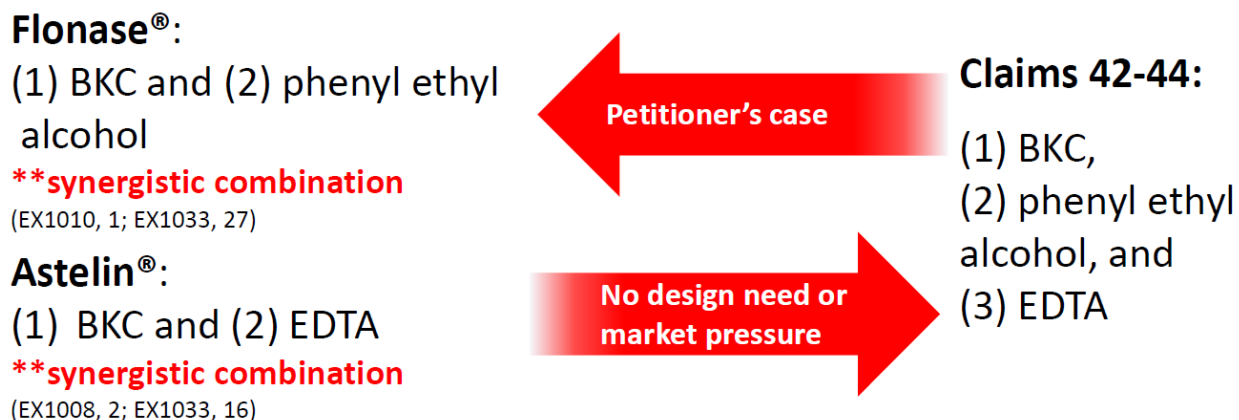
Claims 42-44 each require a three-preservative combination: benzalkonium chloride (“BKC”), edetate disodium (“EDTA”), and phenyl ethyl alcohol.

Petitioner contends that this 3-preservative combination would have been obvious because Hettche discloses BKC and EDTA, and Flonase<sup>®</sup> uses BKC and phenyl ethyl alcohol. Pet. 44-46. The claimed three preservative combination also would not have been obvious to try because (1) there was no design need or market pressure to use the combination of BKC, EDTA, and phenyl ethyl alcohol, (2) there were not a finite number of identified, predictable solutions, or (3) there was no good reason to pursue the claimed three-preservative combination from those

options. CIP2150, ¶50. As discussed below, Petitioner's arguments fail each of these three elements, and thus, Petitioner's selection of BKC, EDTA, and phenyl ethyl alcohol is improperly based on hindsight.

Astelin<sup>®</sup> and Flonase<sup>®</sup> use two different preservative pairings: Astelin<sup>®</sup> uses BKC and EDTA; while Flonase<sup>®</sup> uses BKC and phenyl ethyl alcohol. EX1004, 23; EX1008, 2; EX1010, 1. Because these preservative pairings were used in the commercial embodiments of Hettche and Phillipps, these pairings would have been viewed as the preferred pairings. CIP2150, ¶51. In contrast, claims 42-44 each requires all three preservatives. Petitioner gives no evidence of a deficiency in the preservative pairing in either Astelin<sup>®</sup> or Flonase<sup>®</sup> that would warrant deviating from these two-preservative combinations to a three-preservative one. *Id.*; *Novartis Pharm. Corp. v. Par Pharm., Inc.*, 48 F. Supp. 3d 733, 757-58 (D. Del. 2014) (rejecting obvious-to-try rationale because “[t]here can be no motivation to combine prior art references to solve a problem that no one knows exists.”). And in contrast, Segal teaches minimizing the use and amount of preservatives because “[p]reservative-free compositions are preferred due to reduced sensitivity and increased patient acceptance.” CIP2150, ¶52; EX1012, 6:15-20. As shown below, Petitioner has again improperly used the challenged claims as a blueprint.

Figure 5



Even if there was a design need or market pressure (and there was not), Petitioner has not shown that there were a finite number of identified, predictable solutions. At most, Petitioner unremarkably shows that these preservative excipients were simply *known*, but the art disclosed at least 27 other preservatives that were allegedly suitable with azelastine and fluticasone:

- Hettche discloses lower alkyl p-hydroxybenzoates, chlorohexidine, phenyl mercury borate, thimerosal, quaternary ammonium compounds such as cetrimide, benzethonium chloride, and myristyl-:-picolinium chloride. EX1007, 2-3.
- Cramer discloses benzyl alcohol, parabens, chlorobutanol, and phenylmercuric acetate. EX1011, 5. Cramer also discloses that “[m]ixtures of these preservatives may be used.” *Id.*
- The Handbook of Pharmaceutical Excipients, used by Dr. Donovan, discloses at least 17 more preservatives. CIP2156, 4-5.

CIP2150, ¶53. Because each is a pharmaceutically acceptable preservative that was known to be useful in nasal sprays, by Dr. Donovan's own rationale, a POSA would not have disregarded these options. *Id.*

Lastly, any synergistic activity of the EDTA-BKC and BKC-phenyl ethyl alcohol pairings would not have provided a good reason to pursue a three-preservative combination. CIP2150, ¶54. Importantly, the alleged synergistic activity for the EDTA-BKC and BKC-phenyl ethyl alcohol pairings is consistent with their use in Astelin<sup>®</sup> and Flonase<sup>®</sup>, and Petitioner cites to nothing that would motivate a POSA to include an additional preservative. *Id.* And Petitioner fails to explain why a POSA would arrive at the claimed three-preservative combination when Cramer discloses that "the most preferred preservative system for use herein comprises a combination of benzalkonium chloride, chlorhexidine gluconate, and disodium EDTA" *Id.*; EX1011, 5.

**C. It would not have been obvious to try the claimed glycerine as an isotonicity agent.**

Claims 42-44 each require glycerine. Petitioner asserts that glycerine would have been an obvious excipient because it was a known isotonicity agent and humectant, and Hettche discloses its use as a solvent in azelastine formulations. Pet. 44, 47. But glycerine's solvent and humectant functions would not have motivated a POSA to select glycerine. CIP2150, ¶59. Petitioner cites to no need for an additional solvent or a humectant in an azelastine/fluticasone combination



formulation. Even if a POSA were to consider glycerine's other properties, a POSA would know that glycerine is used to thicken formulations and thus would potentially render the azelastine/fluticasone too thick.

A POSA also would not have selected glycerine as a isotonicity agent. Astelin<sup>®</sup> uses NaCl as its isotonicity agent, and Flonase<sup>®</sup> uses dextrose. CIP2150, ¶¶55-56; EX1008, 2; EX1010, 1. Petitioner gives no evidence of any design need or market pressure to deviate from the commercially acceptable, and preferred, isotonicity agents in Astelin<sup>®</sup> and Flonase<sup>®</sup>. *Id.* There was no known shortcoming with those isotonicity agents, and Petitioner does not identify one. *Novartis*, 48 F. Supp. 3d at 757-58. And beyond Astelin<sup>®</sup> and Flonase<sup>®</sup>, the art generally disclosed a preference for sodium chloride and dextrose as isotonic agents for nasal formulations. CIP2150, ¶¶56; CIP2112, 19.

Even if there was a design need or market pressure (and there was not), there were not a finite number of predictable solutions. Beyond sodium chloride and glycerine, Hettche discloses saccharose, glucose, sorbitol, and 1,2-propylene glycol can be used. CIP2150, ¶¶57; EX1007, 3. Besides dextrose, Cramer discloses that boric acid, citric acid, sodium tartrate, sodium phosphate, and potassium phosphate can be used. CIP2150, ¶¶57; EX1011, 4. Dr. Donovan even went so far as to admit at her deposition that “*any material* that dissolves in solution contributes to the tonicity of the solution” and therefore “by its own dissolution behavior” would

adjust the tonicity of an azelastine/fluticasone formulation. CIP2159, 94:1-95:1 (emphasis added).

Nor would there have been a good reason to pursue glycerine as an option. Petitioner identifies no art that would have motivated a POSA to use glycerine with a fluticasone formulation. Indeed, during the *Apotex* trial, Dr. Donovan testified in response to why a POSA would not select sodium chloride or dextrose as isotonicity agents: “I don’t believe that a formulator would necessarily immediately select one of those agents for any particular reason over any of the others.” CIP2020, 30:12-22; 2159, 7:10-9:7. Unlike glycerine, dextrose was known to be compatible with both azelastine and fluticasone. CIP2150, ¶¶58; EX1007, 4:31-35; CIP2135, 3.

## **VII. UNEXPECTED RESULTS CONFIRM NON-OBVIOUSNESS OF THE CHALLENGED CLAIMS.**

Dymista<sup>®</sup> is the commercial embodiment of challenged claims 1, 4-6, 24-26, 29, and 42-44 in the United States. It is a nasal spray comprising both azelastine hydrochloride and fluticasone propionate used to treat AR (CIP2147, ¶¶151-152); has a particle size less than 10 µm; is an aqueous suspension containing azelastine and fluticasone; contains pharmaceutically acceptable carriers and excipients, including EDTA, glycerin, MCC/CMC, polysorbate 80, BKC, phenyl ethyl alcohol, and water. CIP2150, ¶¶62-64.

Dymista<sup>®</sup> has been proven to “exhibit [several] superior propert[ies] or

advantage[s] that a person of ordinary skill in the relevant art would have found surprising or unexpected.” *Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009). The importance of Dymista<sup>®</sup>’s unexpected superiority and benefits is straightforward and undeniable—“that which would have been surprising to one of ordinary skill in a particular art would not have been obvious.” *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995).

The closest prior art for all clinical purposes is the prior art studies of the co-administration of an antihistamine and a steroid. CIP2147, ¶¶101-106.

**Faster onset:** Nothing in the prior art studies investigating co-administration of antihistamines and steroids suggested that either component drug would have an improved onset. CIP2147, ¶113. But Dymista<sup>®</sup> has an unexpectedly fast onset of action compared to either azelastine or fluticasone alone. CIP2147, ¶115. Whereas azelastine was thought to have an onset of three hours across all four primary symptoms of AR (CIP2147, ¶115; EX1008, 3; CIP2021, 94:23-95:17) and fluticasone had an onset of action of at least twelve hours (EX1010, 3), Dymista<sup>®</sup> surprisingly has an established onset of action of **thirty minutes**. CIP2147, ¶116; CIP2066, 18.

Moreover, Petitioner cites to Bousquet (EX1024) to support its claim that azelastine has a 15-minute onset. Pet., 37. Bousquet contains no data, and the only study cited in that portion of ARIA does not claim a 15-minute onset. Instead, the

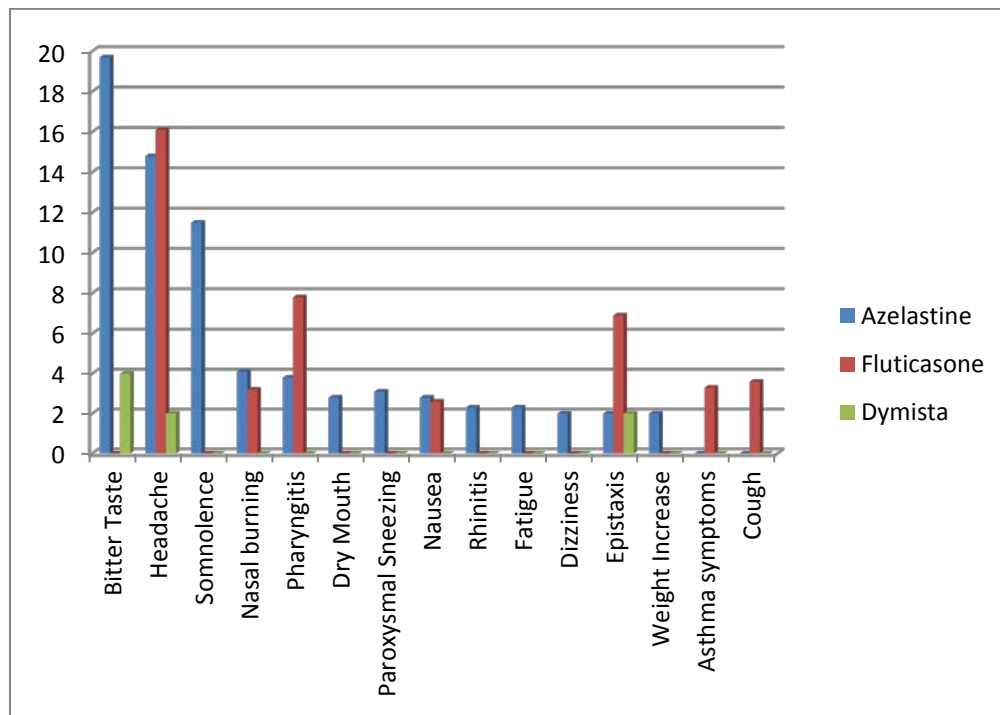
study explains that azelastine showed a “*trend* toward statistical significance” at two hours. CIP2147, ¶117; CIP2046, 1 (emphasis added). In other words, clinical onset (i.e., actual statistical significance versus placebo) was not shown even at two hours. CIP2147, ¶117. Falser, furthermore, says nothing about the onset of the drugs investigated; instead, it explains that the “15 minute” point Petitioner relies upon is merely a test of efficacy fifteen minutes after the second application of azelastine each day (while the first dose is theoretically still working). CIP2147, ¶¶118-120; EX1015, 2, 6. A POSA would have understood that this does not suggest that azelastine had a 15-minute onset (CIP2147, ¶118); instead, it merely states that it was still working 15 minutes after the second daily dose. Nor does Ratner 2008 show an accelerated onset of the kind seen in Dymista<sup>®</sup>. CIP2147, ¶121; EX1045.

**Reduced side effects:** Dymista<sup>®</sup> has a surprisingly improved side effect profile. Azelastine had a 19.7% incidence of bitter taste, 14.8% of headache, and 11.5% of somnolence, among more than a dozen side effects that appeared in greater than 2% of the population. CIP2147, ¶123-124; EX1008, 3. Meanwhile, fluticasone, when administered alone at the same dose amount used in Dymista<sup>®</sup>, caused headache in 16.1% of patients, pharyngitis in 7.8% of patients, and epistaxis in 6.9% of patients. CIP2147, ¶123; EX1010, 7. Moreover, Shenfield explains that it was thought that combination drugs would exhibit increased side

effects as compared to either component drug alone. CIP2147, ¶122; CIP2043, 13. And studies confirmed this concern, showing increased incidence of side effects in patients co-administering two drugs. CIP2137, ¶121; EX1035, 8; EX1036, 5; EX1039, 6. This expectation is further confirmed by Ratner 2008, which shows a synergistic increase in bitter taste of azelastine and a near-additive increase in headache associated with fluticasone when azelastine and fluticasone are co-administered. CIP2147, ¶122; EX1045, 5. Nothing in the prior art co-administration studies suggested a reduced side effect profile.

Figure 6 shows that Dymista<sup>®</sup> surprisingly exhibits bitter taste in only 4% of patients. CIP2147, ¶¶123, 126; CIP2066, 6. Even though the same concentration of fluticasone is present in the prior art Flonase<sup>®</sup> product and Dymista<sup>®</sup>, the incidence of headache is surprisingly reduced from 16.1% for Flonase<sup>®</sup> to 2% for Dymista<sup>®</sup>. CIP2147, ¶¶123, 125, 127. No other side effect—including somnolence—occurred in more than 2% of patients. CIP2147, ¶¶123, 128.

Figure 6



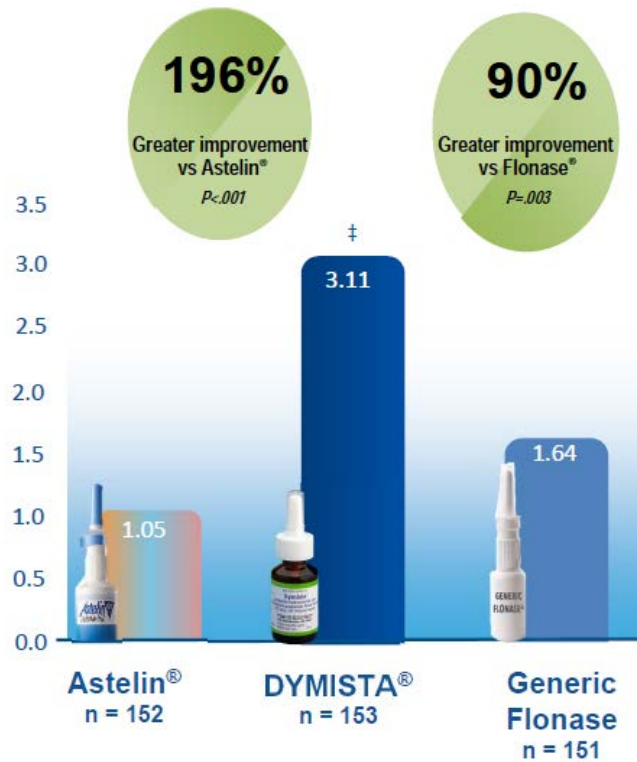
EX1008, 3; EX1010, 7; CIP2066, 6. This dramatic reduction in side effects was surprising (CIP2147, ¶129), and wholly unexplained by Petitioner even though it and its expert each were aware of them.

**Improved clinical efficacy:** It was widely understood in 2002 that each antihistamine was approximately equal in efficacy. CIP2147, ¶102; EX1041, 9; CIP2042, 4. It was also thought that all steroids were equally effective in clinical practice. CIP2147, ¶103; CIP2047, 3. Petitioner's reliance on potency is not a clinical factor; it is irrelevant in clinical practice. CIP2147, ¶103. Further, the weight of the prior art showed that there was no meaningful clinical benefit to co-administering an antihistamine with a steroid (*see* § IV.A), so a POSA would not

have expected a combination like Dymista<sup>®</sup> to yield any meaningful improvement. CIP2147, ¶¶107-108.

Yet, Figure 7 shows that, when compared to the Astelin<sup>®</sup> and generic Flonase<sup>®</sup> prior art products after the placebo effect is removed, Dymista<sup>®</sup> surprisingly exhibited nearly twice the therapeutic effect of fluticasone and almost three times the therapeutic effect of azelastine. CIP2147, ¶¶109-110.

**Figure 7**



To the extent that Petitioner suggests that the co-administration of azelastine and fluticasone are the closest prior art (Pet. 55; EX1045, 1), and that the improvement shown by Dymista<sup>®</sup> is similar to that shown in Ratner 2008

(EX1045), Ratner 2008, published six years the invention, is not prior art.

CIP2147, ¶111. Nor is Ratner's study indicative of the prior art use of azelastine and fluticasone: Ratner 2008 studied the co-administration of azelastine and fluticasone 15-30 minutes apart (EX1045, 2-3) but the prior art recommended azelastine be used "on demand." CIP2147, ¶111; EX1024, 90; EX1022, 5.

Ratner 2008 only shows a statistically significant difference between co-administration and the monotherapies after four days of consistent fixed dosing. EX1045, 5. But Petitioner's cited art explicitly recommends stepwise, "on demand," or as-needed therapy, not the fixed dosing regimen tested in the Ratner 2008 study. CIP2147, ¶111; EX1019, 34; EX1022, 5; EX1024, 90. Petitioner's own art proves that Ratner 2008 was not practiced as of 2002, and Cipla has no obligation to show unexpected results over art that did not exist prior to 2002. *In re Geiger*, 815 F.2d 686, 690 (Fed. Cir. 1987) (J. Newman, concurring). Indeed, the authors of Ratner 2008 themselves expressed surprise at their results: that the co-administration of azelastine and fluticasone showed an "unanticipated magnitude" of improvement. CIP2147, ¶112; EX1045, 7.

Moreover, these unexpected results are a difference in kind, not degree, further supporting patentability. Specifically, because the prior art taught that Dymista<sup>®</sup> should have: (1) no faster onset but it unexpectedly does; (2) an *increased* side effect profile, but it unexpectedly has reduced side effects; and (3)



no greater clinical efficacy, but it unexpectedly does. All three of these results are unexpected and are differences in kind. *Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1306 (Fed. Cir. 2015) (finding a difference in kind when a property improves when the art taught no improvement or a decline).

**VIII. OTHER OBJECTIVE INDICIA COMPEL NON-OBVIOUSNESS OF THE CHALLENGED CLAIMS.**

Petitioner was obligated to address all available objective indicia evidence but failed to do so. *Apple Inc. v. Samsung Elecs. Co.*, 839 F.3d 1034, 1048 (Fed. Cir. 2016) (*en banc*) (“A determination of whether a patent claim is invalid as obvious under § 103 requires consideration of all four *Graham* factors, and it is error to reach a conclusion of obviousness until all those factors are considered...Objective indicia of nonobviousness must be considered in every case where present.”).

Despite both of Petitioner’s declarants stating: “I understand that when considering the obviousness of an invention, one should also consider whether there are *any* secondary considerations that support the nonobviousness,” both declarants failed to address the objective indicia evidence that they had already addressed in open court in the *Apotex* case approximately seven weeks earlier. EX1004, ¶11; EX1003, ¶92 (emphasis added).

Petitioner’s failure to address these objective indicia was not through a lack of awareness—it was a strategic decision. CIP2158, 98:8-17. Petitioner’s

representative attended trial. CIP2127, 1. Dr. Schleimer testified that he recalled discussions at trial regarding Dymista<sup>®</sup>'s unexpected results, skepticism, industry praise, and commercial success. CIP2158, 94:10-96:10. Dr. Donovan likewise admitted during deposition that she observed Cipla's evidence regarding copying and Dr. Alexander D'Addio's testimony about Meda's skepticism and later failure to formulate an azelastine/fluticasone combination formulation. CIP2159, 119:12-121:5, 123:7-126:13. Yet, none of these indicia appears in either the Petition or declarations.

Besides attending trial (CIP2127, 1), Petitioner should also have been aware of Cipla's objective indicia evidence through the multiple public court filings extensively discussing them. CIP2017, 84-118; CIP2022, 39-52; CIP2023, 41-54; CIP2024, 45-56. To the extent Petitioner in its Reply tries to address the objective indicia evidence of which it was aware, but chose to ignore in its Petition, such arguments should be stricken from the record, or Cipla should be given leave for a sur-reply to address Petitioner's new arguments. *See Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1369 (Fed. Cir. 2016) ("It is of the utmost importance that petitioners in the IPR proceedings adhere to the requirement that the initial petition identify 'with particularity' the 'evidence that supports the grounds for the challenge to each claim.'").

Petitioner's failure to address these objective indicia is important. Objective indicia "can be the most probative evidence of non-obviousness in the record, and enable[] the court to avert the trap of hindsight." *Leo Pharma. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1358 (Fed. Cir. 2013) (quoting *Crocs, Inc. v. Int'l Trade Comm'n*, 598 F.3d 1294, 1310 (Fed. Cir. 2010)) (internal quotations omitted). And particularly given Petitioner's hindsight-driven arguments in this case, "objective criteria help inoculate the obviousness analysis against hindsight." *InTouch Technologies, Inc. v. VGO Commc'ns, Inc.*, 751 F.3d 1327, 1347 (Fed. Cir. 2014).

And as explained below, Dymista<sup>®</sup>, Duonase (and the Duonase copycats) satisfy a long-felt but unmet need in the treatment of AR, are a commercial success, exhibit unexpected properties, received industry praise, were the subject of industry skepticism, were the subject of royalty-bearing licenses, and were copied. These powerful objective indicia of nonobviousness are present that confirm the patentability of the challenged claims.

**A. Commercial embodiments of the claimed invention Dymista<sup>®</sup> and Duonase have a nexus to the challenged claims.**

Meda's Dymista<sup>®</sup> product and Cipla's Duonase product (and the Duonase copycats) are commercial embodiments of the challenged claims. Specifically, Dymista<sup>®</sup> embodies challenged claims 1, 4-6, 24-26, 29, and 42-44, while Duonase embodies claims 1, 4-6, 24-26, and 29 because it is a nasal spray comprising both azelastine hydrochloride and fluticasone propionate; has a particle size less than 10

µm; is an aqueous suspension containing azelastine and fluticasone; and contains pharmaceutically acceptable carriers and excipients. CIP2150, ¶¶61-65. And each of the Duonase copycat products Azeflo, Nazomac, Floresp, Ezicas, and Nasocom embodies claims 1, 4-5, and 24-25; while Duonase copycat product Combinase embodies claims 1, 4-5, 24-25, and 42-44. CIP2150, ¶¶66-74. Each product is used to treat conditions for which antihistamines and steroids are indicated. CIP2147, ¶¶150-161.

**B. Dymista<sup>®</sup> meets long-felt but unmet medical needs for more effective, faster, and safer treatment of AR.**

“[A] long felt but unresolved need tends to show non-obviousness because it is reasonable to infer that the need would have not persisted had the solution been obvious.” *WBIP, LLC v. Kohler CO.*, 829 F.3d 1317, 1332 (Fed. Cir. 216). As of 2002, studies showed that adding an antihistamine along with a steroid provided little or no benefit. CIP2147, ¶¶61-63; EX1034; EX1036; EX1039; EX1040; CIP2041; CIP2042. Accordingly, 74% of patients did not believe their symptoms were controlled by existing drugs and 65% of patients avoided drugs because of fear of side effects. CIP2170, 3. Patients and clinicians wanted an AR treatment that worked faster across all symptoms (CIP2147, ¶¶133-135), provided greater relief than steroids (CIP2147, ¶¶131-132), and yielded reduced side effects when compared to existing treatments. CIP2147, ¶¶136-140. Dymista<sup>®</sup> satisfied these needs. CIP2147, ¶¶132, 135, 141. To date, it is the only treatment in the U.S. that

is proven to be more effective than a steroid alone. CIP2147, ¶148; CIP2052, 1.

**C. Dymista<sup>®</sup> faced industry skepticism from both Meda and FDA.**

“If industry participants or skilled artisans are skeptical about whether or how a problem could be solved or the workability of the claimed solution, it favors nonobviousness.” *WBIP*, 829 F.3d at 1335.

First, from a clinical perspective, not only had FDA never before approved a fixed-dose nasal spray formulation, but FDA did not even have a procedure in place in 2002 to approve this type of product. CIP2147, ¶¶142-143. More critically, FDA’s skepticism corroborates Cipla’s arguments above because FDA explained that “mechanisms of action, [and] onset of symptom relief” are not sufficient to justify approval of a combined formulation like Dymista<sup>®</sup>. CIP2147, ¶144; CIP2165, 5. This statement, made in May 2008, was consistent with pre-invention findings that, simply because two drugs work differently, they do not necessarily work better together. CIP2147, ¶144. Indeed, FDA’s “combination rule,” which requires that both drugs in a fixed-dose combination contribute to efficacy, was cited against Dymista<sup>®</sup> as an expected basis for denial of approval. *Id.* Dymista<sup>®</sup> overcame this skepticism and obtained approval.

Similarly, FDA expressed concerns over reduced flexibility similar to those stated above (§IV). FDA told Meda that its proposed product “**eliminates flexibility with dosage titration and potentially exposes patients to**

**unnecessary medication, and thus unnecessary risk.”** CIP2147, ¶145; CIP2165, 5 (emphasis added). FDA’s skepticism mirrors the teachings in the prior art. Specifically, FDA’s concern regarding loss of flexibility reflects Shenfield’s pre-invention teaching that “[o]ne of the major problems [with a fixed-dose combination] is that the prescribing doctor loses flexibility in patient management.” CIP2043, 12. Similarly, FDA’s concern over increased side effects is the same as Shenfield’s teaching that patients “may be exposed to additional ingredients with little therapeutic benefit and major potential side effects.” CIP2043, 13. FDA’s post-invention skepticism confirms the doubt a POSA would have had over developing a combination of the sort claimed. CIP2147, ¶146. These issues are not the sort typically raised in the FDA-approval process. CIP2147, ¶147.

Second, from the formulation perspective, Meda’s skepticism provides real-world corroboration that a POSA would have been skeptical in 2002 that an azelastine/fluticasone combination formulation could be “suitable for nasal administration.” CIP2150, ¶76. In 2002, Meda concluded that developing an azelastine/steroid combination formulation would have a “high degree of difficulty” and a low probability of success at least because of (1) the anticipated incompatibility of a solution formulation, like azelastine, in combination with a suspension formulation, like fluticasone, (2) the anticipated dosing

incompatibilities between Astelin<sup>®</sup> and Flonase<sup>®</sup>, and (3) the lack of guidance in the art in 2002 about suspending one active ingredient in a solution of another active ingredient. CIP2150, ¶75; CIP2148, ¶¶10-15; CIP2054, 11; CIP2056, 11.

Meda's skepticism led it to pursue other research avenues, like dual-chamber devices, rather than attempt a combination formulation. CIP2148, ¶¶16-17. Then, in 2006 when it learned of Cipla's invention, Meda was genuinely surprised that anyone had successfully overcome the incompatibilities that had dissuaded Meda years earlier. CIP2148, ¶26. Meda's concerns, expressed by individuals falling within the definition of a POSA, confirm the skepticism with which a POSA would have viewed Cipla's invention. CIP2148, ¶¶6-7, 9, 18, 21; CIP2150, ¶76. And there is a nexus between the skepticism and the challenged claims. CIP2150, ¶77.

**D. Dymista<sup>®</sup> has enjoyed industry praise as the new “gold standard” for treatment of AR.**

After Dymista<sup>®</sup>'s launch and clinical results, the editors of the world's leading allergy journal—*Journal of Allergy and Clinical Immunology*—declared that Dymista<sup>®</sup> “can be considered the drug of choice for the treatment of AR.” CIP2147, ¶¶148-149; CIP2052, 1. They also declared that “[t]he improvement of [Dymista<sup>®</sup>] over standard therapy was substantial, occurred faster (up to 5 days faster than fluticasone and up to 7 days faster than azelastine), and was more complete, with 1 of 8 [Dymista<sup>®</sup>]-treated patients exhibiting complete/near-complete symptom resolution.” CIP2052, 1.

Likewise, in 2015, GlobalData—a leading clinical market analysis company—published a “Strengths Weaknesses Opportunities Threats” (“SWOT”) analysis for Dymista<sup>®</sup>. CIP2053, 133. Dymista<sup>®</sup>’s strengths included a “demonstrated superior efficacy in clinical trials compared to azelastine, fluticasone, and placebo,” a rapid onset on the order of minutes, and “good safety and tolerability.” *Id.* It also declared Dymista<sup>®</sup> the “gold standard of AR therapy.” *Id.* The IMS report also predicted that Dymista<sup>®</sup> is the branded product with the most growth potential, specifically highlighting that it is the first intranasal combination AR treatment approved in the U.S. *Id.*

**E. Failure by Cramer, Segal, and Meda to develop a combination nasal spray confirms nonobviousness.**

“[T]here can be little better evidence negating an expectation of success than actual reports of failure.” *Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.*, 320 F.3d 1339, 1354 (Fed. Cir. 2004). Failure by others “show[s] indirectly the presence of a significant defect in the prior art, while serving as a simulated laboratory test of the obviousness of the solution to a skilled artisan.” *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Lit.*, 676 F.3d 1063, 1082 (fed. Cir. 2012) (internal citations omitted).

Before learning of Cipla’s patent, Meda attempted and failed to formulate an azelastine/fluticasone combination formulation in 2006 because azelastine would not stay dissolved in a solution consisting of Flonase<sup>®</sup> excipients—including the



claimed thickening agent MCC/CMC. CIP2148, ¶¶17-25. Further, Meda tried modifications that would have been thought to be within the grasp of a POSA to enhance the solubility of azelastine in the Flonase<sup>®</sup> excipients, but those modifications also failed. CIP2150, ¶82. After several unsuccessful attempts, Meda ultimately abandoned its efforts. CIP2148, ¶¶25-27; CIP2150, ¶¶78-79, 82; CIP2061, 17-19. Meda's failure is particularly salient here because Meda had more than a decade of experience formulating azelastine and had developed Astelin<sup>®</sup>, so it would have been in the best position of anyone to develop a combination product containing azelastine. CIP2148, ¶10. And because Meda's work was conducted by individuals who fall within both Cipla's and Petitioner's definition of a POSA (CIP2148, ¶¶6-7, 21-22), these efforts reflect what a POSA would have tried and what a POSA would have achieved. CIP2150, ¶80.

Meda's failures also have a nexus to the challenged claims. Dissolving azelastine into the Flonase<sup>®</sup> excipients was only the first step in Meda's plan to formulate an azelastine/fluticasone formulation. CIP2150, ¶81. Because azelastine was not soluble in the Flonase<sup>®</sup> excipients, attempting to dissolve azelastine directly into the Flonase<sup>®</sup> would have been futile. *Id.*; CIP2148, ¶¶25-27.

In addition to Meda, two other sophisticated pharmaceutical companies—Procter & Gamble and Warner-Lambert Co.—both filed, and later abandoned, patent applications—Cramer and Segal—disclosing combination formulations for

the treatment of AR. EX1011; EX1012. The only reasonable inference is that both companies had tried to develop such a product to treat AR but neither company entered the market, evidencing a failure of others. *Pfizer Inc. v. Teva Pharm. USA, Inc.*, 460 F. Supp.2d 659, 662 (D.N.J. 2006) (stating that “not getting to market...is an appropriate benchmark for failure [of others].”); *see also Knoll Pharm. Co. v. Teva Pharm. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004). In addition, the pharmaceutical company CyDex was investigating a product containing azelastine in combination with the steroid budesonide. CIP2048, 215-16. Despite working on since 2009 (CIP2048, 215), no azelastine/budesonide combination formulation has entered the market, again evidencing a failure of others. These repeated failures support the non-obviousness of the challenged claims. *See Boehringer*, 320 F.3d at 1354.

**F. Meda’s royalty-bearing license to the ’620 patent supports patentability.**

Licenses may also constitute evidence of nonobviousness. *In re GPAC Inc.*, 57 F.3d 1573, 1580 (Fed. Cir. 1995). After failing to develop its own formulation, Meda took a license to Cipla’s intellectual property, including the ’620 patent, as the only way that it could obtain a viable azelastine/fluticasone combination formulation. CIP2148, ¶¶26-28; CIP2049, 1; CIP2050, 1. That Meda took a license to the ’620 patent demonstrates its nonobviousness and nexus, and that Meda was willing to later amend the license to increase its royalty payment to 15% further

supports this. CIP2149, ¶¶103-105; CIP2049, 28 (identifying PCT/GB2003/002557); CIP2050, 1-3; EX1001, 1.

**G. Dymista<sup>®</sup> and Duonase were subject to widespread copying.**

The commercial embodiments of the challenged claims were widely copied, which is “another form of flattering praise for inventive features.” *WBIP*, 829 F.3d at 1336. Duonase was subject to wide-spread copying within two years of its market entry. CIP2149, ¶¶101-102. In total, six Duonase copycat products are encompassed by the challenged claims, and ten more azelastine/fluticasone combination nasal sprays have entered the market. CIP2123, 23-26. These competitors had access to the commercial Duonase product and also to the disclosures in Cipla’s published patent application that issued as the ’620 patent. EX1001, 1 (identifying that PCT/GB03/02557 published on June 13, 2003).

**H. Dymista<sup>®</sup> and Duonase are commercially successful.**

Where the embodiment of the patent at issue enjoys commercial success, there is a presumption that the success is due to the patented invention. *Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1392–93 (Fed. Cir. 1988). Here, Dymista<sup>®</sup> is a commercial success in the United States, and Duonase (and copycats) are commercial successes in India.

**Dymista<sup>®</sup>**: Upon launch in 2012, Dymista<sup>®</sup> enjoyed immediate and consistent growth for prescriptions and revenue: amassing by April 2016

approximately 963,299 prescriptions per year and generating approximately \$157 million in annual revenue. CIP2149, ¶¶37-39. Through 2016, Dymista<sup>®</sup>'s share among branded nasal sprays was 27.3%, and it is currently the most prescribed branded nasal spray in the United States. CIP2149, ¶¶44-46. Dymista<sup>®</sup>'s revenue share among branded nasal sprays was 15.6% by that time. CIP2149, ¶46. As measured by market-share or revenue-share, Dymista<sup>®</sup> was the second best branded nasal spray by the end of 2014—its second full year on the market. CIP2149, ¶¶45-46. Even among generic prescription AR treatments, Dymista<sup>®</sup>'s prescriptions, revenues, and market shares are consistently increasing while the footprint of its competitors was shrinking or stagnating. CIP2149, ¶¶47-49. In either of these calculations, over-the-counter treatments were not included because those treatments are not direct competitors to Dymista<sup>®</sup> for two reasons: those treatments (i) do not require a prescription; and (ii) are used before a patient seeks a prescription AR treatment. CIP2149, ¶¶40-43.

Dymista<sup>®</sup>'s performance has a nexus to the challenged claims of the '620 patent because Dymista<sup>®</sup> is an embodiment of those claims, and regardless, is primarily marketed on its patented features: (1) its rapid and sustained symptoms relief, (2) its efficacy over fluticasone, and (3) being the first combination nasal spray. CIP2149, ¶¶57-66, 99-100; CIP2064, 9, 11; CIP2074, 35; CIP2082, 6; CIP2083, 5-7; CIP2084, 4; CIP2085, 25; CIP2086, 3-4. Additionally, Dymista<sup>®</sup>'s

success is not due to extraneous, non-patented factors because (1) Dymista<sup>®</sup> does not have a pricing advantage, and (2) Meda's marketing was not a significant driver of sales of Dymista<sup>®</sup>. CIP2149, ¶¶80-93; CIP2053, 127, 129; CIP2064, 9; CIP2074, 17, 35; CIP2093, 18; CIP2094, 13; CIP2095, 1; CIP2163.

**Duonase and its copycats:** Both the units of Duonase shipped and the revenue generated have steadily grown every year since it was first launched in India in 2004. CIP2149, ¶¶50-54. The Duonase copycats have achieved similar levels of success. *Id.* Collectively, Duonase and its copycats comprise 24-46% of all nasal sprays used to treat AR in the Indian market. CIP2149, ¶¶55-56. And in rebuttal to Petitioner's criticism of the commercial success evidence that Cipla presented to the USPTO, Duonase is a commercial success when limited to only azelastine/fluticasone competitive products. CIP2149, ¶¶108-110. Like Dymista<sup>®</sup>, Duonase is an embodiment of several of the challenged claims, and is primarily marketed on its patented features. CIP2149, ¶¶67-69; CIP2087, 14; CIP2088, 28. And Duonase's success is directly attributable to its patented features. CIP2149, ¶¶94-98.

**I. No alleged “blocking patents” undercut Cipla's commercial success and long-felt need evidence.**

Petitioner asserts that Hettche and Phillipps are “blocking patents” which “undercut[] any nexus” to commercial success and satisfaction of a long-felt but unmet need. Pet. 56. Hettche and Phillipps are not blocking patents, and

Petitioner's theory fails for three reasons. First, Hettche and Phillipps were not owned or licensed by Cipla. EX1009, 1; EX1007, 1. A "blocking patent" scenario occurs when the same patentee also owns the blocking patent and the patent at issue. *See Galderma Labs. L.P. v., Inc.*, 737 F.3d 731, 740 (Fed. Cir. 2013); *Merck & Co., Inc. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1377 (Fed. Cir. 2005).

Second, Hettche expired in May 2012 and Phillipps expired in May 2004 — each before Dymista<sup>®</sup> launched in September 2012. Dymista<sup>®</sup>'s success, therefore, cannot be attributable to any alleged protection conferred by those patents.

CIP2005, ¶¶114-115; *see Merck*, 395 F.3d at 1376 (commercial sales beginning 2003, blocking patent exclusivity expiration 2008); *Galderma Labs.*, 737 F.3d at 740 (commercial sales beginning in 2007, blocking patent expiration in 2010).

Even if a competitor was dissuaded by the Hettche patent, that competitor could have developed a competing product under 35 U.S.C. § 271(e)(1)'s safe harbor provision, then obtain FDA approval, wait for Hettche to expire, and still could have beat Dymista<sup>®</sup> to the market. CIP2149, ¶¶111-112. No one did, so there was no blocking effect.

Third, the record itself reflects that competitors were not blocked. CIP2149, ¶113. Proctor & Gamble and Warner-Lambert filed Cramer and Segal, respectively. *Otsuka Pharm. Co. Ltd. v. Sandoz, Inc.*, 07-1000, 2010 WL 4596324, at \*25 (Nov. 15, 2010 D.N.J) (rejecting "blocking patent" theory because

competitors filed patent applications during the term of the alleged “blocking patent”). In addition, CyDex investigated an azelastine/budesonide combination formulation before Hettche expired, and thus, CyDex was not blocked. CIP2048, 215-216.

## **IX. CONCLUSION**

As shown above, a POSA in 2002 would not have been motivated to combine azelastine and fluticasone into the combination formulation as recited in the challenged claims. A POSA also would not have had a reasonable expectation of successfully doing so. In addition, there was no motivation to deviate from the successfully used excipients in Astelin® and Flonase® to arrive at the excipients recited in claims 42-44. Finally, at least eight powerful objective indicia of nonobviousness exist that are tied to the challenged claims. For at least the foregoing reasons, the Board should find that Petitioner has not carried its burden to prove that each of the instituted claims are unpatentable by a preponderance of the evidence.

Respectfully submitted,  
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**CERTIFICATE OF WORD COUNT**

Pursuant to 37 C.F.R. § 42.24(d), I certify that Cipla Limited's Patent Owner Response contains 13,546 words as counted by the word-processing program used to generate this response. This total does not include the table of contents, the table of authorities, appendix of exhibits, certificate of service, or this certificate of word count.

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**CERTIFICATE OF SERVICE (37 C.F.R. § 42.6(e))**

The undersigned hereby certifies that the above-captioned “Cipla Limited’s Patent Owner Response” was served in its entirety on November 20, 2017, upon the following parties via electronic mail upon the following counsel of record for the Petitioner:

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