

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 PRELIMINARY RESPONSE  
UNDER 37 C.F.R. § 42.107(a)**

***Mail Stop “PATENT BOARD”***

Patent Trial and Appeal Board  
U.S. Patent and Trademark Office  
P.O. Box 1450  
Alexandria, VA 22313-1450

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## SUMMARY OF THE ARGUMENT

Patent Owner Cipla Ltd. (“Cipla”) provides this preliminary response to Petitioner Argentum Pharmaceuticals LLC’s (“Argentum”) Petition for *inter partes* review of claims 1, 4-6, 24-26, 29, and 42-44 of U.S. Patent No. 8,168,620 (“the ’620 patent”; EX1001) in accordance with 37 C.F.R. § 42.107(a). The Board should deny institution on all three grounds identified in Argentum’s Petition—anticipation Ground 1 and obviousness Grounds 2 and 3—for failure to address threshold legal issues, or because its arguments fail on the merits, or both.

The Board should deny instituting trial for the following two threshold failures:

*First*, Ground 1 of Argentum’s Petition presents “the same or substantially the same prior art or arguments [that] previously were presented to the Office.” 35 U.S.C. § 325(d). Argentum relies on WO 98/48839 (“Segal”) to argue that a fixed-dose combination of azelastine and fluticasone was previously disclosed in the prior art. But Segal was already before the U.S. Patent and Trademark Office (“USPTO”) during prosecution, as was the more specific teachings of EP No. 0780127 (“Cramer”), and Cipla overcame both by showing that Cramer did not teach a dosage form “**suitable for nasal administration**” or a “**nasal spray**,” as recited by the claims. Because Argentum has not shown that Segal discloses or enables a “nasal spray” or dosage form that is “suitable for nasal administration,”

the Board should deny institution of Ground 1.

*Second*, Grounds 2 and 3 are also defective as a matter of law because Argentum failed to address significant publicly-available evidence of objective indicia of non-obviousness of which Argentum was indisputably aware. In December 2016, the '620 patent was tried in the District of Delaware. An in-house legal representative of Argentum attended that trial and saw Cipla's evidence of eight objective indicia of non-obviousness. The evidence was also the subject of extensive pre- and post-trial submissions readily available to Argentum and the public.

Additionally, both of Argentum's declarants here—Drs. Schleimer and Donovan—provided expert testimony concerning objective indicia of non-obviousness on behalf of Apotex at trial. CIP2018, 27-28. The Board would be left uninformed of that fact based on Argentum's Petition (despite being filed just over a month after trial ended). Instead of challenging the well-developed trial evidence it witnessed, Argentum's Petition responds only to the objective indicia evidence submitted during patent prosecution. That is not enough. Even Dr. Robert Schleimer, Argentum's expert, acknowledges in his declaration that “one must also consider whether there are any secondary considerations that support the non-obviousness of the invention,” listing many of the indicia presented at trial. EX1003, ¶43. Yet, neither he nor Argentum addressed these considerations it its

Petition.

The law requires Argentum, as the patent challenger, to address all available objective indicia of non-obviousness in its Petition. *See Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1357 (Fed. Cir. 2013) (“Whether before the Board or a court, this court has emphasized that consideration of the objective indicia is *part of* the whole obviousness analysis, not just an afterthought.”) (citations omitted, emphasis in original). Because Argentum knew of this evidence and deliberately chose to ignore it to Cipla’s prejudice, the Board should deny institution on obviousness Grounds 2 and 3.

Argentum’s Petition also fails on the merits because all three asserted grounds suffer fatal substantive shortcomings. Ground 1, asserting that claims 1 and 25 of the ’620 patent are anticipated in view of Segal, is flawed because a person of ordinary skill in the art (“POSA”) would not have immediately envisaged the claimed combination of azelastine hydrochloride (“azelastine”) and fluticasone propionate (“fluticasone”) from the more than 800 million possible combinations Segal discloses. Moreover, Segal provides no disclosure or teaching that would have enabled a POSA to arrive at a pharmaceutical formulation combining azelastine and fluticasone that is “**suitable for nasal administration**” or in a combined “**nasal spray**,” which are required limitations of claims 1 and 25.

Ground 1 is also duplicative of the rejection made and overcome by the



patentee during prosecution. Indeed, the sole teaching for which Argentum relies on Segal—the disclosure of azelastine and fluticasone among millions of other disclosed combinations—was also alleged by the Examiner to have been disclosed in the Cramer reference. Cipla overcame Cramer’s more specific disclosure by demonstrating that it did not teach a combined “nasal spray” formulation that was “suitable for nasal administration.” Accordingly, Segal does not provide an anticipatory disclosure.

Argentum’s Ground 2 asserting obviousness of claims 1, 4-6, 24-26, and 29 in view of U.S. Patent No. 4,335,121 (“Phillipps”), U.S. Patent No. 5,164,194 (“Hettche”), and Segal is equally deficient. The cited references would not have motivated or otherwise provided a POSA any reason to combine azelastine and fluticasone into the claimed fixed-dose combination formulation. Rather, at the time of the invention, the art taught that: (1) co-administering an antihistamine, like azelastine, with an intranasal corticosteroid, like fluticasone, resulted in no meaningful clinical improvement over a steroid alone; (2) co-administering an antihistamine and a steroid was expected to increase side effects experienced by patients, and thus decrease compliance; and (3) a fixed-dose combination decreased the flexibility mandated by the prevailing allergic rhinitis treatment guidelines Argentum cites and the well-established approaches practiced in the art. Argentum’s Petition provides no support for a POSA deviating from what the art

taught.

Indeed, as Argentum's expert Dr. Robert Schleimer admitted at trial, before Cipla's invention, no one, anywhere in the world, had successfully developed a nasal spray with two active ingredients, much less a steroid and an antihistamine in a single nasal spray formulation. CIP2019, 43:5-44:2. And Dymista<sup>®</sup>—the U.S. commercial embodiment—was the first, and still is the only, FDA-approved, fixed-dose combination nasal spray formulation. These facts alone demonstrate the non-obviousness of Cipla's invention. *Leo*, 726 F.3d at 1358.

Moreover, even if a POSA had a reason to combine azelastine and fluticasone into a fixed-dose combination, known formulation difficulties would have dissuaded a POSA from trying it. And, even if it were tried, a POSA would not have had any reasonable expectation of success of formulating the claimed combination. For example, fluticasone was known to aggregate and precipitate from its suspended state when co-formulated with other active ingredients. A POSA following what the USPTO determined to be the closest prior art—Cramer's Example III—would have arrived at a pharmaceutical formulation that was not suitable for nasal administration. A POSA would not have been able to fix all of the shortcomings with any reasonable expectation of success. And, notably, Segal's disclosure is substantially less detailed than Cramer's Example III.

Finally, Argentum's Ground 3 asserting obviousness of claims 42-44 in

view of Hettche, Phillipps, Segal, and the Flonase<sup>®</sup> label is flawed because the Petition provides no evidence that a POSA would have been motivated to combine the cited prior art references to arrive at the claimed invention. While Ground 3 suffers from all the same flaws as Ground 2, Ground 3 goes even further astray in its hindsight selection of claimed excipients, including use of excipients explicitly discouraged by the relevant art.

There are also eight significant objective indicia of non-obviousness that further defeat Grounds 2 and 3. Given that these considerations “must always when present be considered,” Argentum’s obviousness analysis is incomplete as a matter of law. *Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014). Thus, the Board should deny institution of Argentum’s Petition because Argentum failed to meet its legal burden.

## **I. INTRODUCTION**

### **A. The ’620 patent**

The ’620 patent is directed to compositions containing azelastine and fluticasone, along with specific pharmaceutical excipients. CIP2007, ¶21. 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.<sup>1</sup> Duonase, a commercial embodiment in India, was not only the

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<sup>1</sup> Argentum claims to have “preserve[d]” some right to challenge the priority

first-ever fixed-dose nasal spray combination of an antihistamine and a steroid, but it was also the first fixed-dose nasal spray combination of any type, anywhere in the world. Dymista<sup>®</sup>, a commercial embodiment in the U.S., was the first, and today remains the *only*, FDA-approved fixed-dose nasal spray combination formulation.

**B. Background of related litigation**

The '620 patent is listed in the Food and Drug Administration's ("FDA") Orange Book in connection with the drug Dymista<sup>®</sup>, which is approved for the treatment of seasonal allergic rhinitis ("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 Pharmaceuticals) 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.). The Court held a bench trial from December 13-16, 2016, and closing arguments occurred in March 2017.<sup>2</sup> All trial and hearing transcripts, and all post-trial submissions were publicly

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date, but has failed to articulate any basis for any challenge "with particularity" as required under 35 U.S.C. § 312(a)(3). Accordingly, the Board should reject Argentum's unsupported priority challenge and deem it waived.

<sup>2</sup> The parties settled the district court dispute in May 2017.

available to Argentum from the Court's docket. And, moreover, Argentum's declarants in this IPR—Drs. Robert Schleimer and Maureen Donovan—served as testifying experts on behalf of Apotex at trial on the same issue of the '620 patent's validity. Finally, Argentum admitted that "[it] attended the public portions of the trial." CIP2127, 1. Because no part of trial was ever closed to the public, Argentum attended the entire trial.

**C. Statement of relief requested**

Cipla submits that the Board should deny institution of Argentum's Petition for the reasons explained in this preliminary response.

**D. 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 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. CIP2001, ¶19. 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. CIP2007, ¶¶19-20.

Argentum's proposed definition differs in that it incorrectly renders optional

clinical experience in treating patients. Pet. 11. By omitting the critical clinical experience of a POSA, Argentum's arguments seek to rely only on laboratory models. Argentum's limited view is problematic because it overlooks the significant body of clinical literature at the time of invention, discussed below, showing that antihistamines and steroids had redundant activity *in vivo*.

## II. CLAIM CONSTRUCTION

### ***"Conditions"***

The parties agree that "conditions" means "disease(s) or illness(es)," as construed in the related *Apotex* litigation.

### ***"Nasal Spray" / "Suitable for Nasal Administration"***

Argentum's Petition fails to proffer constructions for the terms "**nasal spray**" and "**suitable for nasal administration.**" Those terms each should be construed to require "**pharmaceutical formulations that are tolerable to patients, that are homogeneous, and that can be suitably deposited onto the nasal mucosa,**" consistent with Cipla's arguments during prosecution. CIP2001, ¶26; CIP2007, ¶23.

The Board applies the "broadest reasonable construction" to the terms and phrases of unexpired patents. *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2142 (2016); 37 C.F.R. § 42.100(b). That said, "their broadest reasonable interpretation ... does not include giving claims a legally incorrect interpretation."

*In re Skvorecz*, 580 F.3d 1262, 1267 (Fed. Cir. 2009); *D'Agostino v. Mastercard Int'l Inc.*, 844 F.3d 945, 948 (Fed. Cir. 2016). Here, the Board “should [] consult the patent’s prosecution history in proceedings in which the patent has been brought back to the agency for a second review” to see if a construction would be “legally incorrect.” *Microsoft Corp. v. Proxyconn, Inc.*, 789 F.3d 1292, 1298 (Fed. Cir. 2015); *D'Agostino*, 844 F.3d at 948.

During prosecution, the Examiner initially rejected Cipla’s application under 35 U.S.C. §§ 102 and 103 over the Cramer reference, and specifically the formulation disclosed in Example III. CIP2001, ¶27; CIP2007, ¶¶23-24; EX1002, 507-522. In response, Cipla submitted a declaration from co-inventor Geena Malhotra recreating Cramer’s Example III. The declaration and recreation demonstrated that Cramer’s Example III 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 effected homogeneity of the formulation. EX1002, 286-287, 220-221. Together, these problems rendered Example III unsuitable for use as a nasal spray. *Id.*; CIP2001, ¶28; CIP2007, ¶25.

In view of this testing, and to overcome the prior art rejection, Cipla also amended the claims to recite “said pharmaceutical formulation is in a dosage form

**suitable for nasal administration,”** and likewise noted that certain pending claims recited a “nasal spray.” EX1002, 203-231; CIP2001, ¶¶29-30; CIP2007, ¶25.

Cipla argued that the Malhotra declaration established that “Example 3 of *Cramer* (identified by the April 28, 2010 Office Action, page 16, as the closest example) is inoperable and unacceptable as *a pharmaceutical formulation in a dosage form suitable for nasal administration*” because it exhibited an unacceptable osmolality, unacceptable spray quality, and unacceptable settling and that “the inoperability of *Cramer*’s closest example as cited by the Office Action is a further basis for the novelty of independent claims 1 [and] 56....” EX1002, 220-21 (emphasis added).

Based on the declaration, arguments, and amendments, the Examiner later allowed the pending claims over *Cramer*. EX1002, 38-40. A POSA would have understood from Cipla’s claim amendments, declaration, and arguments that the formulations recited in the challenged claims do not suffer from unacceptable osmolality, unacceptable spray quality, and unacceptable settling, as distinguished from *Cramer*’s Example III which was proven inoperable. CIP2001, ¶31; CIP2007, ¶¶25, 44-47.



**III. THE BOARD SHOULD DENY TRIAL ON GROUNDS 1, 2, AND 3 BECAUSE EACH HAS A THRESHOLD FAILURE.**

**A. Anticipation Ground 1 presents the same anticipation argument using substantially the same art as was overcome during prosecution**

The Board should deny trial on Argentum's anticipation Ground 1 as redundant under 35 U.S.C. § 325(d) because it presents the same arguments on substantially the same prior art that was already overcome during prosecution. Because Cipla already overcame these same arguments in view of substantially the same prior art during prosecution, the Board should deny institution here.

As discussed above (§II), Cipla overcame Cramer's alleged anticipatory disclosure by *inter alia*, (1) demonstrating that Cramer's Example III formulation was not a nasal spray suitable for nasal administration, and (2) amending the claims. Aware of Cramer's shortcomings, Argentum relies on Segal, a reference its expert, Dr. Schleimer, testified is "less specific" than Cramer, to assert the same anticipation argument. CIP2019, 65:17-20.

As shown in the chart below, each teaching in Segal to which Argentum points in its Petition was also before the Examiner during prosecution by way of Cramer:

'620 Patent Claims	Segal (Pet. 19-21)	Cramer (EX1011)
1. A pharmaceutical formulation comprising:	"The present invention provides <u>topically applicable nasal compositions</u>	"The present invention relates to novel <u>nasal spray compositions</u> ," EX1011,

	comprising a therapeutically effective amount of a topical antiinflammatory agent and a therapeutically effective amount of at least one agent suitable for topical nasal administration and selected from the group consisting of a vasoconstrictor, a neuramidinase inhibitor, an anticholinergic agent, a leukotriene inhibitor, an antihistamine, an antiallergic agent, an anesthetic, and a mucolytic agent.” EX1012, 4:10-15; <i>see also id.</i> cl.1.	2:5; EX1002, 511.
(a) azelastine, or a pharmaceutically acceptable salt thereof, and	“Suitable antihistamines are diphenhydramine, chlorpheniramine, cetirizine, terfenadine, fenofexadine, astemizole, norastemizole, <u>azelastine</u> , and azatidine.” EX1012, 5:19-20; <i>see also id.</i> cl.4 (depending from Segal claim 1).	The present invention comprises an “antihistamine selected from the group consisting of cetirizine, loratadine, <u>azelastine</u> , pharmaceutically acceptable salts thereof, optically active racemates thereof and mixtures thereof.” EX1011, 2:36-43; EX1002, 511.
(b) a pharmaceutically acceptable ester of fluticasone,	“In a preferred embodiment the topical antiinflammatory agent is beclomethasone dipropionate, budesonide, dexamethasone, mometasone furoate, <u>fluticasone propionate</u> or triamcinolone acetonide.” EX1012, 4:23-26; <i>see also id.</i> cl.2 (depending from Segal claim 1).	The present invention comprises a “glucocorticoid selected from the group consisting of beclomethasone, flunisolide, triamcinolone, <u>fluticasone</u> , mometasone, budesonide, pharmaceutically acceptable salts thereof and mixtures thereof.” EX1011, 2:36-40; EX1002, 511.

(c) wherein said pharmaceutical formulation is in a dosage form suitable for nasal administration.	<p>“The compositions of the present invention are formulated as aqueous solutions comprising an antiinflammatory agent and at least one additional therapeutic agent and further comprising a pharmaceutically acceptable nasal carrier...Preferred nasal formulations are nose drops or <u>nasal sprays</u> containing a water buffered aqueous solution as a carrier.”</p> <p>EX1012, 5:29-4:5; see also id. cl.15 (depending from Segal claim 1 or 11).</p> <p>Segal provided no exemplary formulations.</p>	<table><tr><th>Component</th><th>Wgt %</th></tr><tr><td>triamcinolone acetonide</td><td>0.050</td></tr><tr><td>azelastine HCl</td><td>0.070</td></tr><tr><td>polysorbate 80</td><td>0.050</td></tr><tr><td>glycerin</td><td>2.000</td></tr><tr><td>hydroxypropyl methyl cellulose</td><td>1.000</td></tr><tr><td>sodium chloride</td><td>0.900</td></tr><tr><td>ethylenediamine tetraacetic acid</td><td>0.050</td></tr><tr><td>benzalkonium chloride</td><td>0.020</td></tr><tr><td>distilled water</td><td>q.s. to vol.</td></tr></table> <p>EX1011, 6:30-41. This purported nasal spray example from Cramer discloses an aqueous carrier, the same formulation information Argentum identified in Segal. <i>See also</i> EX1011, 3:34-35 (describing aqueous saline solution carriers).</p> <p>The above exemplary formulation from Cramer, Example III, is the closest prior art as confirmed by the PTO (EX1002, 519-520), and was shown during prosecution and again during litigation to be unsuitable for nasal administration due to its unacceptable acidity, instability, and inconsistent dosage delivery. EX1002, 284-287; <i>see also</i> CIP2029; CIP2030.</p>	Component	Wgt %	triamcinolone acetonide	0.050	azelastine HCl	0.070	polysorbate 80	0.050	glycerin	2.000	hydroxypropyl methyl cellulose	1.000	sodium chloride	0.900	ethylenediamine tetraacetic acid	0.050	benzalkonium chloride	0.020	distilled water	q.s. to vol.
Component	Wgt %																					
triamcinolone acetonide	0.050																					
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sodium chloride	0.900																					
ethylenediamine tetraacetic acid	0.050																					
benzalkonium chloride	0.020																					
distilled water	q.s. to vol.																					
25. A nasal spray formulation comprising	<p>“The compositions of the present invention are formulated as aqueous solutions comprising an antiinflammatory agent and at</p>	<p><i>See supra</i> claim limitation 1(c).</p>																				

	<p>least one additional therapeutic agent and further comprising a pharmaceutically acceptable nasal carrier...Preferred nasal formulations are nose drops or <u>nasal sprays</u> containing a water buffered aqueous solution as a carrier.”</p> <p>EX1012, 5:29-6:5; <i>see also id.</i> cl.15 (depending from Segal claim 1 or 11).</p>	
(i) azelastine, or a pharmaceutically acceptable salt thereof,	<p>“Suitable antihistamines are diphenhydramine, chlorpheniramine, cetirizine, terfenadine, fenofexadine, astemizole, norastemizole, <u>azelastine</u>, and azatidine.”</p> <p>EX1012, 5:19-20; <i>see also id.</i> cl.4 (depending from Segal claim 1).</p>	<i>See supra</i> claim limitation 1(a).
(ii) a pharmaceutically acceptable ester of fluticasone,	<p>“In a preferred embodiment the topical antiinflammatory agent is beclomethasone dipropionate, budesonide, dexamethasone, mometasone furoate, <u>fluticasone propionate</u> or triamcinolone acetonide.”</p> <p>EX1012, 4:23-26; <i>see also id.</i> cl.2 (depending from Segal claim 1).</p>	<i>See supra</i> claim limitation 1(b).
and (iii) a pharmaceutically acceptable carrier or excipient therefor.	<p>“Preferred nasal formulations are nose drops or <u>nasal sprays</u> containing a <u>water buffered aqueous solution</u> as a carrier.”</p> <p>EX1012, 6:4-5.</p>	<p>“One other essential component of the present invention is a pharmaceutically-acceptable intranasal carrier. Preferred for use herein are aqueous saline solution carriers.”</p> <p>EX1011, 3:34-35.</p>

Moreover, Argentum's Petition makes no mention of the above claim amendments or Cipla's arguments, nor their importance in overcoming Cramer during prosecution. Nor has Argentum proffered any evidence to suggest that Segal discloses a dosage form that is "suitable for nasal administration" or a "nasal spray" as required by the challenged claims.

The Board should deny Ground 1 because it presents "the same or substantially the same prior art [and] arguments" that Cipla already overcame during prosecution. *See, e.g., Yotrio Corp. v. Lakesouth Holdings, LLC*, IPR2017-00298, Paper 12, 7-14 (PTAB May 15, 2017); IPR2017-00299, Paper 7, 9-14 (PTAB May 15, 2017).

**B. Obviousness Grounds 2 and 3 are fatally deficient as a matter of law because Argentum failed to address various evidence of objective indicia of which it had knowledge.**

**1. Argentum knew of Cipla's well-developed objective indicia evidence because it observed, and its experts testified about, the same evidence in the *Apotex* trial.**

The Board has repeatedly denied institution when a Petition fails to address known objective indicia of nonobviousness from prior related proceedings or the prosecution history. *Robert Bosch Tool Corp. v. SD3, LLC*, IPR2016-01751, Paper 15, 22-32 (PTAB March 22, 2017); *Praxair Distr., Inc. et al v. Mallinckrodt Hosp. Prods.*, IPR2016-00777, Paper 10 , 9-10 (PTAB Sept. 22, 2016); *Coal. for Affordable Drugs V LLC v. Hoffman-LaRoche Inc.*, IPR2015-01792, Paper 14, 17-

18 (PTAB March 11, 2016). In the *Robert Bosch* proceeding, the Board confirmed that all known objective indicia evidence must be considered at the institution stage where (1) the petitioner is aware of the objective indicia evidence from having participated in a related ITC action, and (2) that evidence was fully developed in that proceeding. *Robert Bosch*, IPR2016-01751, Paper 15, 22-32. The same is true here.

As discussed here and in further detail in §IV.D, Argentum's Petition ignores the compelling objective indicia evidence that (1) its own in-house representative witnessed in open court, and (2) that its own declarants observed and testified about at trial. There is no question that the objective indicia evidence that Cipla presented at trial was well-developed. On this basis alone, institution on Grounds 2 and 3 should be denied.

At trial in the related *Apotex* case, Cipla presented evidence of eight objective indicia of the nonobviousness of the '620 patent's claims (each objective indicia is discussed in more detail below in §IX.D): (1) unexpected results; (2) failure of others; (3) licensing; (4) industry skepticism; (5) commercial success; (6) copying; (7) long-felt need; and (8) industry praise. Despite having affirmative knowledge of this evidence from attending trial, Argentum neither attempts to address nor even mention this evidence in its Petition.

Besides attending trial, Argentum also had knowledge of Cipla's objective indicia evidence from multiple public court filings that discussed them extensively, including: (1) Cipla's redacted Pretrial Order that was publicly filed on November 21, 2016,<sup>3</sup> more than two months before Argentum's Petition (CIP2017, 84-118); (2) Apotex's and Cipla's post-trial findings of fact that were publicly filed on January 10, 2017, several weeks before Argentum's Petition (CIP2022, 39-52; CIP2023, 41-54); and (3) Apotex's opening post-trial brief that was filed nine days before Argentum's Petition. CIP2024, 45-56. Argentum also had constructive knowledge of this evidence through its declarants' participation in the *Apotex* trial and testimony concerning most of these objective indicia. In fact, in the related *Apotex* case, Dr. Schleimer addressed unexpected results, long-felt need, industry praise, industry skepticism, and failure of others, and Dr. Donovan addressed unexpected results too. CIP2011, 46-48; CIP2012, 10-21; CIP2013, 22-26; CIP2015, 61-66.

Contrary to Argentum's assertion, this case is not like the situation presented in *Amneal Pharm. Inc. v. Supernus Pharm. Inc.*, IPR2013-00368, where patent

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<sup>3</sup> While Apotex, Cipla, and Meda confidential information was redacted in the Joint Pretrial Order, Cipla's and Meda's objective indicia evidence was subsequently disclosed in open court and unredacted post-trial briefing.

owner's objective evidence of non-obviousness was sealed by the Court's protective order in a related co-pending litigation. *See Amneal*, IPR2013-00368, Paper 2, 47-48 (Petitioner, June 20, 2013). Unlike *Amneal*, no part of the *Apotex* trial was closed to the public. Moreover, even in the *Amneal* case, the petitioner *still addressed the publicly-available objective considerations evidence* from trial in its petition. *See Amneal*, IPR2013-00368, Paper 2, 47-54. Argentum should have—but failed—to do the same here.

Argentum's failure to address the relevant evidence presented by Cipla in the related *Apotex* trial is fatal to Grounds 2 and 3 of its Petition as a matter of law. A determination that there is a likelihood of succeeding on an obviousness position requires consideration of Cipla's objective indicia evidence. *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."); *see also WBIP, LLC v. Kohler, Co.*, 829 F.3d 1317, 1329 (Fed. Cir. 2016).

**2. Cipla will be severely prejudiced if trial is instituted despite Argentum's failure to address Cipla's objective indicia evidence in its Petition.**

Argentum's decision not to address Cipla's objective indicia evidence in its



Petition was purposeful, and will severely prejudice Cipla if trial is instituted. By avoiding this evidence, Argentum improperly shifts the burden onto Cipla to establish objective indicia in its preliminary response and/or in its patent owner response. Argentum can then respond to Cipla's evidence in its petitioner's reply—with little or no opportunity for Cipla to respond to those arguments. On similar facts, the Board denied institution in *Merial v. Virbac*, recognizing this same fundamental “unfair[ness],” finding “it unfair to impose on [patent owner] in the first instance the burden of establishing unexpected results in a trial” when petitioner “was aware of the unexpected results showing” and “should have addressed unexpected results in the first instance.” *Merial*, IPR2014-01279, Paper 13, 26-27 (PTAB Jan. 22, 2015). That same rationale warrants denial of Argentum's Petition.

**IV. THE BOARD SHOULD ALSO DENY TRIAL ON GROUNDS 1-3 BECAUSE THEY LACK SUBSTANTIVE MERIT.**

Beyond threshold failures, each Ground presented in Argentum's Petition also fail on the substantive merits. Argentum's anticipation Ground 1 fails because Segal neither discloses nor enables a fixed-dose nasal spray formulation comprising azelastine and fluticasone. Argentum's Grounds 2 and 3 are defective because they fail to establish a motivation or reasonable expectation of success; indeed, the art taught away from the claimed combinations.

**A. Ground 1 Fails: Argentum has not established a reasonable likelihood that Claims 1 and 25 are anticipated by Segal.**

**1. Segal does not describe azelastine and fluticasone in single formulation.**

A POSA would not have immediately envisaged the claimed azelastine/fluticasone combination. Segal contains minimal disclosure of combination products for the treatment of allergic rhinitis. It teaches compositions comprising “a topical antiinflammatory [sic] agent and...*at least one agent*...selected from the group consisting of a vasoconstrictor, a neuramidinase inhibitor, an anticholinergic agent, a leukotriene inhibitor, an antihistamine, an antiallergic agent, an anesthetic, and a mucolytic agent.” CIP2001, ¶79; EX1012, 4:10-15. Segal further discloses four decongestants, three antileukotrienes, one neuramidinase inhibitor, nine antihistamines, three antiallergic agents, one anticholinergic, three anesthetics, and three mucolytic agents. CIP2001, ¶80; EX1012, 5:13-28. Because Segal also teaches that the “anti-inflammatory agent” can be combined with “at least one agent” from the list (CIP2001, ¶81), it teaches more than 800 million combinations total within its broad genus.<sup>4</sup>

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<sup>4</sup> Segal teaches combinations with “at least one” of the twenty-seven disclosed agents. The formula for calculating the number of possible combinations of  $r$  agents from a set of  $n$ , where  $r$  is 1-27 and  $n$  is 27, is as follows:

Consistent with its overbroad disclosure, Segal does not provide any preference for combinations of anti-inflammatory agents with any of the other 8 drug classes, let alone any preference for a particular species like azelastine and fluticasone. CIP2001, ¶81. Accordingly, a POSA would have been unable to envision the specific species—azelastine plus fluticasone—from among the 800 million disclosed combinations. *Id.*

Recognizing the problematic breadth of Segal's disclosure, Argentum attempts to limit that disclosure by referring only to Segal's claims 1, 2, and 4. This is unavailing. Segal's claim 1 recites an anti-inflammatory agent with "at least one agent" from the eight other disclosed drug classes. Segal's claim 2 limits the "topical antiinflammatory agents" to six (suggesting that claim 1 is broader<sup>5</sup>), so it does nothing to narrow the 134,217,727 possible combinations of "at least one" of the other agents. Likewise, Segal's claim 4 limits the "antihistamines" to nine

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$$\sum_{k=1}^{27} \binom{27}{k}, \text{ where } \binom{27}{k} = \frac{27!}{k!(27-k)!}$$

The solution to this formula is 134,217,727. Multiplying the number of non-steroid combinations by six (for each steroid) yields **805,306,362** possible combinations. CIP2035, 6-8.

<sup>5</sup> A dependent claim must "set forth and then specify a further limitation of the subject matter claims." 35 U.S.C. § 112, ¶4.

(again, suggesting that claim 1 is broader), so it, too, does nothing to narrow the 134,217,727 possible disclosed combinations of other agents.

Because each of the drug classes listed in claim 1 are, as a matter of law, broader than the options disclosed in Segal's specification, claims 2 and 4 serve only to show that the 805,306,362 combinations disclosed in Segal are merely *exemplary*; the true number of combinations among these classes is incalculable. Accordingly, these claims do not salvage Argentum's case; they disprove it.

Likewise, Argentum's *In re Petering* anticipation theory fails. Pet. 18-19. In *Petering*, the anticipatory reference disclosed "specific preferences" that would have limited its broad disclosure. *In re Petering*, 49 C.C.P.A. 993, 1000 (1962). But neither Segal generally, nor Segal's claims 1, 2, and 4 specifically, disclose *any preference* for the anti-inflammatory agent or what to combine with it. *See, e.g., Sanofi-Synthelabo v. Apotex, Inc.*, 470 F.3d 1368, 1377 (Fed. Cir. 2006) (rejecting *Petering* anticipation theory for bisulfate salt despite prior art disclosing 50 pharmaceutically acceptable salts because the anticipatory reference did not disclose any preference for bisulfates). Indeed, Cipla already overcame a similar *In re Petering* argument when the Examiner cited the more specific disclosure of Cramer. EX1002, 512.

Accordingly, a POSA would not immediately envisage a fluticasone/azelastine combination nasal spray formulation from Segal (CIP2001, ¶81), so Segal does not anticipate either claim 1 or claim 25.

**2. Segal does not enable the “nasal spray” / “dosage form suitable for nasal administration” of claims 1 and 25.**

To be anticipatory, Segal must enable a POSA to practice its allegedly anticipatory disclosure. *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1082 (Fed. Cir. 2008). Segal does no such thing.

Segal does not disclose sufficient information which a POSA could use as guidance for formulating a solution formulation—like azelastine—with a suspension formulation—like fluticasone—because Segal contains no formulation examples. CIP2007, ¶29. Beyond Segal’s explicit disclosures, the art generally in 2002 did not enable such a combination because general texts that a POSA would have turned to did not teach how to combine solution formulations and suspension formulations into a nasal spray. CIP2007, ¶29.

Segal’s lack of an enabling disclosure is underscored by the fact that the Cramer reference—which contains more detailed formulation guidance than Segal—is not enabling. CIP2007, ¶¶30-31. During prosecution, Segal was rejected because it “cannot be considered novel or cannot be considered to involve an inventive step” over Cramer. EX1012, 10-11. Segal’s disclosure of a “topically applicable nasal composition” comprising triamcinolone and azelastine—with no

disclosure of how to co-formulate these ingredients—is encompassed within Cramer’s disclosure of an “intranasally administered pharmaceutical composition” comprising triamcinolone and azelastine as set out in Cramer’s Example III. CIP2007, ¶¶27-28; EX1011, 7; EX1012, 4:23-5:28. Dr. Schleimer testified in the related *Apotex* case that Segal’s disclosure is actually a “less specific” version of Cramer’s disclosure. CIP2007, ¶31; CIP2019, 66:17-20.

As Cipla established during prosecution, Cramer’s Example III formulation exhibits unacceptably high osmolality, poor spray quality, and unacceptable settling and caking. CIP2007, ¶31; EX1002, 286-287. Moreover, Cramer Example III’s shortcomings were later confirmed by testing completed in the related *Apotex* case, including testing conducted by Apotex’s expert Dr. Ram Govindarajan, which Dr. Donovan relied upon in that case, showing: (i) unacceptable acidity; (ii) unacceptable settling and caking; and (iii) unacceptably high osmolality. CIP2007, ¶¶44-47; CIP2029; CIP2030.

Because Cramer’s more specific teaching is not enabled, neither is Segal’s significantly broader disclosure. Importantly, Segal is a non-patent prior art publication so no presumption of enablement applies. *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1355 n.22 (Fed. Cir. 2003). Therefore, Argentum carries the burden of establishing that Segal contains an enabling anticipatory disclosure, but Argentum’s Petition has not done so.

First, Argentum offers unsupported testimony from Dr. Schleimer that “Segal was enabling at the time of the invention,” (Pet. 17 (citing EX1003, ¶41)), but Dr. Schleimer has no demonstrable qualification or experience in formulating pharmaceutical compositions. EX1051, 1; CIP2025, 27:3-11.

Second, Argentum asserts that the '620 patent “admits” that the art enables a POSA to formulate Segal’s compositions because the '620 patent contains the following statement preceding its formulation examples: “*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.” Pet. 17; EX1001, 7:67-8:2 (emphasis added). But this statement refers to how to formulate the subsequent Examples of the '620 patent; it does not reference the prior art, and would not be understood to enable prior art that was otherwise not enabled. CIP2007, ¶32. And unlike the formulation examples of the '620 patent, Segal contains no formulation examples. There is no “list[]” of “ingredients of the formulation according to [Segal’s] invention.” *Id.*

Third, Argentum pivots to assert that Segal is enabled by the art because Segal states that the disclosed combination products contain “a water buffered aqueous solution as a carrier.” Pet. 18. Not so. Segal’s anti-inflammatory agents, like fluticasone, are “practically insoluble in water” and are therefore formulated as suspension formulations. CIP2007, ¶33; EX1012, 6:4-5; EX1010, 1; CIP2039.

That is, Segal's anti-inflammatory agents could not have been "water buffered aqueous solutions." CIP2007, ¶33.

Fourth, and lastly, Argentum hopes to bolster its enablement contention with unsupported testimony from Dr. Donovan, (Pet. 18), but the cited passages from Dr. Donovan have no relation to Segal and, in fact, relate only to claim limitations not found in challenged claims 1 and 25. EX1004, ¶¶35, 59-61. Accordingly, the evidence relied upon by Argentum to assert enablement does not support Argentum's arguments, and certainly does not overcome the errors in Argentum's analysis presented above.

**B. Ground 2 fails: Argentum has failed to establish a reasonable likelihood that Claims 1, 4-6, 24-26, and 29 are obvious over Segal, Hettche, and Phillipps.**

The challenged claims would not have been obvious to a POSA at the time of invention. The justifications Argentum relies upon for selecting azelastine and fluticasone, and the alleged motivations to combine them, were either contradicted by the art, or rejected by experts in the field at the time of invention. Argentum's arguments, thus, amount to nothing more than textbook hindsight. Simply put, at the time of invention, there was no clinical justification for combining these two agents into a single formulation; rather, the art taught away from such a pairing. Moreover, the art also taught that technical difficulties, including fluticasone's known aggregation behavior when formulated with a second active ingredient,



would have undercut any motivation or reasonable expectation of success.

**1. The clinical art taught away from the co-administration of an antihistamine and a steroid.**

Argentum's Petition advances three alleged motivations for a POSA to pursue a fixed-dose combination of azelastine and fluticasone. First, Argentum alleges, "the clinical use of antihistamines and corticosteroids together for treating allergic rhinitis was well established before June 2002." Pet. 35. Second, Argentum claims that "a POSA would have wanted to take advantage of the known complementary mechanisms of action of azelastine and fluticasone working together." Pet. 36. And third, Argentum alleges that "a POSA would have expected a combined azelastine/fluticasone nasal spray to improve patient compliance over use of the individual monotherapies." Pet. 38.

Each of these purported "motivations" are belied by the art at the time of invention. First, the alleged "complementary mechanisms of action" that Argentum relies upon were actually tested—and explicitly rejected—in the art prior to the date of invention. Second, the clinical art Argentum relies upon explicitly taught that azelastine should be used as a *flexible*, "on demand" therapy, and not in a fixed regimen. The art also taught that fixed-dose combinations eliminated the type of flexibility required here. Finally, the references cited in Argentum's Petition actually show that there was no need to improve compliance of an azelastine-fluticasone "on demand" co-therapy.

**(a) The art established that antihistamines and steroids had redundant mechanisms of action *in vivo*.**

In the late eighties through the late nineties, investigators studied the primary premise of Argentum's argument: whether theorized differences in the mechanisms of action of antihistamines and steroids would provide patients greater symptom improvement than either drug alone. CIP2001, ¶¶46-48. The findings showed that antihistamines and steroids did not have complementary mechanisms. Instead, they showed antihistamines and steroids had redundant activity *in vivo*. CIP2001, ¶61; CIP2041, 5.

Four studies—Juniper 1989, Simpson, Benincasa, and Ratner 1998—all considered different pairs of antihistamines and steroids and each found no meaningful clinical improvement between the use of both drugs and steroids alone. CIP2001, ¶¶52, 55-57; EX1039, 1; EX1036, 3; EX1040, 1; EX1034, 1. These were not ambiguous teachings; the authors consistently found no reason to use antihistamines and steroids together in a fixed dosing regimen, *i.e.*, in a manner consistent with the fixed-dose combinations of the challenged claims. Juniper found that the co-administration of beclomethasone and astemizole “provided no better control of rhinitis than beclomethasone alone.” CIP2001, ¶52; EX1039, 1. Simpson found that “budesonide and terfenadine combination treatment produced a similar effect to treatment with budesonide alone.” CIP2001, ¶55; EX1036, 1, 3. Benincasa found that there was “no significant difference in efficacy between

[**fluticasone** alone] ... and [**fluticasone**] in combination with oral cetirizine.”

CIP2001, ¶56; EX1040, 1. Ratner 1998 concluded that “adding loratadine to [**fluticasone**] does not confer meaningful additional benefit.” CIP2001, ¶57; EX1034, 1. That is, two of these studies investigated treatment regimens with the claimed steroid fluticasone, which yielded no meaningful improvement. These studies also found that combining steroids and antihistamines exhibited a similar or greater incidence of side effects. CIP2001, ¶45 (citing EX1035, 8; EX1036, 5; EX1039, 6).

Two other studies—Drouin and Brooks—studied the specific combination of loratadine and beclomethasone against beclomethasone alone. EX1035, 1; EX1038, 1. Although these studies claimed some benefit, the data in each showed that no meaningful benefit was actually obtained. Drouin reflects only a 7% difference between the steroid-only and the co-administration treatment arts, and this minor difference is not clinically relevant. CIP2001, ¶59 (citing EX1035, 5). Meanwhile, there were no observed differences in efficacy between the steroid and antihistamine monotherapies in Brooks. EX1038, 3. As Dr. Schleimer explains, a POSA would have known that steroids are much more effective than antihistamines. EX1003, ¶54. The co-administration data presented in Brooks is consistent the typical efficacy of a steroid alone, and thus a POSA would immediately recognize that the reported data is flawed by the ineffectiveness of the

steroid monotherapy. CIP2001, ¶60. Because the only notable increase from these studies was an increase in side effects, a POSA would have been deterred from using an antihistamine and steroid together in a fixed manner. CIP2001, ¶¶59-60. This understanding is confirmed by Nielsen 2001, a meta-analysis that expressly considered Brooks and nevertheless concluded that “[c]ombining antihistamines and intranasal corticosteroids in the treatment of allergic rhinitis ***does not provide any additional effect to intranasal corticosteroids alone.***” CIP2001, ¶63 (citing CIP2042, 2) (emphasis added).

Cramer and Segal applications published before most of these studies were published. Both applications described a theoretical benefit to combining antihistamines and steroids without any data, but clinical studies that actually tested this theory demonstrated no such benefits. Indeed, these studies included many of the antihistamine/steroid pairs apparently disclosed in Cramer and Segal, including: beclomethasone and astemizole (EX1039, 1); budesonide and terfenadine (EX1036, 1); fluticasone and cetirizine (EX1040, 1); and fluticasone and loratadine (EX1034, 1). CIP2001, ¶52.

Argentum’s assertion that a POSA would have perceived benefits to combining an antihistamine with a steroid are not just refuted by the primary studies themselves, but also by retrospective meta-analyses in the art. In 2000 and 2001, two articles reviewed the available literature and both concluded that there

was ***no reason*** to add an antihistamine to a steroid to treat AR because the combination had been repeatedly shown to confer no benefit over the steroid alone. CIP2041, 4-5; CIP2042, 2. Nielsen, in particular, explicitly considered Argentum's art—Juniper 1989, Simpson, Brooks, Juniper 1997, and Ratner 1998. CIP2001, ¶62; CIP2042, 10. Nielsen concluded that these studies show “no or a marginal clinical benefit,” and that the use of the two drugs classes together “has no support in clinical evidence, as the combination has not provided effects beyond [steroids] alone.” CIP2001, ¶62; CIP2042, 11. A POSA, aware of the studies and review articles, would have seen no reason to develop a fixed-dose combination of an antihistamine and a steroid.

Notably, these studies each tested whether a steroid (with its theoretical effect on late phase) and an antihistamine (with its theoretical effect on early phase) would confer any benefit due to their different mechanisms of action. The answer was no. Indeed, in 2000, Howarth squarely rejected Argentum's claim that antihistamines and steroids had complementary mechanisms of action, concluding instead that their mechanisms were redundant:

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***.

CIP2001, ¶61; CIP2041, 5 (emphasis added). Argentum's expert, Dr. Schleimer,

relied on both Howarth and Nielsen in the related *Apotex* case (CIP2011, 116 (citing Howarth); CIP2012, 26 (citing Nielsen)), and they undermine Argentum's arguments here. Notably, Argentum has not produced or even acknowledged these references, which further exposes the hindsight in Argentum's motivation theory.

(b) **Based on the results of the fixed co-administration studies, the prevailing clinical treatment Guidelines recommended using azelastine only as an “on demand” adjunct therapy.**

Argentum's remaining references—the Cauwenberge and ARIA treatment guidelines—are consistent with the teachings of the Howarth and Nielsen. Coincidentally, the authors of Howarth and Nielsen were also authors of the guidelines. CIP2001, ¶63; CIP2133, 3. Although it was known that fixed dosing co-administration of antihistamines and steroids yielded no improvement over a steroid alone, an antihistamine might be useful in a flexible, “on demand” treatment—*i.e.*, used as needed for their fast onset when a patient's symptoms peak. Indeed, Cauwenberge and ARIA (two versions of the same document) specifically taught that this practice should be used for topical antihistamines like azelastine:

Topical antihistamines usually require bidaily administrations to maintain satisfactory clinical effect. Their use may therefore be recommended for organ-limited mild disease and as an “***on demand***” treatment in addition to a continuous medication.

EX1022, 5; *see also* EX1024, 90 (emphasis added). Dykewicz taught a similar

approach, recommending “both step-up and step-down approaches” along with “modifications” to a patient’s treatment. EX1019, 34. A POSA would understand that these approaches allowed for a patient to increase or decrease treatment as needed. CIP2001, ¶¶66-67.

Argentum’s Juniper 1997 reference, which contains no efficacy data (CIP2001, ¶68), illustrates this approach. One patient group was told to use fluticasone consistently and add an antihistamine when needed. CIP2001, ¶69; EX1031, 3. These patients used an overage of 5.5 antihistamine pills over the course of the entire 6-week study period—less than one pill a week. CIP2001, ¶69; EX1031, 7. The use portrayed in Juniper 1997 (and recommended in Dykewicz, Cauwenberge, and ARIA) thus resulted in one antihistamine use per seven steroid uses. CIP2001, ¶69. This practice does not suggest to a POSA to use a fixed-dose combination of an antihistamine and steroid.

**(c) A POSA would have expected azelastine to decrease compliance with a fluticasone therapy.**

Insofar as Argentum argues that a POSA would have been motivated to select azelastine (Pet. 33-34), that allegation is contrary to the alleged motivation of improved compliance that Argentum and its expert, Dr. Schleimer, rely on. *See, e.g.*, Pet. 38-39; EX1003, ¶72. Not only was azelastine known to have several side effects that deterred compliance, but a POSA would also have known that azelastine’s duration of action would reduce compliance.

First, azelastine exhibited greater side effects than three popular oral antihistamines combined. The table below includes the adult adverse event data from the 2000 FDA labels for Astelin® (azelastine), Allegra® (fexofenadine), Zyrtec® (cetirizine), and Claritin® (loratadine).

Listed Side Effect	Azelastine	Fexofenadine	Cetirizine	Loratadine
Bitter Taste	19.7			
Headache	14.8			12
Somnolence / Drowsiness	11.5	1.3	13.7	8
Nasal Burning	4.1			
Pharyngitis	3.8		2.0	
Dry Mouth	2.8		2.3	3
Paroxysmal Sneezing	3.1			
Nausea	2.8	1.6		
Rhinitis	2.3			
Fatigue	2.3		2.6	4
Dizziness	2.0		2.0	
Epistaxis	2.0			
Weight Increase	2.0			
Viral infection (cold, flu)		2.5		
Dysmenorrhea		1.5		

CIP2001, ¶73; EX1008, 3; CIP2034, 4, 6, 9. A POSA would have known from these labels that azelastine exhibits (1) as many side effects as the other three drugs combined, including multiple systemic side effects; (2) systemic side effects (somnolence, nausea, fatigue, dizziness, and weight increase) equal to or greater than its oral counterparts; and (3) a much higher incidence of side effects than oral



drugs. CIP2001, ¶¶74-76. At the Apotex trial, Cipla presented evidence (unrebutted here) that increasing side effects decreases compliance. CIP2022, ¶30; CIP2020, 124:14-20. This explains the overwhelming preference for *oral* antihistamines—which had a 57% market share, more than twice that of intranasal steroids and approximately thirty times that of intranasal antihistamines. CIP2001, ¶77; CIP2138, 29.

Second, as Dr. Schleimer explained in his declaration, “compliance is enhanced when ... fewer number of daily doses is required.” EX1003, ¶72. The opposite is also true: when more daily doses are required, compliance decreases. CIP2001, ¶91. As explained in Shenfield, “the vital factor [for improved compliance] is not the number of tablets [or sprays] taken but the number of doses prescribed.” CIP2001, ¶90; CIP2043, 6. A POSA would have understood from these two references that a single “dose” could be multiple drugs so long as they are taken at the same time. CIP2001, ¶90.

And here is where Argentum’s theory unravels: fluticasone only needs to be taken once a day. CIP2001, ¶91; EX1010, 8. But azelastine, which has a short duration of action, must be taken *twice* per day. CIP2001, ¶91; EX1022, 5; EX1024, 90 (“Topical H1-antihistamines usually require bi-daily (BID) administrations to maintain a satisfactory clinical effect.”). A POSA would understand that, by keeping the two drugs separate, a patient would be more likely

to comply with the steroid by taking it all in one daily dose. Putting the products together in a single formulation would be expected, per Dykewicz, to reduce compliance with the more effective steroid. CIP2001, ¶91; EX1019, 35.

**2. The art as a whole taught away from a fixed-dose combination of an antihistamine and a steroid.**

The art taught that “general considerations produce very few good reasons for using combination products.” CIP2043, 14. Shenfield, which Argentum’s counsel and Dr. Schleimer ignore even though it was prominently discussed during the Apotex trial (CIP2021, 41:18-42-1, 47:18-48:21), establishes that fixed-dose combinations eliminated dosing flexibility from treating physicians. CIP2001, ¶88; CIP2043, 12. As explained above, the clinical references on which Argentum relies taught that AR treatment requires flexibility. §IV.B.1.b; CIP2001, ¶¶66-69. The flexible approach unanimously recommended in the art would have led a POSA in a direction divergent from the inflexible path that the inventors took. CIP2001, ¶88. Accordingly, the art taught away from an inflexible fixed-dose combination. *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326-27 (Fed. Cir. 2009) (finding that a “reference may be said to teach away when a [POSA], upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant”) (citations omitted).

Shenfield further taught that “[t]he use of 2 drugs will always increase the

risk of adverse drug reactions both idiosyncratic and pharmacological.” CIP2001, ¶89; CIP2043, 13. It also taught that a fixed-dose combination should not be used in “circumstances [where] patients may be exposed to additional ingredients with little therapeutic benefit and major potential side effects.” CIP2043, 13. As shown above, the fixed dosing co-administration of an antihistamine and a steroid added no additional benefit, but *did* frequently expose the patients to additional side effects. CIP2001, ¶¶52, 55, 59; EX1035, 8; EX1036, 5; EX1039, 6. Accordingly, the art as a whole taught away from a fixed-dose combination of an antihistamine and a steroid because it would confer no additional benefit while risking significant drawbacks. CIP2001, ¶89. Again, Shenfield and the co-administration studies would have discouraged a POSA from pursuing the co-administration of antihistamines/steroids and led the POSA down a divergent path. *DePuy Spine*, 567 F.3d at 1326-27.

**3. In view of the anticipated formulation difficulties, a POSA would not have been motivated to formulate azelastine and fluticasone into a nasal spray with a reasonable expectation of success.**

Aside from Dr. Schleimer’s testimony concerning the alleged “clinical motivations” to combine Hettche, Phillipps, and Segal to arrive at the claimed invention, Argentum offers no testimony or arguments from the *formulation* perspective. In light of the anticipated formulation difficulties of formulating azelastine and fluticasone into a fixed-dose combination formulation, a POSA

would not have been motivated to do so, nor would a POSA have had a reasonable expectation of success.

**(a) Argentum fails to establish that co-formulating azelastine and fluticasone into a combination formulation was known in 2002.**

Argentum wrongly asserts that the '620 patent somehow “admits” that the prior art taught how to combine azelastine and fluticasone into a combination formulation. Pet. 39; EX1001, 7:67-8:2. Not so. As it did above (§IV.A.2), Argentum omits critical context for the passage from the '620 patent it cherry picks: the statements apply in Examples of the '620 patent where the ingredients of the formulations are listed. CIP2007, ¶¶32, 39; EX1001, 3:4-6:28. So while the statement is true in the context of the specific examples disclosed and described in the '620 patent itself, the same is not true of the art in general at the time, where there was not specific knowledge of the requisite formulation excipients and their concentrations. CIP2007, ¶¶32, 35-37.

Moreover, Argentum cites *In re Epstein* to bolster its admission argument, but that case is inapposite. There, the Federal Circuit rejected the patentee's argument requiring an anticipatory reference to provide a more detailed enabling disclosure than was contained in the patent at issue. 32 F.3d 1559, 1568 (Fed. Cir. 1994). But here the '620 patent provides a level of detail that Segal does not—multiple examples of formulations of the claimed invention, including specific

listing of excipients and their concentrations. *See* EX1012, 3:4-6:28. Similarly, Argentum cites *Amgen Inc. v. Hoechst Marion Roussel* for the proposition that Hettche and Phillipps are presumed enabled. Pet. 39-40. But *Amgen* is equally inapplicable for at least the reason that neither Hettche nor Phillipps even disclose combination formulations, so there is no disclosure of combination formulations to enable.

Nor would a POSA be able to arrive at the claimed “nasal spray” / “dosage form suitable for nasal administration” simply because azelastine and fluticasone had been previously separately formulated, as Argentum’s Petition alleges. CIP2007, ¶¶37-38; Pet. 39-40. There was no guidance in 2002 of how to combine a solution formulation—like azelastine—with a suspension formulation—like fluticasone. CIP2007, ¶¶36-38. And from the little guidance that existed—Cramer and Segal—in 2002, that guidance led a POSA to formulations not suitable for nasal administration. *See* §IV.B.3.c below and CIP2007, ¶¶36-37.

- (b) **No reasonable expectation of success exists because a POSA knew that combining fluticasone with another active ingredient in a suspension formulation led to aggregation.**

Further, a POSA in 2002 would have known that fluticasone would aggregated when co-formulated with a second active ingredient. CIP2007, ¶¶40-41. Specifically, by 2002, Glaxo—the developer of fluticasone—found that when fluticasone and a second active ingredient were co-formulated in a suspension

formulation, aggregation resulted. CIP2111,1; CIP2044,1. Glaxo recognized—as would a POSA—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. This explicit teaching would have undermined any reasonable expectation of combining fluticasone with a second active ingredient, like the challenged claims.

**(c) No reasonable expectation of success exists because Cramer’s Example III—the USPTO’s asserted closest prior art—is not suitable for nasal administration.**

A POSA following the closest prior art formulation, Cramer Example III, would have arrived at a formulation that: (1) exhibit unacceptable settling and caking (CIP2007, ¶¶42-43), (2) possesses an unacceptably high osmolality for long-term use of multiple sprays per day (CIP2007, ¶¶44-45), (3) is unacceptably acidic (CIP2007, ¶¶46-47), and (4) demonstrates an unacceptable spray quality. EX1002, 286-287. Argentum and Dr. Donovan assert two reasons why Example III’s osmolality of over 500 mOsm/kg would not be unacceptable: (1) because the FDA-approved migraine treatment Imitrex has an osmolality of over 700 mOsm/kg, and (2) hypertonic saline nasal irrigation treatments were acceptable for daily use. EX1004, ¶75. First, Imitrex is only approved for acute use, not consistent, long-term use like the type needed for treating allergic rhinitis. CIP2007, ¶44. Second, nasal irrigation treatments are used to flush the nasal cavity

and the hypertonic (high osmolality) nature of those treatments helps clear the nasal cavity. CIP2007, ¶45. A POA, however, would understand from this that such a high osmolality may be useful for nasal clearance, but would understand that the goal of intranasal drug delivery is for the formulation to be deposited on and stay on the nasal mucosa, not be cleared from it. *Id.* Therefore, an osmolality similar to Example III would be unacceptable for treatment of allergic rhinitis.

Additionally, routine modifications available to a POSA in 2002 were unable to remedy the multiple shortcomings, including applying heat, increasing and decreasing the viscosity of the thickening agent, and using high-speed mixing. CIP2007, ¶¶48-50; CIP2030, 27 (identifying Hypromellose, Type 2910, Pharmacoat 606); CIP2105, 4-6 (identifying a viscosity of 6 cP); CIP2110, 4-7; CIP2040, 4 (identify 6 cP as a low viscosity); CIP2029, 3; EX1002, 285-286; CIP2030, 30-31, 33, 36, 37.

**C. Ground 3 Fails: Argentum has failed to establish a reasonable likelihood that claims 42-44 would have been obvious over Segal, Hettche, Phillipps, and Flonase<sup>®</sup> Label.**

**1. The Petition does not articulate a motivation to combine Hettche, Phillipps, Segal, and Flonase<sup>®</sup> Label.**

The only testimony Argentum presents as a reason why a POSA would combine the Hettche, Phillipps, Segal, and the Flonase<sup>®</sup> label references to arrive at the invention of claims 42-44 comes from Dr. Donovan, who states “*I have been asked by counsel to assume it was obvious to combine azelastine hydrochloride and*

fluticasone propionate into a single nasal spray” and therefore “[Dr. Donovan] *considered only whether it would have been obvious to coformulate* azelastine hydrochloride and fluticasone propionate as a nasal spray with the excipients claimed in the ’620 patent.” EX1004, ¶40 (emphasis added). Argentum is required to identify “where each element of the claim is found in the prior art patents or printed publications relied upon.” 37 C.F.R. § 42.104 (emphasis added). For claims 42-44, Argentum has failed to do so.

Dr. Schleimer’s testimony does not correct this omission. Dr. Schleimer’s obviousness testimony relates *only* to whether “[c]laims 1, 5-6, 24-26, and 29 were obvious as of at least June 2002.” EX1003, §XI. That is, Dr. Schleimer provides no opinion on claims 42-44 at all. And on this point, Argentum’s Petition tries to fill its gap in testimony by incorporating its Ground 2 by reference. Pet. 43-44. But Ground 2 is not directed to claims 42-44 or the Flonase<sup>®</sup> label, so even accepting the incorporation by reference, the Petition is devoid of any showing “where each element of [claims 42-44 are] found in the prior art patents or printed publications relied upon.”<sup>6</sup> See 37 C.F.R. § 42.104. In addition, Ground 3 suffers from the same flaws as Ground 2 due to Argentum’s incorporation by reference.

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<sup>6</sup> If the Board accepts Argentum’s incorporation by reference, Cipla incorporates the above §IV.B herein by reference.



**2. The Board should deny trial on Ground 3 because the art taught away from the excipients recited in claims 42-44.**

Ground 3 asserts that the four-reference combination of Hettche, Phillips, Segal and the Flonase® label renders claims 42-44 unpatentable on a “obvious to try” theory. Pet. 44. But to succeed, Argentum 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). Argentum failed in this standard.

For the reasons below, a POSA would not have been motivated to select the excipients recited in claims 42-44 of the '620 patent—in fact the prior art would have dissuaded a POSA from selecting the claimed excipients—nor would the prior art have offered a reasonable expectation of successfully formulating a combination product within the scope of claims 42-44.

**(a) The art taught away from using microcrystalline cellulose and sodium carboxymethyl cellulose with cationic drugs like azelastine salts.**

A POSA formulating an azelastine/fluticasone combination formulation would have been led away from using either microcrystalline cellulose (“MCC”) or sodium carboxymethyl cellulose (“CMC”) as the thickening agent because of the expected incompatibility of azelastine with CMC and/or MCC. CIP2007, ¶52.

By 2002, it was known that CMC and MCC were incompatible with cationic

drugs. CIP2007, ¶53. Lieberman teaches that “[c]arboxymethylcellulose solutions have poor tolerance for electrolytes . . . as they precipitate the polymer. CMC is compatible with other nonionic cellulose derivatives, clays, and commonly used preservatives *but is incompatible with cationic drugs.*” CIP2113, 24 (emphasis added). Similarly, MCC was also known to be “incompatible with cationic drugs and electrolytes.” *Id.*

In addition, azelastine was known in the art to be formulated as a salt. CIP2007, ¶54; EX1007, 3:48-56. When formulated as a salt, azelastine would dissociate into its anionic and cationic electrolytes, with azelastine being a cation. CIP2007, ¶54. That is, CMC and MCC would be in the presence of both electrolytes and a cationic drug if formulated with the claimed azelastine salts. Given that the CMC or MCC polymers were expected to precipitate out of the formulation—thereby eliminating their activity as a thickening agent to keep fluticasone in suspension—a POSA would have been led away from MCC or CMC. *DePuy Spine*, 567 F.3d at 1326-27.

This fear was confirmed by third party Meda’s work with azelastine formulations. As stated in §IV.D.3, Meda tried and failed in 2006 to dissolve azelastine crystals into the Flonase<sup>®</sup> (commercial fluticasone) nasal spray vehicle which contains both CMC and MCC. CIP2003, ¶¶23-26; CIP2061, 17-19. Across several attempts, Meda continually observed a precipitant, which it believed was

azelastine. CIP2061, 19. In response to this same argument in the related *Apotex* case, Dr. Donovan stated that the precipitant was likely the MCC in the Flonase<sup>®</sup> vehicle, 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>.” CIP2007, ¶55; CIP2014, 240:15-21. Regardless of whether it was the azelastine crystals precipitating as Meda believed, the MCC precipitating as Dr. Donovan believes, or the CMC precipitating as the prior art teaches, there appears to be no dispute that azelastine would be incompatible with MCC and/or CMC.

Argentum cites to Hettche’s disclosure in an effort to overcome this concern, but it cannot. *See* Pet. 47. Although Hettche lists CMC as a possible thickening agent for azelastine formulations, the Lieberman reference was published *after* Hettche and would therefore be viewed as the current understanding. Lieberman is also a more explicit disclosure (“is incompatible”) compared to Hettche’s permissive language that CMC “may, for example, be” used. CIP2007, ¶56; CIP2113, 24; EX1007, 4:54-61.

**(b) The art taught away from using three preservatives: benzalkonium chloride, edetate disodium, and phenyl ethyl alcohol.**

The prior art would have taught a POSA to reduce preservatives in a formulations, and not toward using three preservatives.

Argentum's own prior art reference—Segal—discloses that “[p]reservative-free compositions are preferred due to reduced sensitivity and increased patient acceptance.” EX1012, 6:15-19. In 2002, however, it was known that Astelin<sup>®</sup> (the commercial embodiment of azelastine) contains two pharmaceutically and commercially acceptable preservatives, benzalkonium chloride (“BKC”) and edetate disodium (“EDTA”), and that Flonase<sup>®</sup> contains two pharmaceutically and commercially acceptable preservatives, BKC and phenyl ethyl alcohol. EX1008, 2; EX1010, 1. Faced with combining azelastine and fluticasone into a combination formulation, a POSA would have been led away from using all three preservatives because doing so would (1) run counter to conventional wisdom trending towards preservative-free compositions, and (2) run counter to Argentum's and Dr. Schleimer's stated motivation of using azelastine and fluticasone in a single combination formulation to increase patient compliance. CIP2007, ¶¶57-58. That is, a POSA would have been discouraged from attempting the claimed three preservative combination. *DePuy Spine*, 507 F.3d at 1326-27.

**(c) The art taught away from using glycerin as a isotonic agent.**

A POSA formulating an azelastine/fluticasone combination formulation would not have been motivated to use glycerin as an isotonic agent. CIP2007, ¶59. First, Astelin<sup>®</sup> used sodium chloride as its isotonic agent, and Flonase<sup>®</sup> used dextrose. CIP2007, ¶60; EX1008, 2; EX1010, 1. Beyond that, the art generally

disclosed a preference for sodium chloride and dextrose as isotonic agents for nasal formulations. CIP2007, ¶60; CIP2112, 19. And unlike glycerin, dextrose was known to be compatible with both azelastine and fluticasone. CIP2007, ¶61; EX1007, 4:31-35; CIP2135, 3. Finally, glycerin's other functions (solvent and humectant) would not have interested a POSA because glycerin was also known to thicken formulations, which would make the azelastine/fluticasone formulation potentially too thick. CIP2007, ¶62.

**D. Grounds 2 and 3 Fail: Compelling objective indicia of non-obviousness support the validity of the challenged claims.**

As explained above, Argentum failed to address objective indicia which its counsel heard at trial and on which its experts testified at trial. Below are the objective indicia that Argentum knew of, that its experts previously addressed, and which Argentum should have rebutted in its Petition.

**1. Cipla's objective indicia evidence has a nexus to the challenged claims.**

When a commercial product embodies the entirety of a claim, a presumption of nexus exists. *WBIP*, 829 F.3d at 1329. Argentum does not dispute that Dymista<sup>®</sup> is an embodiment of the challenged claims. CIP2007, ¶¶64-65; CIP2001, ¶143; CIP2021, 178:4-179:20. Similarly Duonase is an embodiment of claims 1, 4-6, 24-26, and 29. CIP2007, ¶¶64-65, 68; CIP2001, ¶143; CIP2021, 178:4-179:20. And, the various generic products that copied Duonase also are embodiments of many of

the challenged claims, and therefore a nexus exists to the '620 patent. CIP2007, ¶¶66-74; CIP2001, ¶143. Argentum does not dispute that Dymista<sup>®</sup> and Duonase meet every limitation of the challenged claims. Therefore, there is a nexus to the claims.

**2. Unexpected results: The claimed formulation exhibits unexpected formulation and clinical results.**

The formulations of the challenged claims exhibit unexpected clinical and formulation results. From the clinical perspective, the commercial embodiment of the claims—Dymista<sup>®</sup>—is the first product to exhibit greater efficacy than a steroid alone. From the formulation perspective, Dymista<sup>®</sup> overcomes several known incompatibilities between the excipients and active ingredients to form a safe, stable formulation suitable for nasal administration.

- (a) Dymista<sup>®</sup> unexpectedly surpasses the efficacy of both commercial and reformulated fluticasone.**
  - (i) The closest prior art from a clinical perspective is the fixed dosing studies, which are the only evidence of an antihistamine and steroid being dosed consistently prior to the date of invention.**

The closest prior art from a clinical perspective are the fixed dosing co-administration studies (and subsequent review articles), which showed no benefit to the co-administration of antihistamines and steroids.

For example, it was widely thought at the time of invention that each antihistamine was approximately equal in efficacy. CIP2001, ¶199; EX1041, 9;

CIP2042, 4. These drugs worked in generally the same ways, and thus there was no reason to expect one antihistamine to work differently from another when used in combination with a steroid.

It was also thought that all steroids were equally effective in clinical practice. CIP2001, ¶100; CIP2047, 3. Argentum's reliance on potency is not a clinical factor; it is irrelevant in clinical practice. CIP2001, ¶101. And because these drugs also worked in similar manner, there was no reason to expect one steroid to work differently from another when used in combination with an antihistamine. CIP2001, ¶101.

Accordingly, a POSA would have expected the specific selections of antihistamine and steroid used in the co-administration studies to be indicative of the efficacy of other selections. And, because these studies showed what happens when antihistamines and steroids are used together in a fixed manner, consistent with the fixed-dose combination of the challenged claims, these studies are the closest prior art.

**(ii) Dymista<sup>®</sup> is unexpectedly more effective, faster-acting, and safer than the prior art.**

Given that the closest prior art established no meaningful clinical benefit to the fixed dosing of an antihistamine and a steroid as compared to the steroid alone, it was unexpected in 2002 that Dymista<sup>®</sup> achieves a nearly 40% improvement in efficacy over fluticasone alone. CIP2001, ¶¶105-106; CIP2045, 3. This meaningful

improvement is different in kind from a POSA's expectation of no meaningful improvement. CIP2001, ¶104.

To the extent that Argentum suggests that the improvement shown by Dymista<sup>®</sup> is similar to the improvement shown in Ratner 2008, which was published in 2008 and tested co-administration of azelastine and fluticasone monotherapies (EX1045, 1), Argentum has failed to show that the dosing regimen in Ratner 2008 was consistent with any practice prior to the date of invention. Indeed, Ratner 2008 only shows a statistically significant difference between co-administration and the monotherapies after *four days* of consistent fixed dosing. EX1045, 5. But Argentum's cited art explicitly recommends stepwise, "on demand," or as-needed, therapy. CIP2001, ¶107; EX1019, 34; EX1022, 5; EX1024, 90. And Juniper 1997 shows what that meant prior to the date of invention: use the antihistamine once every week—*not* twice a day, as in Ratner 2008. EX1031, 7. Argentum's own art proves that Ratner 2008 was not practiced prior to the date of invention, and Cipla has no obligation to show unexpected results over art that did not exist prior to the date of invention. *In re Geiger*, 815 F.2d 686, 690 (Fed. Cir. 1987) (J. Newman, concurring).

Dymista<sup>®</sup> also has an unexpectedly fast onset of action. It was known that azelastine had an onset of three hours across all four primary symptoms of AR. CIP2001, ¶¶110-11; EX1008, 3; CIP2021, 94:23-95:17. Dymista<sup>®</sup>, on the other



hand, has an established onset of action of thirty minutes. CIP2001, ¶112; CIP2066, 18.

The references cited by Argentum regarding a 15 minute onset do not actually support that claim; they contain no data, and referring to the study cited in ARIA, for example, one sees that it claims only a “trend toward statistical significance” (i.e., an onset) “beginning at two hours.” CIP2001, ¶113; CIP2046, 1. As for the Falser reference Argentum relies upon, it does not say anything about the actual onset of the drugs; instead, it clearly explains that the “15 minute” point Argentum relies upon is merely a test of efficacy fifteen minutes after the second application of azelastine each day. CIP2001, ¶114-115; EX1015, 2, 6. A POSA would have understood that this does not suggest that azelastine had a 15-minute onset; instead, it merely states that it was still working 15 minutes after the second daily dose. CIP2001, ¶¶114-115. In fact, Falser could not establish onset because it lacks a placebo group, and onset of action in AR treatment was defined as a statistically significant improvement *over placebo*. CIP2001, ¶116; CIP2129, 17. Nor does Ratner 2008 show an accelerated onset of the kind seen in Dymista<sup>®</sup>. CIP2001, ¶117. This onset is a difference in kind from what was known in the art. CIP2001, ¶110.

Finally, as explained in Shenfield, it was thought that the use of two drugs would increase side effects as compared to either alone. CIP2001, ¶118; CIP2043,

13. This expectation was confirmed by the closest prior art studies, which showed increases in side effects in the co-administration groups. CIP2001, ¶¶52, 55, 59; EX1035, 8; EX1036, 5; EX1039, 6. It is further confirmed by Ratner 2008, which shows a synergistic increase in bitter taste and a near-additive increase in headache. CIP2001, ¶137; EX1045, 5. The Dymista<sup>®</sup> label, on the other hand, shows a dramatic reduction in side effects as compared to the prior art azelastine and fluticasone formulations. CIP2001, ¶¶121-125. This, too, is a difference in kind that was unexpected at the time of invention. CIP2001, ¶126.

**(b) The claimed formulations are unexpectedly suitable for nasal administration in light of the prior art.**

The prior art taught a POSA to expect (1) that co-formulating fluticasone with a second active ingredient would lead to aggregation, and (2) that formulating azelastine with either CMC or MCC would be incompatible. CIP2007, ¶83. But unexpectedly, Dymista<sup>®</sup>, Duonase, and the Duonase Imitator Products all contain fluticasone co-formulated with azelastine, and azelastine formulated with CMC and MCC, and unexpectedly none of the expected negative interactions occur. *Id.*

**3. Failure of Others: sophisticated pharmaceutical companies failed to develop a combined formulation.**

“[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). Here, before learning of

Cipla's patent, Meda attempted to formulate an azelastine/fluticasone combination formulation in 2006 but found that azelastine would not stay dissolved the a formulation consisting of Flonase<sup>®</sup> excipients—including the claimed thickening agent MCC/CMC. CIP2003, ¶¶18-25. Meda was ultimately unsuccessful and abandoned its efforts. CIP2003, ¶¶26-27; CIP2007, ¶¶78-79, 82; CIP2061, 17-19. And because Meda's work was conducted by individuals who fall within both Cipla's and Argentum's definition of a POSA, these efforts reflect what a POSA would have tried. CIP2007, ¶80. Further, Meda used routine modifications within the grasp of a POSA to enhance the solubility of azelastine in the Flonase<sup>®</sup> excipients, but those modifications were also unsuccessful. CIP2007, ¶82.

Meda's failures also have a nexus to the challenged claims because dissolving azelastine into the Flonase<sup>®</sup> excipients was only the first step to formulating an azelastine/fluticasone formulation. CIP2007, ¶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. CIP2007, ¶81; CIP2003, ¶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. The only reasonable inference is that both companies had

tried to develop such a product to treat AR but neither company entered 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 the product for over eight years, no azelastine/budesonide combination formulation has entered the market, again evidencing a failure of others. The failure of these companies to successfully formulate and develop antihistamine/steroid combination formulations in general, and an azelastine/budesonide formulation in particular, supports the non-obviousness of the challenged claims.

**4. Acquiescence: Meda’s decision to take a royalty-bearing license to Cipla’s patents supports nonobviousness.**

After failing to develop its own formulation, Meda licensed Cipla’s intellectual property relating to Cipla’s Duonase product. CIP2003, ¶¶26-28; CIP2049, 1; CIP2050, 1. Without the license agreement, Meda would not have been able to develop and market Dymista<sup>®</sup>. CIP2003, ¶28. But Meda’s licensing decision was not without cost: licensing and royalty fees would accompany any license. The fact that Meda was unable to make its own formulation and decided to take a license from Cipla despite the costs evidences the strength of the ’620

patent. CIP2005, ¶¶106-108. And because the Cipla-Meda licenses included rights to the '620 patent, this objective indicia has a nexus to the challenged claims. CIP2005, ¶106; CIP2049, 28 (identifying PCT/GB2003/002557); CIP2050, 1; EX1001, 1.

**5. Skepticism: Both Meda and FDA were skeptical of the feasibility and desirability of a fixed-dose azelastine/fluticasone formulation.**

From the formulation perspective, a POSA would have been skeptical in 2002 that an azelastine/fluticasone combination formulation could be “suitable for nasal administration.” First in 2002, Meda considered an azelastine/steroid combination formulation to 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 combining solution and suspension formulations. CIP2003, ¶¶11-15; CIP2007, ¶75; CIP2054, 11; CIP2056, 11. In fact, Meda was so skeptical in 2002 that it pursued other research avenues, like dual-chamber devices, rather than attempt a combination formulation. CIP2003, ¶16. Then in 2006 after Meda found Cipla’s Duonase product, Meda was surprised that anyone had successfully overcome Meda’s anticipated incompatibilities. CIP2003, ¶26.

This skepticism has a nexus to the challenged claims because it goes to the core of whether a single formulation containing azelastine and a steroid (like fluticasone) would be “suitable for nasal administration.” CIP2007, ¶77. And because this skepticism is how a POSA would have viewed the claimed combination formulation in 2002 and 2006 it is related to non-obviousness. CIP2007, ¶76.

**6. Commercial Success: Sales of Dymista<sup>®</sup> in the U.S. and Duonase in India demonstrate nonobviousness.**

When a patentee can demonstrate commercial success, usually shown by significant sales in a relevant market, and that the successful product is the invention disclosed and claimed in the patent, it is presumed that the commercial 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, Meda’s Dymista<sup>®</sup> is a commercial success in the United States, and Cipla’s Duonase and the Imitator Products 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 approximately 963,299 prescriptions per year in April 2016 and generating approximately \$157 million in annual revenue by that time. CIP2005, ¶¶39-41. By April 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. CIP2005, ¶¶46-47. Dymista<sup>®</sup>’s revenue

share among branded nasal sprays was 15.6% by that time. CIP2005, ¶48. As measured by market-share or revenue-share, Dymista® was the second best branded nasal spray by the end of 2014—its second full year on the market. CIP2005, ¶¶47-48. Even among generic prescription AR treatments, Dymista®'s prescriptions, revenues, and market shares are consistently increasing while the footprint of its competitors was shrinking or stagnating. CIP2005, ¶¶49-51. In either of these calculations, over-the-counter treatments were not included because those treatments are not direct competitors to Dymista® because those treatments do not require a prescription and are used before a patient seeks a prescription AR treatment. CIP2005, ¶¶43-44.

Dymista's performance has a nexus to the challenged claims of the '620 patent because Dymista® 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 first combination nasal spray. CIP2005, ¶¶59-68; CIP2064, 9, 11; CIP2074, 35; CIP2082, 6; CIP2083, 5-7; CIP2084, 4; CIP2085, 25; CIP2086, 3-4. Additionally, Dymista®'s success is not due to extraneous, non-patented factors because (1) Dymista does not have a pricing advantage, and (2) Meda's marketing was not a significant driver of sales of Dymista®. CIP2005, ¶¶83-95; CIP2053, 127, 129; CIP2064, 9; CIP2074, 17, 35; CIP2093, 18; CIP2094, 13; CIP2095, 1.

**Duonase and the Imitator Products:** Both the units of Duonase shipped and the revenue generated have steadily grown every year since it was first launched in India in 2004. CIP2005, ¶¶52-56. The Duonase Imitator Products have achieved similar levels of success. CIP2005, ¶¶56. Collectively, Duonase and its Imitators comprise 24-46% of all nasal sprays in the Indian market. CIP2005, ¶¶57-58. And in rebuttal to Argentum'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 (CIP2005, ¶¶111-113), as well as looking at all nasal sprays used for treatment of allergic rhinitis.

Like Dymista®, Duonase is an embodiment of many of the challenged claims, and is primarily marketed on its patented features. CIP2005, ¶¶69-71. Furthermore, Duonase's success is not due to non-patented features because (1) Cipla's brand recognition is not a significant driver of sales, and also would not drive sales of the Duonase Imitator Products, and (2) Duonase's reformulation in 2010 to add a sweetener did not driver significant sales, nor would it have driven sales of the Imitator Products. CIP2005, ¶¶96-101.

**7. Unmet Need: Dymista® satisfied a long-felt but unmet need for better AR treatment.**

Dymista® satisfies the long-felt needs for more effective, faster, and safer AR treatments. First, the long-felt need for a therapy better than a steroid is established by the co-administration studies discussed above. CIP2001, ¶¶128-129.



These studies show that steroids alone, despite being the most effective treatment option, were inadequate to treat the worst cases of AR. *Id.* Thus, the art established, beginning in at least 1989, that there was a need for improved AR treatments. Dymista<sup>®</sup> satisfies that need.

There was also a need for a faster-acting treatment. Again, steroids were the most effective treatment, but as Argentum acknowledges, they had a slow onset. Pet. 37. The other drugs, which had faster onsets, did not adequately treat all symptoms. For example, intranasal decongestants had an onset of 10 minutes, but only worked on one symptom. EX1024, 96. It was, therefore, important to obtain a drug with a very rapid onset that worked on all symptoms. CIP2001, ¶131. Dymista<sup>®</sup> is just such a drug: it works in 30 minutes. CIP2001, ¶132.

Finally, there was a need for safer AR treatment. The development of second-generation antihistamines and topical steroids showed a need for AR treatments with reduced side effects. CIP2001, ¶¶134-136; EX1024, 82, 84-85, 92. Ratner 2008 confirms that separate co-administration of azelastine and fluticasone did not satisfy this need because it found synergistic and near-additive increases in bitter taste and headache, respectively. CIP2001, ¶137; EX1045, 5.

Continuing that trend toward reduced side effects, Dymista<sup>®</sup> inexplicably exhibits reduced side-effects as compared to either of its monotherapies. For example, 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. EX1008, 3. Meanwhile, fluticasone at the dose 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. EX1010, 7. Dymista<sup>®</sup>, by contrast, exhibits bitter taste in only 4% of patients, while only 2% of patients experience headache or epistaxis. CIP2066, 6. No other side effect—including somnolence—occurred in more than 2% of patients. *Id.* This dramatic reduction satisfies the long-felt need for reduced side effects. CIP2001, ¶138.

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

With respect to evidence of commercial success and satisfaction of a long-felt but unmet need, Argentum asserts that the Hettche and Phillipps references are “blocking patents” which “undercuts any nexus” to the challenged claims. Pet. 56. But Hettche and Phillipps are not blocking patents.

First, Hettche and Phillipps were not owned or licensed by Cipla. EX1009, 1; EX1007, 1. A “blocking patent” scenario occurs when a patentee also owns a prior art patent that precludes development of the later claimed invention. *See Galderma Labs. L.P. v., Inc.*, 737 F.3d 731, 740 (Fed. Cir. 2013) (“no entity other than Galderma could have successfully brought to 0.3% [adapalene gel] to market prior to 2010”); *Merck & Co., Inc. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1377 (Fed. Cir. 2005) (“Merck had a right to exclude others...”); *Warner Chilcott Co.*,

*LLC v. Teva Pharm. USA, Inc.*, 37 F. Supp. 3d 731, 739 (D. Del. 2014) (“P & G’s U.S. Patent No. 5,583,122...would have discouraged development of risedronate products.”). This is dispositive, and defeats Argentum’s flawed theory.

Second, Hettche (expired May 2012) and Phillipps (expired May 2004) both expired before Dymista<sup>®</sup> launched in September 2012, so Dymista<sup>®</sup>’s success cannot be attributable to the protection offered by those references. 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); *Warner Chilcott*, 37 F. Supp. 3d at 739 (commercial sales beginning in 2005, blocking patent expiration in 2013). And even if a competitor was concerned about the Hettche patent, the competitor could develop a product under the FDA’s safe harbor, get FDA approval, wait for Hettche to expire, and beat Dymista<sup>®</sup> to the market. CIP2005, ¶114-115. No one did.

Third, the record reflects that competitors were not blocked. CIP2005, ¶116. 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 dissuaded by Hettche.

**9. Copying: Duonase was subjected to widespread copying in India.**

Duonase was widely copied by multiple imitators, which is “another form of flattering praise for inventive features...and thus evidence of copying tends to show nonobviousness.” *WBIP*, 829 F.3d at 1336. In the U.S., Apotex has sought to market a generic version of Dymista<sup>®</sup>, and has stipulated to the infringement of many of the challenged claims. CIP2005, ¶103; CIP2017, 3; CIP2001, ¶145. Apotex’s efforts are noteworthy because Apotex already markets a generic version of Astelin<sup>®</sup> and a generic version of Flonase<sup>®</sup>, suggesting that Apotex views their combination into a single product to be competitively advantageous. CIP2005, ¶103. In India, Duonase was subject to copying after only two years of market success. CIP2005, ¶¶104-105. These competitors had access to the Duonase product and to Cipla’s published patent application that issued as the ’620 patent. EX1001, 1 (identifying that PCT/GB03/02557 published on June 13, 2003).

**10. Praise: Industry leaders praised Dymista<sup>®</sup>.**

After reviewing the clinical data used by FDA to approve Dymista<sup>®</sup>, the editors of the world’s leading allergy journal—the *Journal of Allergy and Clinical Immunology*—declared that Dymista<sup>®</sup> “can be considered the drug of choice for the treatment of AR.” CIP2001, ¶139; 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 September of 2015, a market report published a “Strengths Weaknesses Opportunities Threats” (“SWOT”) analysis for Dymista<sup>®</sup>. CIP2053, 133. The publication, by IMS—a leading clinical market analysis entity—declared that 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.

## **V. CONCLUSION**

For the foregoing reasons, Cipla respectfully requests that the Board deny institution with respect to each Ground presented in Argentum’s Petition. All three Grounds suffer from legal and factual defects. The legal defects include Argentum’s failure to explain how its art teaches a claim term in accordance with its use in the claims and its failure to address objective indicia. Similarly, each Ground is defective on the merits. In Ground 1, Argentum fails to distinguish the

Segal reference from Cramer, which was already used for the same teachings and overcome during prosecution. And in Grounds 2 and 3, Argentum not only failed to address objective indicia, but it failed to establish a motivation or reasonable expectation for success.

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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 Preliminary Response contains 13,915 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 Preliminary Response” was served in its entirety on May 30, 2017, upon the following parties via electronic mail upon the following counsel of record for the Petitioner:

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