UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GLAXOSMITHKLINE CONSUMER HEALTHCARE HOLDINGS (US), LLC,

Petitioner,

v.

CIPLA LTD.,

Patent Owner.

Case IPR2020-00371

Patent No. 9,901,585

PATENT OWNER PRELIMINARY RESPONSE

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2001	Excerpts from the Image File Wrapper for the ’620 Patent
2002	Drugs@FDA entry for Flonase
2003	Drugs@FDA entry for Astelin
2004	Apotex Products (Apr. 29, 2020)
2005	Drugs@FDA entry for Dymista
2006	Dymista Prescribing Information
2007	Duonase Nasal Spray Prescribing Information, available at https://www.ciplamed.com/content/duonase-nasal-spray
2008	Center for Drug Evaluation and Research, Cross Discipline Team Leader Review for Dymista, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202236Orig1s000CrossR.pdf
2009	Aria Workshop Report
2010-11	Intentionally Left Blank
2012	Mylan Press Release, *Mylan Completes Acquisition of Meda* (Aug. 5, 2016), *http://newsroom.mylan.com/2016-08-05-Mylan-Completes-Acquisition-of-Meda*
2013-17	Intentionally Left Blank
2018	Akerlund et al., *Clinical Trial Design, Nasal Allergen Challenge Models, and Considerations of Relevance to Pediatrics, Nasal Poyposis, and Different Classes of Medication*, 115 J. ALLERGY CLIN. IMMUNOL. S460 (2005)
2019	Astelin Approval Letter
2020	Flonase Label
2021	Commercial and Stakeholder Perspectives: Allergic Rhinitis, Is there life after Claritin (Sept. 2004)
2022	Blais, *Efficacy, Safety, and Patient Preference of Inhaled Nasal Corticosteroids: A Review of Pertinent Published Data*, 22 ALLERGY & ASTHMA PROC. S5 (2001)

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2023	Carr et al., *A Novel Intranasal Therapy of Azelastine with Fluticasone for the Treatment of Allergic Rhinitis*, 129 J ALLERGY CLIN. IMMUNOL. 1282 (2012)
2024	Barnes et al., *Effects of Levocetirizine as add-on Therapy to Fluticasone in Seasonal Allergic Rhinitis*, 36 CLINICAL & EXPERIMENTAL ALLERGY 676 (2006)
2025	Proposed Joint Pretrial Order (Public Version), *Meda Pharm. Inc. v. Apotex Inc.*, No. 14-1453-LPS (D. Del Nov. 21, 2016), ECF No. 137
2026	Allergic Rhinitis-Global Drug Forecast and Market Analysis to 2024
2027	Glaxo EPO Opposition, EP 1519731 (Jan. 14, 2010)
2028	2006 Cipla-Meda License Agreement with Quality Agreement (PTX1016)
2029	2011 First Amendment to Cipla-Meda Agreement (PTX0282)
2030	EP 1519731
2031	Astelin Day Life Cycle Plan (Nov. 1, 2002)
2032	Email regarding Astelin Nasal Spray Life Cycle Management Projects (Oct. 30, 2002)
2033	Wikipedia entry for "Physician's Desk Reference," available at https://en.wikipedia.org/wiki/Physicians%27_Desk_Reference
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2040	https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202236Orig1s000SumR.pdf

I. INTRODUCTION

Patent Owner Cipla Ltd. ("Patent Owner") submits this Preliminary Response to GlaxoSmithKline Consumer Healthcare Holdings (US), LLC's ("Petitioner") Petition seeking *inter partes* review of U.S. Patent No. 9,901,585 ("the '585 patent"). Petitioner's request should be denied because it fails both on threshold issues and the merits.

At the outset, the Petition fails to particularly cite to the prior art such that the Patent Trial and Appeal Board ("Board") and Patent Owner can determine the art upon which the Petition relies. While the Petition purports to identify prior art that when combined render the claims obvious, it does little more than portray a collage of teachings across numerous references. The Petition compounds this error by attempting to incorporate dozens of additional references cited only in expert declarations and nowhere described in the Petition.

The Petition also suffers from another significant threshold shortcoming—it fails to address, much less overcome, the fact that the U.S. Patent and Trademark Office ("Office") has already considered and rejected the arguments and art set forth in the Petition. The Board's precedent demands that where a petitioner relies on substantially the same prior art and arguments considered during prosecution, that petitioner must establish error in the Examiner's analysis. Petitioner made no effort to make this showing, simply parroting previously rejected arguments. As set

forth in Section III, *infra*, the prior art and arguments relied upon in the Petition's Grounds were considered, "of record" and had been "previously evaluated, or disclose[d] information redundant to information of record." Ex. 1008, 37. Cramer was considered extensively during prosecution, forming the basis of multiple rejections. And Petitioner's additional art—Segal and PDR 1999—were either expressly considered and rejected, or cumulative of information considered and rejected during prosecution. Petitioner points to nothing new to distinguish the arguments and art examined—and overcome—during prosecution. For this reason alone, the Petition should not be instituted pursuant to 35 U.S.C. § 325(d).

Setting aside the Petition's defects, Petitioner's obviousness assertion is rooted in a fundamentally flawed principle: that a combination of known elements is obvious even though the prior art provided no impetus to create—and in fact taught away from—that combination. The '585 patent's claims cover Dymista®, a novel nasal spray formulated by combining two active ingredients: the antihistamine, azelastine, and the corticosteroid, fluticasone. Dymista® was a breakthrough: it was the first fixed-dose combination nasal spray to treat allergic rhinitis ("AR"). Prior to Dymista®, and despite myriad available AR treatments, no one had successfully combined an intranasal antihistamine with an intranasal corticosteroid in a fixed-dose formulation.

There was a good reason for this. Indeed, the prior art discouraged such combinations because a fixed-dose formulation presented patients and physicians several treatment difficulties. Namely, a fixed-dose formulation prevented: 1) dose adjustments, 2) use of only one of the two medications, and 3) use of different medications. Moreover, the two medications had incompatible dosing regimens. The prior art provided no motivation to make such a combination. To the contrary, the prior art taught skilled artisans that a combined steroid-antihistamine product would offer *no* advantage over a steroid alone. And with no guidance in the prior art, the inventors created a formulation that not only overcame those challenges, but also invented a formulation that combined a medication delivered as a *suspension* with a different medication delivered as a *solution*. Petitioner fails to address at all why—in the face of these obstacles—a skilled artisan would be motivated to do what the inventors did. Notably, FDA recognized that the development of Dymista® was particularly complex and one that raised issues that had "not been previously encountered" in the development of nasal sprays with just one active ingredient. Ex. 2008, 4.

Petitioner nonetheless asserts the '585 patent is purportedly obvious because the inventors merely combined two known therapies. But, an "invention is not obvious just because all of the elements that comprise the invention were known in the prior art." *Broadcom Corp. v. Emulex Corp.*, 732 F.3d 1325, 1335 (Fed. Cir.

2013) (internal quotations and citation omitted). Rather, "a finding of obviousness at the time of invention requires a plausible rational[e] as to why the prior art references would have worked together." *Id.* (internal quotations and citation omitted). This requirement is absent here—Petitioner's overly-simplistic obviousness theory fails to provide any motivation to first select these two specific monotherapies, out of all the myriad possibilities, and then combine them. There was no suggestion in the prior art as to why one might want to bring fluticasone and azelastine together into a single formulation. Quite the opposite, the prior art provided many reasons *not* to make such a combination. It was only the inventors' ingenuity that brought Dymista to the market, where some 20 years later, it remains the only fixed-dose combination nasal spray approved by FDA for the treatment of AR.

The nonobviousness of the '585 patent is bolstered by objective evidence, including the extensive record demonstrating commercial success (ignored by Petitioner), unexpected results, and the satisfaction of a long-felt need. This evidence was relied on by the Examiner in the original prosecution of the earlier '620 patent and *was* addressed in the prior Argentum IPR, which the Examiner reviewed during prosecution of the '585 patent. *See* Section III.D, *infra*. Petitioner's failure to address the known record evidence is, alone, another basis sufficient to deny institution here.

The Board should decline to institute this proceeding.

II. THE PETITION FAILS TO MEET ITS THRESHOLD SHOWING BECAUSE IT FAILS TO CITE PRIOR ART IN SUPPORT OF UNPATENTABILITY

At the outset, the Petition makes two substantial errors for which the Board should deny institution. *First*, the Petition does not cite any prior art with specificity but rather improperly canvases the prior art in support of its arguments. *Second*, the Petition fails to explain *in the Petition* why the prior art renders the patent unpatentable and instead resorts to circular citations to multiple, lengthy expert declarations. For either, or both, of these reasons, the Board should decline to institute.

A. The Board Should Deny the Petition under 35 U.S.C. § 314(a) Because It Lacks the Required Specificity.

The Petition should be denied because Petitioner does not adequately put Patent Owner on notice of the precise grounds for alleged unpatentability. Petitioner posits two primary grounds under which the challenged claims are allegedly obvious—each purportedly resting on the combination of two references. The Petition, however, creates a confounding record with a discussion of a multitude of additional references and does not identify precisely which claim elements are allegedly present in which references.

To merit institution, the statute requires that "the petition identif[y], in writing and *with particularity*, each claim challenged, the grounds on which the

challenge to each claim is based, and the evidence that supports the grounds for challenge to each claim....” 35 U.S.C. § 312(a)(3) (emphasis added). Moreover, “[t]he petition must specify where each element of the claim is found in the prior art patents or printed publications relied upon.” 37 C.F.R. § 42.104(b)(4). Here, the Petition does not adequately put Patent Owner on notice of the precise grounds for alleged unpatentability.

In Grounds 1 and 2, Petitioner challenges the patentability of the ’585 patent’s claims with each ground purportedly resting on a combination of two references: PDR 1999 in view of Segal and Cramer in view of PDR 1999.

The Petition, however, creates a confounding record with a discussion of a multitude of additional references and does not identify precisely which claim elements are allegedly present in which references. For example, in Ground 1, the Petition identifies at least 7 additional references that appear to form the basis of the Ground. *See* Pet. 8 (citing Drouin, Brooks, Dykewicz, Berger, Cauwenberge, Spector, and Bousquet as supporting Ground 1). More references are then discussed in the Petition’s discussion of the independent and dependent claims. *See, e.g.*, Pet. 10-30. The Petition does not particularize the teaching from the art in the Ground, but instead cites numerous citations to other prior art references (often in string cite form) absent explanation. Likewise, Petitioner does not include any claim charts that map the cited references to the language of the claims. Neither the

Board nor Patent Owner should be expected to fill in the blanks to uncover Petitioner's arguments. *See Teoxane S.A. v. Allergan, PLC*, IPR2017-02002, 2018 WL 1247024, at *8 (PTAB Mar. 9, 2018) (citing *DeSilva v. DiLeonardi*, 181 F.3d 865, 866–67 (Fed. Cir. 1999) ("A brief must make all arguments accessible to the judges, rather than ask them to play archeologist with the record.")).

The Board should reject Petitioner's invitation to play archeologist and should instead follow the path of *Zetec, Inc. v. Westinghouse Electric Co.*, IPR2014-00384, 2014 WL 3704254 (PTAB July 23, 2014), and exercise its discretion under 35 U.S.C. § 314(a) and 37 C.F.R. § 42.108(b) to deny institution. *Zetec*, 2014 WL 3704254, at *7-10 (denying institution because "attempting to evaluate fully the…underdeveloped assertions in the Petition to determine whether Petitioner has shown that it would be likely to prevail in any unpatentability challenge would place a significant burden on the Board and contravene the efficient administration of the Office"); s*ee also Schumer v. Lab. Comput. Sys., Inc.*, 308 F.3d 1304, 1316 (Fed. Cir. 2002) ("It is not our task . . . to attempt to interpret confusing or general testimony to determine whether a case of invalidity has been made out."). As in *Zetec*, the Board should decline to expend its resources scouring the numerous references cited by Petitioner to determine if the identified combinations (or some other, unidentified combination) demonstrate a reasonable likelihood that Petitioner would prevail. *Zetec*, 2014 WL 3704254, at *9

("Appellant's Brief is at best an invitation to the court to scour the record, research any legal theory that comes to mind, and serve generally as an advocate for the appellant. We decline the invitation." (citations omitted)).

B. The Board Should Not Consider Evidence Included in Expert Declarations But Not Cited in the Petition.

In deciding whether to institute this review, the Board should not consider arguments included in the expert declarations but not discussed in the Petition. 37 C.F.R. § 42.6(a)(3) prohibits arguments being incorporated by reference from one document to another in an IPR proceeding. This includes information in expert declarations. *See Tempur Sealy Int'l Inc. v. Select Comfort Corp.*, IPR 2014-01419, Paper 7 at 7-8 (PTAB Feb. 17, 2015); *Cisco Sys., Inc., v. C-Cation Techs., LLC*, IPR2014-00454, 2014 WL 4352301, at *5-6 (PTAB Aug. 29, 2014) (expanded panel decision explaining that arguments not made in the Petition will not be considered); *Fidelity Nat'l Info. Servs., Inc., v. DataTreasury Corp*., IPR2014-00489, 2014 WL 4059220, at *5 (PTAB Aug. 13, 2014) ("Under our rules, the petition must contain a 'full statement of the reasons for the relief requested, including a detailed explanation of the significance of the evidence....' We, therefore, decline to consider information presented in a supporting declaration, but not discussed sufficiently in a petition." (citation omitted)); *see also* Trial Practice Guide Update (August 2018) at 4.

Just as Petitioner glosses over the Grounds, Petitioner also incorporates by reference vast swaths of expert declarations with little, and often no, discussion in the Petition. Indeed, in this Petition, setting aside Exhibits 1001-1008 which contain the four challenged patents and excerpts from their file histories, the Petition's exhibit list identifies 52 exhibits, only 19 of which are cited in the Petition. The remaining 33 exhibits[1] are omitted from discussion in the Petition. None of these omitted exhibits should be considered by the Board.

Petitioner's attempts to impermissibly incorporate by reference is well illustrated in the Petition's limited discussion of certain secondary indicia of nonobviousness. *See* Pet. 63-66. For example, the Petition gives short shrift to overcoming the established unexpected results of the '585 patent—devoting just over two pages to the issue. Yet, the Petition incorporates 59 paragraphs spanning 24 pages from the Schleimer Declaration. Pet. 64 (incorporating paragraphs 473-531 from the Schleimer Declaration). Worse, in those 59 paragraphs at least six references are discussed in detail and ***none*** of them are cited in the Petition. The Petition suffers the same problems with respect to the criticisms of the declaration by one of the named inventors, Malhotra ("Malhotra Declaration"), submitted

[1] The non-referenced exhibits are Exhibit Nos. 1014-1015, 1017-1018, 1020, 1025-1031, 1034, 1036-1037, and 1039-1056.

during prosecution of the earlier ’620 patent that evidenced the inoperability of Example III in Cramer. *See* Pet. 65-66.

Petitioner’s attempts to discount the claimed invention’s satisfaction of a long-felt and unmet need provide an even more egregious example. There, the Petition includes just four lines, yet cites to 7 paragraphs in the Schleimer declaration spanning three pages with reference to several additional exhibits in that section, which are again not cited in the Petition. *See* Pet. 66. The line and a half of argument on industry praise is similar facially improper. *See* Pet. 66.

Consistent with *Tempur Sealy*, the Board should decline to consider information presented in the Schleimer and Donovan declarations, but not sufficiently discussed in the Petition.

C. The Petition Likely Fails to Name a Real Party-in-Interest.

Petitioner names GlaxoSmithKline Consumer Healthcare Holdings (US) LLC as the sole real party-in-interest. Pet. 66. Previously, a related entity, Glaxo Group Limited, filed an EPO opposition against a European patent related to the ’585 patent. Ex. 2027. That opposition named other Glaxo entities as well, including GlaxoSmithKline (the entity apparently responsible for payment of the fees associated with the opposition) and GlaxoSmithKline Services Unlimited (on whose letterhead the opposition was filed). Ex. 2027, 4. The EPO opposition record suggests additional entities are likely real parties-in-interest here. This likely

failure provides yet another basis for the Board to exercise its discretion by declining to institute.

III. BACKGROUND

A. The ’620 Patent Prosecution History and the Examiner’s Consideration of Cramer, Segal and the Teachings of the PDR 1999 During Prosecution

U.S. Patent No. 8,168,620, entitled *Combination of Azelastine and Steroids*, was filed in the United States as a national stage entry of PCT Application No. WO03/105856 on December 14, 2004. The PCT Application was filed on June 13, 2003, but the ’620 patent is entitled to the earlier priority date of June 14, 2002 based on Great Britain Application No. 0213739.6. The patent lists Amar Lulla and Geena Malhotra as the named inventors, and Cipla Ltd. as the assignee. Meda is the exclusive licensee of the patent. Ex. 2028. As originally filed, the ’620 patent application had 50 claims, all claiming a pharmaceutical formulation, preparation, or medicinal use of azelastine and a steroid, including fluticasone. Ex. 2001, 831-39.

1. *Cramer Was Extensively Considered during Prosecution.*

During prosecution of the ’620 patent, spanning more than seven years, Patent Owner addressed and ultimately traversed, or overcame, each of the Examiner’s four anticipation and obviousness-based rejections, all of which addressed the same Cramer patent application that Petitioner relies on in Ground 2.

Ex. 2001, 751-73, 721-42 (rejecting claims as anticipated, or rendered obvious, by Cramer, alone or in combination), 603-22 (rejecting claims as rendered obvious by Cramer, alone or in combination), 497-512 (rejecting claims as anticipated, or rendered obvious, by Cramer, alone or in combination). Cramer was also specifically discussed during an Examiner interview. Ex. 2001, 494 (8/4/2011 Interview Summary).

According to the Examiner, "Cramer teaches a nasal spray composition comprising about 0.001 to about 0.2% concentration of a glucocorticosteroid (i.e. beclomethasone, flunisolide, triamcinolone, fluticasone, mometasone, bedusonide [sic] and pharmaceutically acceptable salts), 0.01 to about 4% concentration of an antihistamine (i.e. azelastine or pharmaceutically acceptable sale thereof, and an intranasal carrier)." Ex. 2001, 721-42 (1/23/2009 Non-Final Office Action). The Examiner argued that Cramer's composition can be formulated as a nasal spray designed to deliver both medications. *Id.* The Examiner recognized that "Cramer does not exemplify a composition comprising azelastine and fluticasone," but concluded that "one of ordinary skill in the art would have been motivated to make a composition comprising azelastine and fluticasone because Cramer suggests that the combination of a glucocorticoid (i.e. fluticasone) and antihistamine (i.e. azelastine) provide improved relief of symptoms associated with seasonal or perennial allergic rhinoconjunctivitis." *Id.* at 733.

In its response, Patent Owner argued, *inter alia*, that the Examiner's obvious-to-try rationale was improper and that "the broad genus disclosed in the primary reference does not render obvious the Applicants' claimed species directed to a pharmaceutical formulation comprising azelastine and fluticasone." Ex. 2001, 669-70. Patent Owner additionally offered the Malhotra Declaration (7/23/2009 Applicant Arguments/Remarks; decl. under 37 C.F.R. § 1.132) and statements from medical practitioners, which explained the invention's advantages and superior results. *See*, *e.g.*, Ex. 2001, 698-720.

2. *Segal Was Also Considered during Prosecution.*

In addition to the years-long consideration of Cramer, the Examiner also considered Segal (WO 98/488391). Patent Owner disclosed Segal in an IDS filed October 5, 2005, a full three-years before the first Office Action. Ex. 2001, 787-88. The Examiner thereafter identified Segal, and just a handful of other references, as "considered" on January 23, 2008, by initialing next to the reference in the IDS. Ex. 2001, 786. This was confirmed later in prosecution when the Examiner stated that Segal was evaluated and considered during earlier prosecutions. Ex. 1008, 36-37 (stating that "all references cited by the Argentum Petition [which included Segal in its grounds] are of record and have been previously evaluated, or disclose information redundant to information of record"). Segal was also considered during the '428 patent's prosecution. *See* § II.C, *infra*. Segal is coextensive with,

but even less informative than, Cramer in that it is even more conclusory and does not contain a single example.

3. *PDR 1999 Is Cumulative of the Azelastine and Fluticasone Monotherapy References Considered by the Examiner.*

Petitioner relies on the PDR 1999 reference for the uncontroversial proposition that azelastine as a monotherapy and fluticasone as a monotherapy were each separately approved for nasal administration. Pet. 4-5, 46-47. This was already considered by the Examiner.

At the outset, the specification itself recognizes that azelastine and fluticasone as monotherapies to treat allergy-related conditions were known in the art:

> It is known to use antihistamines in nasal sprays and eye drops to treat allergy-related conditions. Thus, for example, it is known to use the antihistamine **azelastine** (usually as the hydrochloride salt) as a nasal spray against seasonal or perennial allergic rhinitis, or as eye drops against seasonal and perennial allergic conjunctivitis.
>
> It is also known to treat these conditions using a corticosteroid, which will suppress nasal and ocular inflammatory conditions. Among the corticosteroids known for nasal use are, for example, beclomethasone, mometasone, **fluticasone**, budesonide and cyclosenide.

Ex. 1001, 1:20-30 (emphases added). During prosecution Cipla traversed the Examiner's rejection with, *inter alia*, the Malhotra Declaration. *See*, *e.g.*, Ex. 2001, 568-96. Notably, the Malhotra Declaration included stability data for five compositions, including azelastine and fluticasone as *separate* agents. *Id.* at 571-

72. Statements from medical practitioners submitted with the Malhotra Declaration likewise made clear that, just as is disclosed in the PDR 1999, fluticasone and azelastine were available to practitioners to treat AR. *Id.* at 577 ("Especially in seasonal allergic rhinitis,' **Fluticasone alone or azelastine alone** also has been tried." (emphasis added)), 581 ("I have used Beclomethasone, Budesonide, **Azelastine**, **Fluticasone**, Mometasone…." (emphasis added)). Other declarations, including a declaration from Dr. Sujeet Rajan ("Rajan Declaration"), described in detail the prior art practices of using corticosteroids and antihistamines as monotherapies. Ex. 2001, 460; *id*., 279 (discussing use of single-agent antihistamines and steroids in Applicant Remarks). And Cramer itself described the prior art practice of using antihistamines and corticosteroids as monotherapies. Ex. 1011, 2:19-24. The Examiner also stated that at least the fluticasone label was evaluated and considered during earlier prosecutions. Ex. 1008, 36-37 (stating that "all references cited by the Argentum Petition [which included the Flonase label in its grounds] are of record and have been previously evaluated, or disclose information redundant to information of record").

Finally, numerous prior art references were submitted during prosecution that similarly disclosed fluticasone and azelastine. Ex. 1001, 1-7 (identifying references cited). Indeed, in the Notice of Allowance, the Examiner specifically

noted the prior art practice of using corticosteroids alone, going so far as to both bold and italicize "***corticosteroids alone***" in her comments. Ex. 2001, 196**.**

4. ***Objective Indicia of Nonobviousness.***

In response to the Examiner's objections, Patent Owner provided extensive objective evidence of nonobviousness, including not only unexpectedly beneficial properties, but also commercial success, and fulfillment of long-felt, but unsolved, need.

For evidence of the unexpected stability of the claimed combination, including azelastine and fluticasone as monotherapy, the Malhotra Declaration included statements by medical professionals demonstrating the unexpected efficacy of the claimed combination, particularly as compared to "fluticasone alone or azelastine alone." Ex. 2001, 707-08 (7/23/2009 Ex. B3 to Declaration Under 37 C.F.R. § 1.132 of Geena Malhotra). A second declaration by Dr. Joachim Maus ("Maus Declaration"), was also submitted and provided evidence that "the superior results obtained with the combination of nasal fluticasone propionate and azelastine HCl would have been unexpected at the time of the filing of the application." Ex. 2001, 197 "Thus the invention [wa]s unexpectedly and surprisingly unobvious over, different from, and superior to the prior art of record." *Id.* at 198. Patent Owner buttressed this evidence with a declaration by Nikhil Chopra ("Chopra Declaration") demonstrating the commercial success of the

claimed composition as well as the presence of copying, as explained in the Notice of Allowance. Ex. 2001, 192-99 (10/3/2011 Notice of Allowance). A fourth declaration, the Rajan Declaration, demonstrated the claimed composition's fulfillment of long-felt, but unmet need for improved treatment of allergic rhinitis, particularly as compared to "**corticosteroids alone**." *Id.* (10/3/2011 Notice of Allowance) (emphasis in original).

Based on the Patent Owner's arguments and declarations, the Examiner allowed the claims on October 3, 2011, concluding that "the invention [wa]s unexpectedly and surprisingly unobvious over, different from, and superior to the prior art of record." Ex. 2001, 198 (10/3/2011 Notice of Allowance). After further references were filed by the Applicant, the '620 patent issued on May 1, 2012.

B. The '723 Patent Prosecution History

U.S. Patent No. 8,163,723 ("the '723 patent"), entitled *Combination of Azelastine and Steroids*, was filed on September 10, 2010 as a divisional application of the earlier '620 patent application. Like the '620 patent, Amar Lulla and Geena Malhotra are named as the inventors, Cipla Ltd. is the assignee and Meda is the exclusive licensee of the '723 patent. Ex. 2028.

During prosecution of the '723 patent's application, the Examiner initiated an interview where he suggested the claims be amended to "accord with prior art identified during prosecution of the ['620 patent]." Ex. 1006, 3. Cipla made the

suggested amendments (Ex. 1006, 5-14) and in allowing the claims, the Examiner stated that the claims were "free of the prior art of record." Ex. 1006, 22. Just as with the allowance of the '620 patent, the Examiner again clearly stated that patentability of the claims was supported by the Chopra, Rajan, and Maus Declarations, which evidenced the commercial success of the product, its satisfaction of a long-felt need, and the unexpected clinical benefits derived from the invention. *Id*.

C. The '428 Patent Prosecution History

U.S. Patent No. 9,259,428 ("the '428 patent"), entitled *Combination of Azelastine and Fluticasone for Nasal Administration*, was filed on March 18, 2015, as a continuation application that has a priority claim to the '620 patent. The patent also names Amar Lulla and Geena Malhotra as the inventors, Cipla Ltd. as the assignee, and Meda is the exclusive licensee of the patent. Ex. 2028.

In the prosecution of the '428 patent's application, the Examiner initially rejected the pending claims for obviousness-type double patenting over claims of the '620 and '723 patents. Ex. 1007, 4-6. After a terminal disclaimer was filed and after again bringing to the Examiner's attention the Chopra, Rajan, and Maus Declarations (Ex. 1007, 12-32), the Examiner allowed the claims to issue (Ex. 1007, 38-40).

D. The ’585 Patent Prosecution History

U.S. Patent No. 9,901,585, entitled *Combination of Azelastine and Fluticasone for Nasal Administration*, was filed on March 15, 2016, as a continuation application that has a priority claim to the ’620 patent. The patent again names Amar Lulla and Geena Malhotra as the inventors, Cipla Ltd. as the assignee and Meda is the exclusive licensee of the patent. Ex. 2028.

In the prosecution of the ’585 patent’s application, the Examiner rejected all claims “for reasons of record” in the parent applications, particularly the ’620 patent. Ex. 1008, 4-5. Specifically, the claims were rejected as anticipated or obvious in view of Cramer alone or in view of other references. *Id*. Based on Cipla’s response to those rejections (Ex. 1008, 11-29), the Examiner ultimately allowed the pending claims to issue, once again crediting and discussing in detail the Chopra, Rajan, and Maus Declarations (Ex. 1008, 39-42).

The Examiner also reviewed the Argentum IPR petition and supporting declarations (declarations from the same experts relied upon by Petitioner here). Specifically, Argentum’s petition relied on Segal, Hettche and a Flonase (fluticasone) label, which is duplicative of the fluticasone section of PDR 1999 relied upon by Petitioner’s here. Argentum IPR, Paper 2 at 2. The Examiner found the claims allowable over the art and arguments made therein, including purported anticipation and obviousness over Segal. Ex. 1008, 36-39; *see also* Argentum IPR,

Paper 2 at 2 (identifying grounds). Notably, when providing his analysis of the Argentum IPR, the Examiner stated "*all the references cited by the Argentum Petition are of record and have been previously evaluated, or disclose information redundant to information of record*." Ex. 1008, 37 (emphasis added).

E. Background of Related Proceedings

More than a decade ago, Petitioner[2] filed an Opposition of EP 1519731, a patent covering Dymista® in the European Patent Office ("EPO"). Ex. 2027; Ex. 2030. Despite challenging that European patent and having demonstrated a clear interest in patents covering Dymista®, Petitioner failed to join the earlier Argentum IPR. Argentum IPR, Paper 2. As noted above, Petitioner here relies on the same experts, Drs. Schleimer and Donovan, as Argentum relied upon back in 2017. Argentum IPR, Exs. 1003, 1004. The Argentum IPR was resolved prior to a final written decision. Argentum IPR, Paper 60.

IV. BOARD SHOULD DENY INSTITUTION OF THE PETITION BECAUSE IT PRESENTS SUBSTANTIALLY THE SAME ART PREVIOUSLY CONSIDERED BY THE OFFICE

The Office has already evaluated—and rejected—Petitioner's arguments. The Petition turns on three references – Cramer, Segal and PDR 1999. But Cramer

[2] The entity that filed the Opposition before the EPO was Glaxo Group Limited. Ex. 2027, 46. The Petitioner and only real party-in-interest identified here is GlaxoSmithKline Consumer Healthcare Holdings (US) LLC. Pet. 66; *see also* Section II.C, *supra* (objecting to the limited disclosure of GlaxoSmithKline Consumer Healthcare Holdings (US) LLC as the only real party in interest).

and Seagal were already addressed by the Examiner in detail (and overcome by Cipla) during prosecution of the earlier ’620 patent as well as for the ’585 patent. *See* Section III, *supra*. While Petitioner adds PDR 1999 to the mix, its teachings are cumulative of information already considered (and rejected) by the Office. *See* Section III, *supra*. And notably, Petitioner fails to identify any material error in the Office’s analysis. Accordingly, the Board should defer to the Office’s earlier rejection of these same arguments and art and exercise its discretion under 35 U.S.C. § 325(d) to deny institution.

A. Absent a Showing of Material Error, the Director May Decline Institution Where the Petition Merely Rehashes Arguments and Art Already Considered in Prosecution.

Under 35 U.S.C. § 325(d), the Board may decline to institute trial where “the same or substantially the same prior art or arguments previously were presented to the Office.” 35 U.S.C. § 325(d); *see also Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, 2017 WL 6405100, at *6, *8, *14 (PTAB Dec. 15, 2017) (precedential) (denying institution of grounds that were based on arguments and art considered during prosecution); *Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019-01469, 2020 WL 740292 (Feb. 13, 2020) (precedential) (same); *Kayak Software Corp. v. Int’l Bus. Machs. Corp.*, CBM2016-00075, 2016 WL 11034653, at *3-4 (PTAB Dec. 15, 2016) (same); *Regeneron Pharm., Inc. v. Kymab Ltd.*, IPR2019-01580, 2020 WL

1312961 (PTAB Mar. 18, 2020) (same). In evaluating whether to exercise discretion, precedential decisions require the Board to weigh the nonexclusive *Becton Dickson* factors:

> (a) the similarities and material differences between the asserted art and the prior art involved during examination;
>
> (b) the cumulative nature of the asserted art and the prior art evaluated during examination;
>
> (c) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection;
>
> (d) the extent of the overlap between the arguments made during examination and the manner in which Petitioner relies on the prior art or Patent Owner distinguishes the prior art;
>
> (e) whether Petitioner has pointed out sufficiently how the Examiner erred in its evaluation of the asserted prior art; and
>
> (f) the extent to which additional evidence and facts presented in the Petition warrant reconsideration of prior art or arguments.

NHK Spring Co. v. Intri-Plex Techs., Inc., IPR2018-00752, 2018 WL 4373643, at *4 (PTAB Sept. 12, 2018) (precedential).

The Board further addressed discretionary non-institution under 35 U.S.C. § 325(d) in *Advanced Bionics*. Under *Advanced Bionics*, if the "same or substantially the same prior art or arguments previously were presented to the Office," then the petitioner must establish that the Office erred in evaluating the art or arguments. *Advanced Bionics*, 2020 WL 740292, at *3 (citation omitted). If petitioner fails to show that the Office erred, the Director may exercise his

discretion not to institute *inter partes* review. *Id.* (citing *Becton, Dickinson*, 2017 WL 6405100, at *8 (discretion appropriate where "Petitioner has not pointed to error by the Examiner")).

In *Advanced Bionics*, the Board applied a two-part framework to make this determination:

> (1) whether the same or substantially the same art previously was presented to the Office or whether the same or substantially the same arguments previously were presented to the Office; and
>
> (2) if either condition of first part of the framework is satisfied, whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims.

Id. Thus, under the *Advanced Bionics* framework, if a petitioner offers substantially the same arguments or art previously presented to the Office, the petitioner must make a showing of material error. *Id*. Examples of a material error may include misapprehending or overlooking specific teachings of the relevant prior art where those teachings impact patentability of the challenged claims or an error of law, such as misconstruing a claim term, where the construction impacts patentability of the challenged claims. *Id*. If reasonable minds may disagree regarding treatment of the art or arguments, however, material error has not been established. *Id*. Absent this showing, the Director generally will exercise discretion ***not*** to institute *inter partes* review. *Id*. At bottom, this framework reflects a

commitment to deference to prior Office evaluations of the evidence of record absent material error. *Id*.

B. Petitioner Relies on Substantially the Same Art and Arguments Overcome During Prosecution.

The art and arguments relied above are substantially the same as the grounds Petitioner asserts. To illustrate, in Ground 1, Petitioner relies on PDR 1999 for its teaching that both azelastine and fluticasone were known in the prior art as monotherapies. Pet. 4-6. Petitioner relies on Segal for its purposed suggested of a formulation combining fluticasone and azelastine. Pet. 6. In Ground 2, Petitioner pivots and instead relies on Cramer for its purported suggestion of a formulation combining fluticasone and azelastine. Pet. 31-32. However, Petitioner again relies on PDR 1999 for its teaching that both azelastine and fluticasone were known in the prior art as monotherapies—i.e., separately approved agents. Pet. 33-34. But in light of the prosecution history, *see* Section III, *supra*, neither ground differs in any material way from the art and arguments already considered and overcome during prosecution and the *Becton Dickinson* factors each support non-institution for these grounds.

The similarities and material differences between the asserted art and the prior art involved during examination: Petitioner has failed to identify any material differences between the art and arguments considered in prosecution and those offered in the Petition. Indeed, as explained above, Cramer was the primary

reference used to reject claims during prosecution of the ’585 patent, as well as the earlier ’620 patent upon which the ’585 patent claims priority, based on a purported suggestion of a nasal spray combining two agents. *See* Sections III.A and D, *supra*. This is the same alleged teaching Petitioner offers here. And Petitioner offers Segal (also considered by the Examiner) for substantially the same alleged (and rejected) teaching. Notably, however, Segal provides even less relevant information than Cramer.

Petitioner also offers PDR 1999 as a reference disclosing the prior art use of fluticasone and azelastine. But, as addressed above in Section III.A.3, *supra*, this monotherapy use was disclosed in the specification, during prosecution, and in dozens of references submitted to the Office.

***The cumulative nature of the asserted art and the prior art evaluated during examination*:** Just as with factor (a), factor (b) favors non-institution for the same reasons. Both Cramer and Segal were considered by the Examiner, and the Examiner was unambiguously aware of the use of fluticasone and azelastine in the treatment of AR. *See* Sections III.A, B, C, D. It is of no moment that Segal and PDR 1999 were not the basis of a rejection—both references are presented for the same prior art teachings as those of references that were overcome during prosecution. *See CSL Behring GmBH v. Shire Viropharma Inc*., IPR2019-00459, 2019 WL 2866004, at *7 (PTAB July 2, 2019) (exercising discretion not to

institute where, even though the Examiner did not reject claims based on the IPR art during prosecution, the Examiner's rejection using other references relied on prior art teachings and a rationale which, although not entirely cumulative, were very similar to those presented in the petition). Again, the Examiner expressly stated that these references were considered. Ex. 1008, 36-39.

The extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection**:** This factor also supports non-institution. Cramer was the basis for multiple rejections during prosecution for the earlier '620 patent, as well as a rejection for the '585 patent. *See* Section III, *supra*. Segal is substantially the same as Cramer, albeit providing even less disclosure, and was considered during prosecution. *See* Section III.A.2, *supra*. The combination of the prior art use of fluticasone and azelastine was the basis for the Examiner's Cramer-based rejections. Therefore, the substance of PDR 1999 was fully evaluated during examination. *See* Section III.A.3. Moreover, the Examiner stated unequivocally that all of these references were evaluated. Ex. 1008, 36-39.

The extent of the overlap between the arguments made during examination and the manner in which petitioner relies on the prior art or patent owner distinguishes the prior art: As explained above, the arguments and art

relied upon by Petitioner are used in the same manner as was the prior art evaluated during prosecution. This again favors non-institution.

Whether petitioner has pointed out sufficiently how the examiner erred in its evaluation of the asserted prior art: Petitioner has not attempted to identify whether the Examiner erred in the evaluation of the art, let alone how any such error would be material. Petitioner asserts Grounds that merely repeat what was addressed at considerable length during prosecution. The Grounds here differ in no material way from the rejections overcome during prosecution; the art and arguments presented here are substantially the same as those previously overcome during prosecution. This favors non-institution.

The extent to which additional evidence and facts presented in the petition warrant reconsideration of prior art or arguments: Petitioner identifies no new facts or evidence that warrant reconsideration. To the contrary, Petitioner ignored much of the evidence considered during the original prosecution. This favors non-institution.

Petitioner Has Not Identified Any Error by the Examiner. Petitioner does not present any new teachings that were not already considered (and rejected) by the Examiner. And fatally, Petitioner makes no effort to distinguish its relied-upon art from the art already carefully considered during prosecution. Instead, after acknowledging that the same Cramer reference that formed the basis of rejections

during prosecution is relied upon here, the Petitioner states that non-institution under § 325(d) is avoided only because the Petitioner disagrees with the Examiner's careful and fully-explained consideration of objective indicia of non-obviousness. Pet. 68. That is not a material error allowing Petitioner to circumvent the Board's "commitment to defer to previous Office evaluations of the evidence of record unless material error is shown." *Advanced Bionics*, 2020 WL 740292, at *3; *CSL Behring*, 2019 WL 2866004, at *8 (finding that petitioner failed to demonstrate that the Office erred in considering a declaration submitted during prosecution even where the petitioner submitted an expert declaration).

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When taken as a whole, the *Becton Dickinson* factors and the complete absence of any suggestion that the Examiners erred in their consideration of substantially the same prior art addressed here, demonstrate that it is not an efficient use of the Board's time and limited resources to revisit the same disclosures evaluated by the Office over the course of years of prosecution. *Aquestive Therapeutics, Inc. v. Neurelis, Inc*., IPR2019-00450, 2019 WL 3504247, at *9 (PTAB Aug. 1, 2019) (denying intuition where Board found "[i]t is simply not an efficient use of the Board's time and resources to revisit the same prior art disclosures that were examined in detail by the Examiner over eight years of patent prosecution.")

V. THE BOARD SHOULD DENY THE PETITION UNDER 35 U.S.C. § 314(a) BECAUSE INSTITUTION WOULD RESULT IN AN INEFFICIENT USE OF BOARD RESOURCES

"The decision whether to institute inter partes review is committed to the Director's discretion." *Oil States Energy Servs., LLC v. Greene's Energy Grp., LLC*, 138 S. Ct. 1365, 1371 (2018). The August 2018 Update to the Office Patent Trial Practice Guide "invites parties to address additional factors that may bear on the Board's discretionary decision to institute or not institute under §§ 314(a) and 325(d)." *NHK Spring*, 2018 WL 4373643, at *8 n.4. Here, at least three such factors further counsel against institution.

A. The Board Should Exercise Its Discretion Not to Institute Follow-On Petitions

This is just the latest challenge to one of the Dymista Patents. Previously, Argentum petitioned for *inter partes* review of the earlier '620 patent, making arguments like those made in the present Petition and using the same expert declarants submitted here. *See* Section III.E. Petitioner had ample opportunity and motivation to join that petition. Indeed, a related entity of Petitioner previously challenged a European patent covering Dymista® in 2010, demonstrating a long-standing interest in Dymista and the patents covering it. Ex. 2027.

In *General Plastic Industrial Co. v. Canon Kabushiki Kaisha*, IPR2016-01357, 2017 WL 3917706, at * 6-7 (PTAB Sept. 6, 2017) (precedential), the Board articulated a non-exhaustive list of factors to be considered in determining whether

to exercise discretion under § 314(a) to deny a petition that challenges the same patent as a previous petition. However, this is "not limited solely to instances when multiple petitions are filed by the same petitioner." *Valve Corp. v. Elec. Scripting Prods., Inc.*, IPR2019-00062, 2019 WL 1490575, at *1 (PTAB Apr. 2, 2019) (precedential); *NetApp Inc. v. Realtime Data LLC*, IPR2017-01195, 2017 WL 4574548, at *4 (PTAB Oct. 12, 2017) ("[T]he *General Plastic* factors provide a useful framework for analyzing the facts and circumstances present in this case, in which a different petitioner filed a petition challenging a patent that had been challenged already by previous petitions.").

Under *General Plastics*, the Board looks to seven factors, each of which, but for factor seven, which is neutral, favor denying institution here.

Factor (1): Whether the same petitioner previously filed a petition directed to the same claims of the same patent. While Petitioner did not previously file a petition for *inter partes* review, it did oppose a European patent covering Dymista®.

Factor (2): Whether at the time of filing of the first petition the petitioner knew of the prior art asserted in the second petition or should have known of it. Petitioner should have been aware of Cramer and the prior art use of fluticasone as a single agent when the Argentum IPR was filed. *See* Ex. 2001, 751-773 (office action citing Cramer); Ex. 2002 (identifying GlaxoSmithKline as the marketer of

Flonase)

Factor (3): Whether at the time of filing of the second petition the petitioner already received the patent owner's preliminary response to the first petition or received the Board's decision on whether to institute review in the first petition. Petitioner had received the preliminary response, the patent owner response, deposition transcripts and all evidence filed in the Argentum IPR. Indeed, Petitioner's exhibit list includes several documents submitted in the Argentum IPR. Ex. 1043; Ex. 1046; Ex. 1054.

Factor (4): The length of time that elapsed between the time the petitioner learned of the prior art asserted in the second petition and the filing of the second petition. Nearly 11 years have passed since Petitioner challenged the EP counterpart to the Dymista Patents and more than three years have passed since the Argentum IPR was filed.

Factor (5): Whether the petitioner provides adequate explanation for the time elapsed between the filings of multiple petitions directed to the same claims of the same patent. Petitioner offers no explanation for the delay between the filing this Petition and either the EPO opposition or the Argentum IPR.

Factor (6): The finite resources of the Board. Petitioner had ample opportunity to join the Argentum IPR.

Factor (7): The requirement under 35 U.S.C. Section 316(a)(11) to issue a final determination not later than one year after the date on which the Director notices institution of review. The Board, should it elect to institute, presumably would be able to issue a final written decision within one year of institution.

Continued, serial *inter partes* review challenges to the Dymista Patents undermine the policy rationale underlying § 315(b), which is to ensure that *inter partes* review acts as a cost-effective alternative to litigation, not a tool for harassment through serial litigation and administrative attacks. H.R. Rep. No. 112-98, at 48 (2011), r*eprinted in* 2011 U.S.C.C.A.N. 67, 78 (legislative history noting "the importance of quiet title to patent owners to ensure continued investment resources," and made clear that inter partes review and other post-grant proceedings were "not to be used as tools for harassment … through repeated litigation and administrative attacks on the validity of a patent"). Given that Petitioner uses the same experts as did Argentum, had a clear interest in challenging the Dymista Patents as demonstrated by the EPO opposition, and was unquestionably aware of the prior art relied upon here, when considered as a whole, the *General Plastics* factors favor non-institution.

VI. PETITIONER HAS NOT DEMONSTRATED A REASONABLE LIKELIHOOD THAT THE CHALLENGED CLAIMS WOULD HAVE BEEN OBVIOUS

Setting aside the threshold issues, the Petition fails on the merits.[3] Indeed, Petitioner's argument rests on several flawed premises regarding the state of the art at the time of the claimed invention. Petitioner attempts to characterize the invention of a nasal spray combining two different classes of medications—a steroid and an antihistamine—into a single fixed-dose nasal spray as merely combining two medications into one. But the prior art reveals a far more complex reality. Even the FDA recognized that "[t]he development of an intranasal antihistamine/corticosteroid combination raised certain issues that had not been previously encountered in development programs for single-component nasal sprays." Ex. 2008, 4. Indeed, the FDA recognized that the development of Dymista was unusually complex. Ex. 2040, 3 ("[G]iven the complexity surrounding the development of a fixed-dose combination product containing an intranasal corticosteroid and antihistamine for treatment of AR….").

[3] With respect to the threshold issues of the level of skill in the art, Patent Owner does not challenge Petitioner's level of skill (Pet. 2-3) only for the limited purpose of this Preliminary Response. Patent Owner reserves the right to offer a different definition later, if necessary, including in its Patent Owner Response.

With respect to claim construction, Petitioner has not offered a construction of any term of the challenged claims. Patent Owner does not offer any claim construction for the limited purpose of this Preliminary Response. Patent Owner reserves the right to offer constructions in its Patent Owner Response, if necessary.

To start, Duonase was the first ever fixed-dose combination nasal spray marketed anywhere in the world. Practitioners understood there were a multitude of well-known agents and classes of agents that could be used to treat AR. Yet, quite tellingly, prior to Cipla's invention, no one had ever combined any of these therapies into a fixed-dose combination. And the reasons for that are many: the prior art suggested there was no benefit of making such a combination; the fixed-dose combination prevented patients and physicians from adjusting the dose of the two medications; and the two agents at issue here were formulated as a suspension and as a solution, respectively, creating formulation difficulties the prior art simply did not address.

Even when the prior art teaches or suggests the limitations of the claims, that fact is not enough to render the claims obvious. *Reactive Surfaces Ltd. v. Toyota Motor Corp.*, IPR2019-00867, 2019 WL 4492905, at *3 (PTAB Sept. 18, 2019). "An invention is not obvious just 'because all of the elements that comprise the invention were known in the prior art.'" *Broadcom*, 732 F.3d at 1335 (quoting *Power-One, Inc. v. Artesyn Techs., Inc.*, 599 F.3d 1343, 1351 (Fed. Cir. 2010)); *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (A patent claim "is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art."). Instead, "a finding of obviousness at the time of invention requires a 'plausible rational[e] as to why the prior art references

would have worked together.'" *Broadcom*, 732 F.3d at 1335 (quoting *Power-One*, 599 F.3d at 1351). Even when an obviousness argument relies on "combining multiple embodiments from a single reference,...there must be a motivation to make the combination and a reasonable expectation that such a combination would be successful, otherwise a skilled artisan would not arrive at the claimed combination." *In re Stepan Co.*, 868 F.3d 1342, 1346 n.1 (Fed. Cir. 2017). Here, both that motivation to combine fluticasone and azelastine into a single fixed-dose formulation and reasonable expectation of success in doing so is lacking. Indeed, the prior art pointed away from the claimed invention; POSAs expected the drawbacks of a fixed-dose combination nasal spray formulation to far outweigh any expected benefit, which the prior art did not even identify.

Moreover, numerous objective indicia of non-obviousness—long-felt but unmet need, unexpected results, industry skepticism, industry praise, failure of others, licensing, and commercial success—support the patentability of the challenged claims. This real-world evidence confirms the inventive nature of the claimed formulations.

A. Clinical Treatment Options for Allergic Rhinitis As of the Priority Date Were Numerous.

AR is a common condition that afflicts millions of people. Characterized by nasal congestion, rhinorrhea, sneezing, itching of the nose and/or postnasal drainage, AR is an inflammation of the membranes lining the nose. Ex. 1019, 6;

Ex. 2009, 17. AR is extremely prevalent: in June 2002, it was estimated that 20-40 million people in the U.S. alone, or 10% to 30% of the adults and 40% of children, suffered from AR. Ex. 1019, 6.

AR is the body's reaction to the inhalation of an allergen, typically pollens, molds, house dust mites, and animal and insect allergens. Ex. 1019, 23. Due to the complexity of the condition, treating physicians did not base their treatment analysis on mechanisms, but instead on managed symptoms. Ex. 1019, 23; Ex. 2010, 1-2; 2009, 93-107 (describing drug efficacy in terms of symptoms managed).

As of June 2002, the priority date, doctors had an arsenal of AR treatment options (in systemic or topical forms), including: (1) antihistamines, (2) decongestants, (3) anticholinergics, (4) mast cell stabilizers, (5) leukotriene receptor antagonists, and (6) corticosteroids. Ex. 1019; Ex. 2009.

24 Antihistamine Options	Phenbenzamine	Chlorpheniramine	Diphenhydramine	Promethazine	Triprolidine	Pyrilamine maleate	Tripelennamine	Cetirizine	Loratadine
	Azatadine	Azelastine	Ebastine	Fexofenadine	Mizolastine	Hydroxyzine	Acrivastine	Emedastine	Epinastine
	Levocabastine	Mequitazine	Ketotifen	Oxatomide	Dexchlorpheniramine maleate		Brompheniramine		
9 Decongestants	Phenylephrine	Oxymetazoline	Xylometazoline	Naphazoline	Ephedrine	Pseudo-ephedrine	Amphetamines	Tricyclic anti-depressants	Phenylpropanolamine
2 Mast Cell Stabilizers	Disodium cromoglycate						Sodium nedocromil		
4 Anticholinergics	Ipratropium bromide	Oxitropium bromide		Tiotropium bromide			Glycopyrrolate		
3 Leukotriene receptor antagonists	Zileuton			Zafirlukast			Montelukast		
7 Corticosteroids	Beclomethasone dipropionate	Budesonide	Flunisolide	Fluticasone propionate		Mometasone furoate	Ciclesonide	Triamcinolone acetonide	
At least 49 treatment options									

Systemic forms included oral, parenteral, and other dosage forms. Ex. 2009, 91. These systemic forms exhibited systemic side effects, e.g. sedation, but were able to target multiple organs at once. Ex. 2009, 91-109 (describing efficacy and side effects of AR medications). Topical dosage forms included skin creams, nasal sprays and eye drops. Topical dosage forms exhibited localized side effects and had efficacy limited to the treated organ. *Id*.

Antihistamines. In 2002, oral or intranasal antihistamines were known to be effective AR treatments and were available in systemic and topical dosage forms. Ex. 2009, 92-99, 138. Antihistamines were known to work well for itching, sneezing, and runny nose, but they had little effect on congestion. Ex. 1019, 27. Several "second-generation" antihistamines—including well-known oral drugs Claritin (loratadine), Zyrtec (cetirizine), and Allegra (fexofenadine)—were largely indistinguishable in onset, efficacy, and side-effects. Ex. 1041, 8. Azelastine, another second-generation intranasal antihistamine, was well-known to have several significant side-effects, including sedation, headaches, and a uniquely bitter taste that led many patients to avoid it. Ex. 2019, 14; Ex. 1019, 31.

Decongestants. As of the priority date, there were also several decongestants available in both intranasal, oral and topical dosage forms at the time of invention. Ex. 2009, 105; Ex. 1019, 31. Decongestants were known to be

effective in treating congestion, but they had little effect on itching, sneezing, or runny nose. Ex. 1019, 31.

Corticosteroids. There were several intranasal corticosteroids known at the time of invention, one of which was Fluticasone. Ex. 2009, 102-103; Ex. 1001, 6:56. Corticosteroids were known to be the most effective treatment for AR because they worked well on all symptoms. Ex. 1019, 32; Ex. 2009, 99. Aside from minor variations in patient preference and safety profiles, intranasal corticosteroids were largely indistinguishable. Ex. 2022, 4. The primary drawbacks of corticosteroids were safety issues and slow onset of action. Ex. 2020, 5.

Additional Treatment Options. As of the priority date, physicians had several additional choices, such as anticholinergic agents, mast cell stabilizers and leukotriene receptor antagonists. Each were known at the time of invention for use in the treatment of AR. Ex. 2009, 104, 106-07; Ex. 1019, 34, 36, respectively. Collectively they were available in topical and/or systemic dosage forms. Ex. 2009, 107.

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Physicians at the time of invention frequently had to prescribe multiple medications to control a patients' symptoms. Ex. 1019, 37. And, given the large number of monotherapies available at the time of invention, the POSA would have been presented with hundreds of possibilities for the co-administration of these

monotherapies. Physicians often cycled through each of these options to find a treatment that worked. Due to patient variability, however, appropriate combinations of separate monotherapies were often different for each patient. Ex. 1019, 37. There is no evidence in the art that any one combination of drugs was viewed as more promising than any other combination, much less a combination that employed the little-used azelastine. Rather, the art supported individualized patient treatment, which could then only be obtained by way of the co-administration of separate monotherapies. Ex. 1019, 26-27. Treatment guidelines at the time of invention recommended a patient-tailored practice. Ex. 2009, 120-21, 125. The guidelines also recognized the overarching desire to minimize the patient's drug exposure by reducing the dose after symptom control was achieved. Ex. 2009, 120; Ex. 1019, 26-27.

B. Dymista and Duonase Were Breakthrough Combination AR Therapies.

Meda[4], the exclusive licensee to the '585 patent, received FDA approval in 2012 for Dymista, a 137mcg azelastine hydrochloride/50mcg fluticasone propionate combination nasal spray, which is marketed by Mylan Specialty L.P. Exs. 2005, 2006. Dymista is indicated for the relief of symptoms of seasonal AR in patients at least six years of age. Ex. 2006. Dymista is a fixed-dose combination of azelastine hydrochloride ("azelastine") and fluticasone propionate ("fluticasone").

[4] Mylan N.V. acquired Meda in 2016. Ex. 2012.

A fixed-dose combination product is one where two or more medications are incorporated into a single dosage form, here a nasal spray. In a fixed-dose combination product, the patient cannot separate the two medications or adjust the amount of either medication in a given dose. Dymista is the first fixed-dose combination nasal spray for the treatment of AR approved in the U.S. Ex. 2008, 1-2. Dymista is a commercial embodiment of the claims of the '585 patent. *See* Ex. 2037, 41-55.

Duonase, marketed by Cipla in India, is a fixed-dose combination of azelastine and fluticasone and is also an embodiment of the claims of the '585 patent. Ex. 2007. Released in 2004, Duonase was the first fixed-dose combination nasal spray for the treatment of AR anywhere in the world. As a result of its surprising efficacy and commercial success, soon after its introduction, several azelastine/fluticasone copycat products ("Duonase copycats") entered the market. Ex. 2001, 328-334.

C. Overview of the Asserted Art.

Cramer: Cramer is a European patent application titled "*A nasal spray containing a steroid and a antihistamine*." Ex. 1011, 1. Cramer explained that AR was traditionally treated with an antihistamine or a decongestant. *Id.* at 2:9-20. Cramer also explained that corticosteroids could be used in the treatment of AR, as could other types of therapies. *Id.* at 2:20-24. Recognizing the need for improved

formulations, Cramer generally suggests a formulation comprising a corticosteroid and an antihistamine. *Id.* at 2:25-32. Cramer broadly proposes that any of at least six steroids (and salts and mixtures thereof) might be combined with any of at least three antihistamines (and salts, racemates, and mixtures thereof). *Id.* at 3:15-20, 3:24-30. Cramer explains that a host of other components may also be included, such as decongestants, antiallergics, analgesics, lipoxygenase inhibitors and receptor antagonists, leukotriene receptor antagonists, aromatic components, isotonicity agents, thickeners, humectants, surfactants, preservatives, antioxidants, colorings, among others. *Id.* at 4:6-5:30. Cramer provides just three examples, none of which include fluticasone, much less the claimed combination of fluticasone and azelastine. *Id.* at 5:32-6:51. None of the examples provide any safety, tolerability or efficacy data. *Id.*

Segal: Segal is an International Patent Application publication (WO 98/48839) titled *Topical Nasal Antiinflammatory Compositions*. Ex. 1012. Segal broadly disclosed "topically applicable nasal compositions comprising a therapeutically effective amount of an antiinflammatory agent and a therapeutically effective amount of at least one agent selected from the group consisting of a vasoconstrictor, a neuramidinase [sic] inhibitor, a leukotriene inhibitor, an antihistamine, an antiallergic agent, an anticholinergic agent, an anesthetic and a mucolytic agent." *Id.*, Abstract. Segal is a patent application with a specification

spanning just 3.5 pages. It does not include a single working example, it does not include any clinical or pre-clinical data, it does not provide a POSA instruction on how to formulate any of the various combinations, nor does it provide any scientific rationale as to why any of the many medications should be combined, much less the specific combination of azelastine and fluticasone. *Id*. Segal broadly attempts to disclose every possible iteration of combination therapy that might be used in the treatment of AR—as the Board previously found, Segal discloses more than 800 million iterations. Ex. 1055, 13.

In its short specification, Segal states that an anti-inflammatory agent can be a corticosteroid. Ex. 1012, 4:22–23. Segal lists at least six corticosteroids (beclomethasone diproprionate [sic], budesonide, dexamethasone, mometasone furoate, fluticasone proprionate [sic], and triamcinolone acetonide) as preferred anti-inflammatory agents, but the disclosure is not limited to those six. *Id*. at 4:23–26. As the "at least one additional therapeutic agent," Segal lists eight preferred classes of compounds and examples of each: (1) vasoconstrictors (oxymetazoline, naphazoline, xylometazoline, and phenylephrine); (2) leukotriene inhibitors (zafirlukast, pranlukast, and zileuton); (3) neuramidinase [sic] inhibitor (zanamivir); (4) antihistamines (diphenhydramine, chlorpheniramine, cetirizine terfenadine, fenofexadine, astemizole norastemizole, azelastine, and azatidine); (5) antiallergic agents (cromolyn sodium, and nedocromil levocabastine); (6) an

anticholinergic agent (ipratropium bromide); (7) local topical anesthetics (dyclonine, pramoxine, and benzocaine); and (8) mucolytic agents (acetylcysteine, guaifenisin [sic], and mucocysteine). *Id.* at 5:3–25.

PDR 1999: The PDR is a commercially published compilation of manufacturers' prescribing information (i.e., labels) of prescription drugs. Ex. 2033. The prescribing information for the commercial product Flonase (fluticasone propionate) appears in the PDR 1999 from pages 1122-1125. Ex. 1010. More than 2,000 pages later (at pages 3191-3192), the prescribing information for Astelin (azelastine), is reproduced. *Id*. Had the full text of the PDR 1999 been provided by Petitioner, at least dozens of treatments for AR would have been disclosed across multiple therapeutic classes.

D. Petitioner's Prior Art References Do Not Render the Challenged Claims Obvious.

None of the references relied upon by Petitioner teach or suggest formulations combining azelastine with fluticasone, and the specific excipients claimed in the asserted claims of the patents-in-suit. As the Examiner recognized during prosecution, "Cramer does not exemplify a composition comprising azelastine and fluticasone." Ex. 2001 at 607, 733, 763. Likewise, Neither Segal nor PDR 1999 contain such a teaching. Exs. 1010, 1012. In suggesting that the prior art encouraged the combination of fluticasone and azelastine, Petitioner improperly employs the benefit of hindsight to pick and choose from among broad disclosures

to recreate the invention with neither a motivation to do so nor a reasonable expectation of success. *Akzo N.V. v. USITC*, 808 F.2d 1471, 1481 (Fed. Cir. 1986) (patent challengers "cannot pick and choose among individual parts of assorted prior art references 'as a mosaic to recreate a facsimile of the claimed invention'" (citation omitted)).

1. *Rather than Motivate the POSA to Combine Azelastine and Fluticasone into a Fixed-Dose Combination Nasal Spray, the Prior Art Taught Away from This Combination*

Both fluticasone and azelastine were known in the art for years prior to the invention. Fluticasone, marketed by the Petitioner as Flonase, was first approved by FDA in 1994. Ex. 2002. Azelastine, marketed as Astelin, was approved by FDA in 1996. Ex. 2003. Until Cipla developed a fixed-dose combination of these two medications, no one succeeded in combining these two medications into a single fixed-dose nasal spray. The prior art provided no rationale to make this combination and was replete with reasons *not* to do so.

To start, the POSA was not motivated by the prior art to select a nasal spray to develop as an AR treatment. Nasal sprays were known to have multiple drawbacks, including (1) the inability to treat multiple target organs; (2) suboptimal drug distribution on the nasal mucosa; (3) nasal irritation; (4) an inability to provide treatment when the nasal passage is completely blocked; (5)

medication specific-side effects; and (6) lesser patient compliance as compared to oral treatments. Ex. 2009, 91-92.

And, patients preferred oral dosage forms, as shown by the market shares of products available at the time of invention: oral antihistamines controlled a 56.7% share of the total global AR market, whereas all intranasal products—including intranasal corticosteroids—controlled approximately 30% of the market. Ex. 2021, 29. Intranasal antihistamines—including azelastine—controlled only a small fraction of the overall AR market. Ex. 2021, 29. Given the patient preference for oral treatments and the known drawback of nasal sprays, the POSA would instead have been motivated to select an oral dosage form for a new treatment, not a nasal spray.

Additionally, the POSA would not have selected either fluticasone as the starting point for an improved treatment of AR, or azelastine as the antihistamine to combine it with. Fluticasone monotherapy was no more efficacious than any other corticosteroid available at the time of invention and its mechanism of action was unknown, such that there would have had no expectation that fluticasone would be beneficial in use with any other drugs. Ex. 2022, 4; Ex. 2020, 3. Indeed, the POSA would have known that fluticasone had both an undesirable taste and an undesirable odor that led patients in comparative clinical studies to prefer other corticosteroids. Ex. 2022. Azelastine was likewise disfavored as it was known to

have a similar bad taste and several severe side effects, including sedation and headaches. Ex. 2019, 14. For these very reasons, azelastine was not widely used until Cipla learned to combine it into the claimed composition. Ex. 2021, 29.

b. The Prior Art Discouraged the Conjunctive Use of Corticosteroids and Antihistamines

It was well-established that conjunctive use of an antihistamine (like azelastine) and a corticosteroid (like fluticasone) yielded no benefit over the use of a corticosteroid alone. Juniper 1989 considered conjunctive use of the antihistamine, astemizole, and the corticosteroid, beclomethasone dipropionate. Ex. 1039, 4. There, the authors concluded that "[b]eclomethasone plus astemizole provided no better control of rhinitis than beclomethasone alone." *Id*. Likewise, Benincasa 1994 considered the conjunctive use of the antihistamine cetirizine and the corticosteroid fluticasone. Ex. 1040, 1. The authors of this paper concluded that "there is no significant difference in efficacy between [fluticasone], taken once daily in the morning, and [fluticasone] once daily in combination with oral cetirizine 10 mg, in the prophylactic treatment of seasonal allergic rhinitis." *Id.* Simpson 1994 considered the conjunctive use of the antihistamine terfenadine and the corticosteroid budesonide and concluded that "[b]udesonide alone is a highly effective treatment for hay fever with few side effects." Ex. 1036, 4. Simpson 1994 stated that "[b]udesonide and terfenadine combination treatment produced a similar effect to treatment with budesonide alone." *Id.* at 6. Ratner 1998 considered the

conjunctive use of the antihistamine loratadine and the corticosteroid fluticasone. Ex. 1034, 4. Ratner 1998 concluded that "adding loratadine to [fluticasone] does not confer meaningful additional benefit." *Id.*

In a 2000 survey of the literature, researchers concluded that studies of the conjunctive use of an antihistamine and a corticosteroid "do not support a superior effect with long-term regular therapy with the combination [of an antihistamine and corticosteroid] compared with topical corticosteroid alone." Ex. 1037, 4-5. The 2000 Howarth survey further concluded that "[t]he lack of additional clinical benefit when antihistamines are used in combination with corticosteroids indicates that, *in vivo*, the anti-inflammatory effects on the airway of corticosteroids overlap those of the H_1- antihistamines, making the action of the latter redundant." *Id.* at 5.

In a 2001 survey of the literature, other researchers concluded that "[t]he common clinical practice of combining [inhaled corticosteroids] and oral antihistamines in the treatment of allergic rhinitis has no support in clinical evidence, as the combination has not provided effects beyond [inhaled corticosteroids] alone and so it cannot be considered cost effective." Ex. 1042, 14. In reaching this conclusion, the 2001 Nielsen survey team explicitly considered Juniper 1989, Ratner 1998, and Simpson 1994, among other references. *Id.* at 13, Table III.

Based on these studies, a POSA would have seen no meaningful benefit to the conjunctive use of antihistamines and corticosteroids over corticosteroids alone. Ex. 1037; Ex. 1042. The POSA would not have been motivated to attempt a fixed-dose nasal spray combining two drug classes known in the art to confer no benefit when used together.

c. The Prior Art Did Not Motivate the Combination of Azelastine and Fluticasone in a Fixed-Dose Combination Nasal Spray

Likewise, the combination of fluticasone and azelastine in a fixed-dose combination was not motivated, but rather taught away from by the prior art. The POSA would not have expected any clinically relevant difference between the administration of azelastine and fluticasone as conjunctive nasal spray monotherapies or in a fixed-dose nasal spray combination. *See* Section VI.D.1.b. The formulation difficulties and clinical drawbacks of such a combination product would have discouraged the claimed formulations.

And the POSA knew that there were more clinical reasons not to employ a fixed-dose combination product—the patient would receive the same dose of each separate component with each administration. Neither the patient nor the physician could adjust the dosage of either medication in view of the patient's needs. Indeed, FDA recognized that Dymista created concerns left unaddressed by the prior art:

> [A]zelastine/FP will be the first fixed-dose combination nasal spray approved for allergic rhinitis. ***The development of an intranasal***

> ***antihistamine/corticosteroid combination raised certain issues that had not been previously encountered in development programs for single-component nasal sprays***….Specifically, the Division expressed concerns regarding the following: 1) identification of an appropriate patient population for the proposed product; 2) ***the loss of dose titration flexibility***; 3) the ***use of two components to treat the same symptoms of allergic rhinitis***; and 4) the need for pharmaceutically comparable monocomparators to be used in the key factorial-design trials.

Ex. 2008, 3 (emphases added). The POSA, understanding this basic proposition, would not have been motivated to combine azelastine and fluticasone into a single, fixed-dose nasal spray. A fixed-dose combination nasal spray product prohibits physicians from controlling their patient's dosing and achieving optimum dosing of each drug. Ex. 1019, 29-30. The POSA would have known that the inability to titrate to an optimal dosage would subject patients to unnecessarily high drug exposure and increase the risk of undesirable side effects. *Id.* Still further, a fixed-dose combination product would not allow for substitution of one medication for another, e.g., the substitution of budesonide for fluticasone.

The POSA would have also known that a combination nasal spray product including azelastine would require patients to take azelastine even if that drug was unnecessary while needlessly exposing patients to the significant side effects of dysgeusia, somnolence, and headache. Ex. 1010, 13; Ex. 1019, 29. The POSA would not have been motivated to combine azelastine and fluticasone into a single, fixed-dose combination nasal spray product because the sole expected benefit to

such a combination—a modest improvement in convenience—is outweighed by the needless exposure of patients to significant side effects, the physician's inability to titrate dosing, and the inability to account for patient-to-patient variability in response to azelastine or fluticasone therapies.

d. Azelastine And Fluticasone Have Incompatible Dosing Schedules

A fixed-dose combination was further complicated and discouraged by the different dosing schedules for azelastine and fluticasone. As described in PDR 1999, the FDA-approved dose of azelastine nasal spray was two sprays per nostril twice a day, and the FDA-approved dose of fluticasone nasal spray was two sprays per nostril once a day or one spray per nostril twice a day. Ex. 1010.

	Astelin® Label	Flonase® Label – Option 1	Flonase® Label – Option 2
Number of sprays	Two sprays	Two sprays	**One spray**
Active per spray	137 mcg/nostril	50 mcg/nostril	50 mcg/nostril
Times per day	Twice	**Once**	Twice
Therapeutically effective dosage per day	1096 mcg	200 mcg	200 mcg

As illustrated in the table above, to combine azelastine and fluticasone into a fixed-dose nasal spray required altering the FDA-approved quantity of azelastine, fluticasone, or both. Altering the quantities of azelastine and fluticasone known to be safe and effective would require time-consuming and expensive testing of safety and efficacy. As shown below, given the irreconcilable dosing schedules for

azelastine and fluticasone, any combination of one of the drug's dosing schedules would result in either more fluticasone than was known to be safe in the art, or less azelastine that was known to be effective.

	Azelastine	Fluticasone	Problem
Option 1: Two sprays per nostril, twice a day	1096 mcg per day	**400** mcg per day	400 mcg fluticasone not shown to be safe
Option 2: Two sprays per nostril, once a day	**548** mcg per day	200 mcg per day	548 mcg azelastine not shown to be therapeutically effective

2. *The POSA Would Not Have Had a Reasonable Expectation of Success*

The prior art did not provide the POSA with a reasonable expectation of success in creating a fixed-dose combination nasal spray containing azelastine and fluticasone. As the Examiner recognized during prosecution, the prior art did not include any working examples of a nasal spray that combined two different therapeutically active pharmaceutical ingredients. *See generally* Sections III.A, B, C, D. The specific combination here required the POSA to combine azelastine—a product traditionally formulated as a solution—with fluticasone—a product traditionally formulated as a suspension. The prior art provided no guidance as to of how to formulate a nasal spray in which one active ingredient remained in solution and another active ingredient remained in suspension. Formulations concerns aside, the POSA would not have had any expectation that fluticasone and

azelastine could be used in the same nasal spray formulation without deleterious effects on the efficacy, safety, or both, of either fluticasone or azelastine, further diminishing any reasonable prospect that this previously-unknown combination of medication would succeed.

VII. SECONDARY CONSIDERATIONS SUPPORT NON-OBVIOUSNESS

For at least the reasons set forth above, Petitioner has not established a reasonable likelihood of a *prima facie* case of obviousness. At a minimum, however, objective indicia of nonobviousness rebut any *prima facie* case. In fact, during the '585 patent's, and the earlier '620 patent's, prosecution, the Examiner correctly found that the claimed invention was a commercial success, satisfied a long-felt need and exhibited unexpected results, leading to his conclusion that the invention here was "unexpectedly and surprisingly unobvious over, different from, and superior to the prior art of record." *See* Sections III.A and D, Ex. 2001, 198; Exs. 1006, 1007, 1008.[5]

A. The Claimed Invention Exhibits Unexpected Results.

As explained above, the invention exhibits unexpected results. *See* Sections III.A, B, C, D, *supra*. Prior to the invention, studies found no clinical benefit to the co-administration of a steroid and an antihistamine. Exs. 1034, 1036, 1039, 1040.

[5] The Petition presents no argument that there is not a nexus between the claimed invention and any secondary consideration.

Dymista nevertheless exhibits a surprising significant and clinically relevant improvement over both of its constituent active ingredients. Ex. 2023.

B. Others Failed to Develop the Claimed Invention.

"[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. 2003). Here, before learning of Cipla's patent, Meda attempted to formulate an azelastine/fluticasone combination formulation but failed in its efforts. Ex. 2037, ¶¶78-82; Ex. 2038, ¶¶18-27; Ex. 2039. Two other sophisticated pharmaceutical companies—Procter & Gamble and Warner-Lambert—filed, and later abandoned, patent applications—Cramer and Segal—disclosing combination formulations for the treatment of AR, strongly suggesting they too failed to develop a combination product. In addition, CyDex was investigating a product containing azelastine in combination with the steroid budesonide. Ex. 2034, 215-16. Yet this product likewise has not reached the market. The failure of these companies supports the non-obviousness of the challenged claims. *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]"); *Knoll Pharm. Co. v. Teva Pharm. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004).

C. Meda Licensed the Challenged Patents.

After failing to develop its own formulation, Meda took a royalty-bearing license to the Dymista Patents. Ex. 2038, ¶¶26-28[6]; Ex. 2028; Ex. 2029. That Meda was unable to make its own formulation and decided to take a license from Cipla, despite the costs, further evidences the non-obviousness of the Dymista Patents.

D. The Prior Art Was Skeptical of the Claimed Invention.

Dymista was subject to skepticism before it was ever released. 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 and Flonase, and (3) the lack of guidance in the art in 2002 about combining solution and suspension formulations. Ex. 2038, ¶¶11-15; Ex. 2037, ¶75; Ex. 2031, 11; Ex. 2032, 11. In fact, Meda was so skeptical in 2002 that it pursued other research avenues, like dual-chamber devices. Ex.

[6] Mr. D'Addio submitted a declaration for the Argentum IPR. Ex. 2038. Mr. D'Addio's declaration is not one "prepared for this proceeding." 37 C.F.R. 42.51(b)(1)(ii); *Mexichem Amanco Holdings S.A. de C.V. v. Honeywell Int'l, Inc*., IPR2013–00576, 2014 WL 3977112 (PTAB Aug. 15, 2014) ("[I]f the declaration was not prepared for purposes of the instant i*nter partes* review—such as preexisting documentary evidence filed previously in another proceeding—cross-examination of the witness would not be provided as routine discovery."). Similarly, Mr. Jarosz's declaration (Ex. 2035) and the declarations of Dr. Carr (Ex. 2036) and Dr. Smyth (Ex. 2037) were likewise not prepared for this proceeding.

2038, ¶16. In 2006 after Meda found Cipla's Duonase product, Meda was surprised that anyone had successfully overcome Meda's anticipated incompatibilities. *Id.* ¶26.

Others in the art shared Meda's skepticism. Before 2002, experts in the field of AR had concluded that the addition of an antihistamine to a corticosteroid yielded no benefit over the corticosteroid alone. Ex. 1037, Ex. 1042. In 2003, experts stated that the conjunctive use of antihistamines and corticosteroids "offer[s] no or a marginal clinical benefit compared with intranasal corticosteroids alone." Ex. 1029, 10. In 2005, another expert in the field stated that the use of antihistamines and corticosteroids together "is not supported by controlled clinical trials." Ex. 2018, 17. In 2006, others determined that adding an antihistamine to corticosteroid therapy was "inappropriate." Ex. 2024, 1, 5, 8.

E. Embodiments of the Claimed Invention Were Commercially Successful.

When a patent owner 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 is a commercial success in the U.S. and Cipla's Duonase and the Duonase copycats are commercial successes in India. *See generally* Ex. 2035. Indeed, in allowing the

patents to issue, the Examiner found commercial success (*see* Sections III.A, B, C, D, *supra*), an issue left unaddressed and unchallenged in the Petition.

F. The Invention Satisfied a Long-Felt But Unmet Need for Better AR Treatment.

Dymista satisfied the long-felt needs for more effective, faster, and safer AR treatments.

More Effective. There was a long-felt but unmet need for a more effective treatment for AR. Ex. 1034; Ex. 1036; Ex. 1039; Ex. 1040. Studies of the conjunctive use of two or more treatments for AR, beginning in the mid-1980s and continuing through the date of invention, confirm that physicians saw a need for a more effective AR treatment. Ex. 1034; Ex. 1036; Ex. 1039; Ex. 1040; Ex. 2009. Dymista satisfied that need. The *Journal of Allergy and Clinical Immunology*, the leading journal in the field of AR, published an article, "*[Dymista]: A major advancement in the treatment of allergic rhinitis*," which found that Dymista "is significantly more effective than intranasal fluticasone," such that Dymista "can be considered the drug of choice for the treatment of AR." Ex. 1052.

Faster-Acting: There was also a need for a faster-acting treatment. Again, steroids were the most effective treatment, but they had a slow onset. Ex. 2009, 101; Ex. 1019, 29. Antihistamines had a delayed onset of action on the order of hours. Ex. 1041, 6. Faster-acting drugs, such as intranasal decongestants, had an onset of 10 minutes, but only worked on one symptom. Ex. 1024, 98. It was,

therefore, important to obtain a medication with a rapid onset that worked on all symptoms. Ex. 2036, ¶131. Dymista is that drug; it has an FDA-approved onset of action of 30 minutes, meets the need for faster onset than was available from the drugs known at the time of invention. Ex. 2036, ¶132.

Safer: 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. Ex. 1024, 82, 84-85, 92; Ex. 2036, ¶¶134-136. 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. Ex. 1045, 5; Ex. 2036, ¶137. Dymista inexplicably exhibits reduced side-effects as compared to either of its components administered as 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. Ex. 3. Meanwhile, fluticasone at the dose used in Dymista caused headache in 16.1% of patients, pharyngitis in 7.8% of patients, and epistaxis in 6.9% of patients. Ex. 1010, 9. Dymista, by contrast, exhibits bitter taste in only 4% of patients, while only 2% of patients experience headache or epixtaxis. Ex 2006, 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. Ex. 2036, ¶138.

G. The Invention Was Widely Copied.

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, LLC v. Kohler Co*., 829 F.3d 1317, 1336 (Fed. Cir. 2016) (citation omitted). In the U.S., Apotex sought to market a generic version of Dymista, and stipulated to the infringement of many of the challenged claims. Ex. 2025, 3, 5. Apotex's efforts are noteworthy because Apotex already markets a generic version of Astelin (Ex. 2004, 4) and a generic version of Flonase (Ex. 2004, 20), suggesting that Apotex views their combination into a single product to be competitively advantageous. In India, Duonase was subject to copying after only two years of market success. Ex. 2001, 328-334.

H. Industry Leaders Praised the Invention.

Praise by others in the industry can also be an important secondary indicia of non-obviousness. *WBIP*, 829 F.3d at 1334; *Lassen Therapeutics 1, Inc. v. Singapore Health Servs. PTE Ltd*., PGR2019-00053, 2020 WL 603883, at *15 (PTAB Feb. 6, 2020). After reviewing the clinical data used by FDA to approve Dymista, the editors of the world's leading allergy journal declared that Dymista "can be considered the drug of choice for the treatment of AR." Ex. 1052, 1. Those

same editors also declared that "[t]he improvement of [Dymista] 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]-treated patients exhibiting complete/near-complete symptom resolution." Ex. 1052, 1. Likewise, in September of 2015, a market report published by IMS—a leading clinical market analysis entity—declared that Dymista's strengths included a "[d]emonstrated superior efficacy in clinical trials compared with azelastine, fluticasone, and placebo," a rapid onset on the order of minutes, and "[g]ood safety and tolerability." Ex. 2026, 133. It also declared Dymista the "*gold standard* of AR therapy." *Id.* (emphasis added). The IMS report also predicted that Dymista 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.

I. The Board Should Not Institute Because Petitioner Ignored Objective Evidence Credited in the Prosecution History.

Consistent with the above, during prosecution, Patent Owner presented evidence of (1) unexpected results with the Maus Declaration, Ex. 2001, 358-457; (2) long-felt but unsolved need with the Rajan Declaration, *id.*, 458-77; and (3) commercial success and long-felt but unsolved need with the Chopra Declaration,

id., 328-57.[7] The Examiner carefully considered and credited each of these declarations, finding that they support the patentability of the claimed invention. Ex. 2001, 192-99; Ex. 1006, 22; Ex. 1007, 38-40; Ex. 1008, 39-42; *see also* Sections III.A, B, C, D, *infra*. Yet, Petitioner did not address the evidence presented to, and credited by, the Examiner during prosecution.[8] Petitioner failed to do so, even though the Board has "cautioned petitioners in prior proceedings that known evidence of secondary considerations should be addressed in the petition." *Robert Bosch Tool Corp. v. SD3, LLC*, IPR2016-01751, 2017 WL 1096609, at *10 (PTAB Mar. 22, 2017).

The Board has previously denied institution where petitioner fails to address secondary considerations in a petition, just as Petitioner did here. *Coalition for*

[7] Cipla also submitted evidence of commercial success and other secondary indicia in the Argentum IPR, Ex. 1046; Exs. 2035-2038. While not considered by the Examiner during the original prosecution, that evidence is nonetheless part of the prosecution record for the '585 patent, *see* Section III.E, *supra*. *Aylus Networks, Inc. v. Apple Inc*., 856 F.3d 1353, 1361 (Fed. Cir. 2017) (finding that the IPR record constitutes part of the intrinsic record); *Anglefix, LLC v. Wright Med. Tech., Inc*., No. 13-2407, 2015 WL 9581865, at *7 (W.D. Tenn. Dec. 30, 2015) (prosecution history includes IPR proceedings); *Signal IP, Inc. v. Fiat U.S.A., Inc*., No. 14-13864, 2016 WL 5027595, at *16 (E.D. Mich. Sept. 20, 2016) (same).

[8] The Petition includes one conclusory sentence contending that there was not a long-felt but unmet need. Pet. 66. That single sentence improperly incorporates evidence from the Petitioner's declarants that should not be considered in determining whether to institute review. *See* Section II.B. Petitioner's only effort to address the Maus Declaration is to suggest that Cipla was required to compare its invention of a nasal spray combining azelastine and fluticasone with a nasal spray combining azelastine and fluticasone—the very subject matter of the claims. Pet. 64-65.

Affordable Drugs V LLC v. Hoffman-LaRoche, Inc., IPR2015-01792, 2016 WL 1081666 (PTAB Mar. 11, 2016) (denying institution for failure to address objective indicia considered by examiner during original prosecution); *Merial Ltd. v. Virbac*, IPR2014-01279, 2015 WL 331290 (PTAB, Jan. 22, 2015) (denying institution for failure to address objective indicia considered by Examiner during original prosecution and noting "[petitioner] was aware of the unexpected results showing which the Examiner found persuasive…[petitioner] should have addressed unexpected results in the first instance."); *Omron Oilfield & Marine Inc. v. MD/TOTCO*, IPR2013-00265, 2013 WL 8595961 (PTAB Oct. 31, 2013) (denying institution for failure to address objective indicia successfully argued in a reexamination). Petitioner should likewise be denied, particularly where Petitioner merely rehashes prior art and arguments overcome during the original prosecution.

VIII. CONCLUSION

For at least the reasons set forth above, Patent Owner respectfully requests that this Petition not be instituted.

Dated: May 5, 2020

Respectfully submitted,

/s/ Brandon M. White
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Counsel for Cipla Ltd.

CERTIFICATE OF COMPLIANCE WITH WORD COUNT

Pursuant to 37 C.F.R. § 42.24(d), the undersigned certifies that this *Patent Owner Preliminary Response* complies with the type-volume limits of 37 C.F.R. § 42.24(b)(1), because it contains **13,727** words, according to the word-processing system used to prepare this Preliminary Response, excluding the words in the Table of Contents, Table of Authorities, List of Exhibits, Mandatory Notices, Certification Under § 42.24(d), and Certificate of Service, as set forth in 37 C.F.R. § 42.24(a)(1). 179 words were added to the word count generated by the word-processing system for the images in Section VI.

Date: May 5, 2020

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Counsel for Cipla Ltd.

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6, I hereby certify that the foregoing Patent Owner Preliminary Response was served on May 5, 2020, by filing this document through the Patent Trial and Appeal Board End-to-End System, as well as delivering a copy via electronic mail upon the following attorneys of record for the Petitioner:

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