

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ARGENTUM PHARMACEUTICALS LLC,
Petitioner,

v.

CIPLA LTD.,
Patent Owner.

Case IPR2017-00807
Patent 8,168,620 B2

Before BRIAN P. MURPHY, ZHENYU YANG, and
KRISTI L. R. SAWERT, *Administrative Patent Judges*.

SAWERT, *Administrative Patent Judge*.

DECISION
Institution of *Inter Partes* Review
37 C.F.R. § 42.108

I. INTRODUCTION

Argentum Pharmaceuticals LLC (“Petitioner”) filed a Petition for an *inter partes* review of claims 1, 4–6, 24–26, 29, and 42–44 of U.S. Patent No. 8,168,620 B2 (“the ’620 patent,” Ex. 1001). Paper 2 (“Pet.”). Cipla Ltd. (“Patent Owner”) timely filed a Preliminary Response. Paper 7 (“Prelim. Resp.”).

Institution of an *inter partes* review is authorized by statute when “the information presented in the petition . . . and any response . . . shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition.” 35 U.S.C. § 314(a); *see also* 37 C.F.R. §§ 42.4, 42.108.

For the reasons provided below, we determine that Petitioner has satisfied the threshold requirement set forth in 35 U.S.C. § 314(a) as to claims 1, 4–6, 24–26, 29, and 42–44 of the ’620 patent, and we institute an *inter partes* review of those claims.

A. Related Proceedings

The parties identify the following district court actions as related matters under 37 C.F.R. § 42.8(b)(2): *Meda Pharms. Inc. v. Apotex Inc.*, 14-cv-01453 (D. Del.); *Meda Pharms. Inc. v. Teva Pharms.*, 15-cv-00785 (D. Del.); *Meda Pharms. Inc. v. Perrigo UK Finco Ltd.*, 16-cv-00794 (D. Del.). Pet. 1; Paper 9, 1. Patent Owner also identifies U.S. Patent Application Nos. 15/070,839 and 13/284,836 as claiming or potentially claiming priority to the ’620 patent. Paper 4, 1; Paper 9, 1.

B. Real Parties-in-Interest

Petitioner identifies Argentum Pharmaceuticals LLC, Intelligent Pharma Research LLC, APS GP LLC, APS GP Investors LLC, and KVK-TECH, Inc. as real parties-in-interest under 37 C.F.R. § 42.8(b)(1). Pet. 1. Patent Owner identifies Cipla Limited, Meda Pharmaceuticals Inc., Meda AB, Mylan N.V., Mylan Inc., Mylan Pharmaceuticals, Inc., and Mylan Specialty L.P. as real parties-in-interest under 37 C.F.R. § 42.8(b)(1). Paper 9, 1.

C. The '620 Patent

The '620 patent discloses and claims pharmaceutical compositions comprising azelastine (or its pharmaceutically acceptable salt) and fluticasone (or its pharmaceutically acceptable ester) in a dosage form suitable for nasal administration. *See generally* Ex. 1001. The '620 patent teaches that azelastine is an antihistamine useful for treating 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” *Id.* at 1:21–24. The '620 patent also teaches that it was known in the art to treat allergic rhinitis with corticosteroids, “which will suppress nasal and ocular inflammatory conditions.” *Id.* at 1:26–28. The '620 patent lists fluticasone as a corticosteroid “known for nasal use.” *Id.* at 1:28–30.

“It would be highly desirable, however,” the '620 patent continues, “to provide a treatment that combines the effects of anti-histamine treatments and steroid treatments, in a pharmaceutically acceptable formulation.” *Id.* at 1:34–36. The '620 patent teaches that these

formulations should be “tolerated in situ, without significantly disrupting the potency of the constituent pharmaceuticals.” *Id.* at 1:37–38. The ’620 patent then states that the inventors “found that, very surprisingly, azelastine . . . can advantageously be combined with a steroid . . . to provide a stable, very effective combination product or formulation” for nasal treatment. *Id.* at 1:39–48. The combination of azelastine and a steroid such as fluticasone, the ’620 patent explains, “can provide, in a single administration or dosing regime, the antihistaminic properties of azelastine and the anti-inflammatory (and/or other) properties of the steroid, without any significant interference between the two, or adverse reaction in situ.” *Id.* at 1:48–53.

The ’620 patent teaches that the disclosed pharmaceutical compositions are preferably in the form of nasal drops, eye drops, nasal sprays, nasal inhalation solutions, aerosols, or insufflation powders. *Id.* at 2:14–16. Of these, the ’620 patent states that a nasal spray is a particularly preferred form. *Id.* at 2:23–25. The ’620 patent also teaches that the formulations may contain pharmaceutically acceptable excipients, such as preservatives, stabilizers, auxiliary substances, isotonic agents, thickening agents, and buffers. *Id.* at 2:31–4:3.

D. Challenged Claims

Petitioner challenges claims 1, 4–6, 24–26, 29, and 42–44 of the '620 patent. Pet. 2. Claims 1 and 25 are independent and illustrative of the claimed subject matter:

1. A pharmaceutical formulation comprising:
azelastine, or a pharmaceutically acceptable salt thereof,
and
a pharmaceutically acceptable ester of fluticasone,
wherein said pharmaceutical formulation is in a dosage form suitable
for nasal administration.
25. A nasal spray formulation comprising (i) azelastine, or a
pharmaceutically acceptable salt thereof, (ii) a pharmaceutically
acceptable ester of fluticasone, and (iii) a pharmaceutically acceptable
carrier or excipient therefor.

Ex. 1001, 11:46–51, 13:24–27.

E. The Asserted Grounds of Unpatentability

Petitioner challenges the patentability of claims 1, 4–6, 24–26, 29, and 42–44 of the '620 patent on the following grounds:

Claims	Basis	Reference(s)
1 and 25	Anticipation under 35 U.S.C. § 102(b)	Segal ¹
1, 4–6, 24–26, and 29	Obviousness under 35 U.S.C. § 103	Hettche, ² Phillipps, ³ and Segal
42–44	Obviousness under 35 U.S.C. § 103	Hettche, Phillipps, Segal, and Flonase Label ⁴

Pet. 2. Petitioner also relies on the Declarations of Robert P. Schleimer, Ph.D. (Ex. 1003), and of Maureen D. Donovan, Ph.D. (Ex. 1004). Patent Owner disputes Petitioner's asserted grounds. *See generally* Prelim. Resp. Patent Owner relies on the Declarations of Warner Carr, M.D. (Ex. 2001), Alexander Dominic D'Addio, Ph.D. (Ex. 2003), John C. Jarosz (Ex. 2005), and Hugh David Charles Smyth, Ph.D. (Ex. 2007).

¹ Catherine A. Segal, Int'l Publication No. WO 98/48839 (Nov. 5, 1998) ("Segal"). Ex. 1012.

² Helmut Hettche, U.S. Patent No. 5,164,194 (Nov. 17, 1992) ("Hettche"). Ex. 1007.

³ Gordon H. Phillipps, et al., U.S. Patent No. 4,335,121 (Jun. 15, 1982) ("Phillipps"). Ex. 1009.

⁴ FLONASE® (fluticasone propionate) Nasal Spray, 50 mcg Product Information (Dec. 1998) ("Flonase Label"). Ex. 1010.

II. ANALYSIS

A. Broadest Reasonable Interpretation

At this stage of the proceeding, and based on the record before us, we determine that no claim terms require express interpretation for purposes of this Decision. *See Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) (only those claim terms that are in controversy need to be construed, and only to the extent necessary to resolve the controversy).

B. Priority Date of the '620 Patent

Before turning to the asserted grounds of unpatentability, we briefly dispose of Petitioner's argument that the '620 patent is not entitled to priority to foreign application GB 0213739.6 ("the GB application"). *See* Pet. 8–10 (citing Ex. 1006). Although Petitioner correctly notes that we do not presume the '620 patent is entitled to the priority date of the GB application, Pet. 9, we find Petitioner's priority challenge legally irrelevant to this proceeding.

The '620 patent claims priority pursuant to 35 U.S.C. § 119 to the GB application, which was filed on June 14, 2002. *See* Ex. 1001, [30]. Petitioner argues that the '620 patent is not entitled to that 2002 priority date because the GB application fails to provide adequate written description for a "pharmaceutically acceptable ester of fluticasone," as recited in, e.g., claim 1 of the '620 patent. Pet. 9–10.

We find it unnecessary to determine whether the '620 patent is entitled to the foreign priority date of the GB application, because every reference Petitioner relies upon to allege unpatentability in the Petition—

Segal, Hettche, Phillipps, and the Flonase Label—has an undisputed publication date well before June 14, 2002. Pet. 8; *see also* Exs. 1007, 1009, 1010,⁵ 1012. Thus, regardless of whether the '620 patent is entitled to the 2002 foreign-priority date, Segal, Hettche, Phillipps, and the Flonase Label all qualify as prior art under 35 U.S.C. § 102(b) (pre-AIA). Pet. 8. Finally, because the priority date of the '620 patent is not relevant to the grounds instituted herein, we do not consider this issue “preserved” for trial, as Petitioner contends. *See* Pet. 8.

C. Alleged Anticipation by Segal

Petitioner contends that claims 1 and 25 are unpatentable as anticipated by Segal. Pet. 2. Relying on Dr. Schleimer's and Dr. Donovan's Declarations, Petitioner asserts that Segal teaches each and every limitation of claims 1 and 25. *See* Pet. 16–21 (citing Ex. 1003; Ex. 1004).

Patent Owner argues that we should invoke our discretion under 35 U.S.C. § 325(d) and deny the anticipation challenge over Segal, because Petitioner presents “the same arguments on substantially the same prior art” raised during prosecution. Prelim. Resp. 12–15. We decline to exercise our discretion under § 325(d). But we find that, on the merits, Petitioner fails to show a reasonable likelihood that it would prevail in its anticipation challenge to claims 1 and 25 by Segal.

⁵ Page 9 of the Flonase Label is marked “December 1998.” Patent Owner does not dispute that the Flonase Label constitutes prior art under § 102(b). *See, e.g.*, Prelim. Resp. 42.

1. Overview of Segal

Segal, titled “Topical Nasal Antiinflammatory Compositions,” “provides 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.” Ex. 1012 (Abstract). Segal teaches that the disclosed compositions are “useful as nasal sprays and nose drops for the treatment of nasal and sinus conditions,” such as allergic rhinitis and the common cold. *Id.*; *see also id.* at 2:20–21.

Segal states that the anti-inflammatory agent is a corticosteroid that is known in the art to suppress inflammation. *Id.* at 2:22–23. Segal lists beclomethasone dipropionate [sic], budesonide, dexamethasone, mometasone furoate, fluticasone propionate [sic], and triamcinolone acetone as preferred anti-inflammatory agents. *Id.* at 2:23–26. 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, nedocromil, and 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 3:3–25. Segal states that the use of the additional therapeutic agent with a corticosteroid “provides additive and synergistic effects in the treatment of nasal and sinus conditions.” *Id.* at 3:9–12.

Segal teaches that the disclosed compositions “are formulated as aqueous solutions comprising an antiinflammatory agent and at least one additional therapeutic agent and further comprising a pharmaceutically acceptable nasal carrier.” *Id.* at 3:29–31. Segal states that nose drops and nasal sprays containing a water-buffered aqueous solution as a carrier are preferred formulations. *Id.* at 4:4–5. Segal also teaches that the formulations may contain pharmaceutically acceptable preservatives, stabilizers, flavoring agents, and pH adjusters, or may be preservative free. *Id.* at 4:12–19.

2. Analysis

Petitioner contends that Segal anticipates claims 1 and 25 of the ’620 patent. Pet. 16–21. As to claim 1, Petitioner states that Segal “discloses a nasal formulation having both a topical anti-inflammatory and an antihistamine,” *id.* at 17 (citing Ex. 1012, 2:10–15, 5 (claim 1); Ex. 1003 ¶ 32), with “fluticasone propionate as a preferred embodiment of the topical anti-inflammatory agent, along with azelastine as a suitable antihistamine,” *id.* (citing Ex. 1012, 2:23–26, 3:19–20, 5 (claims 1, 2, 4); Ex. 1003 ¶¶ 33–34, 37–38). As to claim 25, Petitioner states that Segal “teach[es] a formulation containing a ‘water buffered aqueous solution as a carrier,’ which is a pharmaceutically acceptable carrier or excipient.” *Id.* (citing Ex. 1012, 4:4–5; Ex. 1004 [sic, 1003] ¶ 39).

A claim is anticipated and therefore unpatentable under 35 U.S.C. § 102, if all its limitations are disclosed either explicitly or inherently in a single prior art reference. *In re Schreiber*, 128 F.3d 1473, 1477 (Fed. Cir. 1997). That single prior art reference must disclose all of the limitations of the claim “arranged or combined in the same way as in the claim.” *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1370 (Fed. Cir. 2008). Moreover, “[a]n anticipating reference must be enabling; that is, the description must be such that a person of ordinary skill in the field of the invention can practice the subject matter based on the reference, without undue experimentation.” *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1082 (Fed. Cir. 2008).

Having reviewed the record, we determine that Petitioner has not shown a reasonable likelihood of prevailing in its assertion that claims 1 and 25 of the ’620 patent are anticipated by Segal. Specifically, we find that Petitioner has not shown sufficiently that an ordinarily skilled artisan would immediately envision from Segal’s disclosure the combination of fluticasone and azelastine as recited in claims 1 and 25 of the ’620 patent. When the allegedly anticipatory disclosure is found in separate lists, as here, “[t]he question for purposes of anticipation is . . . whether the number of categories and components in [the single prior-art reference is] so large that the combination of [one item from each list] would not be immediately apparent to one of ordinary skill in the art.” *Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC*, 683 F.3d 1356, 1361 (Fed. Cir. 2012).

As the anti-inflammatory agent, Segal lists six preferred corticosteroids: beclomethasone dipropionate, budesonide, dexamethasone,

mometasone furoate, fluticasone propionate, and triamcinolone acetonide. *Id.* at 2:23–26, 5 (claim 2). Thus, fluticasone propionate, a pharmaceutically acceptable ester of fluticasone, is one of six possibilities for the anti-inflammatory agent. *Id.* As the “at least one additional therapeutic agent,” Segal lists eight preferred classes of compounds: a vasoconstrictor, a neuraminidase inhibitor, a leukotriene inhibitor, an antihistamine, an antiallergic agent, an anticholinergic agent, an anesthetic, and a mucolytic agent. *Id.* at 3:3–9, 5 (claim 1). And for each class of compounds, Segal lists 1 to 9 preferred examples: four vasoconstrictors, three leukotriene inhibitors, one neuraminidase inhibitor, nine antihistamines, three antiallergic agents, one anticholinergic agent, three anesthetics, and three mucolytic agents. *Id.* at 3:13–25, 5–6 (claims 2–10); *see also* Ex. 2001 ¶ 80.⁶ Thus, Segal lists 27 preferred therapeutic agents. Ex. 2001 ¶ 80. For antihistamines in particular, Segal lists: diphenhydramine, chlorpheniramine, cetirizine, terfenadine, fenofexadine, astemizole, norastemizole, azelastine, and azatidine. *Id.* at 3:19–20, 5 (claim 4).

As to the number of categories and components disclosed in Segal, Petitioner argues that “Segal discloses at most 54 discrete compositions, of which the combination of fluticasone propionate [sic] and azelastine is

⁶ Some compounds in Segal’s lists are not properly separated by commas. For example, in the listing of suitable vasoconstrictors, Segal lacks a comma between “oxymetazoline” and “naphazoline,” which implies that “oxymetazoline naphazoline” is a single compound. We credit Dr. Carr’s undisputed testimony that “oxymetazoline” and “naphazoline” are, in fact, two separate compounds. *See* Ex. 2001 ¶ 80. Our understanding is also supported by claim 3 of Segal, where “oxymetazoline” and “naphazoline” are separated by a comma. Ex. 1012, 5 (claim 4).

one.” Pet. 19. Petitioner arrives at this number by “taking claims 1, 2 and 4 together.” *Id.* Specifically, Petitioner asserts that claim 1 of Segal limits the pharmaceutical composition to a topical anti-inflammatory agent and “one of seven types of therapeutic agents, of which an antihistamine is one.” *Id.* at 18. Petitioner further asserts that claim 2 “limits the anti-inflammatory agent to six compounds, of which fluticasone propionate [sic] is one” and that “claim 4 limits the antihistamine to one of nine compounds, of which azelastine is one.” *Id.* at 18–19. Petitioner then calculates “54 discrete components” by multiplying the number of anti-inflammatory agents in claim 2 by the number of antihistamines in claim 4 (i.e., $6 \times 9 = 54$).

The fault in Petitioner’s analysis, however, is that claim 4 of Segal does not depend from claim 2. Put differently, Petitioner arrives at the “54 discrete components” number by improperly reading claim 4 as dependent upon claim 2, when, in fact, claim 4 depends from claim 1. Ex. 1012, 5 (claims 2, 4). Contrary to Petitioner’s arguments, therefore, Segal does not limit the number of possible combinations of an anti-inflammatory agent and at least one therapeutic agent to 54 possibilities. Instead, as Patent Owner explains, Segal teaches the combination of an anti-inflammatory agent and “at least one” additional therapeutic agent, Ex. 1012, 2:12, 2:19, 3:3, 3:5, 3:30, 4:16, 5 (claim 1), and thus, literally discloses more than 800 million combinations within its broad genus, Prelim. Resp. 21 & n.4 (citing Ex. 2001 ¶¶ 79–81). We find that Petitioner has failed to show with persuasive evidence or reasoning that an ordinarily skilled artisan would immediately envision the combination of fluticasone and azelastine from the broad genus disclosed in Segal.

Thus, for the reasons explained above, we determine that the present record, including the information presented in the Petition and supporting evidence, does not establish a reasonable likelihood that Petitioner would prevail in showing that claims 1 and 25 of the '620 are unpatentable under 35 U.S.C. § 102(b) as anticipated by Segal.

D. Obviousness over Hettche, Phillipps, and Segal

Petitioner contends that claims 1, 4–6, 24–26, and 29 are unpatentable as obvious over Hettche, Phillipps, and Segal. Pet. 2. Relying on the Declarations of Drs. Schleimer and Donovan, Petitioner explains how the references teach or suggest the claim limitations and provides reasoning for combining the references. *See* Pet. 21–43 (citing Ex. 1003; Ex. 1004).

1. Overview of Hettche

Hettche, titled “Azelastine Containing Medicaments,” teaches a “medicament for nasal use . . . which contains as [an] active ingredient azelastine or a physiologically acceptable salt.” Ex. 1007 (Abstract). Hettche teaches that azelastine “is used in particular for prophylactic treatment of asthma” and has “anti-allergic and antihistamine properties.” *Id.* at 1:28–30.

Hettche teaches that the disclosed pharmaceutical compositions are preferably formulated as solutions in water or mixtures of water with other physiologically acceptable solvents, and preferably in the form of a nasal spray. *Id.* at 2:12–17 & 41–43. Hettche states that the formulations contain 0.0005 to 2% of azelastine. *Id.* at 3:26–31. Hettche also teaches that the formulations may contain preservatives, stabilizers, auxiliary substances,

isotonization agents, thickening agents, buffers, and carrier substances. *Id.* at 2:46–5:68.

2. *Overview of Phillipps*

Phillipps, titled “Androstane Carbothioates,” discloses a genus of androstane compounds and claims S-fluoromethyl 6 α , 9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -propionyloxyandrosta-1,4-diene-17 β -carbothioate (i.e., fluticasone propionate).⁷ Ex. 1009, 36:7–10 (claim 13). Phillipps teaches that the disclosed androstane compounds are useful as pharmaceutical compositions for anti-inflammatory therapy, and may be formulated with one or more pharmaceutical carriers or excipients. *Id.* at 32:46–50. Phillipps states that the pharmaceutical compositions may be formulated as topical sprays for the nose. *Id.* at 32:57–60. Such spray compositions, Phillipps teaches, “may for example be formulated as aqueous solutions or suspensions.” *Id.* at 33:12–14. Phillips also teaches that “formulations for administration by inhalation or insufflation are intended for administration on a prophylactic basis to humans suffering from allergic and/or inflammatory conditions of the nose, throat or lungs such as asthma and rhinitis, including hay fever.” *Id.* at 33:40–44.

3. *Analysis*

Petitioner has shown sufficiently for the purpose of institution that the combination of Hettche, Phillips, and Segal discloses each and every limitation of claims 1, 4–6, 24–26, and 29. *See* Pet. 26–33 (citing Exs. 1007,

⁷ S-fluoromethyl 6 α , 9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -propionyloxyandrosta-1,4-diene-17 β -carbothioate is the chemical name for fluticasone propionate. Ex. 1010, 1.

1009, 1012). Specifically, we have reviewed Petitioner’s claim chart and find that sufficient evidence supports Petitioner’s contention that the cited references collectively disclose the limitations of the challenged claims. *Id.* We also note that, in its Preliminary Response, Patent Owner does not identify any particular claim limitation as not disclosed in the prior art. *See generally* Prelim. Resp. 27–42 (Patent Owner’s response to obviousness ground over Hettche, Phillipps, and Segal).

We also find that Petitioner has shown sufficiently for the purpose of institution that an ordinarily skilled artisan would have been motivated to combine the disclosures of Hettche, Phillips, and Segal to provide an improved treatment for allergic rhinitis (“AR”) using a nasal dosage formulation of azelastine and fluticasone. *See* Pet. 33–39 (discussing reasons to select azelastine and fluticasone and to combine these compounds into a single nasal product).

For example, Petitioner contends that the ordinarily skilled artisan would have had a reason to attempt a combination drug formulation comprising a nasal corticosteroid and an antihistamine based upon the prior clinical use of these compounds together for treating AR. Pet. 35–36 (citing Ex. 1019, 505 (stating that intranasal antihistamines “are appropriate for use as first line treatment for the symptoms of allergic rhinitis, or as part of combination therapy with nasal corticosteroids or oral antihistamines”), Ex. 1021, 536 (stating that “for those patients whose symptoms [of AR] are not adequately controlled by either treatment often a combination of both an antihistamine with an intranasal corticosteroid is prescribed”); Ex. 1022, 125 (stating that “a combination of nasal steroids and antihistamines (oral and/or

topical) is recommended” for treatment of patients with severe seasonal AR)).

Petitioner also contends that an ordinarily skilled artisan would have had a reason to select azelastine as an antihistamine, due to its alleged superior qualities over other known antihistamines. *See* Pet. 33–34 (citing Ex. 1003 ¶¶ 63–67; Ex. 1015, 387, 391–92; Ex. 1016, Fig. 2, 99–100; Ex. 1007, 1:44–48 & 53–55, 1:63–2:2; Ex. 1050, 823–24). And Petitioner contends that an ordinarily skilled artisan would have had a reason to select fluticasone as the corticosteroid, in part because it was known as the “most potent FDA-approved corticosteroid available.” *Id.* at 34 (citing Ex. 1017, 623; Ex. 1018, S434; Ex. 1003 ¶¶ 59, 61).

Petitioner also asserts that a skilled artisan “would have wanted to take advantage of the known complementary mechanisms of action of azelastine and fluticasone” in creating a combined drug formulation. *Id.* at 36–37 (citing Ex. 1011, 2:25–27; Ex. 1021, 535; Ex. 1023, S386–87; Ex. 1024, S226, S230–32; Ex. 1003 ¶¶ 53–55, 57–58, 70, 78–79). Petitioner contends that “[t]aking advantage of complementarity of mechanisms of action of two therapeutics was a known technique in the art,” and specifically points to the combination drug product Advair® (fluticasone propionate and salmeterol) as evincing this motivation. *Id.* at 37–38 (Ex. 1020, 223; Ex. 1025, 1213; Ex. 1003 ¶¶ 52, 58, 73, 83–84). In addition, Petitioner points out that it was well known in the art to combine drugs into a single nasal spray to improve patient compliance. *Id.* at 38–39 (citing Ex. 1012, 1:15–20, 2:2–3, 3:3–9; Ex. 1020, 224; Ex. 1003 ¶¶ 80, 82).

Patent Owner disputes Petitioner's assertion that an ordinarily skilled artisan would have been motivated to combine the teachings of Hettche, Phillipps, and Segal to create a combination drug formulation comprising azelastine and fluticasone. *See* Prelim. Resp. 27–42. First, Patent Owner contends that the clinical art, and the art as a whole, taught away from co-administration of an antihistamine and a steroid. *Id.* at 27–38. Second, Patent Owner contends that the ordinarily skilled artisan would not have had a reasonable expectation of success in formulating a combination drug for nasal administration. *Id.* at 38–42.

As part of its teaching-away argument, Patent Owner points out that before the earliest-possible filing date of the '620 patent, several clinical studies showed that antihistamines and corticosteroids had redundant mechanisms of action *in vivo* and, thus, several prior art references discouraged their combined use. *Id.* at 29–31 (citing Ex. 1039, 1 (study finding that the co-administration of the corticosteroid beclomethasone with the anti-histamine astemizole “provided no better control of rhinitis than beclomethasone alone”); Ex. 1036, 1, 3 (study finding that “budesonide [corticosteroid] and terfenadine [anti-histamine] combination treatment produced a similar effect to treatment with budesonide alone”); Ex. 1040, 1 (study finding “no significant difference in efficacy between [fluticasone] alone . . . and [fluticasone] in combination with oral [antihistamine] cetirizine”); Ex. 1034, 1 (study finding that “adding [antihistamine] loratadine to [fluticasone] does not confer meaningful additional benefit”)).

Patent Owner adds that, even if the prior art would have suggested to try antihistamines and corticosteroids, “clinical studies that actually tested

this theory demonstrated no . . . benefits.” Prelim. Resp. 31 (citing Ex. 2001 ¶ 52). Patent Owner points to Howarth⁸ and Nielsen⁹—two reviews published in 2000 and 2001, respectively—for concluding that “[c]ombining antihistamines and intranasal corticosteroids in the treatment of allergic rhinitis does not provide any additional effect to intranasal corticosteroids alone,” Ex. 2042, 2, and that “[t]he lack of additional clinical benefit when antihistamines are used in combination with corticosteroids” indicates that the action of antihistamines is “redundant,” Ex. 2041, 5.

Patent Owner also disputes that an ordinarily skilled artisan would have had a reason to select azelastine as the antihistamine, and asserts that combining azelastine and a steroid would, in fact, decrease patient compliance. Prelim. Resp. 34–37. For example, Patent Owner shows through a graph that “azelastine exhibited greater side effects than three popular oral antihistamines combined.” *Id.* at 35 (citing Ex. 2001 ¶ 73; Ex. 1008, 3; Ex. 2034, 4, 6, 9). Patent Owner argues that an ordinarily skilled artisan would have understood that these side effects would have deterred patient compliance. *Id.* at 34.

As part of its lack-of-reasonable-expectation-of-success argument, Patent Owner contends that “[t]here was no guidance in 2002 of how to combine a solution formulation—like azelastine—with a suspension

⁸ P.H. Howarth, “A comparison of the anti-inflammatory properties of intranasal corticosteroids and antihistamines in allergic rhinitis,” *Allergy*, 62:6–11 (2000) (“Howarth”). Ex. 2041.

⁹ Lars Peter Nielsen et al., “Intranasal Corticosteroids for Allergic Rhinitis Superior Relief?,” *Drugs*, 61(11):1563–79 (2001) (“Nielsen”). Ex. 2042.

formulation—like fluticasone.” *Id.* at 40 (citing Ex. 2007 ¶¶ 36–38). Patent Owner points to what is described as known formulation difficulties with combined drug formulations, *see id.* at 40–41 (citing Ex. 2007 ¶¶ 40–41; Ex. 2111, 1; Ex. 2044, 1–2), as well as to Example III of Cramer,¹⁰ a prior art disclosure of a combination drug formulation containing azelastine and a corticosteroid, that when formulated exhibited unacceptably high osmolality, poor spray quality, and unacceptable settling and caking, *id.* (Ex. 2007 ¶¶ 42–47; Ex. 1002, 268–87).

Upon considering the record developed at this stage of the proceeding, we are of the opinion that Patent Owner’s arguments and expert testimony highlight disputed issues of fact about whether the skilled artisan would have been motivated to combine the teachings of Hettche, Phillipps, and Segal to arrive at the claimed subject matter, and would have had a reasonable expectation of success. We conclude that these issues are best resolved following trial with the benefit of a full record. Thus, based on the limited record before us and the application of the “reasonable likelihood” standard, we are persuaded that Petitioner has articulated sufficient reasoning with rational underpinning for combining the teachings of Hettche, Phillipps, and Segal for instituting trial.

¹⁰ Ronald Dean Cramer, European Patent (EP) Application No. 0,780,127 A1 (published June 25, 1997) (“Cramer”). Ex. 1011. Cramer was thoroughly considered and relied upon by the Examiner during prosecution of the application leading to the ’620 patent. *See generally* Ex. 1002.

E. Obviousness over Hettche, Phillipps, Segal, and the Flonase Label

Petitioner contends that claims 42–44 are unpatentable as obvious over Hettche, Phillipps, Segal, and the Flonase Label. Pet. 2. Relying on the Declaration of Dr. Donovan, Petitioner explains how the references teach or suggest the claim limitations and provides reasoning for combining the references. *See* Pet. 43–52.

1. Overview of the Flonase Label

The Flonase Label states that Flonase® is an aqueous suspension of microfine fluticasone propionate, and also contains microcrystalline cellulose and carboxymethylcellulose sodium, dextrose, 0.02% w/w benzalkonium chloride, polysorbate 80, and 0.25% w/w phenylethyl alcohol. Ex. 1010, 1.

2. Analysis

Claims 42, 43, and 44 depend from claims 1, 24, and 25, respectively, and require edetate disodium, glycerine, a thickening agent comprising microcrystalline cellulose and sodium carboxymethyl cellulose, polysorbate 80, benzalkonium chloride, phenyl ethyl alcohol, and purified water as additional ingredients of the claimed pharmaceutical formulations. Ex. 1001, 14:24–38.

We have reviewed the information presented in the Petition and supporting evidence with respect to these challenged dependent claims and determine that the information presented establishes a reasonable likelihood that Petitioner would prevail in showing that these claims are unpatentable under 35 U.S.C. § 103. At this stage in the proceeding, Patent Owner's contention that the Petition fails to articulate a motivation to combine

Hettche, Phillipps, and Segal with the Flonase Label is an issue for trial. *See* Prelim. Resp. 42–43. We are satisfied on this record that the Petition provides adequate support for Petitioner’s obviousness contention, through a detailed claim chart and expert testimony. Pet. 44–46; Ex. 1004 ¶¶ 52–68, 71.

Finally, although we acknowledge Patent Owner’s teaching-away arguments and evidence about the additional composition excipients recited in claims 42–44, *see* Prelim. Resp. 44–48, we determine that Patent Owner’s arguments and evidence raise a disputed issue of fact that is best resolved on a complete record. *Compare* Prelim. Resp. 44–46 (citing Ex. 2007 ¶¶ 52–56), *with* Pet. 44–45 (citing Ex. 1004 ¶¶ 57–60); *see also* 37 C.F.R. § 42.108(c).

F. Secondary Considerations

Patent Owner argues that the Petition is deficient because it does not address various evidence of secondary considerations of patentability of which Petitioner had knowledge. Prelim. Resp. 16–20. Specifically, Patent Owner contends that Petitioner does not address evidence of eight objective indicia of nonobviousness presented during trial proceedings in the District of Delaware.¹¹ *Id.* at 2. Patent Owner asserts that Petitioner’s in-house representative witnessed Patent Owner’s evidence of secondary considerations in open court, that Petitioner’s “own declarants observed and testified about” that evidence during trial, and that Petitioner had access to

¹¹ Patent Owner refers to the trial proceeding as “the *Apotex* trial” and “the *Apotex* case.” Prelim. Resp. 16–17. The Board assumes that the trial was *Meda Pharms. Inc. v. Apotex Inc.*, 14-cv-01453 (D. Del.), which settled before judgment. *Id.* at 7 n.2.

multiple court filings discussing Patent Owner's evidence. *Id.* at 17–18. Patent Owner contends that it will be severely prejudiced if trial is instituted despite Petitioner's failure to address its objective indicia of nonobviousness in the Petition. *Id.* at 19–20.

Evidence of secondary considerations “must always when present be considered en route to a determination of obviousness.” *Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc.*, 699 F.3d 1340, 1349 (Fed. Cir. 2012) (quotation omitted); *see also Apple Inc. v. Samsung Elecs. Co.*, 839 F.3d 1034, 1048 (Fed. Cir. 2016) (*en banc*) (“A determination of whether a patent claim is invalid as obvious under § 103 requires consideration of all four *Graham* factors, and it is error to reach a conclusion of obviousness until all those factors are considered.”). Secondary considerations may include long-felt but unsolved need, failure of others, unexpected results, commercial success, copying, licensing, industry praise, and expert skepticism. *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1379 (Fed. Cir. 2012). “[O]bjective indicia may often be the most probative and cogent evidence of nonobviousness in the record,” and “help turn back the clock and place the claims in the context that led to their invention.” *Id.* at 1378 (quotation omitted).

Patent Owner is correct that the Board has previously denied institution of an *inter partes* review where the Petitioner failed to address secondary considerations in the Petition. *See Robert Bosch Tool Corp. v. SD3, LLC*, IPR2016-01751 (PTAB Mar. 22, 2017) (Paper 15) (denying institution for failure to address objective indicia introduced during a related ITC proceeding between Petitioner and Patent Owner) (“*Robert Bosch*”);

Coalition for Affordable Drugs V LLC v. Hoffman-LaRoche, Inc., IPR2015-01792 (PTAB Mar. 11, 2016) (Paper 14) (denying institution for failure to address objective indicia considered by Examiner during original prosecution) (“*Coalition V*”); *Omron Oilfield & Marine Inc. v. MD/TOTCO*, IPR2013-00265 (PTAB Oct. 31, 2013) (Paper 11) (denying institution for failure to address objective indicia successfully argued in a reexamination). Our *Trial Practice Guide* also explains that “[t]he Board expects that most petitions will raise issues of obviousness. In determining whether the subject matter of a claim would have been obvious over the prior art, the Board *will review* any objective evidence of nonobviousness proffered by the patent owner *where appropriate*.” *Office Patent Trial Practice Guide*, 77 Fed. Reg. 48,756, 48,763 (Aug. 14, 2012) (“*Trial Practice Guide*”) (emphases added); *see also* 37 C.F.R. § 42.107(a) (“a preliminary response . . . can include supporting evidence”).

Upon review of the record at this stage of the proceeding, however, we determine that, in this case, a better course of action is to permit the parties to develop a more complete record during trial before considering Patent Owner’s evidence of objective indicia of nonobviousness for the following reasons. *First*, this Decision is not a “determination of obviousness,” but rather a decision on whether a “reasonable likelihood” exists for such a determination to be made following trial. *Compare* 35 U.S.C. § 314(a) (authorizing *inter partes* review only if “there is a reasonable likelihood that the petitioner would prevail”), *with* 35 U.S.C. § 316(e) (placing the burden on petitioner of “proving a proposition of unpatentability by a preponderance of the evidence”). Thus, our analysis in

this Decision focuses on whether Petitioner has established a reasonable likelihood of success based on the current record. *Id.* § 314(a); *see also Trial Practice Guide* at 48,765 (“The ‘reasonable likelihood’ standard is a somewhat flexible standard that allows the Board room to exercise judgment.”).

Second, contrary to Patent Owner’s arguments, we find that the facts of this case differ from those in *Robert Bosch*. *See* Prelim. Resp. 17. In *Robert Bosch*, the Board “determined it is appropriate to review and address the objective evidence of nonobviousness proffered by the Patent Owner” “*because Petitioner was a party to the ITC proceeding and the evidence was developed fully during that proceeding.*” *Robert Bosch*, Paper 15 at 24 (emphasis added). Here, in contrast, Petitioner was not a party to the *Apotex* trial and therefore did not have an opportunity in that case to respond to Patent Owner’s evidence. We also note that in *Robert Bosch*, the Board relied upon the Administrative Judge’s determination in the corresponding ITC proceeding that “the evidence of secondary considerations was ‘very strong’ in favor of Patent Owner.” *Id.* at 23 (quoting Initial Determination on Violation of Section 337, 120–21). Here, however, there is no similar determination by the District Court because the *Apotex* case settled before judgment. Prelim. Resp. 7 n.2.

We note that the Board may consider secondary-considerations evidence that was presented during prosecution at the institution stage, *see, e.g., Coalition V*, Paper 14, 18, and Petitioner addresses this evidence in its Petition, *see* Pet. 52–59. But, in its Preliminary Response, Patent Owner does not appear to rely on any evidence that it previously submitted during

prosecution. Specifically, during prosecution, Patent Owner presented evidence of (1) unexpected results with the Declaration of Joachim Maus, M.D., Ex. 1002, 306–12; (2) long-felt but unsolved need with the Declaration of Sujeet K. Rajan, M.D., *id.* at 406–10; and (3) commercial success with the Declaration of Mr. Nikhil Chopra, *id.* at 276–82. Here, however, Patent Owner presents testimony and evidence from different declarants, and Petitioner has not yet had an opportunity to respond to those declarants.

As to Patent Owner’s remaining evidence of secondary considerations, although extensive, we determine that it would be premature at this stage of the proceeding to deny institution based on that evidence. Any final decision will be based on the full record developed during the trial.

III. CONCLUSION

For the foregoing reasons, we are persuaded that the Petition establishes a reasonable likelihood that Petitioner would prevail in showing that claims 1, 4–6, 24–26, 29, and 42–44 of the ’620 patent are unpatentable under 35 U.S.C. § 103.

Our determinations at this stage of the proceeding are based on the evidentiary record currently before us. This decision to institute trial is not a final decision as to patentability of any claim for which *inter partes* review has been instituted. Our final decision will be based on the full record developed during trial.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that pursuant to 35 U.S.C. § 314(a), an *inter partes* review is hereby instituted on the following grounds:

Claims 1, 4–6, 24–26, and 29 as unpatentable under 35 U.S.C. § 103 for obviousness over Hettche, Phillipps, and Segal; and

Claims 42–44 as unpatentable under 35 U.S.C. § 103 for obviousness over Hettche, Phillipps, Segal, and the Flonase Label;

FURTHER ORDERED that no other proposed grounds of unpatentability are authorized; and

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial commencing on the entry date of this Decision.

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