

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

APOTEX INC.,
Petitioner,

v.

UCB BIOPHARMA SPRL,
Patent Owner.

IPR2019-00400
Patent 8,633,194 B2

Before ROBERT A. POLLOCK, RYAN H. FLAX, and
KRISTI L. R. SAWERT *Administrative Patent Judges*.

POLLOCK, *Administrative Patent Judge*.

Final Written Decision

Determining No Challenged Claims Unpatentable
35 U.S.C. § 318(a)

Denying Patent Owner's Motion to Exclude Evidence
37 C.F.R. § 42.64

Denying Petitioner's Corrected Motion to Exclude Evidence
37 C.F.R. § 42.64

Decisions on Motions to Seal
37 C.F.R. §§ 42.1 and 42.54

I. INTRODUCTION

This is a Final Written Decision in an *inter partes* review challenging the patentability of claims 1–11 of U.S. Patent No. 8,633,194 B2 (“the ’194 patent,” Ex. 1001). We have jurisdiction under 35 U.S.C. § 6.

Petitioner has the burden of proving unpatentability of a claim by a preponderance of the evidence. 35 U.S.C. § 316(e) (2018). Having reviewed the arguments of the parties and the supporting evidence, we find that Petitioner has not demonstrated by a preponderance of the evidence that claims 1–11 are unpatentable. For the reasons set forth below, we also deny the parties’ motions to exclude evidence and grant, in-part, the proffered motions to seal.

A. Procedural History

Apotex Inc. (“Petitioner”) filed a corrected Petition for an *inter partes* review of claims 1–11 of the ’194 patent. Paper 4 (“Pet.”). UCB Biopharma Sprl (“Patent Owner” or “UCB”) timely filed a Preliminary Response. Paper 11 (“Prelim. Resp.”). The parties further submitted an authorized Reply and Sur-Reply to the Preliminary Response. Paper 13; Paper 16. In view of the then-available, preliminary record, we concluded that Petitioner satisfied the burden, under 35 U.S.C. § 314(a), to show that there was a reasonable likelihood that Petitioner would prevail with respect to at least one of the challenged claims. Accordingly, on behalf of the Director (37 C.F.R. § 42.4(a) (2018)), and in accordance with *SAS Inst. Inc. v. Iancu*, 138 S. Ct. 1348, 1353 (2018) and the Office’s Guidance on the Impact of SAS on AIA

Trial Proceedings (Apr. 26, 2018),¹ we instituted an *inter partes* review of all the challenged claims, on all the asserted grounds. Paper 17 (“Inst. Dec.”), 21.

After institution, Patent Owner filed a Response. Paper 22 (“PO Resp.”). Petitioner filed a Reply. Paper 33 (“Reply”). Patent Owner filed a Sur-reply. Paper 38 (“Sur-reply”).

Petitioner filed a Corrected Motion to Exclude Evidence directed to Exhibits 2024, 2030, 2031, and 2034. Paper 43. Patent Owner opposed that motion (Paper 48) and Petitioner filed a Reply (Paper 49). Patent Owner filed a Motion to Exclude Exhibits 1031–1038, 1040, 1041, and 1044. Paper 44. Petitioner opposed that motion (Paper 47) and Patent Owner filed a Reply (Paper 50). Also before us are three motions to seal pursuant to the default protective order. Papers 18, 28, 35.

On April 22, 2020, the parties presented arguments at oral hearing, the transcript of which is of record. Paper 56 (“Tr.”).

B. Real Parties-in-Interest

Petitioner identifies itself, Apotex Corp., Apotex Holdings Inc., and Apotex Pharmaceuticals Holdings Inc. as real parties-in-interest. Pet. 3. Patent Owner asserts that its real parties-in-interest are UCB Biopharma Sprl, UCB, Inc., UCB Pharma S.A., UCB S.A., and UCB Manufacturing Inc. Paper 7, 2; Ex. 2008 (public version).

¹ <https://www.uspto.gov/patents-application-process/patent-trial-and-appeal-board/trials/guidance-impact-sas-aia-trial>.

C. Related Proceedings

The '194 patent is at issue in *UCB, Inc. v. Apotex Inc.*, No. 0-18-cv-60846 (S.D. Fla.). *See* Paper 7, 2; Paper 10, 2. On April 1, 2019, the district court in this related litigation issued an Order staying that case pending our review of the '194 patent. Ex. 3001 (order granting Apotex, Inc.'s motion to stay pending *inter partes* review and administratively closing the case); *see also* Paper 43, 6 (noting that the concurrent district court case remains stayed).

Patent Owner also notes the '194 patent was previously at issue in *UCB, Inc. v. Apotex Inc.*, 1:18-cv-03404 (S.D.N.Y.), which was voluntarily dismissed. Paper 7, 2.

D. Asserted Grounds of Unpatentability

Petitioner asserts two grounds of unpatentability (Pet. 7, 8):

Ground	Claims Challenged	35 U.S.C. §	Reference(s)/Basis
1	1–11	103(a) ²	Handbook ³ , WO '094 ⁴

² The Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284 (2011) (“AIA”), amended 35 U.S.C. §§ 102 and 103. Because the challenged claims of the '194 patent have an effective filing date before the effective date of the applicable AIA amendments, we refer to the pre-AIA versions of 35 U.S.C. § 103 throughout this Decision.

³ AMERICAN PHARMACEUTICAL ASSOCIATION, HANDBOOK OF PHARMACEUTICAL EXCIPIENTS (Arthur H. Kibbe, Ph.D. ed., 3d ed. 2000). Ex. 1006.

⁴ International Patent Application Publication No. WO 2004/050094, published June 17, 2004. Ex. 1007.

Ground	Claims Challenged	35 U.S.C. §	Reference(s)/Basis
2	1–11	103(a)	Handbook, EP '203, ⁵ US '558 ⁶

In support of its patentability challenges, Petitioner relies on, *inter alia*, the testimony of Dr. Paul A. Laskar, Ph.D. *See* Exs. 1002, 1050 (first and second Declarations, respectively); Ex. 1003 (curriculum vitae); Exs. 2010 and 2037 deposition transcripts). In opposition to these challenges, Patent Owner relies on, *inter alia*, the testimony of Dr. Sarfaraz K. Niazi, Ph.D. *See* Ex. 2014 (Declaration); Ex. 2098 (curriculum vitae); Ex. 1043 (deposition transcript).

E. The '194 Patent and Relevant Background

According to the '194 patent's specification, its "invention is based on the unexpected recognition that a pharmaceutical composition comprising an active substance belonging to the family of substituted benzhydryl piperazines and a reduced amount of preservatives is stable during a long period of time." Ex. 1001, 1:60–64; *see also id.* at 1:64–65 (defining stability as "the capacity to resist[] . . . microbial contamination"). Such combinations can be administered orally, by spray inhalation, and nasal installation and may be formulated as drops, nasal drops, eye drops, ear drops, and oral preparations such as a syrup. *Id.* at 5:8–29.

⁵ European Patent Application Publication No. 0605203 A2, published July 6, 1994. Ex. 1004.

⁶ U.S. Patent No. 5,698,558, issued Dec. 16, 1997. Ex. 1015.

The Specification further states that “[p]referably, the active substance is selected from the group of cetirizine, levocetirizine, and their pharmaceutically acceptable salts.” *Id.* at 2:19–21. By way of background, we understand that these compounds have antihistamine activity. Cetirizine, the active ingredient in the commercially available allergy relief product Zyrtec, is a racemic mixture of (R) and (S) enantiomers; the levorotary R-enantiomer (as levocetirizine dihydrochloride) is the active ingredient in the commercially available Xyzal and Xyzal Allergy 24HR products. *See* Ex. 1001, 2:22–48; Ex. 1008, 1123;⁷ Ex. 1011; Ex. 2007; and Ex. 3003.

The Specification suggests that compositions including cetirizine or levocetirizine can employ a wide variety of preservatives (*see, e.g.*, Ex. 1001, 3:19–44), but “[b]est results have been obtained with a mixture of methyl parahydroxybenzoate and propyl parahydroxybenzoate in a ratio of 9/1 expressed in weight” (*id.* at 3:45–48). And, whereas the Specification asserts that 3 mg/ml of parahydroxybenzoate esters is “a normal concentration to preserve aqueous solutions” (*id.* at 1:64–2:4), it highlights embodiments in which

the pharmaceutical composition contains an amount of p-hydroxybenzoate esters (methyl p-hydroxybenzoate/propyl p-hydroxybenzoate in a ratio of 9/1 expressed in weight) selected in the range of 0.0001 and 1.5 mg/ml of the composition. Preferably, it contains an amount selected in the range of 0.01

⁷ Jean-Paul Tillement *et al.*, *Compared pharmacological characteristics in humans of racemic cetirizine and levocetirizine, two histamine H1-receptor antagonists*, 66(7) BIOCHEM. PHARMACOL. 1123–26 (2003).

and 1.125 mg/ml. More preferably it contains an amount of preservatives selected in the range of 0.1 and 1 mg/ml.

Id. at 3:49–56; *see also id.* at 9:38–11:7 (Example 4 including oral levocetirizine solution having 9/1 ratio of methyl p-hydroxybenzoate/propyl p-hydroxybenzoate which comprise 0.75 mg/ml of the composition).

With respect to terminology, we accept Dr. Laskar’s testimony that the methyl parahydroxybenzoate and propyl parahydroxybenzoate recited in the ’194 patent are also known as methylparaben and propylparaben, respectively, and generically as “parabens.” *See, e.g.*, Ex. 1002 ¶¶ 53, 54, 80 n.14 (citing Ex. 1006, 340, 450); *see also, e.g.*, Ex. 1013, 536 (alternative spelling as “methyl paraben” and “propyl paraben). Methyl- and propylparaben are also referred to as MP and PP, respectively, in the prosecution history. *See, e.g.*, Ex. 1013, 536–37.

F. Challenged Claims

The ’194 patent includes 12 claims. Of these, Petitioner challenges claims 1–11, of which only claim 1 (reproduced below with paragraphing added) is independent:

1. A liquid pharmaceutical composition comprising
 - (i) levocetirizine or a pharmaceutically acceptable salt of levocetirizine, and
 - (ii) a preservative mixture consisting essentially of a mixture of methyl parahydroxybenzoate and propyl parahydroxybenzoate in a ratio of 9/1 expressed in weight, said mixture being present in an amount of more than 0 and up to 0.75 mg/ml of the composition,wherein said composition is substantially free of bacteria.

Ex. 1001, 13:6–13.

Among the dependent claims before us, claim 4 recites that “the composition is in the form of oral solutions, nasal drops, eye drops or ear drops”; claim 11 is limited to “an oral solution comprising 0.50 mg/ml levocetirizine dihydrochloride, 0.675 mg/ml methyl p-hydroxybenzoate, and 0.075 mg/ml propyl p-hydroxybenzoate”; and claims 8–10 are cast as methods of making the composition according to claim 1. *Id.* at 13:19–21, 14:5–22.

G. Relevant Prosecution History

During the prosecution leading to the issuance of the '194 patent, the Examiner rejected certain claims as obvious over the combination of Dietrich, DeLongueville, Doron, Gilliland I, Gilliland II, and Routlege. Ex. 1013, 454–463; Exs. 2001–2006 (references cited in full at Prelim. Resp., i). In response, Applicants amended then-pending claim 1 to include the “consisting essentially of” and “substantially free of bacteria” limitations. *See* Ex. 1013, 492, 495 (emphasis added). With these additions, claim 1 recited:

1. A liquid pharmaceutical composition comprising

(i) levocetirizine or a pharmaceutically acceptable salt of levocetirizine, and

(ii) a preservative mixture consisting essentially of a mixture of methyl parahydroxybenzoate and propyl parahydroxybenzoate in a ratio of 9/1 expressed in weight, said mixture being present in an amount of more than 0 and **up to 1.125 mg/ml** of the composition,

wherein said composition is substantially free of bacteria.

See id. at 492 (paragraphing and emphasis added). In conjunction with these amendments, Applicants submitted a Declaration of named inventor Domenico Fanara, asserting that “[t]he combined parabens in typical pharmaceutical preparations is at least about 2 mg/ml, as shown by an accepted pharmaceutical treatise (see, Remington, The Science and Practice of Pharmacy, 21st ed., 2005, pp. 748–749, Ex. B, hereinafter ‘the Remington treatise’).” *Id.* at 536, ¶ 7. Mr. Fanara testified, however, that “[i]n the course of developing liquid pharmaceutical formulations of levocetirizine and its salts, we were surprised to discover that levocetirizine itself can act as an anti-microbial.” *Id.* at ¶ 8. Mr. Fanara also submitted evidence purporting to show the antibacterial efficacy of levocetirizine solutions having 0.375 mg/ml or 0.750 mg/ml of parabens consisting of methylparaben (MP) and propylparaben (PP) in a 9/1 ratio. *See id.* at 536–37, ¶¶ 10–11. Upon distinguishing the specific teachings of DeLongueville, Doron, Gilliland I, and Gilliland II, Mr. Fanara stated that the combination of those references “does not teach or suggest that a pharmaceutical formulation could be prepared that is maintained substantially free of bacteria and having the a [sic] total of MP and PP of no greater than 1.125 mg/ml, and no other preservative.” *Id.* at 537–39, ¶¶ 12–17.

A subsequent Interview Summary Record shows that the Examiner was not persuaded by Applicants’ argument that Remington taught a combined paraben concentration of at least about 2 mg/ml. *Id.* at 571. Rather, the Examiner found that “Remington discloses that parabens are common preservatives used in liquid pharmaceutical dosage forms and their typical concentrations levels range from about 0.1% [1 mg/ml] and up.”

Based on this reading of Remington—and Gilliland II’s teaching that methylparaben and propylparaben have synergistic effects in combination—the Examiner determined that one of ordinary skill in the art at the time of the invention “would expect that MP/PP [methylparaben and propylparaben] in a dose of about 1 mg/ml and slightly below would be . . . antimicrobial in view of the prior art,” but “would not expect that amounts of MP/PP much less than 1 mg/ml would be effective.” *Id.*

The Examiner then indicated that claims reciting a combined paraben concentration of 0.75 mg/ml would be patentable, as follows:

A review of the data provided in the Declaration demonstrate that compositions containing [levocetirizine] and MP/PP with ratio of 9/1 and total concentration of 0.675 mg/ml and 0.375 have antimicrobial effects. This is deemed to be surprising and unexpected. Examiner noted that one of ordinary skill in the art would not expect to have antimicrobial effects at these concentrations based on the art of record, however based on the art of record the upper limit of MP/PP amount of 1 mg/ml in claim 5 and 1.125 mg/mg in claim 1 would not be unexpected. The upper limit of claim 15 of 0.75 mg/ml is also considered to be unobvious in view of the prior art. Examiner suggests incorporating the upper limit of claim 15 (i.e.,] 0.75 mg/ml) as the upper limit in claim 1 to make the instant claims allowable.

Id. In light of the above, claim 1 was amended to recite the combined paraben concentration of 0.75 mg/ml, as issued. *Id.* at 590, 612.

II. ANALYSIS

A. Principles of Law

“In an [*inter partes* review], the petitioner has the burden from the onset to show with particularity why the patent it challenges is

unpatentable.” *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016) (citing 35 U.S.C. § 312(a)(3) (requiring *inter partes* review petitions to identify “with particularity . . . the evidence that supports the grounds for the challenge to each claim”)). This burden of persuasion never shifts to Patent Owner. *See Dynamic Drinkware, LLC v. Nat’l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015) (discussing the burden of proof in *inter partes* review).

A claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which that subject matter pertains. *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved based on underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness, if present. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

In analyzing the obviousness of a combination of prior art elements, it can be important to identify a reason that would have prompted one of skill in the art “to combine . . . known elements in the fashion claimed by the patent at issue.” *KSR*, 550 U.S. at 418. A precise teaching directed to the specific subject matter of a challenged claim is not necessary to establish obviousness. *Id.* Rather, “any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed.” *Id.* at 420.

Accordingly, a party that petitions the Board for a determination of unpatentability based on obviousness must show that “a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so.” *In re Magnum Oil Tools Int’l, Ltd.*, 829 F.3d 1364, 1381 (Fed. Cir. 2016) (internal quotation marks and citations omitted). Under the proper inquiry, “obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success.” *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007).

Evidence of unexpected results and other objective indicia of nonobviousness “must always when present be considered,” and can serve as an important check against hindsight bias. *See Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litigation*, 676 F.3d 1063 1075–76, 1079 (Fed. Cir. 2012) (quoting *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538–39 (Fed. Cir. 1983)). Unexpected results must be shown to be unexpected compared with the closest prior art. *Kao Corp. v. Unilever U.S., Inc.*, 441 F.3d 963, 970 (Fed. Cir. 2006). There is, however, no requirement that the closest prior art be commercialized. *See In re Merchant*, 575 F.2d 865, 869 (CCPA 1978).

In addition, unexpected properties, even if found, do not necessarily control the obviousness conclusion. *See, e.g., Pfizer, Inc. v. Apotex, Inc.* 480 F.3d 1348, 1372 (Fed. Cir. 2007). For example, a “marked superiority” in an expected property may be enough in some circumstances to demonstrate patentability, whereas a “mere difference in degree” may be insufficient. *In*

re Papesch, 50 CCPA 1084, 315 F.2d 381, 392 (CCPA 1963); *In re Merck*, 800 F.2d 1091, 1099 (Fed. Cir. 1986) (evidence that a new drug had more potent sedative and anticholinergic effects than the prior art insufficient to outweigh the evidence of obviousness).

We analyze the instituted grounds of unpatentability in accordance with these principles.

B. Person of Ordinary Skill in the Art

In determining the level of skill in the art, we consider the type of problems encountered in the art, the prior art solutions to those problems, the rapidity with which innovations are made, the sophistication of the technology, and the educational level of active workers in the field. *Custom Accessories, Inc. v. Jeffrey-Allan Indus. Inc.*, 807 F.2d 955, 962 (Fed. Cir. 1986); *Orthopedic Equip. Co. v. U.S.*, 702 F.2d 1005, 1011 (Fed. Cir. 1983).

Petitioner contends that a person of ordinary skill in the art as of the relevant date would have

(i) a Pharm. D. or Ph.D. in chemistry, biochemistry, pharmacy, pharmaceuticals, or in a related field, and at least two years of relevant experience in developing and formulating aqueous pharmaceutical formulations; (ii) a master's degree in the same fields and at least five years of the same relevant experience; or (iii) a bachelor's degree in the same fields and at least seven years of the same relevant experience.

Pet. 6 (citing Ex. 1002, ¶ 32–33); *see* Reply 7–8. Patent Owner does not dispute Petitioner's proposed definition of the skilled artisan. *See* Prelim. Resp. 2 n.1; PO Resp. 8–9; Ex. 2034 ¶ 21–23. And as Petitioner's proposed definition is consistent with the cited prior art and the Specification, we

adopt it here. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (explaining that specific findings regarding ordinary skill level are not required “where the prior art itself reflects an appropriate level and a need for testimony is not shown” (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp.*, 755 F.2d 158, 163 (Fed. Cir. 1985))).

C. Claim Construction

We interpret the challenged claims “using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. [§] 282(b).” *See* 37 C.F.R. § 42.100(b) (2019). Under that standard, we presume that a claim term carries its “ordinary and customary meaning,” which “is the meaning that the term would have to a person of ordinary skill in the art in question” at the time of the invention. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007) (quoting *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005)). Any special definition for a claim term must be set forth in the specification with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994). Limitations, however, may not be read from the specification into the claims (*In re Van Geuns*, 988 F.2d 1181, 1184 (Fed. Cir. 1993)), nor may the Board “construe claims during [an *inter partes* review] so broadly that its constructions are unreasonable under general claim construction principles” (*Microsoft Corp. v. Proxyconn, Inc.*, 789 F.3d 1292, 1298 (Fed. Cir. 2015), *overruled on other grounds by Aqua Products, Inc. v. Matal*, 872 F.3d 1290 (Fed. Cir. 2017)).

As noted by Petitioner, columns 2 and 3 of the '194 patent's Specification provide express definitions for some terms. Pet. 6; *see also* Ex. 1001, 2:22–3:48 (defining, e.g., cetirizine, levocetirizine, pharmaceutically acceptable salts, and preservatives). The parties agree that no terms require express construction. Pet. 6; Prelim. Resp. 2 n.1., PO Resp. 8.

In our Institution Decision, however, we construed the claim term “substantially free of bacteria,” as “having, at most, a low, but clinically acceptable, level of bacteria, which would have been its ordinary meaning to the skilled artisan because the claimed composition is a pharmaceutical, but the term ‘substantially’ leaves some flexibility from absolute sterility.” Inst. Dec. 12. We also noted that “claim 1 does not recite any requirement for the level of resistance to bacterial contamination provided by the invention, nor require that the composition is at any point exposed to bacteria, merely that it is ‘substantially free of bacteria.’” *Id.* at 17. Neither party disputes our initial definition, or offers an alternative, and we apply it here for clarity. *See* Pet. Reply 16; PO Resp. 8. And, although Patent Owner further proposes that “whether a particular formulation meets this requirement would be guided by antimicrobial effectiveness testing set for by the United States and/or European Pharmacopoeia,” such further construction is not necessary here. *See* PO Resp. 8 (citing Ex. 2034 ¶ 27; Ex. 2010 77:14–78).

No other terms require express construction. *See Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) (“[O]nly those terms need be construed that are in controversy and only to the extent necessary to resolve the controversy.”); *see also Nidec Motor Corp. v.*

Zhongshan Broad Ocean Motor Co. Matal, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (applying *Vivid Techs.* in the context of an *inter partes* review).

D. Obviousness in view of the Handbook and WO '094 (Ground 1)

As Ground 1, Petitioner challenges claims 1–11 as obvious in view of WO '094 and the Handbook. Pet. 19–43; Reply 3–24. Petitioner's challenge includes a detailed claim chart mapping the teachings of these references to each element of claim 1. Pet. 19–21. Patent Owner Opposes. PO Resp. 26–52; Sur-reply 2–21. We have reviewed the evidence of record including the Petition and Petitioner's expert declarations and Patent Owner's arguments and evidence, including its experts' declarations. We begin our analysis with an overview of the references asserted under Ground 1.

1. Overview of the Handbook (Exhibit 1006)

The Handbook teaches that methylparaben and propylparaben are “widely used as . . . antimicrobial preservative[s] in cosmetics, food products, and pharmaceutical formulations.” Ex 1006, 340, 450.⁸ According to the Handbook, antimicrobial activity and solubility vary inversely with increasing paraben chain length. *Id.* at 340, 341. “A mixture of parabens is thus frequently used to provide effective preservation,” moreover, “[a]ctivity may be improved by using a combination of parabens, since additive effects occur.” *Id.* “Activity may also be enhanced, due to synergistic effects, by

⁸ Where possible, we refer to native page numbers published in the cited documents.

using combinations of parabens with other antimicrobial preservatives such as imidurea.” *Id.*⁹

The Handbook teaches that methylparaben and propylparaben “are affirmed GRAS [(generally regarded as safe)] Direct Food Substances in the US at levels up to 0.1% [1 mg/ml]”¹⁰ and “[i]ncluded in the FDA Inactive Ingredients Guide (IM, IV, and SC injections, inhalations, ophthalmic preparations, oral capsules, solutions, suspensions and tablets, otic, rectal, topical, and vaginal preparations).” *Id.* at 342, 452. The Handbook teaches, for example, that “[m]ethylparaben (0.18%) [1.8 mg/ml] together with propylparaben (0.02%) [0.2 mg/ml] has been used for the preservation of

⁹ Despite Petitioner’s initial assertion (and the ’194 patent’s Applicants’ failure to dispute the Examiner’s finding) that combinations of parabens have synergistic antibacterial effects, we do not read the Handbook as teaching that combinations of parabens alone have such properties. *See* Pet. 17, 23, 26, 29, 51; Ex. 1002 ¶¶ 85, 94, 102, 146; Ex. 1013, 339–40; PO Resp. (citing excerpts of Dr. Laskar’s deposition testimony); Tr. 68:8–10. Moreover, for the reasons set forth at pages 18–19 of Patent Owner’s Sur-reply, Petitioner has not established that it was known in the art that methyl- and propylparaben have synergistic effects. In any event, given that combinations of methyl- and propylparaben were well known in the prior art, any potential synergism has little relevance to the patentability of the asserted claims. *See In re Huellmantel*, 324 F.2d 998, 1003 (CCPA 1963) (“[W]e attribute no magic status to synergism per se since it may be expected or unexpected.”); Tr. 59:3–6.

¹⁰ Dr. Laskar explains, and we accept, that the percentages of methyl- and propylparabens in a solution may be converted from w/v percent to milligrams per ml by multiplying the % value by a factor of 10. Ex. 1002 ¶¶ 71–73. Thus, for example, “0.015% w/v of methylparaben corresponds to 0.15 mg/ml.” *Id.* ¶ 72. Dr. Niazi applies similar calculations. Ex. 2034 ¶ 135. Bracketed amounts reflect that conversion.

various parenteral pharmaceutical formulations,” thus disclosing 2 mg/ml total parabens with a 9:1 ratio of methyl- to propylparaben. *Id.* at 340, 450 (same). The Handbook, however, notes:

Although parabens have also been used as preservatives in injections and ophthalmic preparations[,] they are now generally regarded as being unsuitable for these types of formulations due to the irritant potential of the parabens. These experiences may depend on immune responses to enzymatically formed metabolites of the parabens in the skin.

Id. at 342.

Despite this caution, the Handbook discloses additional information regarding concentrations of methylparaben and propylparaben suitable for particular applications, including “IM, IV, SC injections” and “Ophthalmic preparations.” *Id.* at 340, 450. With respect to methylparaben, the Handbook provides a table indicating the use of 0.065–0.25 % [0.65–2.5 mg/ml], 0.015–0.2 % [0.15–2.0 mg/ml], 0.033 % [0.3 mg/ml], and 0.015–0.2 % [0.15–2.0 mg/ml] for injectable, oral, nasal, and ophthalmic solutions, respectively. *Id.* at 340. A similar table indicates the use of 0.005–0.2 % [0.05–2.0 mg/ml], 0.01–0.2 % [0.1–2.0 mg/ml], 0.017 % [0.17 mg/ml], and 0.005–0.01 % [0.05–0.1 mg/ml] of propylparaben for injectable, oral, nasal, and ophthalmic solutions, respectively. *Id.* at 450. For convenience, we reproduce below a compilation of the data from these two tables in the Handbook for which Dr. Niazi has converted the concentration percentages into mg/ml:

	Methylparaben		Propylparaben	
	Conc. (%)	(mg/mL)	Conc. (%)	(mg/mL)
IM, IV, SC injections	0.065-0.25	0.65-2.5	0.0005-0.2	0.05-2
Inhalation solutions	0.025-0.07	0.25-0.7	0.015	0.15
Intradermal injections	0.1	1	0.02-0.26	0.2-2.6
Nasal solutions	0.033	0.33	0.017	0.17
Ophthalmic preparations	0.015-0.2	0.15-2	0.005-0.01	0.05-0.1
Oral solutions and suspensions	0.015-0.2	0.15-2	0.01-0.02	0.1-0.2
Rectal preparations	0.1-0.18	1-1.8	0.01-0.02	0.1-0.2 ⁵
Topical preparations	0.02-0.3	0.2-3	0.01-0.6	0.1-6
Vaginal preparations	0.1-0.18	1-1.8	0.02-0.1	0.2-1

PO Resp. 23–24 (citing Ex. 2034 ¶ 135). The above table is a compilation of data from the Handbook for which Dr. Niazi has converted the concentration percentages of methyl- and propylparaben into mg/ml.

2. Overview of WO '094 (Exhibit 1007)

WO '094 is directed to the use of levocetirizine for the treatment of persistent allergic rhinitis, wherein: “[a] preferred daily dosage provides from about 0.0005 mg to about 2 mg of levocetirizine or a pharmaceutically acceptable salt thereof, per kg of body weight per patient . . . [and] may be administered once per day of treatment, or divided into smaller dosages.” Ex. 1007, Abstract, 1:10–27, 2:35–3:2.

WO '094 further discloses that levocetirizine compositions may be formulated as, for example, aerosols, solids, creams, and liquids, including oral solutions such as syrups and drops. *Id.* at 4:8–29. Such dosage forms “may be prepared according to conventional methods used by pharmacists,” and include “substances conventionally used as preserving, stabilizing, moisture-retaining, and emulsifying agents.” *Id.* at 3:16–26.

WO '094 discloses that “[b]est results have been obtained with an oral dosage form, in particular liquid formulations such as syrup for children, and film-coated tablet for adults.” *Id.* at 4:24–25. In one preferred embodiment, WO '094 discloses a film coated tablet comprising “levocetirizine dihydrochloride, magnesium stearate, cellulose, lactose and silicon dioxide.” *Id.* at 4:31–32. In another preferred embodiment, WO '094 discloses a syrup formulation of “levocetirizine dihydrochloride, methyl- and propylparaben, saccharinum, and purified water.” *Id.* at 4:33–35.

3. Analysis of Ground 1

For Ground 1, Petitioner argues that one of ordinary skill in the art seeking to make a liquid pharmaceutical composition comprising levocetirizine would have looked first to WO '094, which discloses a preferred oral syrup formulation of “levocetirizine dihydrochloride, methyl- and propylparaben, saccharinum, and purified water.” Pet. 21; Ex. 1007, 4:34–35; *see* section II(D)(2), above. Petitioner argues that because WO '094 is silent as to the ratio and amounts of methyl- and propylparabens in the formulation, the skilled artisan would have looked to the Handbook for guidance. Pet. 22–23.

- a) “a mixture of methyl parahydroxybenzoate and propyl parahydroxybenzoate in a ratio of 9/1 expressed in weight”

With respect to the ratio of methyl- to propylparabens, Petitioner points to the 9/1 ratio taught by the Handbook for non-oral (e.g., injectable) formulations. *Id.* at 23 (quoting Ex. 1006) (“[m]ethylparaben (0.18%) [1.8 mg/ml] together with propylparaben (0.02%) [0.2 mg/ml] has been used for

the preservation of various parenteral pharmaceutical formulations”). According to Petitioner’s expert, Dr. Laskar, the 9/1 ratio is not limited to parenteral formulations, but is “widely used across a variety of dosage forms . . . [and] would logically have commended itself to the attention of the POSA as of the priority date of the ’194 patent.” Ex. 1002 ¶ 88 (referencing exemplary formulations employing the 9/1 ratio).

In response, Patent Owner asserts that one of ordinary skill in the art seeking to make a liquid pharmaceutical composition of levocetirizine would not have been motivated to apply the 9/1 ratio of methyl- and propylparabens recited in the Handbook and in the additional examples provided at paragraph 88 of Dr. Laskar’s first Declaration. PO Resp. 24–25. With respect to the example in the Handbook, Patent Owner asserts that it “does not identify the API for this formulation, nor does it state that the formulation was effective or useful in any manner.” *Id.* at 22 (citing Ex. 2034 ¶ 140). Patent Owner further argues that we should discount the exemplary formulations cited by Dr. Laskar as non-analogous art because they, for example, do not contain antihistamines, refer to gel or jelly formulations, comprise additional preservatives, or lack evidence that they have undergone regulatory testing. *Id.* at 24–25, 42–44 (citations omitted).

We do not find Patent Owner’s arguments on this issue persuasive for the reasons set forth on pages 4 and 5 of Petitioner’s Reply. In short, there is no dispute that the only ratio of methyl- to propylparaben exemplified in the Handbook is 9/1, and that disclosure pertains to a liquid (parenteral)

formulation.¹¹ And despite Patent Owner’s attempt to distinguish the exemplary formulations cited by Dr. Laskar, those examples clearly support his testimony that the 9/1 ratio of methylparaben to propylparaben “is common and is widely used across a variety of dosage forms.” Ex. 1002 ¶ 88; *see* Ex. 2010, 95:4–10, 124:8–14, 134:13–14. Patent Owner does not persuade us to the contrary. *But see* Ex. 2034 ¶ 176 (Dr. Niazi’s testimony that: “In my experience, a 9:1 ratio is not ‘widely used’ in pharmaceutical formulations.”); Ex. 1004 (11:22–42 liquid ophthalmic formulation using 2/1 ratio of methyl- to propylparaben).

Further, and though not necessary to our determination, the obviousness of the 9/1 ratio is further supported by documents and testimony elucidated at Dr. Niazi’s deposition. As Petitioner points out, Dr. Niazi is the sole author of the six volume Handbook of Pharmaceutical Manufacturing Formulations (“Niazi series”) the first edition of which published prior to the filing date of the ’194 patent. *See* Reply 5. Dr. Niazi did not dispute that volumes 3 and 5 of his Niazi Series includes 33 formulations having a 9/1 ratio of methylparaben to propylparaben, including one for cetirizine hydrochloride syrup. *See id.* at 5–6 (citing, *e.g.*, Ex. 1031; Ex. 1043, 171:16–172:14, 173:15–175:19). Accordingly, and considering all the evidence of record, we find that one of ordinary skill in the art seeking to make a liquid

¹¹ Notwithstanding Patent Owner’s statement that “a parenteral formulation is fundamentally different than the formulations of the challenged claims,” we find no support for the suggestion that the liquid pharmaceutical composition of claim 1 excludes parenteral formulations. *See* PO Resp. 43 (citing Ex. 2034 ¶ 38; Ex. 2010, 36:12–37:8); Tr. 17:3–7.

pharmaceutical composition comprising levocetirizine would have found it obvious to use a 9/1 ratio of methylparaben to propylparaben.

- b) “in an amount of more than 0 and up to 0.75 mg/ml of the composition”

With respect to the amount of methyl- and propylparabens, Petitioner points to the Handbook’s teaching to use 0.015–0.2% [0.15–2.0 mg/ml] methylparaben in oral solutions and suspensions. Pet. 27 (citing Ex. 1006, 340, Table 1). Based on this range of methylparaben, Dr. Laskar calculates that a 9/1 ratio of methyl- to propylparaben equates to 0.017–0.22 mg/l of propylparaben. Ex. 1002 ¶¶ 96–97 (cited at Pet. 27–28). Thus, starting with the Handbook’s range for methylparaben in oral solutions and suspensions, and applying a 9/1 ratio to the corresponding amount of propylparaben, Dr. Laskar arrives at total paraben concentration of 0.167 mg/ml–2.22 mg/ml. *Id.* ¶ 98 (cited at Pet. 27–28). Based on this calculation, Dr. Laskar concludes that because “the prior art ranges of the total amount of the p-hydroxybenzoate esters (*i.e.*, 0.167 mg/ml-2.22 mg/ml) overlap with the recited ranges (*i.e.*, > 0 to 0.75 mg/ml),” the range recited in claim 1 would have been obvious to one of ordinary skill in the art. *Id.* ¶¶ 98–101 (cited at Pet. 28–29).

Noting that the range calculated by Dr. Laskar includes total amounts of parabens well above the claimed range, Petitioner further argues that one of ordinary skill in the art would have been motivated to use the lower amounts of parabens “within the workable ranges reported in the Handbook for oral solutions and suspensions” to minimize their irritant potential and as “common sense notion . . . to use as little of a particular compound as

possible to achieve the desired effect.” Pet. 29–30 (citing Ex. 1002 ¶¶ 102–103). In sum, it is Petitioner’s position that “a POSA would have been motivated to use no more paraben than needed, or lower the amounts of parabens while still in the ranges disclosed in the Handbook.” *Id.* at 29. “Thus,” Petitioner asserts, “using the lower amount of “more than 0 and up to 0.75 mg/ml” of total parabens while maintaining the 9/1 ratio would have been obvious.” *Id.* at 29–30 (citing Ex. 1002 ¶ 103).

(1) Dr. Laskar’s Calculation

Patent Owner responds that the Petition’s Ground 1 is predicated on a calculation that “take[s] the range of methylparaben for oral solutions and suspensions listed in the Handbook (0.15-2 mg/mL) and multipl[ies] it by 9 (pursuant to the Handbook’s parenteral example) to determine the appropriate amount of propylparaben (0.017-0.22 mg/mL).” PO Resp. 38 (citing Pet. 27–28, 51–52; Ex. 1002 ¶¶ 95–98, 140–143). Patent Owner contends that this calculation only supports Petitioner’s argument if it uses *methyl*paraben as the starting point for the 9/1 calculation and does not consider what happens if *propyl*paraben is the starting point. *Id.* at 39. Relying on the testimony of Dr. Niazi, Patent Owner reasonably asserts that if propylparaben were instead used as the starting point for Petitioner’s calculation, the range of total parabens would be 1–2 mg/ml, which falls outside of the claims of the ’194 patent. *Id.* (citing Ex. 2034 ¶ 174); *see* Ex. 2034 ¶ 179, n.4.

In our Institution Decision, we expressly suggested that the parties “explore. . . why one of ordinary skill in the art would base the 9/1 calculation upon the Handbook’s range for methylparaben rather than for

propylparaben.” Inst. Dec. 16, n.3. Dr. Lasker declined to do so. Ex. 2010, 75:19–76:3; Ex. 1050. At best, when pressed at his deposition, Dr. Lasker offered the opinion that

methylparaben is more water soluble than propylparaben, as one can see from the information in the Handbook. And to, therefore, base the calculation on the more water soluble of the two parabens makes sense to me. The other is that on those occasions when I have used a combination of methyl and propylparaben, that’s -- the progress sequence that I used is I start with methylparaben and then calculate the amount of propylparaben I would end up using.

Ex. 2010, 76:4–15. Dr. Niazi, in contrast, testifies that if one of ordinary skill in the art were to perform that calculation “they would start with propylparaben because propylparaben is the more active antimicrobial and the POSA would want to ensure that a minimum amount of propylparaben is used.” Ex. 2034 ¶ 174. Weighing the available evidence, we find Dr. Niazi’s explanation more credible. When using Dr. Niazi’s methodology, the claimed paraben amounts are not taught or suggested by the cited prior art. Moreover, even were we to give equal weight to the two possibilities, Petitioner would not prevail as it bears the burden of proving unpatentability by a preponderance of the evidence. Here, Dr. Lasker points to no specific evidence that a POSA would have started with methylparaben, other than his personal opinion that a POSA could have done so. *See Belden Inc. v. Berk-Tek LLC*, 805 F.3d 1064, 1073 (Fed. Cir. 2015) (“[O]bviousness concerns whether a skilled artisan not only *could have made* but *would have been motivated to make* the combinations or modifications of prior art to arrive at the claimed invention.”). Dr. Lasker’s opinion on this matter does not

amount to a preponderance of the evidence and we find Dr. Niazi's opinion on the matter more credible.

(2) Motivation to Explore Low Paraben Concentrations

Noting that the Handbook reports on the "irritant potential of parabens," Petitioner posits that one of ordinary skill in the art "would have been motivated to lower the amounts of parabens within the workable ranges reported in the Handbook for oral solutions and suspensions, because it would have stood to reason that using less parabens would have resolved any irritant issues, while maintaining the widely used 9/1 ratio." Pet. 29 (citing Ex. 1006, 342; Ex. 1002, ¶¶ 102–103); *see* Reply 8–10. According to Dr. Lasker, "[t]his represents nothing more than the common sense notion to a POSA to use as little of a particular compound as possible to achieve the desired effect." Ex. 1002 ¶ 103.

As Dr. Niazi points out, however, every reference cited by Dr. Lasker as exemplifying the use of parabens uses at least 2 mg/ml total parabens—and, thus, well above the upper limit of 0.75 mg/ml recited in claim 1 . Ex. 2034 ¶ 183 (citing Exs. 1017–1020); *see* Sur-reply 2. Moreover, both parties' experts testified that they could not identify any formulation using less than 2 mg/ml total parabens, yet neither expert had experienced irritation due to parabens. *See* PO Resp. 46; Ex. 2034 ¶¶ 181–184; Ex. 2010, 123:22–4, 124:15–19.

We also find supportive of Patent Owner's position the evidence from Dr. Niazi's Handbook of Pharmaceutical Manufacturing presented by Petitioner at Dr. Niazi's deposition and summarized in Exhibit 1031. Sur-

reply 2–3 (citing Ex. 1013, 571, 587–588). Of the 33 formulations presented in the Niazi series, 21 of them used 2 mg/ml total parabens, moreover, even Entry No. 4 for Cetrizine Hydrochloride Syrup uses 1 mg/ml total parabens, which as Patent Owner points out “is the amount the Examiner found obvious during prosecution which caused applicants to lower the claimed amount to 0.75 mg/mL or less.” Sur-reply 2–3 (citing Ex. 1013, 571, 587–588).

One of the 33 Examples from the Niazi Series, Entry No. 33, Vitamin B Complex and Iron Syrup, does recite a combined paraben concentration within the claimed range. We, nevertheless, accord this entry somewhat less weight in our analysis because, having been introduced at such a late stage of the proceeding, the parties have had limited opportunity to explore the underlying properties of Entry No. 33 such as, for example, whether the iron component itself has antibacterial properties. We, nevertheless, credit Dr. Niazi’s testimony that the USP designation for syrup means that it has “66 percent weight by weight and 85 percent weight by volume of sugar, at which point no bacteria can grow in it.” Ex. 1043, 208:17–209:16. Because the challenged claims require “a preservative mixture *consisting essentially of* a mixture of methyl parahydroxybenzoate and propyl parahydroxybenzoate,” the transitional phrase limits the scope of a claim to the specified components “and those that do not materially affect the basic and novel characteristic(s)” of the claimed invention. *In re Herz*, 537 F.2d 549, 551-52 (CCPA 1976) (emphasis in original); *see* Pet. 22, n.12; Sur-reply 20. Accepting, on the limited record before us, Dr. Niazi’s testimony regarding the definition and antibacterial properties of syrups, the Vitamin B Complex

and Iron Syrup example is outside the scope of the claimed invention because the antimicrobial properties of such syrups would materially affect the basic and novel characteristic of the invention, i.e., the maintenance of a composition that is substantially free of bacteria using only the “preservative mixture” recited. *See* Tr. 26:19–22. Accordingly, and, absent additional evidence, the relevance of Entry No. 33 is unclear.

Accordingly, and rather than being motivated to use lower paraben concentrations as Dr. Lasker contends, we find credible Dr. Niazi’s opinion “that a POSA would have deferred to a formulation that includes parabens, specifically in amounts within the ranges found in earlier pharmaceutical formulations, instead of simply seeking to minimize parabens” and “any purported irritant potential would not cause a POSA to eliminate or substantially lessen the amount of parabens given the severe risks of bacterial contamination.” Ex. 2034 ¶¶ 181–182. We further find credible Dr. Niazi’s opinion that the risk-reward benefit of using lower amounts of parabens did not justify such experimentation:

Parabens were inexpensive to obtain and use, and were known to be safe and effective. *See supra* § VIII.C-D. Further, if a POSA used a lower amount of parabens than what was known in the art to be effective and later the formulation became contaminated, the POSA could be exposed to liability for using a lower amount of parabens. *See supra* § VIII. This is especially true when the formulation may be administered to vulnerable patient populations, such as young children. *See supra* § VIII.C.

Id. ¶ 185. Moreover, and despite the parties’ dispute regarding whether the combination of methy- and propylparabens are synergistic, we further note Dr. Niazi’s opinion that “the formulations in question involving mixtures of

parabens and the main advantage of mixing preservatives is that it allows a higher concentration (not a lower concentration) of preservatives in the formulation.” *Id.*; *see also* PO Resp. 20–22, 30–31; Reply 12–14; Sur-Reply 18–19; Ex. 2010, 70:1–71:10.

In sum, we find that Petitioner has not established that one of ordinary skill in the art would have been motivated to use “more than 0 and up to 0.75 mg/ml” of total parabens in a liquid levocetirizine formulation as required by independent claim 1.^{12, 13}

(3) Conclusion as to Ground 1

For the above reasons Petitioner has not carried its burden to establish, by a preponderance of the evidence, that the challenged claims are unpatentable under Ground 1.

¹² Given the limited development of evidence adduced at Dr. Niazi’s deposition, we do not address whether the record as a whole supports Patent Owner’s teaching away argument. *See* PO Resp. 44–46; Sur-reply 3–4.

¹³ We also give little weight to Patent Owner’s unexpected results arguments for lack of comparison to the closest prior art, which would reasonably include the any of the cetirizine hydrochloride formulations of EP ’203, or the levocetirizine syrup formulation of WO ’094. *See* PO Resp. 47–49, 58; Tr. 66:9–15 (Patent Owner’s counsel stating “there is no appropriate closest prior art because it would not be expected that levocetirizine could have [an intrinsic antibacterial] property”) *see also* Ex. 1016, 98 (identifying EP ’203, *inter alia*, as closest prior art in related EPO opposition).

E. Obviousness in view of the Handbook, EP '203, and US '558
(Ground 2)

As Ground 2, Petitioner challenges the '194 patent's claims 1–11 as obvious in light of the Handbook, EP '203, and US '558. Pet. 43–63; Reply 24–27. Petitioner's challenge includes a detailed claim chart mapping the teachings of these references to each element of claim 1. *Id.* at 45–46. Patent Owner Opposes. PO Resp. 52–58; Sur-reply 2–21. As the teachings of the Handbook are discussed in section II(D)(1), above, we begin our analysis with an overview of EP '203 and US '558.

1. Overview of EP '203 (Exhibit 1004)

EP '203 is a European Patent Application titled “Antiallergic composition for ophthalmic or nasal use” and directed to liquid formulations of cetirizine that address stability and irritation problems associated with high and low concentration formulations of cetirizine. Ex. 1004, 2:40–48; Ex. 2034 ¶ 103. EP '203 purports to solve this problem by using cyclodextrin as an additive. Ex. 1004, 3:1–19; Ex. 2034 ¶ 104.

EP '203 broadly discloses an “antiallergic composition for ophthalmic or nasal use, comprising cetirizine or a salt thereof as an active ingredient.” Ex. 1004, Abstract. The reference discloses that such compositions “may further contain any conventional additives in suitable amounts, which are used in ordinary ophthalmic or nasal solutions, e.g., preservatives such as p-hydroxybenzoates The amount of additive to be used can be determined by those skilled in the art within the same range as adopted for ordinary ophthalmic or nasal solutions.” Ex. 1004, 3:52–57.

EP '203 includes eight examples of cetirizine formulations, all of which are either nasal or ophthalmic formulations. *Id.* at 9:44–13:18. Of these, only Examples 5 and 7 contain preservatives. *See* Pet. 44 (citing Ex. 1002 ¶ 131); Ex. 2034 ¶ 106.

Example 5 of EP '203 discloses the following formulation for a cetirizine ophthalmic solution:

Ingredient	Amount
Cetirizine hydrochloride	0.3 g
α -cyclodextrin	0.8 g
Polyvinyl alcohol	0.2 g
Sodium acetate	0.1 g
Propylene glycol	2.0 g
Methylparaben	0.2 g
Propylparaben	0.1 g
Sodium hydroxide	q.s.
Distilled water	ad 100 ml

Id. at 11:22–42. The table above sets forth amounts of cetirizine hydrochloride, methylparaben, propylparaben, and other ingredients. As noted by Patent Owner, “converting the units in EP '203 Example 5 to those used in the '194 patent shows that Example 5 includes 2 mg/ml of methylparaben and 1 mg/ml of propylparaben for a total of 3 mg/ml combined parabens.” PO Resp. 19 (citing Ex. 2034 ¶ 110; Ex. 2010 132:7–16, 138:25–139:3).

Example 7 of EP '203 discloses the following formulation for a cetirizine nasal solution:

Ingredient	Amount
Cetirizine hydrochloride	0.5 g
Hydroxypropyl β -cyclodextrin	1.6 g
Polyvinyl pyrrolidone	1.0 g
Macrogol 4000	1.0 g
Potassium dihydrogenphosphate	0.1 g
Mannitol	5.1 g
Benzalkonium chloride	0.005 g
Potassium hydroxide	q.s.
Distilled water	ad 100 ml

Ex. 1004 12:22–49. The above-disclosed table sets forth amounts of cetirizine hydrochloride, benzalkonium chloride, and other ingredients. As noted in the Petition, EP '203 identifies benzalkonium chloride as a “conventional” preservative. Pet. 44 (citing Ex. 1004, 3:51–53).

2. Overview of the US '558 (Exhibit 1015)

US '558 teaches that cetirizine comprises a mixture of (+) and (-) isomers, where the active, (-) isomer is levocetirizine. *See* Ex. 1015, 1:40–43 (disclosing that cetirizine is a racemic mixture of isomers where “the active compound is the (-) isomer of 2-[4-[(4-chlorophenyl)-phenylmethyl]-1-piperazinyl] ethoxyacetic acid, hereinafter referred to as cetirizine”). US '558 explains that “[t]he prefixes d and l or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the

compound, with (-) or l meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory.” *Id.* at 1:53–56.

US ’558 discloses the use of levocetirizine, i.e., “optically pure (-) cetirizine for the treatment of seasonal and perennial allergic rhinitis in humans while avoiding the concomitant liability of adverse effects associated with the racemic mixture of cetirizine.” *Id.* at Abstract, 1:11–33, 3:47–62. According to the reference, levocetirizine may be administered, e.g., orally or parenterally in a pharmaceutical composition. *Id.* at 6:56–67.

3. Analysis of Ground 2

Petitioner contends that in formulating a liquid pharmaceutical composition of levocetirizine, one of ordinary skill in the art would have focused on Example 5 of EP ’203, which comprises an ophthalmic solution of cetirizine in combination with methylparaben and propylparaben. Pet. 43–44 (citations omitted). Because US ’588 teaches that cetirizine comprises two isomers, of which only the (-) isomer, levocetirizine, is active, Petitioner asserts that one of ordinary skill in the art would have been motivated to use levocetirizine in place of cetirizine in such formulations. *Id.* at 46–48 (citations omitted). Petitioner further argues that one of ordinary skill in the art would have been motivated to look to the Handbook for guidance regarding the amount of parabens in various liquid formulations. *Id.* at 50. For essentially the same reasons as set forth with respect to Ground 1, discussed above, Petitioner asserts that the skilled artisan would have arrived at the claimed ratio and amounts of methyl- and propylparaben set forth in independent claim 1. *See id.* at 48–52.

According to Patent Owner, “Ground 2 is largely the same as Ground 1, except that Ground 2 uses two references (EP ’203 and US ’558) to teach the point Petitioner draws from WO ’094 – a liquid pharmaceutical composition of levocetirizine.” PO Resp. 52. Accordingly, Patent Owner reasons that “Petitioner’s Ground 2 argument fails for the same reasons as Ground 1.” *Id.* at 52–53.

Petitioner does not credibly dispute the similarity between its asserted Grounds (*see* Reply 24–7) and we agree with Patent Owner’s assessment of the similarity of Grounds 1 and 2. For the reasons forth in section II(D)(3)(b), above, we remain unpersuaded by Dr. Laskar’s reasons for calculating ranges for methyl- and propylparabens using methylparaben as a starting point, as well as Petitioner’s explanation of why one of ordinary skill in the art would have been motivated to use the low concentrations of parabens recited in the claimed range.

We also credit Patent Owner’s argument that Petitioner has not adequately explained why one of ordinary skill in the art would have focused on Example 5 of EP ’203. PO Resp. 53–54. EP ’203 discloses eight liquid cetirizine hydrochloride formulations. But according to Petitioner, “Example 5 would have drawn the attention of the skilled artisan,” because “only EP ’203’s Examples 5 (ophthalmic) and 7 (nasal) contain preservatives.” Pet. 44 (citing Ex. 1002 ¶ 131). Petitioner’s expert further asserts that he focused on Example 5 as opposed to Example 7 because it was easier to convert to an oral formulation and “the relevant prior art relates to preservation systems . . . that contain parabens, and not preservation systems comprising benzalkonium.” Ex. 2010, 127:21–128:4; *see* PO Resp.

53–54 (citing Ex. 2010, 127:21–128:10, 129:1–130:16, 126:3–12).

Given that independent claim 1 is not limited to oral formulations, but is broadly directed to a liquid pharmaceutical composition, we do not find Dr. Laskar’s explanation persuasive. Nor are we persuaded by Dr. Laskar’s implication that Example 7 is not relevant prior art insofar as it contains benzalkonium as a preservative.

As is emphasized in Dr. Niazi’s testimony, it is unclear why Dr. Laskar believes one of ordinary skill in the art would focus on the examples in EP ’203 that contain preservatives, on formulations containing parabens specifically, or on those that could be converted to oral solutions. Ex. 2034 ¶¶ 213–214. Considering the evidence of record, we agree with Patent Owner that Dr. Laskar’s selection of Example 5 relies upon impermissible hindsight, which Petitioner does not rebut. *See* PO Resp. 53–54 (citing, e.g., Ex. 2034 ¶¶ 213–215; Ex. 2010, 131:24–132:5.). For this additional reason Petitioner has not carried its burden to establish that the challenged claims would have been obvious under Ground 2.

4. Conclusion as to Ground 2

For the above reasons Petitioner has not carried its burden to establish, by a preponderance of the evidence, that the challenged claims are unpatentable under Ground 2.

III. Patent Owner’s Motion to Exclude Evidence

Patent Owner moves to exclude Exhibits 1031–1038, 1040, 1041, and 1044, where Exhibits 1032–1037 and 1041 are excerpts from volumes 3 and 5 of Dr. Niazi’s Handbook of Pharmaceutical Manufacturing Formulations

(“the Niazi series”), Exhibit 1031 is compilation of formulations set forth in those excerpts, and 1038, 1040, and 1044 were submitted “to establish the publication date of Exhibits 1032–1037, or 1041, or of future, non-prior art edition of the [Niazi series].” Paper 44, 5. Patent Owner bases its motion to exclude on the proposition that, as excerpts, Exhibits 1032–1037 and 1041 are not “original writing[s] . . . required in order to prove [their] content” under Federal Rule of Evidence 1002. *Id.* at 2–3.

Patent Owner’s motion is denied.

As set forth in its Response to the motion, Petitioner fairly used the challenged exhibits as impeachment evidence in Dr. Niazi’s deposition. *See* Paper 47, 1–3, 7–8. Patent Owner does not persuade us that, as excerpts, the subject exhibits run afoul of Rule 1002. As a matter of practicality, the Office, indeed adjudicative bodies in general, would be overwhelmed if every exhibit purporting to be a book chapter, journal article, or dictionary definition further included the entire volume or series from which it was derived. Moreover, in the present case, Dr. Niazi, the sole author of the Niazi series, did not question the accuracy or dispute that those subject exhibits were true and accurate copies of his work. *See id.* at 7–8 (citing Ex. 2034 ¶ 9; Ex. 1043 171:16–175:19). Having elicited testimony thereon, we find that such testimony is best understood in the context of the exhibits themselves.

Patent Owner further requests that we either accept its offer of proof or take judicial notice of certain facts that it contends, “can be readily ascertained from the testimony of Dr. Niazi.” Paper 44, 3–5 (citing Ex. 1043,

255:9–12). Given the apparent inaccessibility of the full Niazi series,¹⁴ and our unwillingness to investigate the length and breadth of the entire six-volume edition, we decline to take judicial notice of the asserted facts. In the alternative, however, we acknowledge and reproduce below, Dr. Niazi’s testimony which forms the basis for Patent Owner’s request:

Q: How many formulations are in your six series books?

A: If I remember correctly, there are 2,000.

Ex. 1043, 255:9–12. In light of the foregoing, we dismiss Patent Owner’s offer of proof as moot.

IV. Petitioner’s Corrected Motion to Exclude Evidence

Petitioner moves, first, to exclude Dr. Niazi’s declaration (Exhibit 2034) in its entirety based on the premise that in failing to disclose the Niazi series, Dr. Niazi “withheld material information, made affirmative misrepresentations, and breached the requirements of 37 C.F.R. § 45.51(b)(1)(iii).” Paper 43, 1.

As an initial matter, Petitioner employed excerpts and summaries of Dr. Niazi’s own work as deposition exhibits to challenge several of his declaration statements. *See, generally*, Paper 43. Patent Owner responds that Petitioner has not demonstrated any inconsistency between Dr. Niazi’s declaration opinions and those exhibits or subsequent testimony. Paper 48, 2–7. We weighed these arguments and evidence in assessing Dr. Niazi’s

¹⁴ Petitioner indicates that although Dr. Niazi may have access to a personal copy, many libraries have supplanted the prior art first edition of the Niazi series with its second edition. Paper 43, 6; Paper 47, 10–11.

credibility and the parties' positions as a whole.

With respect to the basis of Petitioner's motion, however, we agree with Patent Owner that Dr. Niazi did not withhold any part of the Niazi series. As Patent Owner notes, the Niazi series is a publically available reference; it presents a compilation of formulations from publically available sources; its existence is disclosed in Dr. Niazi's expert declaration; and it is listed on the face of the '194 patent. Paper 48, 7–8 (citations omitted).

For at least these reasons, Petitioner's motion to exclude Exhibit 2034 is denied on the merits.

Petitioner further moves to exclude Exhibits 2024, 2030, 2031 and paragraphs 71–73 and 191–193 of Exhibit 2034, insofar as they rely on those exhibits. Paper 48, 1; Paper 49, 5. Because we did not rely on that material in our analysis, that portion of Petitioner's motion is denied as moot.

V. Motions to Seal

We also address the parties' motions to seal. Papers 18, 28 (by Patent Owner); Papers 35 (by Parties jointly). Relevant to these motions, the Office Patent Trial Practice Guide states:

3. A party intending a document or thing to be sealed may file a motion to seal concurrent with the filing of the document or thing. § 42.14. The document or thing will be provisionally sealed on receipt of the motion and remain so pending the outcome of the decision on motion.

4. *Protective Orders*: A party may file a motion to seal where the motion contains a proposed protective order, such as the default protective order in Appendix B. 37 C.F.R. § 42.54. Specifically, protective orders may be issued for good cause by the Board to protect a party from disclosing confidential information.

37 C. F. R. § 42.54. Guidelines on proposing a protective order in a motion to seal, including a Default Protective Order, are provided in Appendix B. The document or thing will be protected on receipt of the motion and remain so, pending the outcome of the decision on motion.

Consolidated Office Patent Trial Practice Guide November 2019 (“CTPG”) at 19–20.¹⁵

“There is a strong public policy for making all information filed in a quasi-judicial administrative proceeding open to the public, especially in an inter partes review which determines the patentability of claims in an issued patent and therefore affects the rights of the public.” *Garmin Int’l v. Cuozzo Speed Techs., LLC*, IPR2012–00001, Paper 34 at 1–2 (PTAB Mar. 14, 2013). For this reason, except as otherwise ordered, the record of an *inter partes* review trial shall be made available to the public. *See* 35 U.S.C. § 316(a)(1); 37 C.F.R. § 42.14. Motions to seal may be granted for good cause; until the motion is decided, documents filed with the motion shall be sealed provisionally. *See* 37 C.F.R. §§ 42.14, 42.54(a). The moving party bears the burden of showing that there is good cause to seal the record. *See* 37 C.F.R. § 42.20(c); *see Argentum Pharm. LLC v. Alcon Research, Ltd.*, Case IPR2017-01053, Paper 27 (Jan. 19, 2018) (informative) (factors for showing good cause to seal information).

As set forth in the CTPG, confidential information that is sealed subject to a protective order ordinarily will become public 45 days after final judgment in a trial. CTPG at 21–22. A party seeking to maintain

¹⁵ Available at <https://www.uspto.gov/sites/default/files/documents/tpgnov.pdf?MURL=>

confidentiality of information may file a motion to expunge the information before it becomes public; however, if the existence of the information is identified in a final written decision following trial, there is an expectation that the information will be made public. *Id.* at 22. This rule “balances the needs of the parties to submit confidential information with the public interest in maintaining a complete and understandable file history for public notice purposes.” *Id.*

Under the Board’s procedures, there is an expectation that all exhibits, including those filed under seal here, will be made part of the public record. Furthermore, the public’s interest in understanding the basis for our decision on patentability means that any good cause alleged in a motion to seal must overcome this heightened public interest. Confidential information that is subject to a protective order ordinarily becomes public 45 days after final judgment in a trial. A party seeking to maintain the confidentiality of the information may file a motion to expunge the information from the record prior to the information becoming public. 37 C.F.R. § 42.56.

A. Patent Owner’s First Motion to Seal (Paper 18)

In Paper 18, Patent Owner moves to seal Exhibit 3005 pursuant to the Board’s default protective order. Paper 18. According to Patent Owner, “Exhibit 3005 discloses the nature of the relationship between Patent Owner and Sanofi-Aventis with respect to the patent subject to this proceeding and the product Xyzal 24HR[®],” whereas, Exhibit 2008 is “a redacted, non-confidential version of Exhibit 3005.” *Id.* at 1. Patent Owner avers that Petitioner does not oppose the motion and that good cause exists in light of

“the nature of the relationship between Patent Owner and Sanofi-Aventis’ and the “competitively-sensitive, non-public, business information that is itself subject to confidentiality obligations between Patent Owner and Sanofi-Aventis.” *Id.* at 2.

Because the information redacted from Exhibit 3005 as compared to Exhibit 2008 is not necessary to our Decision, we find that Patent Owner’s desire to keep this information confidential is not outweighed by the public interest in maintaining a complete and understandable record of these proceedings. Accordingly, we grant Patent Owner’s motion with respect to Exhibit 3005.

B. Patent Owner’s Second Motion to Seal (Paper 28).

In Paper 28, Patent Owner moves to seal Attachment A to the Parties’ Joint Stipulation Regarding the Deposition of Domenico Fanara (Paper 27). Patent Owner Avers that Petitioner does not oppose the motion. Paper 28, 1. According to Patent Owner,

Attachment A is an excerpted version of the deposition of inventor Domenico Fanara which was taken in the related district court litigation (*UCB, Inc. et al. v. Apotex Inc.*, No. 0-18-cv-60846 (S.D. Fla.)). . . . [and] discloses certain confidential information subject to the district court protective order. Specifically, the deposition testimony contains (1) information relating to a strategic partnership with a pharmaceutical company not party to this proceeding and (2) details regarding Patent Owner’s pharmaceutical formulations.

Paper 28, 1. Patent Owner further states that the information sought to be protected “does not relate to the patentability of claims in an issued patent or

otherwise affect the rights of the public,” and that a parallel version of Paper 27 containing a minimally-redacted version of Attachment A is of record as Paper 26. *Id.*

Considering the Patent Owner’s representation as to nature of the information sought to be protected, and that we do not rely on this information in our Decision, Patent Owner has sufficiently shown good cause for granting this request. We find Patent Owner’s desire to keep this information confidential is not outweighed by the public interest in maintaining a complete and understandable record of these proceedings. Interpreting Patent Owner’s motion as a request to seal Paper 28 in its entirety, Patent Owner’s request is granted.

C. The Parties’ Joint Motion to Seal (Paper 35).

Although Paper 35 is submitted jointly by the parties, we understand that Patent Owner seeks to seal confidential, non-public versions of Exhibits 1039, 1042, 1043, and Paper 33 (“Petitioner’s Reply to Patent Owner’s Complete Response”), whereas Petitioner “takes no position, one way or another, on Patent Owner’s position” and notes that all redactions in the corresponding public versions “were made or approved by Patent Owner.” *See e.g.*, Paper 35, 1, 4. We address the subject documents as follows:

1. Exhibit 1039

According to the motion, Exhibit 1039 is the exhibit labeled version of the Deposition of Domenico Fanera and is thus, substantially identical to Attachment A to Paper 28, addressed in the section above. Having already considered this document in the context of Paper 28, the request is granted.

2. Exhibits 1042, 1043, and Paper 33

Petitioner filed confidential and non-confidential versions of Exhibits 1042 and 1043. Petitioner filed Paper 33 as restricted to be viewed by Board and Parties Only and concurrently filed a redacted, public version entered as Paper 34. With respect to Exhibits 1042 and 1043, Patent Owner takes the position that the redacted portions “relate to confidential information which would reveal details of Patent Owner’s confidential pharmaceutical formulations.” Paper 35, 3–4. With respect to Petitioner’s Reply, Patent Owner further asserts that the redacted portions “may be found in exhibits which Patent Owner has requested be sealed in this matter for the same reason.” *Id.* at 4.

The request to seal Exhibits 1042, 1043, and Paper 33 is denied.

Patent Owner’s terse explanation for why sealing is appropriate is insufficient to determine whether good cause exists to grant the request. Nor is this panel inclined to play seek and find with the record or substitute its judgment on precisely what information Patent Owner considers confidential.

Patent Owner is welcome to renew its request, jointly or upon consultation with Petitioner, within 10 business days of this Decision. Any such request shall be accompanied by a statement that the information sought to be redacted is not cited, directly or indirectly, in this Decision. To the extent such statement cannot be made, Patent Owner shall propose a substitute version of the affected Exhibit(s) and provide an explanation of any differences.

VI. CONCLUSION

For the foregoing reasons, Petitioner has not shown by a preponderance of the evidence that any of the challenged claims of the '194 Patent are unpatentable, as summarized in the following table:

Claims	35 U.S.C §	Reference(s) /Basis	Claims Shown Unpatentable	Claims Not Shown Unpatentable
1-11	103(a)	Handbook, WO '094		1-11
1-11	103(a)	Handbook, EP '203, US '558		1-11
Overall Outcome				1-11

VII. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that claims 1–11 of U.S. Patent No. 8,633,194 B2 are not determined to be unpatentable;

FURTHER ORDERED that Paper 44, Patent Owner's Motion to Exclude Exhibits 1031–1038, 1040, 1041, and 1044 is denied;

FURTHER ORDERED that Paper 43, Petitioner's Corrected Motion to Exclude Exhibits 2024, 2030, 2031, and 2034 is denied;

FURTHER ORDERED that Paper 18, Patent Owner's First Motion to Seal is granted as to Exhibit 3005;

FURTHER ORDERED that Paper 28, Patent Owner's Second Motion to Seal is granted as to Paper 27;

FURTHER ORDERED that Paper 35, the Parties' Joint Motion to Seal is granted as to Exhibit 1039 only;

FURTHER ORDERED that Paper 35, the Parties' Joint Motion to Seal is denied as to Exhibits 1042, 1043, and Paper 33 with leave to renew the request as set forth in section V(C)(2), above;

FURTHER ORDERED that, because this is a final written decision, parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

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