

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

KAMADA, LTD.,
Petitioner,

v.

GRIFOLS THERAPEUTICS INC.,
Patent Owner.

Case IPR2014-00899
Patent 6,462,180 B1

Before RAMA G. ELLURU, SHERIDAN K. SNEDDEN, and
TINA E. HULSE, *Administrative Patent Judges*.

HULSE, *Administrative Patent Judge*.

FINAL WRITTEN DECISION
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

I. INTRODUCTION

Kamada, Ltd. (“Petitioner”) filed a Petition requesting an *inter partes* review of claims 1–33 of U.S. Patent No. 6,462,180 B1 (Ex. 1001, “the ’180 patent”). Paper 1 (“Pet.”). Grifols Therapeutics Inc. (“Patent Owner”) filed a Preliminary Response to the Petition. Paper 7 (“Prelim. Resp.”). On December 18, 2014, we instituted an *inter partes* review of claims 1–5, 10–21, 26–28, 32, and 33 on the grounds of unpatentability alleged in the Petition. Paper 8 (“Dec. Inst.”), 24. Patent Owner filed a Response to the Petition. Paper 23 (“PO Resp.”). Petitioner filed a Reply to Patent Owner’s Response. Paper 31 (“Pet. Reply”).

Patent Owner filed a motion to exclude certain portions of Petitioner’s Reply, certain exhibits, and certain testimony provided by Dr. James Travis. Paper 34. Petitioner filed an opposition to Patent Owner’s motion to exclude. Paper 38. And Patent Owner filed a reply in support of its motion to exclude. Paper 39.

An oral hearing for this proceeding was held on July 23, 2015, a transcript of which has been entered in the record. Paper 40 (“Tr.”)

We have jurisdiction under 35 U.S.C. § 6(c). This Final Written Decision is issued pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73.

For the reasons that follow, we determine that Petitioner has shown by a preponderance of the evidence that claims 1–5, 10–21, 26–28, 32, and 33 of the ’180 patent are unpatentable.

A. Related Proceedings

Petitioner states that the '180 patent is the subject of a reissue proceeding (Reissue Application No. 13/567,678) and an *ex parte* reexamination proceeding (Reexamination Control No. 90/013,008). Pet. 1–2; Paper 6, 2. The proceedings have been merged into a single proceeding. Pet. 2. Of the claims involved in this *inter partes* review, Patent Owner canceled claims 2 and 3, and amended claims 1, 4, and 22–24 during the reissue/reexamination proceeding. Ex. 1037, 6. On October 27, 2015, the Examiner entered a final office action rejecting pending claims 1 and 4–35 of the reissue application. Ex. 1037. Because, as of the time of filing this Final Written Decision, the reissue/reexamination proceeding is still pending and no certificate has been issued, we consider all of the claims in this Decision.

B. The '180 Patent (Ex. 1001)

Alpha-1 proteinase inhibitor (“API”) is a glycoprotein that acts as an inhibitor of endogenous proteases. Ex. 1001, 1:16–23. API is used to treat patients with a genetic deficiency of API, which can lead to chronic lung tissue damage and emphysema. *Id.* at 1:24–32. The '180 patent relates to the purification of API from blood plasma or from plasma fractions, such as Cohn Fraction IV-1.¹ *Id.* at 1:5–9. According to the Specification, “the present invention provides a process of purifying [API] from a blood plasma fraction with a higher

¹ Cohn-Fraction IV-1 is a partially purified plasma fraction enriched for API that also contains other proteins, lipids, lipoproteins, and other substances. Ex. 1010 ¶ 8.

yield, higher purity, shorter production time, and use of less resources than known methods.” *Id.* at 2:54–58.

C. Illustrative Claim

Of challenged claims 1–33, claims 1 and 17 are independent claims. Claim 1 is illustrative of the challenged claims and is reproduced below:

1. A method of purifying α -1 proteinase inhibitor from an aqueous solution containing α -1 proteinase inhibitor comprising:
 - (a) removing a portion of contaminating proteins from the aqueous solution by precipitation in order to obtain a purified solution containing α -1 proteinase inhibitor; then
 - (b) passing said purified solution through an anion exchange resin so that α -1 proteinase inhibitor binds to said anion exchange resin; then
 - (c) eluting α -1 proteinase inhibitor from said anion exchange resin to obtain an eluted solution containing α -1 proteinase inhibitor; then
 - (d) passing the eluted solution through a cation exchange resin; then
 - (e) collecting a flow-through from said cation exchange resin that contains α -1 proteinase inhibitor.

D. Grounds of Unpatentability Instituted for Trial

We instituted trial based on the following grounds of unpatentability:

Claim(s)	Basis	References
1, 2, 5, 10, 11, 16–18, 21, 26, 27, 32, and 33	§ 102(e)	Ralston ²
3, 4, 19, and 20	§ 103	Ralston and Coan ³
12 and 28	§ 103	Ralston and Hwang ⁴
13	§ 103	Ralston, Hwang, and Chen ⁵
14 and 15	§ 103	Ralston, Hwang, Chen, and Coan II ⁶
2–5, 12, 16, 18–21, 28, and 32	§ 103	Lebing ⁷ and Coan

II. ANALYSIS

A. The Level of Ordinary Skill in the Art

The parties disagree on the level of ordinary skill in the art. Petitioner asserts that a skilled artisan would have had at least a Master’s Degree in Chemistry or Biochemistry, with five or more years of experience with large-scale protein purification. Pet. 5.

² Ralston et al., US 6,093,804, issued July 25, 2000 (Ex. 1002).

³ Coan et al., US 4,379,087, issued Apr. 5, 1983 (Ex. 1004).

⁴ Hwang et al., US 5,616,693, issued Apr. 1, 1997 (Ex. 1005).

⁵ Chen et al., *Purification of $\alpha 1$ Proteinase Inhibitor from Human Plasma Fraction IV-1 by Ion Exchange Chromatography*, 74 VOX SANG. 232–41 (1998) (Ex. 1007).

⁶ Michael H. Coan, *Purification of Alpha-1-Proteinase Inhibitor*, 84 AM. J. MED. 32–36 (1988) (Ex. 1008).

⁷ Lebing et al., US 5,610,285, issued Mar. 11, 1997 (Ex. 1003).

Patent Owner argues that a skilled artisan would have had an advanced degree in biochemistry or a related discipline, and would have had at least several years of experience in development, testing, and implementing commercial-scale protein purification methods from human plasma. PO Resp. 16.

As an initial matter, we note that the claims do not require large-scale or commercial-scale protein purification. Moreover, not all claims require plasma-derived API. Accordingly, we determine that a person of ordinary skill in the art would have had at least a Master's Degree in chemistry or biochemistry and at least 3–5 years of experience in protein purification.⁸ We also consider the cited prior art as representative of the level of ordinary skill in the art. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (holding the absence of specific findings on “level of skill in the art does not give rise to reversible error ‘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)).

⁸ Patent Owner alleges that Petitioner's declarants are not qualified to opine on the merits of this proceeding because they have no experience with plasma-derived protein purification. PO Resp. 16–24. In light of our decision that a person of ordinary skill in the art does not require plasma-protein purification experience, we are not persuaded that Petitioner's declarants are not qualified, and will accord their testimony appropriate weight.

B. Claim Construction

In an *inter partes* review, the Board interprets claim terms in an unexpired patent according to the broadest reasonable construction in light of the specification of the patent in which they appear. *See In re Cuozzo Speed Techs., LLC*, 793 F.3d 1268, 1278–79 (Fed. Cir. 2015); 37 C.F.R. § 42.100(b). Under that standard, and absent any special definitions, we give claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention. *See In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Any special definitions for claim terms must be set forth with reasonable clarity, deliberateness, and precision. *See In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

1. “precipitation” or “precipitating”

Either the terms “precipitation” or “precipitating” appears in each of the challenged claims. In the Decision to Institute, we preliminarily construed both terms to mean “a process to separate or cause to separate from a solution or suspension.” Dec. Inst. 7. This construction was based, in part, on our review of several dictionary definitions presented by Petitioner, through its expert Dr. Carl Scandella. Pet. 4; Ex. 1010 ¶ 15.

Patent Owner argues that our preliminary construction is overly broad, and that a person of ordinary skill in the art would understand that the term “precipitation” as used in the ’180 patent refers to “the process of selectively reducing the solubility of particular proteins in the solution by adjusting the solution conditions to facilitate protein aggregation that causes these proteins to fall out of solution or

‘precipitate.’” PO Resp. 27. As support, Patent Owner relies on the testimony of its two declarants, Dr. James Travis and Mr. Michael Fournel. Ex. 2016 ¶¶ 32–43; Ex. 2017 ¶¶ 21–31.

Patent Owner and its declarants argue that proteins generally become insoluble at their isoelectric point or when the water structure surrounding the protein is disrupted. PO Resp. 27; Ex. 2016 ¶ 35; Ex. 2017 ¶ 23. These effects allow proteins to become insoluble and aggregate. PO Resp. 27; Ex. 2016 ¶ 35; Ex. 2017 ¶ 23. According to Patent Owner, typical methods for precipitating proteins include changing the pH, changing the salt concentration, or adding organic solvents. PO Resp. 27; Ex. 2016 ¶ 35; Ex. 2017 ¶ 23. As intrinsic support for its proposed construction, Patent Owner asserts that the Specification discloses removing contaminating proteins with polyethylene glycol (“PEG”) and by changing the pH of the solution, which causes the proteins to become insoluble and precipitate. PO Resp. 28 (citing Ex. 1001, 4:43–65, Example 2).

Patent Owner then argues that the process of precipitating proteins differs from the use of lipid removal agents (“LRA”), which are silicates that specifically bind lipids and lipoproteins through adsorption. PO Resp. 28; *see* Ex. 2016 ¶ 43 (“LRA is an adsorption ‘capture’ phenomenon and does not alter protein or lipid solubility in the solution—the lipoprotein/lipid adsorbs to the insoluble silicate media—and is removed from the solution via the interaction with the LRA media.”). The captured protein is then removed from the solution by centrifugation or filtration. *Id.* at 29; Ex. 2016 ¶ 40; Ex. 2017 ¶ 28. According to Patent Owner, construing “precipitation” to

encompass an LRA adsorption process would be unreasonably broad because “precipitation” is limited to “selectively reducing the solubility of particular proteins in the solution by adjusting the solution conditions to facilitate protein aggregation that causes these proteins to fall out of solution.” PO Resp. 30–31.

Petitioner, on the other hand, argues that our preliminary construction is correct and is supported by the Specification, the testimony of both parties’ declarants, and contemporaneous dictionary definitions. Pet. Reply 4–6. Petitioner cites Example 2 of the Specification, which describes an embodiment of the precipitation step of the claims. *Id.* at 5. Example 2 includes the steps of adding PEG, acetic acid, and Hyflo Supercel[®] to Cohn Fraction IV-1 to form a precipitate. Ex. 1001, 6:63–7:6. Hyflo Supercel[®], like LRA, is a silicate that binds lipids and lipoproteins. Pet. Reply 5; Ex. 1024; Ex. 1032, 85:18–86:16. Petitioner argues that because Patent Owner’s proposed construction would exclude the preferred embodiment’s use of Hyflo Supercel[®], Patent Owner’s construction cannot be correct. Pet. Reply 5–6 (citing *GE Lighting Solutions, LLC v. AgiLight, Inc.*, 750 F.3d 1304, 1311 (Fed. Cir. 2014)).

The parties agree that adding PEG and adjusting the pH of a solution can cause contaminating proteins to precipitate. Pet. Reply 4; PO Resp. 28. The dispute is whether the broadest reasonable interpretation of “precipitation” encompasses removal of proteins that adsorb to lipid removal agents like Hyflo Supercel[®]. We determine that it does.

As an initial matter, we note that Patent Owner’s declarants offer little to no persuasive evidence in support of their opinions regarding how a person of ordinary skill in the art would interpret “precipitation.” *See* Ex. 2016 ¶¶ 34–36, 40–43 (failing to cite persuasive evidence in support of opinions); Ex. 2017 ¶¶ 22–24, 27–28, 30–31 (same). Under our rules, unsupported expert testimony may be given little to no weight. *See* 37 C.F.R. § 42.65(a) (stating opinion testimony that does not disclose underlying facts or data “is entitled to little or no weight”); *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 294 (Fed. Cir. 1985) (finding a lack of objective support for expert opinion “may render the testimony of little probative value in a validity determination”).

In any event, starting with the language of the claims, claim 1 recites the step of “removing a portion of contaminating proteins from the aqueous solution by precipitation.” The language of claim 17 is similar, but replaces “aqueous solution” with “Cohn Fraction IV-I.” Thus, the claim language indicates that “precipitation” is a process for removing contaminating proteins.

Next, we look to the Specification for further guidance. The Specification does not expressly define “precipitation.” The parties, however, both cite Example 2 of the Specification as describing the precipitation step of the claims. Pet. Reply 5; PO Resp. 28. Example 2 “describes one purification step in the process for the removal of contaminating proteins” from a suspension of Cohn Fraction IV-1 (Ex. 1001, 6:60–62):

The Cohn Fraction IV-1 dissolved in the Tris buffer solution, as described above, is again cooled to between 2° and 8° C. To this cooled solution is added NaCl to 0.11 M. To this solution is then added 11.5% PEG MW 3,350 (Carbowax[®], Union Carbide, Danbury, Conn.; suspension weight in kg times 0.115). The pH of the solution is then adjusted to between 5.10 and 5.35 with 1.0 M glacial acetic acid. To this is added 2.5% of Hyflo Supercel[®] (Celite Corporation, Lompoc, Calif.) and the resulting solution is mixed for 10 min. *A precipitate of contaminating proteins and viruses, including prion proteins, is formed.* The precipitate is filtered through a filter press assembled with CP90 Cuno filter pads (Cuno, Meriden, Conn.) at NMT 20 psi. The press is rinsed with 11.5% PEG in a water buffer. The paste obtained by the filtration is discarded. The filtrate contains the α -1 PI in PEG. Alternatively, the precipitate may be centrifuged and then filtered.

Id. at 6:63–7:12 (emphasis added). Petitioner contends that Example 2 is evidence that an adsorbent material, Hyflo Supercel[®], is used in forming a precipitate. Pet. Reply 1 (citing Ex. 1001, 6:53–7:12).

Patent Owner and its declarant argue that Hyflo Supercel[®] is used as a filter aid, and is not used to bind proteins. Tr. 39:13–21; Ex. 1032, 84:18–85:8. Although Dr. Travis agreed that the Specification does not indicate Hyflo Supercel[®]'s mechanism of action, he opined that “[i]f you are a protein chemist, you would assume that’s what it meant.” Ex. 1032, 85:9–14. Without objective evidence to support Dr. Travis’s testimony, the Specification is, at best, ambiguous as to the function of the Hyflo Supercel[®].

Regardless, even if we agreed with Patent Owner that Example 2 describes conditions meant to render proteins insoluble and that the

Hyflo Supercel[®] material was used as a filter aid alone, we do not limit the interpretation of the terms “precipitation” or “precipitating” to a single embodiment.

Rather, we are careful not to limit the claims to particular embodiments appearing in the written description if the claim language is broader than the embodiment. *In re Van Geuns*, 988 F.2d 1181, 1184 (Fed. Cir. 1993); *see also Johnson Worldwide Assocs., Inc. v. Zebco Corp.*, 175 F.3d 985, 992 (Fed. Cir. 1999) (“[J]ust as the preferred embodiment itself does not limit claim terms, mere inferences drawn from the description of an embodiment of the invention cannot serve to limit claim terms, as they are insufficient to require a narrower definition of a disputed term.”) (internal citations omitted).

We further note that Ralston refers to a “precipitate” in relation to the use of LRA: “LRA may be removed by filter press filtration or centrifugation. For filter press filtration, . . . Filter Aid 501 FF is added before the *precipitate* is collected.” Ex. 1002, 10:53–56 (emphasis added).

Patent Owner acknowledges the use of the word “precipitate” in Ralston, but characterizes it as “occasional and idiosyncratic” and concludes that a person of ordinary skill in the art would not interpret the term “precipitation” so broadly. PO Resp. 42 (“The occasional and idiosyncratic use of a term such as ‘precipitate’ in the noun form to refer to any solid removed from a liquid mixture notwithstanding, one of ordinary skill in the art would not interpret the claim term ‘precipitation’ as recited in the claims of the ’180 patent, to

encompass use of a lipid removal agent.”). But Patent Owner’s wholesale (and unsupported) dismissal of the Specification’s and Ralston’s use of the word “precipitate” is not persuasive. Given the definition of “precipitate” is “a substance, usually small crystalline particles, *precipitated* from a solution” (Ex. 3001⁹ (emphasis added)), Patent Owner has not explained why we should not interpret Example 2’s “precipitate” as a substance that was precipitated by the addition of PEG, acetic acid, *and* Hyflo Supercel[®]. Without a reasoned, well-supported explanation to the contrary, we find that the Specification supports a broader construction of “precipitation” that encompasses the use of LRA to remove contaminating proteins by adsorption.

Finally, our construction is supported by the extrinsic evidence. As mentioned above, Ralston’s use of the word “precipitate” to refer to the use of LRA is consistent with our construction. Ex. 1002, 10:53–56. Our construction is also consistent with certain technical dictionaries, which define “precipitate” as “to separate or cause to separate from a solution or suspension” (Ex. 1010 ¶ 15) and define “precipitation” as “the process of depositing a substance from a solution, by the action of gravity or by a chemical reaction” (Ex. 3001). These definitions encompass the removal of proteins from a solution by adsorbing to LRA and filtering or centrifuging the precipitate. Although we acknowledge that these definitions are

⁹ ACADEMIC PRESS DICTIONARY OF SCIENCE AND TECHNOLOGY 1712 (1992).

broader than other definitions of “precipitate” related to forming an insoluble solid that separates from a solution (*see* Ex. 1010 ¶ 15), we are not persuaded that our construction is unreasonably broad in light of the ambiguous description of Example 2 in the Specification.

Patent Owner argues that Kamada’s Bauer patent distinguishes lipid adsorption from precipitation and is, therefore, evidence of how a person skilled in the art would interpret precipitation. PO Resp. 29 (citing Ex. 2009,¹⁰ 6:27–32). First, we agree with Petitioner that the patent is less probative of the meaning of the term “precipitation” in the ’180 patent claims because the earliest effective filing date of the Bauer patent is almost four years after the filing date of the ’180 patent. *See Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005) (en banc) (“[T]he ordinary and customary meaning of a claim term 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, i.e., *as of the effective filing date of the patent application.*”) (emphasis added). Regardless, we note that, unlike the ’180 patent, the Bauer patent specification distinguishes between removal of LRA and removal of the precipitate. *See* Ex. 2009, 6:36–38 (“The pH reduction improves the precipitation, and the lipid removal agents and the precipitate are removed from the suspension.”). That is, Bauer does not refer to the LRA as part of the precipitate, as the ’180 patent does. *See* Ex. 1001, 6:63–7:6. We are, therefore, not persuaded that Bauer is inconsistent with our construction of “precipitation” in the ’180 patent.

¹⁰ Bauer, US 7,879,800 B2, issued Feb. 1, 2011 (Ex. 2009).

In light of the evidence in support and the lack of persuasive evidence to the contrary, we determine that the broadest reasonable interpretation of “precipitation” or “precipitating” encompasses the use of LRA (or an equivalent) to remove contaminating proteins from a solution.¹¹

2. *Order of Steps*

In our Decision to Institute, we determined that each of the steps of the claimed methods must occur in the order stated. Dec. Inst. 7–8. Neither Petitioner nor Patent Owner challenges this construction. Pet. Reply 12 (“As a preliminary matter, Kamada does not dispute that the order of steps is relevant to the claimed methods.”); PO Resp. 31 (“The Board properly determined that the steps of claims 1 and 17 must be performed in the recited order.”). Accordingly, because nothing in the full record developed during trial persuades us to deviate from our prior construction, we adopt the construction for purposes of this Decision.

¹¹ To the extent this construction differs from the construction set forth in the Decision to Institute, we modify our construction accordingly. We need not consider if the construction should be broader, as whether the construction encompasses the use of LRA is determinative in this proceeding. *See Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011) (“[C]laim terms need only be construed ‘to the extent necessary to resolve the controversy.’”) (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng’g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)).

C. Principles of Law

To prevail in this *inter partes* review of the challenged claims, Petitioner must prove unpatentability by a preponderance of the evidence. 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d).

To establish anticipation, each limitation in a claim must be found in a single prior art reference, arranged as recited in the claim. *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369 (Fed. Cir. 2008). While the limitations must be arranged or combined in the same way as in the claim, identity of terminology is not required. *In re Gleave*, 560 F.3d 1331, 1334 (Fed. Cir. 2009); *In re Bond*, 910 F.2d 831, 832 (Fed. Cir. 1990). Moreover, a reference anticipates a claim “if it discloses the claimed invention such that a skilled artisan could take its teachings in combination with his own knowledge of the particular art and be in possession of the invention.” *In re Graves*, 69 F.3d 1147, 1152 (Fed. Cir. 1995). Thus, “it is proper to take into account not only specific teachings of the reference but also the inferences which one skilled in the art would reasonably be expected to draw therefrom.” *In re Preda*, 401 F.2d 825, 826 (CCPA 1968).

A patent claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter 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 said subject matter pertains. *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of 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 skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

“[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art.” *KSR*, 550 U.S. at 418. “[I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine elements in the way the claimed new invention does.” *Id.* Moreover, a person of ordinary skill in the art must have had a reasonable expectation of success of doing so. *PAR Pharm., Inc. v. TWi Pharms., Inc.*, 773 F.3d 1186, 1193 (Fed. Cir. 2014).

We analyze the instituted grounds of unpatentability in accordance with the above-stated principles.

D. Anticipation by Ralston

Petitioner asserts that claims 1, 2, 5, 10, 11, 16–18, 21, 26, 27, 32, and 33 of the ’180 patent are anticipated by Ralston. Pet. 9–13; Pet. Reply 6–8. Petitioner also relies on the Declaration of Dr. Carl Scandella. Ex. 1010 ¶¶16–17, App’x I. Patent Owner disagrees with Petitioner’s assertions (PO Resp. 41–43), relying on the Declarations of James Travis, Ph.D. (Ex. 2016 ¶¶ 39–43, 56–66) and Michael Fournel (Ex. 2017 ¶¶ 27–31, 38–49, 65).

1. Ralston (Ex. 1002)

Ralston relates to a process for purifying API from blood plasma or blood plasma fractions. Ex. 1002, 1:8–11. Ralston’s method generally involves the removal of lipoproteins from an initial

protein suspension using a lipid removal agent (“LRA”), followed by successive separations with anion and cation exchange resins. *Id.* at 4:59–64. Thus, according to Ralston, “the present invention provides a means for achieving high yield isolation and purification of active API from various sources.” *Id.* at 4:57–59.

2. *Analysis*

We have reviewed the arguments and evidence presented by both parties, and we are persuaded that Petitioner has shown by a preponderance of the evidence that the challenged claims are anticipated by Ralston.

For example, claim 1 recites a method of purifying API from an aqueous solution comprising steps (a) through (e). Petitioner asserts that Ralston discloses precipitation step (a) because Ralston teaches that LRA adsorbs contaminating proteins, which together form a precipitate that is removed by filtration or centrifugation. Pet. 11; Ex. 1002, 10:47–48, 10:53–56; Ex. 1010 ¶ 16, App’x I. Petitioner also asserts that Ralston teaches passing the purified solution through an anion exchange resin that binds API (i.e., step (b)), eluting API from the anion exchange resin (i.e., step (c)), and passing the eluted solution through a cation exchange resin (i.e., step (d)). Pet. 11–12; Ex. 1002, 4:53–57; Ex. 1010 ¶ 16, App’x I. Finally, Petitioner asserts that Ralston discloses collecting a flow-through from the cation exchange resin that contains API (i.e., step (e)). Pet. 12; Ex. 1002, 5:40–48. We determine that Petitioner has shown by a preponderance of the evidence that Ralston discloses each limitation of claim 1.

Independent claim 17 recites the same steps as claim 1, but specifies the starting material as Cohn Fraction IV-1. As Petitioner asserts, Ralston discloses the use of Cohn Fraction IV-1 as the starting material. Pet. 12; Ex. 1002, 10:32–37; Ex. 1010 ¶ 16, App’x I. We are persuaded that Ralston discloses every element of claim 17, as well.

Patent Owner’s sole argument is that Ralston fails to anticipate the ’180 patent claims because it fails to disclose a precipitation step before the anion and cation exchange chromatography steps. PO Resp. 41–42. Patent Owner then reargues its claim construction position that “precipitation” does not encompass the use of LRA. *Id.*

For the same reasons stated above, we are not persuaded by Patent Owner’s argument. We determine that the broadest reasonable interpretation of “precipitation” includes the use of LRA. Thus, contrary to Patent Owner’s assertion, Ralston discloses a precipitation step before the anion and cation exchange chromatography steps. *See, e.g.,* Ex. 1002, 4:59–64 (“Generally, the method involves the removal of lipoproteins from an initial protein suspension by use of a lipid removal agent . . . followed by successive separations with anion and cation exchange resins with specific eluants.”).

Accordingly, we determine that Petitioner has shown by a preponderance of the evidence that independent claims 1 and 17 of the ’180 patent are anticipated by Ralston. Regarding dependent claims 2, 5, 10, 11, 16, 18, 21, 26, 27, 32, and 33, we have considered the parties’ arguments and evidence, and determine that Petitioner has shown by a preponderance of the evidence that Ralston discloses each

limitation of those claims as well. *See* Pet. 12–13; Ex. 1010 ¶¶ 16–17, App’x I.

E. Obviousness over Ralston and Coan

Petitioner asserts that claims 3, 4, 19, and 20 of the ’180 patent are unpatentable as obvious over Ralston and Coan. Pet. 15–19; Pet. Reply 8–10. Petitioner relies on the Declarations of Dr. Scandella and Dr. Rainer Bischoff. Ex. 1010 ¶¶ 20–24; Ex. 1011 ¶¶ 8, 10, 18, 19. Patent Owner disagrees with Petitioner’s assertions, relying on the Declarations of Dr. Travis and Mr. Fournel. PO Resp. 43–46; Ex. 2016 ¶¶ 76, 77, 79; Ex. 2017 ¶¶ 64, 66. We incorporate here our earlier findings and discussion regarding the disclosure of Ralston.

1. Coan (Ex. 1004)

Coan relates to a method for separating API from blood plasma or blood plasma fractions. Ex. 1004, 1:7–10. Coan teaches adding PEG to blood plasma or a blood plasma fraction and adjusting the pH of the solution to about 4.6–5.9 “to selectively precipitate unwanted proteins from the effluent in which a substantial proportion of the [API] is retained.” *Id.* at 3:2–4. Coan explains that the “primary advantage of the present method is that [API] may be separated from blood plasma in high yield.” *Id.* at 3:7–8. Moreover, Coan states that the method “can be carried out inexpensively because of the low cost of the agents employed in the present method.” *Id.* at 3:14–16.

2. Analysis

We have reviewed the arguments and evidence presented by both parties, and we are persuaded that Petitioner has shown by a

preponderance of the evidence that the challenged claims are unpatentable as obvious over the combination of Ralston and Coan.

Claims 3 and 19 depend from claims 2 and 18, respectively, and further recite that the precipitating step comprises the steps of adding a polyalkylene glycol to the aqueous solution and adjusting the pH of the aqueous solution to from about 5.0 to about 6.0. Claims 4 and 20 further depend from claims 3 and 19, respectively, and require that the polyalkylene glycol is PEG.

As explained above, we determine that Ralston discloses each limitation of claims 2 and 18. For the limitations of dependent claims 3, 4, 19, and 20, Petitioner relies on Coan's disclosure of adding PEG and adjusting the pH of the solution to precipitate unwanted proteins. Pet. 15; Ex. 1010 ¶ 20; Ex. 1011 ¶ 8. We are persuaded that Petitioner has shown by a preponderance of the evidence that the combination of Ralston and Coan teaches each limitation of claims 3, 4, 19, and 20.

Petitioner then offers several reasons why a person of ordinary skill in the art would have had a reason to combine the teachings of Ralston with Coan. Pet. 15–18; Ex. 1010 ¶¶ 21–24; Ex. 1011 ¶¶ 10, 18, 19. Petitioner's declarant states that a skilled artisan would have been motivated to include Coan's precipitation step in the method of Ralston because it was well known that contaminating proteins in a solution of API may interfere with the ion exchange sites on the resin, thereby making the resin less available for the binding of API. Ex. 1010 ¶ 21. The contaminating materials may also lead to a reduction in flow rate of a solution through the ion exchange column and foul the column. *Id.* According to Dr. Scandella, a person of ordinary

skill in the art would have expected Coan's precipitation step to remove contaminating proteins to allow for increased binding of API to the anion exchange resin and to decrease the likelihood that the contaminating proteins would reduce the flow rate of solution through the column. *Id.* Petitioner also asserts that a person of ordinary skill in the art would have expected to increase yield and purity of API per run by precipitating the contaminating proteins, as disclosed in Coan, from the solution of Ralston. Pet. 17–18; Ex. 1010 ¶ 22. Finally, Petitioner asserts that because both references are directed to methods for purifying API and perform the same purification steps in the same order, a person of ordinary skill in the art would have had a reason to combine the elements because the combination would not change the principle of operation or the intended functions of the combined elements. Pet. 18; Ex. 1010 ¶ 24.

For the reasons stated by Petitioner, we are persuaded that Petitioner has met its burden of showing that a person of ordinary skill in the art would have had a reason to add the precipitation step of Coan to Ralston's method of purifying API with a reasonable expectation of success. *See* Pet. 15–18; Ex. 1010 ¶¶ 21–24. In particular, we are persuaded that adding PEG and adjusting the pH to precipitate contaminating proteins, as disclosed in Coan, to Ralston is simply a combination of a well-known technique to yield predictable results. *KSR*, 550 U.S. at 416 (“The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.”).

In response, Patent Owner argues that a person of ordinary skill in the art would not be motivated to combine Coan and Ralston because Ralston allegedly disparages Coan's use of PEG precipitation:

Several other groups have combined PEG precipitation with other purification methods in an attempt to isolate API. For instance, U.S. Pat. No. 4,379,087, U.S. Pat. No. 4,439,358, U.S. Pat. No. 4,697,003 and U.S. Pat. No. 4,656,254, all employ a PEG precipitation step in processes of isolating API. PEG precipitation is disadvantageous in that PEG will also precipitate hepatitis [sic] B virus. Although viruses are typically inactivated in a heat pasteurization step following purification of API, precaution must be taken, and patients must therefore be immunized before receiving treatments.

Along with PEG precipitation, U.S. Pat. No. 4,379,087 by Coan et al. also reports a concentration step involving phosphate buffer and DEAE SEPHAROSE™. The combined process is quite lengthy, i.e., five days. Furthermore, the final product is only 60% active and only 80% pure.

PO Resp. 43–44 (quoting Ex. 1002, 3:45–59). According to Patent Owner, a skilled artisan reading Ralston would not use Coan's PEG precipitation followed by anion chromatography because Ralston expressly describes it as “disadvantageous.” *Id.*

We are not persuaded. “A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant.” *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994).

Although “known disadvantages in old devices which would naturally

discourage the search for new inventions may be taken into account in determining obviousness,” *United States v. Adams*, 383 U.S. 39, 52 (1966), we are not convinced that Ralston’s description of Coan as “disadvantageous” would discourage a skilled artisan from modifying Ralston’s purification method by adding Coan’s PEG precipitation.

Ralston states that PEG precipitation is disadvantageous because “PEG will also precipitate hepatitis [sic] B virus.” Ex. 1002, 3:50–51. Ralston then states that “[a]lthough viruses are typically inactivated in a heat pasteurization step following purification of API, precaution must be taken, and patients must therefore be immunized before receiving treatments.” *Id.* at 3:51–54. Both Petitioner and Patent Owner’s declarants agree, however, that a person of ordinary skill in the art would have understood in 1999 that virus removal or viral inactivation was a required step of purifying API. Ex. 2011, 81:24–82:10 (Scandella); Ex. 1034, 75:12–21 (Fournel); Ex. 1032; 105:3–10 (Travis). Thus, we are not persuaded that a skilled artisan, reading this passage of Ralston, would have been discouraged from using PEG precipitation, because a skilled artisan would have already been aware of the need for viral inactivation and the precautions that should be taken.

Patent Owner also notes that Ralston states that Coan’s combined process of PEG precipitation along with a concentration step involving phosphate buffer and DEAE SEPHAROSE is “quite lengthy” and the “final product is only 60% active and only 80% pure.” Ex. 1002, 3:55–59. Accordingly, Patent Owner argues that a person of ordinary skill in the art would be discouraged from

following the path set out in Coan, would be led in a direction divergent from the path taken by the applicant, or would not incorporate Coan's PEG precipitation step because it would render the result inoperable. PO Resp. 45–46. We do not find Patent Owner's argument persuasive. Ralston does not “criticize, discredit, or otherwise discourage” the use of Coan's PEG precipitation along with Ralston's purification process with anion and cation exchange resins. *See DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1327 (Fed. Cir. 2009) (quoting *In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004)) (holding that for a reference to teach away, it must state more than a general preference for an alternative invention, it must “‘criticize, discredit, or otherwise discourage’ investigation into the invention claimed.”). Rather, Ralston characterizes Coan's “combined process” as lengthy with an 80% pure final product. Ex. 1002, 3:55–59. Thus, although Ralston may teach away from the use of Coan's entire process, we are not convinced that a person of ordinary skill in the art reading Ralston would be discouraged from using Coan's PEG precipitation step in light of the benefits discussed above.

Accordingly, we determine that Petitioner has shown by a preponderance of the evidence that claims 3, 4, 19, and 20 are unpatentable as obvious over the combination of Ralston and Coan.

F. Obviousness over Ralston and Hwang

Petitioner asserts that claims 12–15 and 28 are unpatentable as obvious over Ralston and Hwang alone or in combination with one or more cited references, relying on the Declarations of Dr. Scandella

and Bischoff. Pet. 19–23, 25–28; Pet. Reply 10–12; Ex. 1010 ¶¶ 26–32, 37–46; Ex. 1011 ¶¶ 8–10, 18, 19. Patent Owner disagrees with Petitioner’s assertions, relying on the Declarations of Dr. Travis and Mr. Fournel. PO Resp. 46–50; Ex. 2016 ¶¶ 76, 79–82; Ex. 2017 ¶¶ 64, 66–69. We incorporate here our earlier findings and discussion regarding the disclosure of Ralston.

1. Hwang

Hwang relates to a process for purifying API. Ex. 1005, 1:8–10. In its method, Hwang teaches virus inactivation by solvent-detergent treatment. *Id.* at 4:15–16. Specifically, Hwang discloses using Tween 80 and tri-n-butyl phosphate to inactivate viruses (*id.* at 2:55–57), and then incubating the solution at pH 8 ± 0.5 to inactivate any viruses (*id.* at 4:20–22). Hwang then discloses diluting the treated solution and applying that solution to an anion exchange medium, which binds API. *Id.* at 4:35–40.

2. Analysis

Petitioner asserts that claims 12 and 28 are unpatentable as obvious over Ralston and Hwang. Pet. 19–23; Pet. Reply 10–11. Claims 12 and 28 depend from claims 1 and 17, respectively, and further recite a diluting step before passing the purified solution through the anion exchange resins. Petitioner asserts that Hwang teaches the diluting step. Pet. 19–20 (citing Ex. 1005, 4:35–36).

Petitioner also asserts that claim 13 is unpatentable as obvious over Ralston, Hwang, and Chen. Pet. 25–28; Pet. Reply 12. Claim 13 depends from claim 12 and further requires diluting the purified solution so that the purified solution has a conductivity of between

about 2.0 mS and about 6.0 mS. Chen relates to a method of purifying large quantities of API from fractionated plasma. Ex. 1007, Abstract. Chen's method includes adjusting the conductivity of the Cohn fraction IV-1 suspension to ≤ 5 mmho/cm with NaCl. *Id.* at 233. Petitioner asserts that Chen teaches this limitation because 5 mmho/cm, as disclosed by Chen, is equivalent to 5 mS/cm and, therefore, falls within the recited range. Pet. 26; Ex. 1010 ¶ 37.

Finally, Petitioner asserts that claims 14 and 15 are unpatentable as obvious over Ralston, Hwang, Chen, and Coan II. Pet. 28–31; Pet. Reply 12. Claims 14 and 15 depend from claims 13 and 14, respectively, and further require that the purified solution is diluted with water (claim 14) and wherein the water contains sodium phosphate (claim 15). Coan II relates to purification of API from Cohn fraction IV-1 by precipitation and ion-exchange chromatography. Ex. 1008, Abstract. As part of its method, Coan II teaches dissolving the plasma fraction in one liter of 0.025 M sodium phosphate. *Id.* at 2. Petitioner asserts that Coan II teaches the limitations of claims 14 and 15, given that a one liter solution of 0.025 M sodium phosphate contains 0.025 moles of sodium phosphate dissolved in approximately one liter of water. Pet. 28–29 (citing Ex. 1008, 2; Ex. 1010 ¶ 42).

For each of the combinations, Petitioner asserts that one skilled in the art would have been motivated to include a diluting step in Ralston's purification method because it was well known that diluting a solution containing API changes variables involved in ion exchange, including the conductivity of the solution. *Id.* at 21, 26–28, 29–31.

Accordingly, Petitioner's declarant concludes that a skilled artisan who wanted to improve the binding of API to an anion exchange resin to improve isolation and purification of API would have had a reason to combine the dilution step of Hwang, Chen, and Coan II with the purification process of Ralston. Ex. 1010 ¶¶ 29–30; 38–40; 44–46.

In response to each asserted combination, Patent Owner argues that Ralston teaches away from the use of PEG precipitation. In particular, Patent Owner focuses on Ralston's discussion of Japanese Patent No. 8-99999, which describes using PEG precipitation in combination with a cation exchanger. Ex. 1002, 3:60–61. According to Ralston, "[t]he methods described therein do not separate fully active API from inactive API." *Id.* at 3:61–62. Moreover, Ralston states that "the best yield, achieved by combining PEG precipitation and SP-cation exchange steps, was only 50%, and does not appear to be easily scaled up to a commercial production level." *Id.* at 3:66–4:2. Patent Owner concludes that this disclosure amounts to a discouragement of using PEG precipitation with ion exchange chromatography. PO Resp. 46–48; Ex. 2016 ¶¶ 76, 80; Ex. 2017 ¶¶ 64, 67.

For similar reasons stated above, we are not persuaded that Ralston's description of Japanese Patent No. 8-99999 teaches away from the use of PEG precipitation with the purification method of Ralston. Specifically, we are not persuaded that Ralston's disclosure of the disadvantages of combining PEG precipitation and cation exchanges steps would discourage a skilled artisan from modifying Ralston's purification method by adding PEG precipitation. *See*

DePuy Spine, 567 F.3d at 1327. As Patent Owner's declarant admitted, Ralston was referring to the entire process being used in that patent, and not to PEG precipitation alone. Ex. 1032, 150:14–21. We, therefore, find that Ralston does not discourage the use of PEG precipitation with its purification method.

Accordingly, we determine that Petitioner has shown by a preponderance of the evidence that claims 12 and 28 are unpatentable as obvious over Ralston and Hwang; claim 13 is unpatentable as obvious over Ralston, Hwang, and Chen; and claims 14 and 15 are unpatentable as obvious over Ralston, Hwang, Chen, and Coan II.

G. Obviousness over Lebing and Coan

Petitioner asserts that claims 2–5, 12, 16, 18–21, 28, and 32 are unpatentable as obvious over Lebing and Coan, relying on the Declarations of Dr. Scandella and Dr. Bischoff. Pet. 31–36; Pet. Reply 12–15; Ex. 1010 ¶¶ 47–51; Ex. 1011 ¶¶ 10, 18, 19. Patent Owner disagrees with Petitioner's assertion, relying on the Declarations of Dr. Travis and Mr. Fournel. PO Resp. 50–51; Ex. 2016 ¶¶ 67–68, 83; Ex. 2017 ¶¶ 50–52, 70. We incorporate here our earlier findings and discussion regarding the disclosure of Coan.

1. Lebing

Lebing relates to a method of purifying API from plasma with flow-through cation exchange chromatography. Ex. 1003, 1:8–10, 2:59–61. The method of the preferred embodiment includes the steps of dialyzing the protein solution, adjusting the pH of the solution, passing the solution through a cation exchange chromatography resin, and collecting the purified API as a flow-through fraction of the

chromatography. *Id.* at 2:66–3:9. Lebing also states that for large-scale productions, “a variety of additional steps, including viral inactivation may be added to optimize yield, improve viral safety, and assure regulatory compliance.” *Id.* at 3:42–45. The additional steps include:

- (1) Initial chromatography on a weak ion exchange resin (DEAE);
- (2) Initial chromatography on a strong anion exchange resin (QAE);
- . . . ; and
- (6) Precipitation steps to partially purify starting material prior to cation chromatography.

Id. at 3:45–58.

2. *Analysis*

For the reasons stated in the Petition and Dr. Scandella’s declaration, we determine that the combination of Lebing and Coan teaches each limitation of dependent claims 2–5, 12, 16, 18–21, 28, and 32. Pet. 31–33; Ex. 1010 ¶ 47, App’x J, P. For example, Lebing teaches passing the solution through an anion exchange resin first and then through a cation exchange resin, as required by independent claims 1 and 17. *See* Ex. 1003, 5:32–35 (“In our presently preferred embodiment, anion exchange chromatography is used to partially purify the [API] from a Cohn Fraction IV-1 (Fr. IV-1) suspension before loading onto the strong cation exchange column.”), Fig. 2. Regarding the initial precipitation step, we find persuasive Petitioner’s assertion that Coan teaches PEG precipitation as the first step in the

purification process. Ex. 1010, App'x P (citing Ex. 1004, 4:20–22, 4:56–59).

Petitioner makes similar arguments as above for why a person of ordinary skill in the art would have had a reason to include Coan's PEG precipitation step to remove contaminating proteins and lipids in the method of Lebing. Pet. 33–36; Ex. 1010 ¶¶ 48–50. For example, Petitioner asserts that a skilled artisan would have included Coan's precipitation step because it was well known that contaminating proteins may interfere with the ion exchange sites on the resin, thereby making the resin less available for binding API, which, in turn, interferes with chromatography. Pet. 34; Ex. 1010 ¶ 48. Petitioner also argues that it was well known that contaminating materials may reduce the flow rate of a solution through an ion exchange column and “foul the column.” Pet. 34–35; Ex. 1010 ¶¶ 48–49. For the same reasons stated above, we are persuaded that Petitioner has made a sufficient showing that a skilled artisan would have had a reason to combine Lebing and Coan.

In response, Patent Owner argues that a person of ordinary skill in the art would not combine Lebing with Coan because the '180 patent Specification criticizes the Lebing process as “too resource intensive for large-scale manufacturing.” PO Resp. 50 (quoting Ex. 1001, 2:46–50). Patent Owner also argues that, according to Ralston, Lebing's process tends to occlude the column, requiring larger columns, additional dialysis/filtration steps, and at least two cation chromatography steps, which “reduce efficiency and practicality of the method for large-scale processes.” Ex. 1002, 4:15–26. Because

Ralston allegedly criticizes both Coan and Lebing, Patent Owner argues that there is no motivation to combine the two references. PO Resp. 51 (citing Ex. 2016 ¶ 83; Ex. 2017 ¶ 70). Finally, Patent Owner asserts that neither Lebing nor Coan teaches or suggests the steps of the claims in the claimed order. *Id.* (citing Ex. 2016 ¶ 83; Ex. 2017 ¶ 70).

We do not find Patent Owner's arguments persuasive. Regarding the order of steps, we have already found that Coan teaches an initial PEG precipitation step. *See* Ex. 1004, 4:20–22, 4:56–59. Moreover, Lebing suggests “[p]recipitation steps to partially purify *starting material* prior to cation chromatography.” Ex. 1003, 3:57–58 (emphasis added). Taken together, we agree with Petitioner that the combination suggests adding Coan's precipitation step to the beginning of Lebing's purification method. Pet. Reply 12–13; *see also* Ex. 1032, 109:16–110:9 (Dr. Travis agreeing that the starting material is a Cohn Fraction IV-1 paste). During oral argument, counsel for Patent Owner agreed that Lebing suggests the precipitation step on the starting material is the first step. Tr. 49:20–24. Counsel disagreed, however, that the precipitation step would come before both an anion and a cation chromatography step. Rather, counsel for Patent Owner asserted that the precipitation step would replace the anion step. Tr. 49:24–50:6. Counsel, however, provided no evidence in support of this assertion, other than attorney argument. Because attorney argument is no substitute for evidence, we decline to give this argument any weight. *See Johnston v. IVAC Corp.*, 885 F.2d

1574, 1581 (Fed. Cir. 1989) (“Attorneys’ argument is no substitute for evidence.”).

Moreover, we are not persuaded that Ralston’s statements regarding Coan and Lebing would discourage a person of ordinary skill in the art from combining the Coan PEG precipitation step with the Lebing method. As explained above, we do not consider Ralston’s statements regarding PEG precipitation as disparaging the incorporation of a PEG precipitation step into a method like Lebing’s. *See DePuy Spine*, 567 F.3d at 1327. Moreover, notwithstanding Patent Owner’s assertions to the contrary, we find that Ralston’s statement that Lebing’s initial anion chromatography step binds numerous contaminating proteins that tend to occlude the column actually supports the combination. *See Ex. 1002*, 4:15–22. As explained above, we are persuaded that a person of ordinary skill in the art would have had a reason to add the Coan PEG precipitation step to Lebing’s method to remove the contaminating proteins to improve yield and purity.

Accordingly, we determine that Petitioner has shown by a preponderance of the evidence that claims 2–5, 12, 16, 18–21, 28, and 32 are unpatentable as obvious over the combination of Lebing and Coan.

H. Secondary Considerations of Nonobviousness

Factual inquiries for an obviousness determination include secondary considerations based on evaluation and crediting of objective evidence of nonobviousness. *See Graham*, 383 U.S. at 17. Notwithstanding what the teachings of the prior art would have

suggested to one of ordinary skill in the art at the time of the invention, the totality of the evidence submitted, including objective evidence of nonobviousness, may lead to a conclusion that the challenged claims would not have been obvious to one of ordinary skill in the art. *In re Piasecki*, 745 F.2d 1468, 1471–72 (Fed. Cir. 1984). Secondary considerations may include long-felt but unmet needs, failure of others, unexpected results, commercial success, copying, licensing, and praise. *See Graham*, 383 U.S. at 17; *Leapfrog Enters., Inc. v. Fisher-Price, Inc.*, 485 F.3d 1157, 1162 (Fed. Cir. 2007).

To be relevant, evidence of nonobviousness must be commensurate in scope with the claimed invention. *In re Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011) (citing *In re Tiffin*, 448 F.2d 791, 792 (CCPA 1971)); *In re Hiniker Co.*, 150 F.3d 1362, 1369 (Fed. Cir. 1998). In that regard, to be accorded substantial weight, there must be a nexus between the merits of the claimed invention and the evidence of secondary considerations. *In re GPAC Inc.*, 57 F.3d 1573, 1580 (Fed. Cir. 1995). “Nexus” is a legally and factually sufficient connection between the objective evidence and the claimed invention, such that the objective evidence should be considered in determining nonobviousness. *Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1392 (Fed. Cir. 1988). The burden of showing that there is a nexus lies with the patent owner. *Id.*; *see Paulsen*, 30 F.3d at 1482. Here, Patent Owner argues that longfelt but unmet need, the failure of others, and the unexpected results of the process claimed in

the '180 patent indicates that the claims would not have been obvious to a person of ordinary skill in the art. PO Resp. 52–59.

1. Longfelt Need and Failure of Others

“Longfelt need is closely related to failure of others. Evidence is particularly probative of obviousness when it demonstrates that a demand existed for the patented invention, and that others tried but failed to satisfy the demand.” *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1082 (Fed. Cir. 2012).

Here, Patent Owner argues that there was a shortage of API and a crucial need for “more efficient and production-ready processes.” PO Resp. 53–54. Patent Owner notes that “the failure of others to mass produce sufficient amounts of [API] to meet the needs created by market demand demonstrates the claims of the '180 patent are not obvious.” *Id.* at 55. Patent Owner asserts that this long-felt but unmet need is the problem that the invention of the '180 patent solved, as evidenced by Prolastin[®]-C, which Patent Owner and its declarants, Dr. Rebbeor and Mr. Fournel, contend is manufactured using the claimed invention. PO Resp. 52–53; Ex. 2018 ¶¶14–15; Ex. 2017 ¶¶ 71–77.

According to Mr. Fournel:

Despite efforts throughout the industry, until the '180 patent no one successfully developed a process that significantly increased yield, did not compromise purity, and was efficient enough for large-scale commercial production. Each proposed method (e.g., Lebing '285, Ralston, etc.) presented various disadvantages, particularly relating to the inability to be scaled up into a commercial process.

Ex. 2017 ¶ 73. Patent Owner further asserts that others have attempted to develop a production-ready purification process for API, but nothing was commercialized. PO Resp. 56; *see also* Ex. 2017 ¶ 13.

The problem with this argument is that the claims do not require large-scale commercial production or specific levels of purity and yield. Regardless, Ralston states:

The present process provides API with a product purity of >90%; and yield at manufacturing scale of >70%. Moreover, of all the API collected by the present method, greater than 90% of it is in its active form. In fact, the method of the present invention can produce API isolates having greater than about 95% active API; and can be as much as 100% active.

Ex. 1002, 4:66–5:5. Thus, to the extent there was a longfelt need for a an API purification process that resulted in high product purity and yield, Ralston—at least on its face—appears to have met that need. *Id.*

During oral argument, counsel for Patent Owner attempted to cast doubt on Ralston’s results, stating vaguely that Dr. Travis “has a reason to disbelieve the claims of Ralston.” Tr. 55:18–20. Counsel also stated “[t]here is no product on the market that we know about that actually practices Ralston” and “[t]here is nothing to suggest that it actually works.” *Id.* at 55:20–23. But there is any number of reasons why Ralston (or anyone else) did not commercialize its process. Patent Owner offers no data of its own, testing Ralston’s method to support its assertion that Ralston’s claims should be disbelieved. Without any evidence to the contrary, we decline to

speculate or question the veracity of Ralston's disclosure based on counsel's offhand remarks during oral argument.

Accordingly, we determine that Patent Owner has not established a long-felt need or the failure of others.

2. Unexpected Results

Patent Owner argues that the challenged claims are nonobvious because the order of steps in the production process and the inclusion of a precipitation step produced API at an unexpected and surprising level of efficiency and purity beyond that achieved by the prior art. PO Resp. 57. According to Patent Owner's declarant, Dr. Rebbeor, the '180 inventors found that adding a precipitation step before anion and cation exchange resins unexpectedly resulted in higher yield, higher purity, shorter production time, and use of less resources than previously known methods. Ex. 2018 ¶ 10 (citing data in Ex. 2019). Dr. Rebbeor states that data shows that Prolastin[®]-C, the product made by the methods of the '180 patent, achieved vast improvements over Prolastin[®], a product made using the best prior art method at the time, in yield, purity, cycle time, and significantly reduced labor hours, machine hours, and the total cost of production. Ex. 2018 ¶ 18; Ex. 2019, 1. Dr. Travis explains that the increase in both yield and purity is unexpected because a person of ordinary skill in the art would expect that an increase in yield would result in a decrease in purity, and vice versa. Ex. 2016 ¶ 87.

In response, Petitioner notes that the '180 patent does not contain any data to support its claim of unexpected results. Pet. Reply 16. Petitioner then criticizes Patent Owner's reliance on newly

generated data from 2014 to show the claimed process yielded unexpected results, asserting that doing so is contrary to the law. *Id.* (citing *Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.*, 769 F.3d 1339, 1340–41 (Fed. Cir. 2014) (per curiam) (Dyk, J., concurring) (“This case presents a question of obviousness, in particular whether evidence postdating the invention can be used to establish unexpected results. The panel holds that it cannot be considered in the circumstances of this case.”)).

Petitioner also argues that Patent Owner fails to account for the unclaimed steps in the Prolastin[®]-C process, and the differences between the process for Prolastin[®] (i.e., the “Hein process”) and for Prolastin[®]-C. Pet. Reply 17.

We find Petitioner’s arguments more persuasive. First, we are persuaded that the Prolastin[®]-C data produced in 2014 does not reflect the results that would have been expected (or unexpected) at the time of the invention in 1999. “To be particularly probative, evidence of unexpected results must establish that there is a difference between the results obtained and those of the closest prior art, and that the difference would not have been expected by one of ordinary skill in the art *at the time of the invention.*” *Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014) (emphasis added); *see also Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.*, 769 F.3d 1339, 1341 (Fed. Cir. 2014) (Dyk, J., concurring in denial of petition for rehearing en banc) (stating under the circumstances of the case that the “decision properly does not allow consideration of post-

invention evidence” regarding unexpected results). Accordingly, we give the 2014 Prolastin[®]-C data little weight in our analysis.

Moreover, even if we did consider the 2014 data, we are persuaded that Patent Owner has not met its burden of establishing a nexus between a novel feature of the claimed invention and the unexpected results. For example, Patent Owner has not accounted for the additional unclaimed steps in the Prolastin[®]-C method, like the dissolution step, which Patent Owner’s declarants admit affect purity and yield. Ex. 1033, 46:3–21 (stating the step of dissolving Cohn Fraction IV-1 “is important with respect to yield”); Ex. 1034, 68:4–11. Furthermore, the Hein process for Prolastin[®] uses heat pasteurization, which negatively affects API yield. Ex. 2017 ¶ 72. Thus, because the Prolastin[®]-C method does not include the heat pasteurization step, that would explain, at least in part, the higher yield of Prolastin[®]-C. Pet. Reply 18.

Given these issues with Patent Owner’s argument, we determine that Patent Owner has not offered sufficient evidence to establish unexpected results.

I. Conclusion

Having considered Petitioner’s prima facie case of obviousness and Patent Owner’s arguments and evidence in rebuttal, we evaluate all of the evidence together to make a final determination of obviousness. *In re Eli Lilly & Co.*, 902 F.2d 943, 945 (Fed. Cir. 1990) (“After a prima facie case of obviousness has been made and rebuttal evidence submitted, all the evidence must be considered anew.”). In doing so, we conclude that Petitioner has shown by a preponderance

of the evidence that each of the challenged claims is unpatentable as obvious over the cited references.

III. PATENT OWNER’S MOTION TO EXCLUDE EVIDENCE

Patent Owner filed a motion to exclude evidence offered by the Petitioner. The party moving to exclude evidence bears the burden of proving that it is entitled to the relief requested—namely, that the material sought to be excluded is inadmissible under the Federal Rules of Evidence (“FRE”). *See* 37 C.F.R. §§ 42.20(c), 42.62(a).

Patent Owner moves to exclude portions of Petitioner’s Reply to Patent Owner’s Response as newly raised material that was not in the Petition, is not part of the grounds in the Decision to Institute, and is outside the scope of Patent Owner’s Response. Specifically, Patent Owner moves to exclude Petitioner’s argument regarding Ralston’s disclosure of purifying the milk of transgenic animals, and the testimony of Dr. Travis and Exhibits 1035–1036, which are related to that argument. Paper 34, 1–2, 7–10. While we agree that that argument is newly raised in the Reply, we did not rely on that argument or any related testimony or exhibits for purposes of this Decision. Patent Owner’s arguments are, therefore, moot.

Patent Owner also seeks to exclude Exhibits 1022 and 1026, which are documents created during the deposition of Dr. Travis, and any testimony regarding those exhibits. *Id.* at 3–5. We did not rely on Exhibits 1022 or 1025 or the related testimony for purposes of this Decision. Patent Owner’s arguments are, therefore, moot.

Because we did not consider any of the evidence that Patent Owner moves to exclude for purposes of this Decision, Patent Owner's motion is dismissed as moot.

IV. CONCLUSION

We conclude that Petitioner has shown by a preponderance of the evidence that claims 1–5, 10–21, 26–28, 32, and 33 of the '180 patent are unpatentable.

V. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that claims 1–5, 10–21, 26–28, 32, and 33 of the '180 patent are held unpatentable;

FURTHER ORDERED that Patent Owner's Motion to Exclude Evidence is *dismissed as moot*; and

FURTHER ORDERED that, because this is a Final Written Decision, the 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.

IPR2014-00899
Patent 6,462,180 B1

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