UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC.,
Petitioner,

v.

SANOFI-AVENTIS DEUTSCHLAND GMBH,
Patent Owner.

Case No. IPR2017-01528
U.S. Patent No. 7,713,930 B2

PATENT OWNER SANOFI-AVENTIS DEUTSCHLAND GMBH'S NOTICE OF APPEAL UNDER 37 C.F.R. § 90.2(a)

Pursuant to 35 U.S.C. §§ 141-144, 319 and 37 C.F.R. § 90.2(a), notice is hereby given that Patent Owner Sanofi-Aventis Deutschland GmbH ("Sanofi") appeals to the United States Court of Appeals for the Federal Circuit from the Final Written Decision (Paper No. 87) (the "Final Written Decision"), in IPR2017-01528, entered on December 12, 2018, by the United States Patent and Trademark Office, Patent Trial and Appeal Board (the "Board"), and from all orders, decisions, rulings, and opinions antecedent to the Final Written Decision. A copy of the Final Written Decision is attached hereto as Exhibit A.

In accordance with 37 C.F.R. § 90.2(a)(3)(ii), Sanofi further indicates that the issues on appeal may include, but are not limited to, the Board's determination that claims 1-20 of U.S. Patent Number 7,713,930 have been shown to be unpatentable under 35 U.S.C. § 103 in view of the grounds of unpatentability identified in the Board's Final Written Decision, challenges to any findings supporting the determination, the Board's failure to provide Sanofi with sufficient due process, the Board's failure to properly consider evidence of record, the Board's legal errors in undertaking the obviousness analysis, the Board's failure to consider Patent Owner's arguments in support of patentability, the Board's procedural errors including its failure to strike and/or exclude certain of Petitioner's arguments and evidence and the Board's failure to provide Patent Owner an opportunity to offer rebuttal argument and evidence, the Board's

findings that conflict with the evidence of record and are not supported by substantial evidence, and other issues decided adversely to Patent Owner.

Simultaneous with this submission, a copy of this Notice of Appeal is being filed through the Patent Trial and Appeal Board End to End ("PTAB E2E") System. In addition, a copy of the Notice of Appeal, along with the required docketing fee, is being filed with the Clerk of Court for the United States Court of Appeals for the Federal Circuit.

Dated: January 4, 2019

Respectfully submitted,

/Elizabeth Stotland Weiswasser/

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CERTIFICATE OF SERVICE

The undersigned certifies that, in addition to being filed electronically through the PTAB E2E System, the original version of Patent Owner Sanofi-Aventis Deutschland GmbH's Notice of Appeal, has been sent via priority mail on January 4, 2019, to the Director of the United States Patent and Trademark Office, at the following address:

Director of the United States Patent and Trademark Office
c/o Office of the General Counsel
United States Patent and Trademark Office
Madison Building East, Room 10B20
600 Dulany Street
Alexandria, VA 22314-5793

The undersigned also certified that a true and correct copy of Patent Owner Sanofi-Aventis Deutschland GmbH's Notice of Appeal and the required filing fee were filed electronically via CM/ECF on January 4, 2019, with the Clerk of Court for the United States Court of Appeals for the Federal Circuit.

The undersigned also certifies that a true and correct copy of Patent Owner Sanofi-Aventis Deutschland GmbH's Notice of Appeal was served on January 4, 2019, via electronic mail, upon the following counsel of record for Petitioner Mylan Pharmaceuticals Inc.:

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EXHIBIT A

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Paper No. 87
Entered: December 12, 2018

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC.,
Petitioner,

v.

SANOFI-AVENTIS DEUTSCHLAND GMBH,
Patent Owner.

Case IPR2017-01528
Patent 7,713,930 B2

Before ERICA A. FRANKLIN, ROBERT A. POLLOCK, and MICHELLE N. ANKENBRAND, *Administrative Patent Judges.*

ANKENBRAND, *Administrative Patent Judge*.

FINAL WRITTEN DECISION

Finding Claims 1–20 Unpatentable
35 U.S.C. § 318(a); 37 C.F.R. § 42.73

Denying-in-part and Dismissing-in-part as Moot Patent Owner's Motion to Strike
37 C.F.R. §§ 42.5(a), 42.20(a)

Dismissing Petitioner's Motion to Exclude and Denying-in-part and Dismissing-in-part as Moot Patent Owner's Motion to Exclude
37 C.F.R. § 42.64(c)

Denying Petitioner's First Motion to Seal, Granting Petitioner's Second Motion to Seal, and Granting Patent Owner's Motions to Seal
37 C.F.R. § 42.54

I. INTRODUCTION

This is a Final Written Decision in an *inter partes* review challenging the patentability of claims 1–20 (collectively, the "challenged claims") of U.S. Patent No. 7,713,930 B2 (Ex. 1002, "the '930 patent"). We have jurisdiction under 35 U.S.C. § 6. For the reasons that follow, we determine that Petitioner demonstrates, by a preponderance of the evidence, that the challenged claims are unpatentable.

A. Procedural History

Mylan Pharmaceuticals, Inc. ("Petitioner") filed a Petition (Paper 2, "Pet.") requesting an *inter partes* review under 35 U.S.C. § 311. Petitioner supported its Petition with the testimony of Samuel H. Yalkowsky, Ph.D. (Ex. 1003). On December 13, 2017, we instituted trial to determine whether:

1. Claims 1–20 of the '930 patent are unpatentable under 35 U.S.C. § 103 as obvious over the combination of Lantus Label[1] and Lougheed[2];
2. Claims 1–18 and 20 of the '930 patent are unpatentable under 35 U.S.C. § 103 as obvious over the combination of Lantus Label and FASS[3];

[1] Physicians' Desk Reference, Lantus entry 709–713 (55th ed. 2001) (Ex. 1004). We refer in this decision to the corrected version of Exhibit 1004.

[2] W.D. Lougheed et al., *Physical Stability of Insulin Formulations*, 32 DIABETES 424–432 (1983) (Ex. 1006).

[3] Farmaceutiska Specialiteter I Sverige ("FASS"), Summary of Product Characteristics Entry for Insuman Infusat (2000) (certified English translation provided as Ex. 1007A; original Swedish version provided as Ex. 1007).

3. Claims 1–18 and 20 of the '930 patent are unpatentable under 35 U.S.C. § 103 as obvious over the combination of Lantus Label and Grau[4];
4. Claim 19 of the '930 patent is unpatentable over the combination of Lantus Label, FASS or Grau, and Lougheed;
5. Claims 1–20 of the '930 patent are unpatentable under 35 U.S.C. § 103 as obvious over the combination of Owens[5] and Lougheed;
6. Claims 1–18 and 20 of the '930 patent are unpatentable under 35 U.S.C. § 103 as obvious over the combination of Owens and FASS;
7. Claims 1–18 and 20 of the '930 patent are unpatentable under 35 U.S.C. § 103 as obvious over the combination of Owens and Grau; and
8. Claim 19 of the '930 patent is unpatentable over the combination of Owens, FASS or Grau, and Lougheed.

Paper 12 ("Institution Decision" or "Inst. Dec.").

Following institution, Sanofi-Aventis Deutschland GmbH ("Patent Owner") filed a Response (Paper 26, "Resp.") and supporting declarations from Bernhardt Trout, Ph.D. (Ex. 2006) and Laurence C. Baker, Ph.D. (Ex. 2039). Petitioner filed a Reply (Paper 41, "Reply") and supporting declarations from Dr. Yalkowsky (Ex. 1181), Robert S. Langer, Sc.D. (Ex. 1111), Deforest McDuff, Ph.D. (Ex. 1169), and William C. Biggs, M.D. (Ex. 1174).

During an interlocutory teleconference on July 17, 2018, we authorized Patent Owner to file a motion to strike certain arguments Petitioner made in the

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[4] Ulrich Grau & Christopher D. Saudek, *Stable Insulin Preparation for Implanted Insulin Pumps – Laboratory & Animal Trials*, 36 DIABETES 1453–59 (1987) (Ex. 1008).

[5] David R. Owens et al., *Pharmacokinetics of ^{125}I-Labeled Insulin Glargine (HOE 901) in Healthy Men – Comparison with NPH insulin and the influence of different subcutaneous injection sites*, 23 DIABETES CARE 813–819 (2000) (Ex. 1005).

Reply. *See* Ex. 2055, 43:3–20 (Transcript of July 17, 2018 teleconference). We also authorized Patent Owner to file a sur-reply as to certain, but not all, arguments in Petitioner's Reply. *Id.* at 42:13–43:2. Subsequently, Patent Owner filed a Sur-reply (Paper 44) and a Motion to Strike (Paper 45, "Mot. to Strike"). Petitioner filed an opposition to Patent Owner's Motion to Strike (Paper 50, "Mot. to Strike Opp.").

Petitioner and Patent Owner also filed several motions to seal certain briefs and exhibits. Paper 43 (Patent Owner's Supplemental Motion to Seal), Paper 76 (Patent Owner's Motion to Seal), Paper 84 (Petitioner's Motion to Seal), Paper 86 (Petitioner's Motion to Seal and for Entry of Proposed Protective Order). Both parties also filed motions to exclude, which have been fully briefed. *See* Papers 55, 62, 69 (briefing related to Petitioner's Motion to Exclude); Papers 59, 65, 68 (briefing related to Patent Owner's Motion to Exclude). Patent Owner also filed Observations on the Cross-Examination Testimony of Petitioner's Reply Declarants, and Petitioner responded. Papers 58, 66. The record further includes a transcript of the final oral hearing conducted on September 27, 2018. Paper 75 ("Tr.").

After the final oral hearing, we authorized Patent Owner to file a second sur-reply and additional evidence, and we authorized Petitioner to file a sur-sur-reply. Paper 75. Subsequently, Patent Owner filed the Sur-reply (Papers 77 (confidential version), 78 (public version)), and Petitioner filed the Sur-sur-reply (Papers 83 (confidential version), 85 (public version)).

B. Related Matters

The parties identify the following pending litigation involving the '930 patent: *Sanofi-Aventis U.S. LLC v. Merck Sharp & Dohme Corp.*, C.A. No. 1:16-cv-00812-RGA (D. Del.); *Sanofi-Aventis U.S. LLC v. Merck Sharp & Dohme*

Corp., C.A. No. 2:17-cv-05914 (D.N.J.); *Sanofi- Aventis U.S. LLC v. Mylan N.V.*, C.A. No. 2:17-cv-09105-SRC (D.N.J); and *Sanofi- Aventis U.S. LLC v. Mylan N.V.*, C.A. No. 1:17-cv-00181-IMK (D.W.V.). Paper 6, 2; Paper 13, 1–2. The parties also identify the following concluded litigation involving the '930 patent: *Sanofi-Aventis U.S. LLC v. Eli Lilly & Co.*, C.A. No. 1:14-cv-00113-RGA (D. Del.); *Sanofi-Aventis U.S. LLC v. Eli Lilly & Co.*, C.A. No. 1:14-cv-00884-RGA (D. Del.). Paper 6, 2; Paper 13, 1.

And the parties identify as related Case IPR2017-01526— an *inter partes* review involving U.S. Patent No. 7,476,652 (Ex. 1001), which issued from a parent application to the application that issued as the '930 patent. Paper 6, 2; Paper 13, 2. Concurrent with this decision, we issue a Final Written Decision in Case IPR2017-01526.

C. The '930 Patent (Ex. 1002)

The '930 patent, titled "Acidic Insulin Preparations Having Improved Stability," issued on May 11, 2010. Ex. 1002, (45), (54). The '930 patent relates to a pharmaceutical formulation comprising a modified insulin—insulin glargine (Gly(A21)-Arg(B31)-Arg(B32)-human insulin); at least one surfactant; at least one preservative; and optionally an isotonicizing agent, buffers or other excipients, wherein the formulation has a pH in the acidic range. *See, e.g.*, Ex. 1002, Abstract, 1:15–23, 11:49–56. The formulation is used to treat diabetes, and is "particularly suitable for preparations in which a high stability to thermal and/or physicomechanical stress is necessary." *Id.* at 1:19–22. According to the specification, insulin glargine was a known modified insulin with a prolonged duration of action injected once daily as an acidic, clear solution that "precipitates on account of its solution properties in the physiological pH range of the subcutaneous tissue as a stable hexamer associate." *Id.* at 2:56–61.

The specification explains that, at acidic pH, insulins exhibit decreased stability and increased susceptibility to aggregation in response to thermal and physicomechanical stress, resulting in turbidity and precipitation (i.e., particle formation). *Id.* at 3:7–11. Such stresses can arise during use or shaking of the insulin solution. *Id.* at 5:43–67. Also contributing to aggregation are hydrophobic surfaces with which the insulin solution comes into contact during storage and administration, including those on glass storage vessels, solution/air boundary layers, sealing cap stopper materials, and siliconized insulin syringes. *Id.* at 3:13–22.

According to the specification, the applicants "surprisingly [] found" that adding surfactants to the insulin solution or formulation "can greatly increase the stability of acidic insulin preparations," thereby producing insulin solutions with "superior stability to hydrophobic aggregation nuclei for several months [u]nder temperature stress." *Id.* at 3:45–49; *see id.* at 5:29–11:47 (examples showing that adding the surfactant polysorbate 20 or polysorbate 80 to an insulin glargine formulation stabilizes the formulation in use and during physicomechanical stressing).

D. Illustrative Claim

We instituted an *inter partes* review of claims 1–20 of the '930 patent, of which claim 1 is independent. Claim 1 is illustrative of the claimed subject matter and recites:

> 1. A pharmaceutical formulation comprising Gly(A21), Arg(B31), Arg(B32)-human insulin;
>
> at least one chemical entity chosen from esters and ethers of polyhydric alcohols;
>
> at least one preservative; and
>
> water,

wherein the pharmaceutical formulation has a pH in the acidic range from 1 to 6.8.

Ex. 1002, 11:49–56.

II. EVIDENTIARY MOTIONS

Patent Owner filed a motion to strike various arguments and evidence. Petitioner and Patent Owner also filed motions to exclude certain evidence. We first address Patent Owner's motion to strike and then turn to the parties' motions to exclude.

A. *Patent Owner's Motion to Strike*

Patent Owner requests to strike what it contends are two new arguments that Petitioner makes based on Lantus Label: (1) that Lantus Label's teaching of different storage requirements for different product sizes would have indicated an aggregation problem and provided a reason to modify the Lantus Label formulation; and (2) that Lantus Label sometimes refers to insulin glargine as "insulin," which would have suggested that it "'behaved similar to other insulins.'" Mot. to Strike 1–2. Patent Owner also seeks to strike paragraphs 100 and 120–26 of Dr. Langer's declaration (Ex. 1111), as well as paragraphs 8 and 20–22 of Dr. Yalkowsky's reply declaration (Ex. 1181). *Id.* at 1. According to Patent Owner, the arguments and testimony are outside the scope of a proper reply. Petitioner opposes. Mot. to Strike Opp. 1–2.[6]

[6] Patent Owner filed a sur-reply addressing Petitioner's argument about the different storage requirements for different Lantus product sizes and additional evidence supporting its sur-reply. Paper 77; Exs. 2060–2069. And Petitioner filed a sur-sur-reply in response to Patent Owner's sur-reply on this issue. Paper 83.

We do not rely on the arguments or evidence that Patent Owner seeks to strike in making our ultimate determination on the patentability of the challenged claims. Thus, we dismiss Patent Owner's request as moot.

Patent Owner next argues that we should strike what it contends are new arguments and evidence (Ex. 1111 ¶¶ 147, 159, 161) based on new insulin references. Mot. to Strike 2–3. Specifically, Patent Owner directs us to Petitioner's argument that an ordinarily skilled artisan would have reasonably expected success because "at least 20 prior art references allegedly show surfactants tried with proteins, and at least 12 references allegedly show surfactants with insulin (not glargine)." *Id.* at 3. Patent Owner contends that this argument and supporting evidence amounts to "a do-over" "with new references presented through a new expert." *Id.* Petitioner opposes, arguing that the Petition provides evidence that the claimed surfactants were commonly used in protein formulations and provides one example for insulin. Mot. to Strike Opp. 2. Petitioner further asserts that the argument and evidence are properly submitted in reply because they directly respond to Patent Owner's argument that an ordinarily skilled artisan would not have reasonably expected success because of "alleged unpredictable effects that surfactants 'could' have or that 'were possible.'" *Id.* at 3 (citing Resp. 48–52).

We agree with Petitioner that its argument and evidence is within the proper scope of a reply. The argument does not raise a new theory of unpatentability or provide new references in support of Petitioner's prima facie obviousness case. Rather, we find that the formulations discussed in the Reply and Dr. Langer's declaration support the initial arguments raised in the Petition and directly respond to Patent Owner's arguments about reasonable expectation of success and further serve to "document the knowledge that skilled artisans would bring to bear in

reading the prior art identified as producing obviousness." *Anacor Pharm., Inc. v. Iancu*, 889 F.3d 1372, 1380–81 (Fed. Cir. 2018); *see Ariosa Diagnostics v. Verinata Health, Inc.*, 805 F.3d 1359, 1365 (Fed. Cir. 2015); *Belden Inc. v. Berk-Tek LLC*, 804 F.3d 1064, 1078–80 (Fed. Cir. 2015) (explaining that the Board may rely on new evidence submitted with a reply because that evidence was responsive to the arguments in patent owner's response). Accordingly, we deny Patent Owner's request to strike Petitioner's argument and Dr. Langer's testimony about additional insulin formulations.

Patent Owner next requests that we strike Petitioner's reply argument and evidence (Ex. 1111 ¶¶ 127–145; Ex. 1133; Ex. 1174) about "'public' knowledge," arguing that Petitioner presents a new theory based on documents about a recall, and hearsay evidence from a new fact witness about a Lantus vial that became turbid in a hot car. Mot. to Strike 4–5. Patent Owner also argues that Petitioner improperly relies on Patent Owner's confidential internal documents to support the obviousness challenge. *Id.* According to Patent Owner, Petitioner's argument is not responsive to anything in the Response. *Id.* at 5. Petitioner opposes, arguing that it has not presented any new theory. Mot. to Strike Opp. 4–5.

We do not rely on the arguments or evidence that Patent Owner seeks to strike in making our ultimate determination on the patentability of the challenged claims. Thus, we dismiss Patent Owner's request as moot.

Finally, Patent Owner requests that we strike the Reply and Dr. Langer's declaration in their entirety. Mot. to Strike 5–7. Patent Owner argues that "Petitioner is attempting a complete re-do of its Petition, contrary to the letter and spirit of the IPR framework." *Id.* at 6. Patent Owner further argues that Dr. Langer's declaration is "an 87-page declaration from a new expert who . . . offers alleged support for a number of new theories and presents almost 60 new

exhibits." *Id.* at 5. Petitioner opposes, arguing that both its Reply and Dr. Langer's declaration are proper. Mot. to Strike Opp. 5–7.

We do not agree with Patent Owner that Petitioner's Reply and Dr. Langer's declaration are improper. Rather, we find that the Reply and Dr. Langer's declaration support the initial arguments raised in the Petition, are in fair response to the arguments Patent Owner raises in the Response, and also fairly respond to Dr. Trout's testimony. *Belden Inc.*, 804 F.3d at 1078. Further, Patent Owner has been granted, and indeed, filed two sur-replies addressing arguments made in Petitioner's Reply and Petitioner's supporting evidence. Papers 44, 77. Accordingly, we deny Petitioner's request to strike the Reply and Dr. Langer's declaration in their entirety.

In sum, we deny-in-part and dismiss-in-part as moot Patent Owner's Motion to Strike.

E. Motions to Exclude

Petitioner and Patent Owner each filed a motion to exclude. We address Petitioner's motion first and then turn to Patent Owner's motion.

1. Petitioner's Motion to Exclude

Petitioner moves to exclude Exhibits 2042–2045 and Exhibits 2051–2052. Paper 55 ("Pet. Mot. to Exclude"). Exhibits 2042–2045 are certain documents Dr. Baker relied upon to support his opinions regarding the commercial success of the Lantus Product. Pet. Mot. to Exclude, 1–2. Exhibit 2051 is an Order from the related Delaware litigation, and Exhibit 2052 is a compilation of excerpts from the trial transcript in that same litigation. *Id.* at 2–4. Petitioner moves to exclude Exhibits 2042–2045 as irrelevant and prejudicial under Federal Rules of Evidence ("FRE") 402 and 403, and as improper summaries under FRE 1006. *Id.* at 1–2. Petitioner moves to exclude Exhibits 2051–2052 as irrelevant and prejudicial under

FRE 402 and 403, and further moves to exclude Exhibit 2052 as an improper summary under FRE 1006. *Id.* at 2–3. Patent Owner opposes. Paper 62.

We do not rely on any of Exhibits 2042–2045 or Exhibits 2051–2052 in making our ultimate determination on the patentability of the challenged claims. Accordingly, we need not decide Petitioner's Motion to Exclude those exhibits, and we dismiss the motion as moot.

2. Patent Owner's Motion to Exclude

Patent Owner moves to exclude the following exhibits, or portions thereof: Exhibits 1144–1161; Exhibit 1111; Exhibit 1169 ¶¶ 13–14, 40–49; Exhibit 1174; Exhibit 1181 ¶¶ 15–16, 18–24, 26, 28, 30–36, 38–51, 53–56; Exhibit 1114; and Exhibits 1057–1058. Paper 59 ("Patent Owner Mot. to Exclude"). Patent Owner notes that the exhibits fall into several categories: (a) documents and testimony related to Patent Owner's confidential information; (b) testimony from witnesses that Patent Owner alleges lack the scientific, technical, or other specialized knowledge required under Federal Rule of Evidence 702; (c) testimony that is not cited in the Petition or Reply; and (d) evidence that Patent Owner alleges is inadmissible hearsay. *Id.* We address each category below.

a. Documents and testimony related to Patent Owner's confidential information

Patent Owner moves to exclude Exhibits 1144–1161 and Dr. Langer's declaration (Ex. 1111) in its entirety. Patent Owner Mot. to Exclude 5–10. Patent Owner argues that we should exclude Exhibits 1144–1161 under FRE 402 and 403 because confidential information is irrelevant to the knowledge of an ordinarily skilled artisan. *Id.* at 5–7. Patent Owner argues that we should exclude Dr. Langer's declaration under FRE 702 because his opinions regarding obviousness are compromised by his reliance on Patent Owner's confidential

documents. *Id.* at 7–10. Although Patent Owner seeks to exclude Dr. Langer's declaration in its entirety, Patent Owner identifies only certain paragraphs of the declaration as containing or relying upon the confidential information. *See id.* at 7–8 (identifying paragraphs 117–126, 130–145, 148, 149, 163–165, 168–172, and 177 of Dr. Langer's declaration). Petitioner opposes, arguing that it does not offer the exhibits as prior art, but rather, to refute Patent Owner's argument that an ordinarily skilled artisan would not have viewed the prior art the way the Petition proposes. Paper 65, 1–2. Petitioner contends that such evidence is relevant to the credibility of Patent Owner's positions and Dr. Trout's testimony. *Id.* at 2.

We deny Patent Owner's request to exclude the entirety of Dr. Langer's declaration because Patent Owner's arguments go to the weight we should accord Dr. Langer's testimony and Dr. Langer's credibility, not the declaration's admissibility. *See, e.g.*, *Liberty Mutual Ins. Co. v. Progressive Casualty Ins. Co.*, Case CBM2012-00002, slip op. at 70 (Paper 66) (PTAB Jan. 23, 2014) ("[T]he Board, sitting as a non-jury tribunal, is well-positioned to determine and assign appropriate weight to the evidence presented in this trial, without resorting to formal exclusion that might later be held reversible error."). Further, although Patent Owner moves to exclude Dr. Langer's declaration under FRE 702, Patent Owner's motion does not discuss why the declaration is inadmissible under that rule.

As to Exhibits 1144–1161 and paragraphs 117–26, 130–45, 148, 149, 163–65, 168–72, and 177 of Dr. Langer's declaration, we do not rely on any of that evidence in making our ultimate determination on the patentability of the challenged claims. Accordingly, we need not decide Patent Owner's motion as to those exhibits and paragraphs, and we dismiss that portion of Patent Owner's motion as moot.

b. Testimony from witnesses that allegedly lack the knowledge required under Federal Rule of Evidence 702

Patent Owner moves to exclude paragraphs 40–43 of Dr. McDuff's declaration (Ex. 1169) and the entirety of Dr. Biggs' declaration (Ex. 1174), arguing that the testimony lacks the scientific, technical, or other specialized knowledge that FRE 702 requires. Patent Owner Mot. to Exclude 10–13. Petitioner opposes. Paper 65, 5–6.

We do not rely on Dr. Biggs' declaration or any of paragraphs 40–43 of Dr. McDuff's declaration in making our ultimate determination on the patentability of the challenged claims. Accordingly, we need not decide Patent Owner's motion as to those exhibits and paragraphs, and we dismiss that portion of Patent Owner's motion as moot.

c. Testimony not cited in the Petition or Reply

Patent Owner moves to exclude portions of Dr. Langer's, Dr. McDuff's, Dr. Biggs' declarations, as well as portions of Dr. Yalkowsky's reply declaration and Exhibit 1114 as irrelevant under FRE 403 because Petitioner did not cite that evidence in its Petition or Reply. Patent Owner Mot. to Exclude 14. Petitioner opposes. Paper 65, 8–9.

As to Exhibit 1114, we do not rely on that evidence in making our ultimate determination of the patentability of the challenged claims. Accordingly, we need not decide Patent Owner's motion as to that exhibits, and we dismiss that portion of Patent Owner's motion as moot.

Turning to the expert declarations, although Patent Owner cites *SK Innovation Co., Ltd. v. Celgard, LLC*, Case IPR2014-00679, slip op. at 49 (Paper 58) (PTAB Sept. 25, 2015) as supporting exclusion of certain information, we do not agree. First, we note that *SK Innovation* is not precedential and, therefore, not

binding. Moreover, in *SK Innovation*, the Board excluded exhibits—not portions thereof—that a party did not cite during the course of the proceeding. Here, Petitioner cites to and relies upon each declaration exhibit its Reply. Accordingly, we deny Patent Owner's motion as to those declarations.

d. Allegedly inadmissible hearsay evidence

Patent Owner moves to exclude paragraphs 20–22 and 25–30 of Dr. Biggs' declaration (Ex. 1174) and Exhibits 1057–1058 under FRE 802 as containing inadmissible hearsay. Patent Owner Mot. to Exclude 13, 15. Petitioner opposes. Paper 65, 7–8, 10.

We do not rely on paragraphs 20–22 and 25–30 Dr. Biggs' declaration or Exhibits 1057–1058 in making our ultimate determination on the patentability of the challenged claims. Accordingly, we need not decide Patent Owner's motion as to those paragraphs and exhibits, and we dismiss that portion of Patent Owner's motion as moot.

In sum, we deny-in-part and dismiss-in-part as moot Patent Owner's Motion to Exclude.

III. DISCUSSION OF UNPATENTABILITY CHALLENGES

Petitioner bears the burden of proving unpatentability of the challenged claims, and that burden never shifts to Patent Owner. *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015). To prevail, Petitioner must establish the facts supporting its challenge by a preponderance of the evidence. 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d). Below, we explain how Petitioner has met its burden with respect to the challenged claims.

A. Principles of Law

Obviousness is a question of law based on underlying determinations of fact. *Graham v. John Deer Co.*, 383 U.S. 1, 17 (1966); *Richardson-Vicks, Inc. v. Upjohn Co.*, 122 F.3d 1476, 1479. The underlying factual determinations include: (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, i.e., secondary considerations. *See Graham*, 383 U.S. at 17–18. Subsumed within the *Graham* factors are the requirements that all claim limitations be found in the prior art references and that the skilled artisan would have had a reasonable expectation of success in combining the prior art references to achieve the claimed invention. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007). "Obviousness does not require absolute predictability of success . . . all that is required is a reasonable expectation of success." *In re O'Farrell*, 853 F.2d 894, 903–4 (Fed. Cir. 1988).

Moreover, "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007). "If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability." *Id.* at 417.

B. Level of Ordinary Skill in the Art

We consider each asserted ground of unpatentability in view of the understanding of a person of ordinary skill in the art. Petitioner contends that, as of June 2002, a person of ordinary skill in the art would have had "an M.S. or Ph.D. or equivalent in pharmacology, pharmaceutical sciences, or a closely related field; or an M.D. with practical academic or industrial experience in peptide injection formulations or stabilizing agents for such formulations." Pet. 13 (citing

Dr. Yalkowsky's testimony, Ex. 1003 ¶¶ 31–34). As an example, Petitioner notes and Dr. Yalkowsky testifies, that a person of ordinary skill in the art would have had experience in surfactants that are commonly used in peptide injection formulations and an understanding of the factors that contribute to the molecule's instability. *Id.*; Ex. 1003 ¶ 33. Petitioner further contends that an ordinary artisan may have "consulted with one or more team members of experienced professionals to develop an insulin formulation resistant to the well-known aggregation propensities of insulin molecules." Pet. 13; *see* Ex. 1003 ¶ 34.

Patent Owner does not offer a separate description for one of ordinary skill in the art. Nevertheless, Patent Owner disputes some aspects of Petitioner's description of the level of ordinary skill in the art. Resp. 18–20. Specifically, Patent Owner contends that Petitioner: (1) describes the field of invention improperly; (2) asserts that the skilled artisan would have been more than ordinarily creative by consulting other team members; and (3) incorrectly suggests that a person of ordinary skill in the art "would have been aware of or expected that the original LANTUS glargine formulation would be prone to aggregation under normal use conditions." *Id.*

The parties' disputes about the person of ordinary skill in the art appear to be directed to an issue at the heart of this case—what an ordinarily skilled artisan would have expected as to aggregation of insulin glargine. We need not—and do not—decide that issue as part of determining the level of ordinary skill in the art. We find that a person of ordinary skill in the art would have possessed an M.S., a Ph.D., or equivalent in pharmacology, pharmaceutical sciences, or a closely related field; or an M.D. with practical academic or industrial experience in peptide injection formulations or stabilizing agents for such formulations. We further find that a person of ordinary skill in the art would have understood instabilities that

affect proteins in formulation, and that proteins may aggregate. *See* Ex. 1003 ¶ 33; Ex. 2006 ¶ 34. This description is consistent with the level of ordinary skill in the art at the time of the invention as reflected in the prior art in this proceeding. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (the prior art, itself, can reflect the appropriate level of ordinary skill in art).

Further, based on Petitioner's and Patent Owner's experts' statements of qualifications and curriculum vitae, we find that Dr. Yalkowsky, Dr. Langer, and Dr. Trout[7] are qualified to opine from the perspective of a person of ordinary skill in the art at the time of the invention. *See* Ex. 1003, Ex. A (Dr. Yalkowsky's curriculum vitae); Ex. 1111A (Dr. Langer's curriculum vitae); Ex. 2007 (Dr. Trout's curriculum vitae).

C. Claim Construction

The Board interprets claims in an unexpired patent using the "broadest reasonable construction in light of the specification of the patent." 37 C.F.R. § 42.100(b) (2016)[8]; *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46

[7] The parties do not offer their additional witnesses as persons of ordinary skill in the art. Petitioner offers Dr. Biggs as a fact witness. Tr. 25:11–26:5. And Petitioner and Patent Owner offer Dr. McDuff and Dr. Baker, respectively, not as persons of ordinary skill in the art, but as economic experts to opine on the commercial success of Patent Owner's reformulated Lantus product. *See* Ex. 1169 ¶¶ 1–5, 7 (detailing Dr. McDuff's qualifications scope of work); Ex. 2039 ¶¶ 1–5, 8 (detailing Dr. Baker's qualifications and assignment).

[8] The Office recently changed the claim construction standard applicable to an *inter partes* review. *See* Changes to the Claim Construction Standard for Interpreting Claims in Trial Proceedings Before the Patent Trial and Appeal Board, 83 Fed. Reg. 51,340 (Oct. 11, 2018). The rule changing the claim construction standard, however, does not apply to this proceeding because Petitioner filed its Petition before the effective date of the final rule, i.e., November 13, 2018. *Id.* at 51,340 (rule effective date and applicability date), 51,344 (explaining how the Office will implement the rule).

(2016). Under that standard, claim terms are given their ordinary and customary meaning in view of the specification, as would be understood by one of ordinary skill in the art at the time of the invention. *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. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

We determined in the Institution Decision that no claim term required express construction based on the record developed at that stage of the proceeding. Inst. Dec. 10–11. Neither party contests our decision not to expressly construe claim terms. *See* Resp. 18; *see generally* Reply. On the full record before us, we can determine the patentability of the challenged claims without expressly construing any claim term. *See Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) ("only those terms need be construed that are in controversy, and only to the extent necessary to resolve the controversy").

D. Summary of Asserted References

Before turning to the instituted grounds, we provide a brief summary of the asserted references.[9]

3. Lantus Label (Ex. 1004)

Lantus Label describes the commercially available Lantus formulation, a solution of insulin glargine (21^{A}-Gly-30^{B}-a-L-Arg-30^{B}-b-L-Arg-human insulin) "a recombinant human insulin analog that is long-acting (up to 24-hr duration of action)" and "produced by recombinant DNA technology." Ex. 1004, 3. The Lantus formulation is prescribed for injection and "consists of insulin glargine

[9] Although we refer to the original pagination associated with each reference in footnotes 1–5, setting forth the full citation of the references, we refer in our discussion to the pagination Petitioner added to each reference.

dissolved in a clear aqueous fluid." *Id.* Each milliliter of Lantus contains 100 IU insulin glargine, 30 mcg zinc, 2.7 mg m-cresol, 20 mg glycerol 85%, and water for injection. *Id.* The pH of Lantus is approximately 4, and is adjusted by adding aqueous solutions of hydrochloric acid and sodium hydroxide to the formulation. *Id.*

Lantus Label also describes the pharmacodynamics of Lantus, explaining that Lantus is "completely soluble" at pH 4, but "[a]fter injection into the subcutaneous tissue, the acidic solution is neutralized, leading to formation of microprecipitates from which small amounts of insulin glargine are slowly released." *Id.* As a result, Lantus has a relatively constant concentration/time profile, which allows once-daily dosing. *Id.*

Lantus Label instructs that Lantus "must only be used if the solution is clear and colorless with no particles visible." *Id.* at 5; *see also id.* at 6 ("You should look at the medicine in the vial. If the medicine is cloudy or has particles in it, throw the vial away and get a new one.").

4. Owens (Ex. 1005)

Owens describes clinical studies designed to determine the subcutaneous absorption rates of insulin glargine with 15, 30, and 80 μg/ml zinc. Ex. 1005, 1. Owens teaches that insulin glargine is "a di-arginine (30^{B}a-L-Arg-30^{B}b-L-Arg) human insulin analog in which asparagine at position 21^{A} is replaced by glycine." *Id.* Owens discloses that such a replacement "achieves an increase in the isoelectric point from pH 5.4 (native insulin) to 7.0 and stabilization of the molecule. When injected as a clear acidic solution (pH 4.0), insulin glargine undergoes microprecipitation in the subcutaneous tissue, which retards absorption." *Id.*

In one of the studies, Owens administers subcutaneously, from 5-ml vials, a formulation containing 100 IU/ml insulin glargine[15] or insulin glargine[80], m-cresol, and glycerol at pH 4.0, with 15 and 80 µg/ml zinc, respectively. *Id.* at 3. In another study, Owens administers subcutaneously a formulation containing 100 IU/ml insulin glargine, 30 µg/ml zinc, m-cresol, and glycerol at pH 4.0. *Id.* at 4.

5. Lougheed (Ex. 1006)

Lougheed explains that "the tendency of insulin to aggregate during storage in and delivery from [infusion] devices remains one of the fundamental obstacles to their prolonged clinical use." Ex. 1006, 1. In an attempt to address that obstacle, Lougheed describes studies carried out to determine "the effects of physiologic and nonphysiologic compounds on the aggregation behavior of crystalline zinc insulin (CZI) solutions." *Id.* In those studies, Lougheed tested anionic, cationic, and nonionic surfactants, "in view of their known protein-solvation characteristics and their potential to constrain the conformation of insulin[ ] . . . in aqueous solution[,]" to determine whether such surfactants stabilized CZI solutions against aggregation. *Id.* at 1–2. Specifically, Lougheed subjected CZI solutions that contained the surfactants to continuous rotation or shaking to determine whether the surfactants enhanced stability of the CZI solutions as compared to a control of insulin in distilled water. *Id.* at 3. Lougheed describes the formulation stabilities (FS) of the solutions in terms of continuous rotation (FSR) or shaking (FSS). *Id.*

Lougheed reports that Tween 20, Tween 80, and other "nonionic and ionic surfactants containing the hydrophobic group, $CH_3(CH_2)_N$, where N = 7–16, remarkably stabilized CZI formulations while those lacking such groups demonstrated little or no effect." *Id.* at 1. In Table 3, Lougheed shows the stabilities of formulations containing Tween 20, Tween 80, and other nonionic

surfactants. *Id.* at 3–4. Table 3 demonstrates that Tween 20 had an FSR value of 68 days, while Tween 80 had an FSR value of 48 days, as compared to 10 days for the insulin control solutions. *Id.* at 3. Lougheed concludes from the stability data that the nonionic surfactants inhibited aggregate formation in the CZI solution. *Id.*; *see also id.* at 7 (explaining that the nonionic surfactants "markedly increased the stability of their respective formulations when these were subjected to continuous rotation at 37°C").

6. FASS (Ex. 1007A)

FASS describes Insuman Infusat insulin, which is administered as a subcutaneous, intravenous, or intraperitoneal infusion with an insulin pump for the treatment of diabetes mellitus. Ex. 1007A, 5. Each milliliter of the injectable solution contains 100 IU of biosynthetic insulin, 0.058 mg zinc chloride, 6 mg trometamol, 20 mg glycerol, 0.01 mg poly(oxyethylene, oxypropylene)glycol, 2.7 mg phenol (a preservative), 3.7 mg hydrochloric acid, and up to 1 ml water. *Id.* FASS discloses that poly(oxyethylene, oxypropylene)glycol is a stabilizer in the formulation that "prevents precipitation and flocculation of the insulin." *Id.* at 7.

7. Grau (Ex. 1008)

Grau explains that insulin stability "has been a significant impediment in the development of mechanical medication-delivery devices for diabetes," pointing to the tendency of insulin to "precipitate, aggregate in high-molecular-weight forms, and denature." Ex. 1008, 1. Searching for an insulin preparation to overcome that obstacle, Grau studies the ability of Genapol, a polyethylene-polypropylene glycol, to inhibit insulin aggregation in pump catheters. *Id.*

For the study, Grau uses a "pH-neutral buffered insulin formulation containing either 100 or 400 IU/ml semi-synthetic human insulin [], 27.8 or 111 µg/ml zinc ions (for U-100 and U-400 insulin, respectively) with 2 mg/ml phenol

as a preservative, 16 mg/ml glycerol as an isotonicity agent, 50 mM of tris-(hydroxymethyl)-aminomethane (Tris) buffer, and 10 µg/ml polyethylene-polypropylene glycol (Genapol, Hoechst AG, Frankfurt, FRG)." *Id.* Grau tests the insulin formulations in two ways: (1) on a shaking apparatus in a programmable implantable medication system ("PIMS"); and (2) *in vivo* in dogs implanted with the PIMS devices. *Id.* at 2–3. The PIMS devices include a fluid handling system through which the insulin travels, making contact with titanium metal surfaces and the catheter tubing. *Id.* at 2.

Grau analyzes the insulin using scanning electron microscopy and x-ray microanalysis (for the PIMS mounted on the shaking apparatus) or high performance liquid chromatography (for implanted PIMS). *Id.* at 3. Grau reports that changes to the Genapol formulations after testing were "comparable to those seen in insulin stored in a glass vial at 37°C without movement," and that the surfaces of the PIMS devices "were clean of apparent precipitate even in remote corners." *Id.* at 4–5. Grau concludes that "Genapol, a surface-active polyethylene-polypropylene glycol, effectively prevents adsorption of insulin to hydrophobic surfaces . . . . The data demonstrate good stability in accelerated laboratory tests and after as long as 5 mo between refills in vivo." *Id.* at 6.

E. Patentability Analysis

Below, we discuss whether Petitioner demonstrates, by a preponderance of the evidence, that the challenged claims are unpatentable as obvious over the asserted combinations of cited references.

1. The Limitations of the Challenged Claims

Petitioner contends that the asserted references in each ground teach each and every limitation of the challenged claims. *See* Pet. 23–63. Patent Owner does not dispute Petitioner's contentions in that regard. *See generally* Resp. We find

that Petitioner establishes, by a preponderance of the evidence, that the references asserted in each ground collectively teach each limitation of the claims challenged in that ground.

a. Grounds 1 and 5: Lantus Label or Owens and Lougheed collectively teach or suggest each limitation of claims 1–20

Petitioner asserts that Lantus Label and Owens teach every limitation of claim 1, except for the limitation requiring "at least one chemical entity chosen from esters and ethers of polyhydric alcohols." Pet. 23–24 (citing Ex. 1002, 4:32–34; Ex. 1003 ¶¶ 98–102, 307–310; Ex. 1004, 3), 45–47 (discussing Owens and citing Ex. 1002, 4:32–34; Ex. 1003 ¶¶ 98–102, 410; Ex. 1005, 3–4). For that limitation, Petitioner points to Lougheed's teaching of adding esters of polyhydric alcohols, such as polysorbate 20 (Tween 20), polysorbate 80 (Tween 80), and/or Brij 35 to insulin formulations. *Id.* at 24 (citing Ex. 1003 ¶¶ 308–317; Ex. 1006, 4, 7, Table 3), 46 (citing Ex. 1003 ¶¶ 412–413; Ex. 1006, 1, 4, 7, Table 3). Petitioner makes similar assertions regarding the limitations of the dependent claims, relying on the disclosure of Lantus Label (Ground 1) or Owens (Ground 5) or Lougheed (Grounds 1 and 5) for teaching the additional limitations of those claims. *See id.* at 26–27, 33–34 (relying on Lantus Label and Lougheed for teaching the additional limitations of claims 2, 3, 8, and 18); *id.* at 27–29, 31 (relying on Lantus Label for teaching the additional limitations of claims 4–7, 9, 12, 13, and 17); *id.* at 30–35 (relying on Lougheed for teaching the additional limitations of claims 10, 11, 14–16, 19, and 20); *id.* at 47 (relying on Owens and Lougheed for teaching the additional limitations of claims 2, 3, and 8); *id.* at 48–49, 50–51 (relying on Owens for teaching the additional limitations of claims 4–7, 9, 12, 13, 17); *id.* at 49–50, 51–54 (relying on Lougheed for teaching the additional limitations of claims 10, 11, 14–16, and 18–20).

Patent Owner does not challenge Petitioner's showing or evidence that Lantus Label and Lougheed or Owens and Lougheed teach or suggest each limitation of claims 1–20. *See generally* Resp.[10]

Based on the full trial record, we find that Lantus Label and Lougheed, as well as Owens and Lougheed, collectively teach or suggest each limitation of the challenged claims. Specifically, we find that Lantus Label or Owens teaches every limitation of independent claim 1, except for the limitation requiring "at least one chemical entity chosen from esters and ethers of polyhydric alcohols." Ex. 1004, 3; Ex. 1005, 3–4; *see* Ex. 1003 ¶¶ 130–132, 308–310, 410–411. As explained above, Lantus Label describes the commercially available Lantus formulation, which is a solution of insulin glargine (21^{A}-Gly-30^{B}-a-L-Arg-30^{B}-b-L-Arg-human insulin) for injection. Ex. 1004, 3. Each milliliter of Lantus contains 100 IU insulin glargine, 30 mcg zinc, 2.7 mg m-cresol (a preservative), 20 mg glycerol 85%, and water for injection. *Id.* The pH of Lantus is approximately 4. *Id.* Owens describes insulin glargine formulations containing 100 IU/ml insulin glargine[15] or insulin glargine[80], m-cresol, and glycerol at pH 4.0, with 15 and 80 μg/ml zinc, respectively. Ex. 1005, 3.

We also find that Lougheed teaches adding polysorbate 20 (Tween 20), polysorbate 80 (Tween 80), and/or Brij 35 to insulin formulations. Ex. 1006, 4, 7, Table 3; Ex. 1003 ¶¶ 308–317). And we find that Lantus Label (Ground 1), Owens (Ground 5) or Lougheed (Grounds 1 and 5) teach or suggest the additional limitations of dependent claims 2–20. *See* Pet. 26–35, 47–54; Ex. 1002, 3:7–12; Ex. 1003 ¶¶ 129–131, 135–137, 311–312, 322–323, 326–327, 330–332, 335, 339, 343, 346–348, 351, 354–355, 424–425, 428–431, 434, 438, 441–442, 445–448,

[10] Patent Owner also does not challenge Petitioner's assertions that Lantus Label, Owens, and Lougheed are prior art printed publications. *See generally id.*

450, 453–454; Ex. 1004, 3; Ex. 1005, 1, 3–4; Ex. 1006, 4–7, Tables 2–6. Accordingly, Petitioner demonstrates, by a preponderance of the evidence, that Lantus Label and Lougheed, and Owens and Lougheed, collectively teach each and every limitation of claims 1–20.

b. Grounds 2, 3, 6, and 7: Lantus Label and FASS or Grau, and Owens and FASS or Grau collectively teach each limitation of claims 1–18 and 20

Petitioner asserts that Lantus Label and FASS (Ground 2) or Grau (Ground 3) collectively teach each limitation of claims 1–18 and 20. Pet. 35–44. Petitioner further asserts that Owens and FASS (Ground 6) or Grau (Ground 7) collectively teach each limitation of claims 1–18 and 20. Pet. 54–62. Petitioner's arguments as to how the references collectively teach each limitation of claim 1 are substantially the same as those for claim 1 in Ground 1 (based on Lantus Label and Lougheed), except that Petitioner cites FASS or Grau instead of Lougheed for Grounds 2, 3, 5, and 6, and Petitioner cites Owens instead of Lantus Label for Grounds 5 and 6.

For Grounds 2 and 3, Petitioner argues that Lantus Label teaches all of the elements of claim 1, except that Lantus Label does not teach the limitation requiring "at least one chemical entity chosen from polysorbate and poloxamers," as recited in both claims. Pet. 35–37 (discussing both grounds together). For that limitation in Ground 2, Petitioner directs us to FASS' teaching that adding the stabilizer poly(oxyethylene, oxypropylene)glycol (i.e., a poloxamer, which is also an ether of a polyhydric alcohol) to an insulin formulation "prevents precipitation and flocculation of the insulin." *Id.* at 36 (quoting Ex. 1007A, 7); *see id.* (citing Ex. 1033A, 6); Ex. 1003 ¶ 359 (identifying poloxamers as "examples of ethers of polyhydric alcohols"). For that limitation in Ground 3, Petitioner directs us to Grau's teaching of adding a poloxamer (Genapol) to insulin formulations "to

inhibit insulin aggregation" for various *in vitro* and *in vivo* tests with PIMS devices. *Id.* at 36–37 (citing Ex. 1008, 2–6).

Petitioner makes similar assertions regarding the limitations of the dependent claims, relying on the disclosure of Lantus Label or FASS and Grau, or the disclosures of Lantus Label, FASS and Grau, for teaching the additional limitations of those claims. *See id.* at 38–42 (relying on Lantus Label for teaching the additional limitations of claims 3, 6, 7, 12, and 13); *id.* at 39–40, 44 (relying on Lantus Label and FASS, or Lantus Label and Grau for teaching the additional limitations of claims 2, 4, 5, 8, 9, 17, and 18); *id.* at 41–43 (relying on FASS and Grau for teaching the additional limitations of claims 10, 11, 14–16, and 20).

For Grounds 6 and 7, Petitioner argues that Owens teaches all of the elements of claim 1, except that Owens does not teach "at least one chemical entity chosen from esters and ethers of polyhydric alcohols." Pet. 54–55. For that limitation in Ground 6, Petitioner directs us to FASS' teaching that adding the stabilizer poly(oxyethylene, oxypropylene)glycol (i.e., a poloxamer, which is also an ether of a polyhydric alcohol) to an insulin formulation "prevents precipitation and flocculation of the insulin." *Id.* at 55 (quoting Ex. 1007A, 6); *see id.* (citing Ex. 1033A, 6); Ex. 1003 ¶ 458 (identifying poloxamers as "examples of ethers of polyhydric alcohols"). For that limitation in Ground 7, Petitioner directs us to Grau's teaching of adding a poloxamer (Genapol) to insulin formulations "to inhibit insulin aggregation" for various *in vitro* and *in vivo* tests with PIMS devices. *Id.* at 55 (citing Ex. 1008, 6).

Petitioner makes similar assertions regarding the limitations of the dependent claims, relying on the disclosure of Owens or FASS and Grau, or the disclosures of Owens, FASS and Grau, for teaching the additional limitations of those claims. *See id.* at 56–60 (relying on Owens for teaching the additional

limitations of claims 2, 3, 6–8, 12, and 13); *id.* at 56–58, 61–62 (relying on Owens and FASS or Owens and Grau for teaching the additional limitations of claims 5, 9 17, and 18); *id.* at 59–61 (relying on FASS and Grau for teaching the additional limitations of claims 10, 11, 14–16, and 20).

Patent Owner does not challenge Petitioner's showing or evidence that Lantus Label and FASS or Grau, and Owens and FASS or Grau teach or suggest each limitation of claims 1–20. *See generally* Resp.[11]

As explained above, based on the full trial record, we find that Lantus Label or Owens teaches every limitation of claim 1, except for the limitation requiring "at least one chemical entity chosen from polysorbate and poloxamers." *See supra* § III.E.1.a; Ex. 1004, 3; Ex. 1005, 3–4; *see also, e.g.*, Ex. 1003 ¶¶ 130–132, 308–310, 410–411 (Dr. Yalkowsky's testimony regarding the teachings of Lantus Label and Owens, which we credit). We further find that FASS and Grau teach adding a poloxamer to insulin formulations. Specifically, FASS teaches adding the stabilizer poly(oxyethylene, oxypropylene)glycol (i.e., a poloxamer) to an insulin formulation (Ex. 1007A, 7), and Grau teaches adding the poloxamer Genapol to insulin formulations (Ex. 1008, 2–6). *See also, e.g.*, Ex. 1003 ¶¶ 224, 232 (Dr. Yalkowsky's testimony regarding the teachings of FASS and Grau, which we credit). Thus, Petitioner demonstrates, by a preponderance of the evidence, that Lantus Label and FASS or Grau, and the collective teachings of Owens and FASS or Grau, collectively teach each and every limitation of claim 1.

We also find that Lantus Label and FASS, or Lantus Label and Grau, and Owens and FASS, or Owens and Grau collectively teach or suggest the additional limitations of dependent claims 2–20. *See* Pet. 35–44, 54–62; Ex. 1002, 3:7–12;

[11] Patent Owner also does not challenge Petitioner's additional assertions that FASS and Grau are prior art printed publications. *See generally id.*

Ex. 1003 ¶¶ 373–374, 377–378, 381–383, 386, 390, 394, 397–400, 403, 466–467, 470–471, 474–476, 479, 483, 486–487, 490–493, 496; Ex. 1004, 3; Ex. 1005, 1, 3–4; Ex. 1007A, 5–6; Ex. 1008, 1–2. Accordingly, Petitioner demonstrates, by a preponderance of the evidence, that Lantus Label and FASS or Grau, and Owens and FASS or Grau, collectively teach each and every limitation of claims 2–18 and 20.

c. Grounds 4 and 8: Lantus Label, FASS or Grau, and Lougheed, or Owens FASS or Grau, and Lougheed teach the additional limitation of claim 19

Petitioner asserts that Lantus Label, FASS or Grau, and Lougheed, or Owens, FASS or Grau, and Lougheed collectively teach the additional limitation of claim 19. Pet. 44–45, 62–63. Claim 19 requires "[T]he pharmaceutical formulation as claimed in claim **18**,[12] wherein the excipient is NaCl which is present in a concentration of up to 150 mM." Ex. 1002, 12:49–51. Petitioner asserts that Lougheed discloses using 154 mM of sodium chloride (NaCl) in insulin formulations. Pet. 44, 62 (citing Ex. 1003 ¶¶ 406, 499; Ex. 1006, 5–6. Tables 4, 6). Petitioner notes that although Lougheed's sodium chloride concentration "is slightly over the claimed range," the '930 patent does not suggest that the particular sodium chloride concentration recited in claim 19 is critical. *Id.* at 44–45, 62–63 (citing *In re Aller*, 220 F.2d 454, 456 (CCPA 1955); *Galderma Labs, LP v. Tolmar, Inc.*, 737 F.3d 731, 739 (Fed. Cir. 2013)). Petitioner further asserts that a person of ordinary skill in the art would have a reason to reduce the amount of sodium chloride in the formulation, i.e., to compensate for other formulation components, with a reasonable expectation of success in achieving the

[12] Claim 18 recites "[t]he pharmaceutical formulation as claimed in claim **1**, further comprising one or more excipients chosen from acids, alkalis and salts." Ex. 1002, 12:46–48.

claimed pharmaceutical formulation. *Id.* at 45, 63 (citing Ex. 1003 ¶¶ 406–408, 500).

Patent Owner does not challenge Petitioner's showing or evidence that Lougheed teaches or suggests a sodium chloride concentration that is close to the range recited in claim 19. *See generally* Resp. Nor does Patent Owner challenge Petitioner's showing that reducing the amount of sodium chloride would have been routine. *Id.*

Based on the full trial record, we find that Lougheed teaches the additional limitation of claim 19 for the reasons provided in the Petition. Pet. 44–45, 62–63; *see In re Aller*, 220 F.2d at 456. Thus we find that Petitioner demonstrates, by a preponderance of the evidence, Lantus Label, FASS or Grau, and Lougheed, or Owens, FASS or Grau, and Lougheed collectively teach the additional limitation of claim 19.

2. Reason to Modify Lantus Label's and Owens's Insulin Glargine Formulations to Include Nonionic Surfactants and Reasonable Expectation of Success

A patent "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. Petitioner must also demonstrate that one of ordinary skill in the art would have had a reason to combine the prior art elements to achieve the claimed invention with a reasonable expectation of success. *Par Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1183 (Fed. Cir. 2014). These factors are subsidiary requirements for obviousness subsumed within the *Graham* factors. *Pfizer*, 480 F.3d at 1361.

a. Petitioner's assertions

Petitioner argues that a skilled artisan would have had several reasons to include esters or ethers of polyhydric alcohols, such as the nonionic surfactants polysorbate 20, polysorbate 80, and/or Brij 35 that Lougheed teaches, or the

poloxamers that FASS and Grau teach (collectively, "nonionic surfactants"), in the insulin glargine formulations that Lantus Label and Owens teach. First, Petitioner asserts it was well-known in the art that insulins had a tendency to aggregate upon storage and delivery. Pet. 24–26 (citing Ex. 1001, 3:2–6; Ex. 1003 ¶¶ 308–317; Ex. 1006, 1). As support, Petitioner points to, *inter alia*, Lougheed's teaching that "the tendency of insulin to aggregate during storage in and delivery from . . . devices remains one of the fundamental obstacles to their prolonged clinical use." Ex. 1006, 1; *see* Pet. 24. Petitioner also identifies what it contends are known insulin aggregation factors, including contact with air present in the vials used to store the insulin glargine, the hydrophobic surfaces of the glass vials and rubber stopper material of the vial seals, insulin glargine's acidic pH environment, and the presence of monomers in the insulin glargine solution. Pet. 6–7, 12 (citing Ex. 1001, 3:7–22; Ex. 1003 ¶¶ 105–123, 126; Ex. 1015, 3); *see* Ex. 1003 ¶¶ 105–108, 126 (citing Ex. 1014, 9; Ex. 1015, 3–4, 6; Ex. 1018, 1, 8 Ex. 1031, 1); Reply 5 (citing Ex. 1181 ¶¶ 9, 25).

Second, Petitioner contends that:

> It is beyond reasonable dispute that non-ionic surfactants were used in commercially-available insulin formulations for inhibiting protein aggregation long before the priority date of the '930 patent's claims. Thus a PHOSITA would have had reason to improve commercially-available insulin glargine formulations (*see*, *e.g,* LANTUS® 2000 label [Ex. 1004] and Owens [Ex. 1005]) by anti-aggregation additives, such as Brij 35, Lubrol WX, Triton X100, Tween 20, Tween 80, poloxamer 171, poloxamer 181 and other known surfactants, which were used routinely to inhibit aggregation and formation of particles in peptide and protein-containing formulations.

Pet. 10 (citing Ex. 1003 ¶ 128). Petitioner points to Lougheed's disclosure that surfactants, such as polysorbate 20, polysorbate 80, and Brij 35 enhance the stability of insulin formulations and decrease insulin aggregation. *Id.* at 24 (citing

Ex. 1003 ¶¶ 308–317; Ex. 1006, 4, 7, Table 3). Petitioner also explains that FASS and Grau teach surfactants (poloxamers) to enhance the stability of insulin formulations and inhibit insulin aggregation. *See, e.g., id.* at 36–37 (citing Ex. 1007A, 7; Ex. 1008, 2–5).

Third, Petitioner asserts that Lantus Label explicitly warns patients not to use the product if aggregation occurs such that Lantus Label itself would have provided a reason to modify the insulin glargine formulation. *Id.* at 25 (citing Ex. 1004, 5–6).

Petitioner further asserts that a person of ordinary skill in the art would have had a reasonable expectation of success in achieving the claimed formulations because surfactants, such as polysorbates, "were commonly used to stabilize other protein and peptide formulations well prior to June 2002[,]" and already were included in the Food and Drug Administration Inactive Ingredients Guide for various pharmaceutical formulations. *Id.* at 24–25 (citing Ex. 1003 ¶¶ 314–317; Ex. 1016, 3, Table I). Thus, argues Petitioner, a person of ordinary skill in the art "would have had ample reason" to add polysorbate 20, polysorbate 80, Brij 35, and/or a poloxamer (e.g., poloxamer 181) to an insulin glargine formulation, "with a reasonable expectation that doing so would successfully inhibit or eliminate insulin's well-known propensity to aggregate." *Id.* at 25 (citing Ex. 1003 ¶¶ 317, 320); *e.g., id.* at 37–38 (citing Ex. 1003 ¶¶ 359–371), 55–56.

b. Patent Owner's assertions

Patent Owner responds that Petitioner fails to provide prior art evidence that glargine had a tendency to aggregate. Resp. 29–31. In that regard, Patent Owner argues that Lantus Label and Owens teach clear, soluble solutions that were stable in an acidic pH, and that Petitioner's reliance on the "use-only-when-clear" patient

instructions in Lantus Label as conveying an aggregation problem is misplaced. *Id.* at 29–30 (citing 1004, 3; Ex. 1005, 1; Ex. 2006 ¶¶ 113–116; Ex. 2008, 30:17–31:10). Patent Owner also notes that the "use-only-when-clear" instruction is found in most labels for injectable drugs. *Id.* at 30 (citing Ex. 2006 ¶ 117). And Patent Owner explains that Petitioner's asserted references relate to chemical and physical instability of human and animal insulin formulations, not the modified, recombinant insulin glargine formulations. *Id.* at 31 (citing generally Ex. 1006; Ex. 1007A; Ex. 1008; Ex. 1014; Ex. 1015; Ex. 1018).

Patent Owner further responds that Petitioner fails to provide evidence that a person of ordinary skill in the art would have expected the same aggregation problem for insulin glargine, as was known for other insulins. Resp. 32–43. Patent Owner presents four arguments in that regard. First, Patent Owner argues a person of ordinary skill in the art would not have expected insulin glargine to aggregate based on prior art disclosing chemical and physical instability in human and animal insulin because insulin and insulin glargine have structural differences resulting in changes in physical and chemical properties of insulin glargine. *Id.* at 33–37 (citing Ex. 2004, 2:51–61; 2006 ¶¶ 59–63, 76–78, 123–124, 148). Second, Patent Owner argues that the evidence of record does not support Petitioner's assertion that a person of ordinary skill in the art would have expected insulin glargine to aggregate due to the prevalence of monomers. *Id.* at 37–39 (citing Ex. 1011, 12; Ex. 1031, 1; Ex. 2006 ¶¶ 116, 136–138, 159; Ex. 2018, 1, 7). Third, Patent Owner argues that the prior art does not teach that insulin glargine formulations are prone to aggregation at acidic pH. *Id.* at 39–41. Fourth, Patent Owner argues that a skilled artisan would not have expected aggregation based on prior art related to insulin pumps (i.e., Lougheed, FASS, and Grau), because insulin for pump formulations "is a special case requiring stabilization that is not

needed in other insulin formulations." *Id.* at 41–43 (citing Ex. 1006, 1; Ex. 1007A, 5; Ex. 1008, 1; Ex. 1015, 6; Ex. 2006 ¶¶ 65, 72–73, 96–97, 106–111, 140).

Patent Owner also argues that the statements in the '930 patent background section cannot be used to support a rationale to modify the insulin glargine formulations because the patent specification distinguishes between insulin and insulin glargine, does not admit that insulin glargine had a known tendency to aggregate, and "simply recites what was known in the art . . . regarding *insulin* aggregation." *Id.* at 43–45.

As to reasonable expectation of success, Patent Owner asserts that there is no support for Petitioner's argument that adding polysorbates and/or poloxamers to insulin glargine formulations would have been routine. Resp. 46. Patent Owner argues that Petitioner's position "ignores the unpredictability of protein formulation," *id.* at 47, and the competing considerations that must be taken into account when introducing an additional component into a formulation. *Id.* at 47–48 (citing Ex. 2003, 28–29; Ex. 2006 ¶¶ 43–45, 149–166). Similarly, Patent Owner contends that Petitioner's analysis fails to address whether introducing a surfactant would interfere with insulin glargine's mechanism of action or efficacy. *Id.* at 49–51. Patent Owner also argues that Petitioner fails to account for the potential negative consequences of adding a nonionic surfactant to the Lantus Label and Owens insulin glargine formulations. *Id.* at 51–56. According to Patent Owner those negative consequences "could" include polysorbate hydrolysis in acidic environments, discoloration of the formulation, interference with the antimicrobial properties and hexamer-stabilizing effects of m-cresol, and the potential for polysorbate to undergo autoxidation reactions during storage to form harmful peroxides in the formulation. *Id.* (citing Ex. 1012, 1; Ex. 1013; Ex. 1019, 5, 30, 41, 43, 46, 50; Ex. 2006 ¶¶ 153–166; Ex. 2015, 4; Ex. 2017, 1; Ex. 2028, 4).

c. Analysis

Turning first to reason to combine, we disagree with Patent Owner that, to meet its burden as a matter of law, Petitioner must provide prior art evidence that insulin glargine had a tendency to aggregate. Resp. 29–31. The prior art need not expressly articulate or suggest that insulin glargine had a tendency to aggregate. Rather, "a patent claiming the combination of elements of prior art" may be shown to be obvious if "the improvement is [no] more than the predictable use of prior art elements according to their established functions." *KSR*, 550 U.S. at 517. Here, Petitioner asserts that a person of ordinary skill in the art would have understood that aggregation generally was a concern in developing insulin formulations and that a surfactant predictably would have been added to the formulations to address that concern. Pet. 6–7, 21–22, 25–26. Based on our review of the full trial record, we find that Petitioner demonstrates a reason to modify the prior art, as explained below.

The '930 patent explains that insulins had a known tendency to aggregate in the presence of hydrophobic surfaces that come into contact with insulin formulations, such as "the glass vessels of the preparations, the stopper material of the sealing caps or the boundary surface of the solution with the air supernatant." Ex. 1002, 3:8–14. The '930 patent further states it was known that "very fine silicone droplets can function as additional hydrophobic aggregation nuclei in the taking of the daily insulin dose by means of customary, siliconized insulin syringes and accelerate the process." *Id.* at 3:14–17. The '930 patent does not exclude insulin glargine when describing the tendency for insulins to aggregate due to interactions with hydrophobic surfaces on vials and insulin delivery devices, including syringes. *See id.* at 3:2–17. And the record supports that an ordinarily skilled artisan would not have suspected insulin glargine to behave differently than

other insulins, due to the differences in amino acids between them, when exposed to hydrophobic surfaces. For example, although bovine, porcine, and human insulin are structurally different, they all were known to aggregate (albeit to different degrees). Ex. 1014, 3 (Figure 1 depicting the primary structure of human insulin and noting that porcine insulin differs by one amino acid and bovine insulin differs by three amino acid); Ex. 1015, 2 (recognizing that human, porcine, and bovine all aggregate, but explaining that bovine insulin has a greater tendency to aggregate than human and porcine insulin).

The '930 patent also does not suggest that aggregation due to hydrophobic surfaces occurred only in pumps, as Patent Owner argues. To the contrary, as noted above, the '930 patent describes the hydrophobic surfaces of glass storage vials, stopper materials of sealing caps, the air-water interface, and siliconized daily use syringes as promoting aggregation. Additional evidence of record is consistent with the background of the '930 patent. *See* Ex. 1006, 1 (silicone rubber promotes insulin aggregation); Ex. 1014, 8; Ex. 1015, 1 (insulin was known to undergo conformational changes when exposed to hydrophobic surfaces, such as the air/water interface in a vial, resulting in aggregation and the formation of a viscous gel or insoluble precipitates), 4; Ex. 1021, 1; Ex. 1026, 3 (insulin aggregates in glass vials); Ex. 2012, 9379 ("It has been suggested that insulin is destabilized at hydrophobic surfaces (air-water or water-pump materials)"). Thus, the background of the '930 patent and the prior art suggests that it is the air-water interfaces and interactions with hydrophobic surfaces that promote insulin aggregation, and not the type of device used to deliver the insulin formulation.

Given this evidence, we credit Dr. Langer's testimony that aggregation "was known in the art not to be unique to pumps," Ex. 1111 ¶ 92, over Dr. Trout's testimony that "[i]nsulin fibrillation was also known to be an issue confined to

insulin pumps," Ex. 2006 ¶ 72. We further find that the evidence Dr. Trout cites does not support the conclusion that insulin aggregation was limited to pumps. *See id.* Rather, the evidence on which Dr. Trout relies indicates that insulin has a *greater tendency* to aggregate in pump delivery devices (i.e., a difference in degree) because it is exposed to a greater hydrophobic surface area. *See, e.g.*, Ex. 1008, 1 ("The problems associated with insulin use in implantable pumps are even greater").

The insulin glargine formulations in Lantus Label and Owens were supplied in vials—the same type of delivery materials that the '930 patent states were known to contain hydrophobic surfaces. *See* Ex. 1004, 6 (Lantus is supplied in 5mL and 10 mL vials); Ex. 1005, 3–4 (explaining that the insulin glargine formulations were administered from 5mL vials and injected subcutaneously). Further, it is not disputed that the vials in which the insulin glargine formulations were stored contained a "headspace" (air above the solution liquid) forming an air-water interface. *See* Ex. 1037, 11 (depicting a 10 mL Lantus vial with stopper and air-water interface); Ex. 1054, 207:6–13, 207:22–208:21 (Dr. Trout's testimony that the headspace in the Lantus vials forming a gas-liquid interface). Thus, we find that a person of ordinary skill in the art would have been concerned about aggregation in the insulin glargine formulations that Lantus Label and Owens disclose.

Further, both parties' experts agree that insulins exist in equilibrium as monomers, dimers, and hexamers, which structure may affect its tendency to aggregate in solution. *See, e.g.*, Ex. 1003 ¶ 106 (citing Ex. 1018, 1); Ex. 2006 ¶¶ 55–56 (quoting Ex. 1018, 1 and citing Ex. 1014, 29). Certain factors such as pH, however, were known to shift the equilibrium toward the monomer, Ex. 1015, 3, whereas other factors, like the presence of zinc in the formulation, were known

to promote hexamer formation, Ex. 1015, 7. *See* Ex. 2006 ¶ 68. As to pH, the background of the '930 patent states that "[e]specially at acidic pH, insulins . . . show a decreased stability and an increased proneness to aggregation on thermal and physicomechanical stress, which can make itself felt in the form of turbidity and precipitation (particle formation) (Brange et al., J. Ph. Sci. 86:517–525 (1997))." Ex. 1001, 3:2–7. And prior to the invention, a number of studies confirmed that although insulin was known to aggregate in neutral solutions, the rate of insulin aggregation increased in acidic solutions, due to the presence of more insulin monomers (than dimers and hexamers) in those solutions—monomers that unfolded exposing hydrophobic interfaces that were normally buried. *See* Ex. 1014, 9–10; Ex. 1015, 3, 6; Ex. 1018, 1; Ex. 2012, 9379.

As described in Lantus Label, insulin glargine was formulated as a clear solution with an acidic pH. Ex. 1004, 3 (Lantus formulation); *see also* Ex. 1001, 2:66–3:2 (describing background information). And Jones[13] described insulin glargine as "monomeric compared to pharmacological insulin preparations in which insulin is usually present as a hexamer." Ex. 1031, 1.

Patent Owner argues that, despite Jones's statement regarding the monomeric nature of insulin glargine, the evidence of record does not support Petitioner's assertion that insulin glargine was believed to have a greater proportion of monomers. Resp. 37–38. First, Patent Owner contends that Jones's statement is erroneous and based on a misreading of another reference that it

[13] Richard Jones, *Insulin glargine Aventis Pharma*, 3 IDRUGS 1081 (2000) (Ex. 1031). Although we refer to the original pagination associated with this reference in setting forth its full citation, we refer in our discussion to the page numbers Petitioner added to the reference.

cites—Hoogwerf.[14] *Id.* Patent Owner bases this argument on what it contends is a particular citation scheme that Jones adopts—citing references at the end of each paragraph, rather than at the end of each sentence. Tr. 54:19–55:5 (Patent Owner's counsel acknowledging that Jones's cite to Hoogwerf does not appear in the sentence on which Petitioner relies, but arguing that it applies to that sentence because Jones "does citations . . . at the end of paragraphs."). But Jones does not appear to employ that citation scheme. Indeed, many paragraphs include citations in the middle of sentences, or at the end of each sentence. Thus, we do not conclude on this record that Jones intended to cite Hoogwerf for the statement that insulin glargine is monomeric. Nor do we conclude that Jones's statement in that regard is erroneous. Rather, we consider Jones for what it would have taught the ordinary artisan—that insulin glargine is more monomeric than other insulin preparations.

Patent Owner also contends that an ordinarily skilled artisan would have expected insulin glargine "to be more hexameric than insulin because [a]lterations to the molecule favor the formation of insulin hexamers" and because the insulin glargine formulations in Lantus Label and Owens include zinc, which was known to promote insulin hexamer formation. Resp. 39 (citing Ex. 1011, 2; Ex. 2006 ¶¶ 116, 159).

As to Patent Owner's argument regarding zinc, although we agree that the presence of zinc in a formulation was known to promote hexamer formation at neutral and basic pH, thus stabilizing the insulin in the formulation (Ex. 1003 ¶¶ 98, 100; Ex. 1168, 77; Ex. 2006 ¶ 57), it was also known that "in acidic solutions[,] insulin does not bind [zinc]" (Ex. 1168, 77). As to Patent Owner's

[14] Hoogwerf et al., *Advances in the Treatment of Diabetes Mellitus in the Elderly – Development of Insulin Analogues*, 6 DRUGS & AGING 438–48 (1996) (Ex. 2018).

argument that insulin glargine's alterations favor hexamer formation, the fact that a chemical alteration favors hexamer formation, does not mean that insulin glargine is predominantly hexameric, especially given Jones's statement that insulin glargine is more monomeric than other insulins. Even assuming that insulin glargine is predominantly hexameric at acidic pH, however, prior art insulin formulations were believed to be hexameric at neutral pH, yet they still were known to aggregate at neutral pH. *See* Ex. 1006, 1 (aggregates formed in insulin preparations "even under normal storage conditions"), Ex. 1014, 8–10; Ex. 1018, 1 ("models have been proposed to describe the self-association [i.e., aggregation] of insulin in solution at both acidic and neutral pH"); Ex. 2012, 9377, 9379 (aggregation occurred in insulin formulations at pH 7). Thus, we find that a person of ordinary skill in the art would have had an additional reason to be concerned about aggregation in the insulin glargine formulations that Lantus Label and Owens disclose.

Turning to whether an ordinary artisan would have added nonionic surfactants to the insulin glargine formulations with a reasonable expectation of success, Patent Owner argues Petitioner's assertion that an ordinarily skilled artisan would have reasonably expected success in achieving the claimed pharmaceutical formulations "ignores the unpredictability of protein formulation" and the competing considerations that must be taken into account when introducing an additional component into a formulation. Resp. 47–48. Patent Owner's arguments regarding unpredictability of protein formulating are not persuasive under the proper legal inquiry regarding reasonable expectation of success. Under the proper inquiry, "obviousness cannot be avoided by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." *Pfizer*, 480 F.3d at 1364.

Based on our review of the full trial record, Petitioner demonstrates, by a preponderance of the evidence, a reasonable probability of success. Specifically, the prior art is replete with examples of nonionic surfactants successfully used to stabilize insulins and other peptides against aggregation. As to insulin, Lougheed teaches formulations comprising insulin and surfactants, including nonionic surfactants (e.g., polysorbate 20 and polysorbate 80). *See* Ex. 1006, 2–3. Lougheed tested those surfactants as "stabilizers in view of their known protein-solvation characteristics and their potential to constrain conformation of insulin[] and other proteins in aqueous solution." *Id.* at 2. Lougheed concluded that the nonionic surfactants "markedly increased the stability of their respective formulations" under rotational testing. *Id.* at 7; *see also id.* at 3–4 (explaining that observed formulation stability continuous rotation values for insulin formulations including Brij 35, Tween 20 (i.e., polysorbate 20), and Tween 80 (i.e., polysorbate 80) are 141 days, 68 days, and 48 days, respectively, as compared with 10 days for insulin controls (i.e., formulations that lacked surfactant additives). And FASS teaches that adding the stabilizer poly(oxyethylene, oxypropylene)glycol (i.e., a poloxamer) to an insulin formulation "prevents precipitation and flocculation of the insulin." Ex. 1007A, 7. Grau further teaches using nonionic surfactants to stabilize insulin formulations. Ex. 1008, 2–6 (adding a poloxamer (Genapol) to insulin formulations "to inhibit insulin aggregation" for various *in vitro* and *in vivo* tests with programmable implantable medication systems); *see also* Ex. 1111 ¶ 159 (Table 1, listing twenty prior art references describing surfactants used in insulin formulations, including two that disclose the use of polysorbates with insulin at acidic pH (e.g., Ex. 1023; Ex. 1125)).

Petitioner also directs us to a number of protein and polypeptide pharmaceutical formulations that include nonionic surfactants as stabilizers.

Pet. 8–9; Ex. 1016, 3 (Table I listing a few of the approved surfactants, including polysorbate 20, polysorbate 80, and Brij); Ex. 1003 ¶¶ 111–123 (discussing several studies showing the stabilizing effect of nonionic surfactants on insulin, including Exs. 1023–1026). And Jones explains that nonionic surfactants "have been traditionally used in formulations to stabilize proteins." Ex. 1016, 2. These surfactants are attractive as additives in producing, purifying and stabilizing drugs because "many have already been approved for use internationally in medicinal products" and exhibit "low toxicity and low reactivity with ionic species." *Id.*

The prior art further discloses that nonionic surfactants such as Genapol (a poloxamer) successfully stabilized bovine, porcine, and human insulins, as well as three additional non-insulin proteins. Ex. 1021, 1, 3. Given the foregoing, we credit Dr. Yalkowsky's testimony that an ordinarily skilled artisan "would have indeed looked at the available protein formulations and what was acceptable to the [Food and Drug Administration ("FDA")]." Ex. 1181 ¶ 38; *see also* Ex. 1003 ¶¶ 115 (explaining that the FDA had listed polysorbate 20 and polysorbate 80 as Generally Recognized As Safe ("GRAS") and they remain listed as GRAS). For the same reason, we find unpersuasive Patent Owner's arguments that an ordinarily skilled artisan would not have reasonably expected success when adding a nonionic surfactant to insulin glargine in view their success stabilizing other insulins and proteins. Resp. 46–51.

As noted previously, Patent Owner also argues that Petitioner fails to account for the potential negative consequences of adding a nonionic surfactant to the Lantus Label and Owens insulin glargine formulations. *Id.* at 51–56. This argument strikes us more as an argument directed to reason to modify and not reasonable expectation of success. To the extent Patent Owner's argument is so directed, we do not agree with Patent Owner that "potential" consequences would

have discouraged an ordinary artisan from adding nonionic surfactants to the prior art glargine formulations. *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) ("[A] given course of action often has simultaneous advantages and disadvantages, and this does not necessarily obviate motivation to combine.").

Nor do we find that, based on the record as a whole, a person of ordinary skill in the art would have considered those potential consequences to have obviated a reasonable expectation of success in achieving the claimed formulations. For example, Patent Owner argues that an ordinarily skilled artisan would have been aware of the potential hydrolysis or saponification of polysorbate in acidic environments, given that "gradual saponification [of polysorbate] occurs with strong acids." Resp. 52 (citing Ex. 1019, 30, 50; Ex. 2006 ¶¶ 153–154). But Patent Owner does not direct us to evidence that a "strong acid" was or would have been present in the prior art Lantus formulations. *See id.*; Ex. 2006 ¶¶ 153–154. And Petitioner points to evidence that polysorbates were used in pharmaceutical formulations at acidic pH. Reply 23–24; *see* Ex. 1139, 2 (disclosing Etoposide parenteral formulation that includes polysorbate 80 and has a pH of 3.0–4.0); Ex. 1054, 265:7–266:13). Further, as noted above, Petitioner identifies nonionic surfactants other than polysorbates (e.g., Brij and poloxamers) that the claims encompass. *See* Pet. 10; Ex. 1003 ¶ 128.

Patent Owner also points to potential negative effects of using nonionic surfactants and phenols (e.g., cresol) in the same formulation. Resp. 53–55 (citing Ex. 1019, 30, 43, 50; Ex. 2006 ¶¶ 157–163). Petitioner, however, provides evidence that phenols and nonionic surfactants had been used together in pharmaceutical formulations. Reply 25 (and evidence cited therein); *see, e.g.*, Ex. 1141, 2 (disclosing Norditropin, a polypeptide hormone parenteral formulation that includes nonionic surfactant poloxamer 188 and phenol).

In sum, Petitioner demonstrates, by preponderance of the evidence, a reason that one of ordinary skill in the art would have modified the insulin glargine formulations that Lantus Label and Owens teach by adding nonionic surfactants to achieve the claimed pharmaceutical formulations with a reasonable expectation of success. That does not end our inquiry, however, because the record includes arguments and evidence regarding objective indicia of nonobviousness that we evaluate before making a final determination on obviousness. *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1328 (Fed. Cir. 2016).

3. Objective Indicia of Nonobviousness

Patent Owner argues that objective evidence of commercial success supports the nonobviousness of the challenged claims. Resp. 56–59. As explained further below, we are not persuaded that Patent Owner's arguments and evidence regarding commercial success support the nonobviousness of the challenged claims.

Patent Owner offers evidence of the success of the Lantus product. Resp. 57–59. Patent Owner explains that that original Lantus vial formulation exhibited aggregation and precipitation during storage, "resulting in the normally clear formulation becoming visibly cloudy." *Id.* at 57. Patent Owner solved this problem by reformulating the original Lantus vial to include a nonionic surfactant "aimed at stabilizing the formulation without interfering with the glargine's unique profile of action." *Id.* Patent Owner asserts that the reformulated Lantus vial practices claims 1–9 and 12–19 of the '930 patent. *Id.*

Patent Owner sells the reformulated Lantus vial, "with U.S. sales growing from $1.1 billion at its introduction to approximately $2.6 billion in 2017"—sales that "have accounted for approximately 33% of all sales of long-acting injectable insulin and/or insulin analog therapies." *Id.* at 57 (citing Ex. 2039 ¶¶ 29–30).

Patent Owner contends that these sales amount to commercial success and that there is a nexus between the commercial success of the reformulated Lantus vial and the invention claimed in the '930 patent because the reformulated Lantus vial is the claimed invention. *Id.* at 58. Patent Owner further contends that a nexus exists because the reformulated Lantus vial "averted potential regulatory action and negative sales impacts that could have occurred had Patent Owner not remedied the aggregation issues with the original [Lantus] vial." *Id.* at 58 (citing Ex. 2006 ¶¶ 162–172; Ex. 2039 ¶¶ 36–39).

"When a patentee can demonstrate commercial success, usually shown by significant sales in a relevant market, and that the successful product is the invention disclosed and claimed in the patent, it is presumed that the commercial success is due to the patented invention." *J.T. Eaton & Co. v. Atl. Paste & Glue Co.*, 106 F.3d 1563, 1571 (Fed. Cir. 1997); *see WBIP*, 829 F.3d at 1329 (finding "a presumption of nexus for objective considerations when the patentee shows that the asserted objective evidence is tied to a specific product and that product 'is the invention disclosed and claimed in the patent'"). That presumption of nexus, however, is rebuttable, as "a patent challenger may respond by presenting evidence that shows the proffered objective evidence was 'due to extraneous factors other than the patented invention.'" *WBIP*, 829 F.3d at 1329.

There appears to be no dispute in this case that the Lantus product is a commercial success. *See* Reply 26 (arguing that "the commercial success of Lantus is attributable to the fact that it contains insulin glargine, not any non-ionic surfactants"). Petitioner, however, contends that any nexus between such success and the claimed invention is rebutted by, among other things, Patent Owner's failure "to account for its patent on the original insulin glargine compound, which blocked market entry of any competing insulin glargine products at least until after

its expiration in September 2014." Reply 25–26 (citing Ex. 1055, 18:21–20:3; Ex. 1111 ¶ 98; Ex. 1169 ¶¶ 29–33).

Petitioner correctly notes that Patent Owner does not account for any patents[15] covering the insulin glargine compound. *See* Resp. 56–59; Ex. 1055, 18:21–20:3 (Dr. Baker's testimony that he generally understands what "blocking patents" are, but did not investigate whether there was a blocking patent). Petitioner, on the other hand, offers testimony that at least two of Patent Owner's patents—the '722 patent and the '376 patent—"are considered to be blocking patents" and that other of Patent Owner's patents had been listed in the Orange Book as covering the Lantus product. Ex. 1169 ¶¶ 30, 32; Ex. 1111 ¶ 98 (citing Ex. 1171; Ex. 1172); *see also* Ex. 1088, 954 (Orange Book entry listing patents covering Lantus). Dr. McDuff testifies that the patents "would have blocked competitors from commercializing a product that embodied" the same technologies and "provided strong disincentives for others to develop and commercialize" the technology described in the '930 patent. Ex. 1169 ¶ 32. We credit Dr. McDuff's testimony and find, on the record before us, that Patent Owner's insulin glargine

[15] Dr. Langer testifies that U.S. Patent No. 6,100, 376 ("the '376 patent") and U.S. Patent No. 5,656,722 ("the '722 patent") are both directed to "certain insulin analogs, including insulin glargine." Ex. 1111 ¶ 98 (citing Ex. 1171 ('376 patent); Ex. 1172 ('722 patent)). The '376 patent has an issue date of August 8, 2000, and expired on November 6, 2009. Ex. 1171 [45]; *see, e.g.*, Ex. 1088, 954 (Food & Drug Administration, *Approved Drugs with Therapeutic Equivalence Evaluations* (27th ed. 2007), also known as the "Orange Book," listing the '376 patent under the entry for "INSULIN GLARGINE RECOMBINANT; LANTUS" and noting that the '376 patent expires on November 6, 2009). The '722 patent has an issue date of August 12, 1997, and expired on September 12, 2014. Ex. 1172 [45]; *see, e.g.*, Ex. 1088, 954 (Orange Book listing the '722 patent under the entry for "INSULIN GLARGINE RECOMBINANT; LANTUS" and noting that the '722 patent expires on September 12, 2014).

patents may have precluded others from entering the market with their own insulin glargine formulation products.

We find Patent Owner's evidence of commercial success weak in light of Patent Owner's blocking patents covering the insulin glargine compound—a required component of the pharmaceutical compositions claimed in the '930 patent. *Acorda Therapeutics, Inc. v. Roxane Labs., Inc.*, 903 F.3d 1310, 1339 (Fed. Cir. 2018); *see Galderma Labs*, 737 F.3d at 740 ("Where market entry by others was precluded [due to blocking patents], the inference of non-obviousness of [the claims], from evidence of commercial success, is weak."). Because Patent Owner could have precluded others from market entry prior to the patents covering insulin glargine expiring, Patent Owner's evidence of commercial success is insufficient to support the nonobviousness of the challenged claims.

4. Conclusion as to obviousness

Having considered the parties' arguments and evidence, we evaluate all of the evidence together to make a final determination of obviousness. *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1075 (Fed. Cir. 2012) (stating that a fact finder must consider all evidence relating to obviousness before finding patent claims invalid). In so doing, we conclude that Petitioner has satisfied its burden of demonstrating, by a preponderance of the evidence, that: (1) claims 1–20 of the '930 patent would have been obvious over the combination Lantus Label and Lougheed; (2) claims 1–18 and 20 of the '930 patent would have been obvious over the combination of Lantus Label and FASS; (3) claims 1–18 and 20 of the '930 patent would have been obvious over the combination of Lantus Label and Grau; (4) claim 19 of the '930 patent would have been obvious over the combination of Lantus Label, FASS or Grau, and Lougheed; (5) claims 1–20 of the '930 patent would have been

obvious over the combination Owens and Lougheed; (6) claims 1–18 and 20 of the '930 patent would have been obvious over the combination of Owens and FASS; (7) claims 1–18 and 20 of the '930 patent would have been obvious over the combination of Owens and Grau; and (8) claim 19 of the '930 patent would have been obvious over the combination of Owens, FASS or Grau, and Lougheed.

IV. MOTIONS TO SEAL

Patent Owner and Petitioner each filed unopposed Motions to Seal portions of certain papers and exhibits. Papers 43, 76, 84, 86. Accompanying Petitioner's second motion to seal is a request to enter an agreed upon protective order. Paper 86, Attachment.

Patent Owner seeks to seal Exhibits 1144–1161 and the portions of Petitioner's Reply (Paper 41) and Dr. Langer's declaration (Ex. 1111) that reference Exhibits 1144–1161 or the information contained in those exhibits. Paper 43 (Patent Owner's supplemental motion). Patent Owner also seeks to seal portions of Exhibits 2065–2068, and the portions of Patent Owner's sur-reply (Paper 77) that reference those exhibits. Paper 76. In support of its motions, Patent Owner asserts that the information it seeks to seal is highly confidential and proprietary, that concrete harm would result upon its disclosure, there is a need to rely on the information they seek to seal, and that its interest in maintaining confidentiality outweigh the public interest in an open record. *See, e.g.*, Paper 43, 2–15.

Petitioner seeks to seal the portions of its sur-sur-reply (Paper 83) that reference Exhibits 2065–2068 and Exhibit 1086. Papers 84 (Petitioner's First Motion to Seal), 86 (Petitioner's Second Motion to Seal). In support of its motion to seal portions of the sur-sur-reply, Petitioner notes that the sur-sur-reply

references information from papers that Patent Owner has moved to seal. Paper 84, 1.In support of its motion to seal Exhibit 1086 (diabetes-treatment market data), Petitioner asserts that the exhibit consists of "third-party proprietary commercial information that would lose [its] value if publicly available." Paper 86, 2–3. Petitioner also asserts that the Board has sealed similar information in other *inter partes* review proceedings, that having the data in the record permits the Board and Patent Owner to assess the basis of Dr. McDuff's opinions, and that the public interest is satisfied because the public can access Dr. McDuff's full expert declaration. *Id.*

Petitioner did not oppose Patent Owner's motions, and Patent Owner did not oppose Petitioner's motions. Additionally, Patent Owner filed a public version of its sur-reply (Paper 78) and proposed redacted public versions of Petitioner's Reply and Dr. Langer's declaration (Paper 43, Attachments 1–2). Petitioner filed a public version of its sur-sur-reply. Paper 85.

"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, slip op. at 1–2 (PTAB Mar. 14, 2013) (Paper 34). 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. The standard for granting a motion to seal is good cause. 37 C.F.R. § 42.54. That standard includes a showing that "(1) the information sought to be sealed is truly confidential, (2) a concrete harm would result upon public disclosure, (3) there exists a genuine need to rely in the trial on the specific information sought to be sealed, and (4) on balance, an interest in maintaining confidentiality outweighs the

strong public interest in having an open record." *Argentum Pharms. LLC v. Alcon Research, Ltd.*, Case IPR2017-01053, slip op. at 4 (Paper 27) (PTAB Jan. 19, 2018) (informative).

After having considered the submissions, we determine that the parties' proposed protective order, although not the Board's default order, is acceptable and will be entered. We also determine that there is good cause for granting the Motions with respect to all information, except the information in Petitioner's sur-sur-reply, as we explain further below. Specifically, the parties demonstrate that the information they seek to seal consists of confidential and proprietary research and development information, confidential packaging specifications, confidential regulatory submissions, and confidential commercial information. And we see little harm to the public's interest in restricting access to the information because we do not rely on any confidential information in this decision. We further note that the public versions of Petitioner's Reply, Dr. Langer's declaration, and Patent Owner's sur-reply appear to redact only that information that the parties seek to seal in their motions.[16]

As to Petitioner's motion to seal the sur-sur-reply (Paper 84), other than noting that it references information from papers that Patent Owner moves to seal, Petitioner provides no justification for why the redacted portions of the sur-sur-reply should be kept confidential. Thus, Petitioner fails to satisfy the good cause requirement and we deny Petitioner's motion without prejudice to Patent Owner.

We authorize Patent Owner to file, with ten (10) business days of the date of this decision, a motion to seal portions of Petitioner's sur-sur-reply, setting forth a

[16] Patent Owner shall file its proposed public version of Petitioner's Reply as a paper in this proceeding and its proposed public version of Dr. Langer's declaration as an exhibit in this proceeding.

showing why the particular portions of those documents the parties seek to seal are confidential and that good cause exists to seal those portions. We instruct the parties to work together to prepare proposed redactions to Petitioner's sur-sur-reply. Any proposed redactions should be narrowly tailored. The parties shall meet and confer in good faith as necessary to comply with our orders in this decision. 37 C.F.R. § 42.11.

V. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that Petitioner establishes, by a preponderance of the evidence, that claims 1–20 of the '930 patent are unpatentable;

FURTHER ORDERED that Patent Owner's Motion to Strike (Paper 45) is denied-in-part and dismissed-in-part as moot;

FURTHER ORDERED that Petitioner's Motion to Exclude (Paper 55) is dismissed as moot;

FURTHER ORDERED that Patent Owner's Motion to Exclude (Paper 59) is denied-in-part and dismissed-in-part as moot;

FURTHER ORDERED that the parties' proposed protective order (Paper 86, Attachment) is entered and governs the treatment and filing of confidential information in this proceeding;

FURTHER ORDERED that Petitioner's first Motion to Seal (Paper 84) is denied without prejudice;

FURTHER ORDERED that Petitioner's second Motion to Seal (Paper 86) is granted;

FURTHER ORDERED that Patent Owner's Supplemental Motion to Seal (Paper 43) and Patent Owner's Motion to Seal (Paper 76) are granted;

FURTHER ORDERED that Patent Owner shall file its proposed public version of Petitioner's Reply as a paper in this proceeding and its proposed public version of Dr. Langer's declaration as an exhibit in this proceeding within five (5) business days of this decision;

FURTHER ORDERED that Patent Owner is authorized to file a motion to seal portions of Petitioner's sur-sur-reply (Paper 83), within ten (10) business days of this decision, and in accordance with the instructions set forth above; and

FURTHER ORDERED that this is a Final Written Decision; therefore, 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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