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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 IPR2017-01526
Patent 7,476,652 B2

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

ANKENBRAND, *Administrative Patent Judge*.

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

I. INTRODUCTION

Mylan Pharmaceuticals, Inc. ("Petitioner") requests an *inter partes* review of claims 1–25 of U.S. Patent No. 7,476,652 B2 (Ex. 1001, "the '652 patent"). Paper 2 ("Pet."). Sanofi-Aventis Deutschland GmbH ("Patent Owner") filed a Preliminary Response. Paper 8 ("Prelim. Resp.").

We have authority to determine whether to institute an *inter partes* review. 35 U.S.C. § 314(b); 37 C.F.R. § 42.4(a). We may not institute an *inter partes* review "unless . . . there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a). Applying that standard, and upon consideration of the information presented in each Petition and Preliminary Response, we institute an *inter partes* review as to claims 1–25 of the '652 patent.

II. BACKGROUND

A. Related Matters

Patent Owner identifies the following pending litigation involving the '652 patent: *Sanofi-Aventis U.S. LLC v. Merck Sharp & Dohme Corp.*, C.A. No. 1-16-cv-00812-RGA (D. Del.); *Sanofi-Aventis v. Merck Sharp & Dohme Corp.*, C.A. No. 2-17-cv-05914 (D.N.J.). Paper 7, 2. Patent Owner also identifies the following concluded litigation involving the '652 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.). *Id.*; Prelim. Resp. 51–52. Patent Owner also identifies as related IPR201-01528— an *inter partes* review Petitioner filed challenging U.S. Patent No. 7,713,930 (Ex. 1002, "the '930 patent"), which issued from continuation application to the application that issued as the '652 patent. Paper 7, 2.

As Patent Owner points out, the Petition does not identify the pending or concluded litigation involving the '652 patent. Prelim. Resp. 51–52. In that regard, the Petition states that Petitioner "is not a party to any litigation related to the '652 patent." Pet. 2. Patent Owner argues that we should deny the Petition due to Petitioner's failure to identify all related matters pursuant to 37 C.F.R. § 42.8(b)(2). Prelim. Resp. 51–52.

We do not find sufficient grounds to deny the Petition on that basis. To be sure, § 42.8(b)(2) requires parties to identify "any other judicial or administrative matter that would affect, or be affected by, a decision in the proceeding." The district court litigation that Patent Owner identifies, however, does not involve Petitioner as a party, and it is not apparent from the record that Petitioner was aware of, but failed to identify, that district court litigation.

Although we do not deny the Petition as Patent Owner requests, we direct Petitioner to update its mandatory notices, within three days of the entry of this Decision, to include the pending and concluded litigation that Patent Owner identifies, as well as IPR2017-01528. We also remind the parties of their continuing obligation to file an updated mandatory notice "within 21 days of a change of the information" required in the notices. 37 C.F.R. § 42.8(a)(3).

B. The '652 Patent (Ex. 1001)

The '652 patent, titled "Acidic Insulin Preparations Having Improved Stability," issued on January 13, 2009. Ex. 1001, (45), (54). The '652 patent relates to pharmaceutical formulations comprising a modified insulin—insulin glargine (Gly(A21)-Arg(B31)-Arg(B32)-human insulin) —and at least one surfactant. *See, e.g.*, Ex. 1001, Abstract, 1:11–19, 11:2–9. 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 3:2–6. Such stresses can arise during use or shaking of the insulin solution. *Id.* at 5:34–56. Also contributing to aggregation are hydrophobic surfaces with which the insulin solution comes into contact, including those on glass vessels storing the insulin solution, sealing cap stopper materials, and siliconized insulin syringes. *Id.* at 3:8–17.

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 3:41–45; *see id.* at 5:20–10:67 (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).

C. Illustrative Claim

Petitioner challenges claims 1–25 of the '652 patent, of which claims 1, 7, and 24 are independent. Claim 1 of the '652 patent 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 polysorbate 20 and polysorbate 80;
>
> at least one preservative; and
>
> water,
>
> wherein the pharmaceutical formulation has a pH in the acidic range from 1 to 6.8.

Ex. 1001, 11:2–9.

D. The Asserted Grounds of Unpatentability

Petitioner asserts that the challenged claims of the '652 patent are unpatentable based on the following grounds:

References	Statutory Basis	Claims Challenged
Lantus Label[1] and Lougheed[2]	§ 103	1–25
Lantus Label and FASS[3]	§ 103	7, 24
Lantus Label and Grau[4]	§ 103	7, 24
Owens[5] and Lougheed	§ 103	1–25
Owens and FASS	§ 103	7, 24
Owens and Grau	§ 103	7, 24

[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).

[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).

Petitioner supports the Petition with the testimony of Samuel H. Yalkowsky, Ph.D. (Ex. 1003).

III. ANALYSIS

A. Discretionary Denial under 35 U.S.C. § 325(d)

Patent Owner argues that we should exercise our discretion to deny all of the asserted grounds under 35 U.S.C. § 325(d) because they present substantially the same prior art and arguments the Office previously considered during the prosecution of the '652 patent. Prelim. Resp. 43–48. Patent Owner points to the Examiner's rejection over a combination of art that included Dörschug[6]—a patent that discloses a plasmid for preparing insulin glargine and various formulation components in aqueous solution. *Id.* at 44. Patent Owner contends that the list of components Dörschug discloses "substantially overlaps with the list of components that Petitioner asserts" Lantus Label and Owens teach. *Id.* Patent Owner also points to several patents disclosing surfactants in formulations of human or animal insulins that the Examiner considered during prosecution of the '652 patent—Massey[7] and Hirai.[8] *Id.* at 44–46 (citing Ex. 1001A,[9] 2406–11; Ex. 1023; Ex. 1024). Patent Owner asserts that the Office, therefore, "previously considered the patentability of the challenged claims over Glargine and non-Glargine insulin art, and concluded that the claimed Glargine formulation would not have been obvious." *Id.* at 46.

[6] Dörschug, U.S. Patent No. 5,656,277, issued Aug. 12, 1997 (Ex. 2004).
[7] Massey et al., U.S. Patent No. 4,839,341, issued June 13, 1989 (Ex. 1024).
[8] Hirai et al., U.S. Patent No. 4,153,689, issued May 8, 1979 (Ex. 1023).
[9] Exhibit 1001A is the prosecution history of the '652 patent. For ease of reference, we refer to the pagination that Petitioner has added to the exhibit.

We have considered Patent Owner's arguments, but decline to exercise our discretion under § 325(d). First, we note that Petitioner's asserted references are not the same references that the Examiner considered during prosecution. *See* Pet. 14 (explaining that the Examiner's rejections did not include Lantus Label, Owens, Lougheed, FASS, or Grau).

Second, even assuming that the art Petitioner asserts is substantially similar to the art that the Office considered during prosecution of the '652 patent, Patent Owner directs us to references that the Examiner considered at different stages of prosecution and in making rejections over claims differing in scope than the issued claims. That is, the Examiner did not reject the claims of the '652 patent over the combination of Dörschug, Massey, and Hirai, or any combination of those references. Rather, the Examiner rejected the applicants' originally-filed claims as anticipated or obvious over Massey, and as anticipated or obvious over Hirai, among other rejections. *See* Ex. 1001A, 2407–09. At a later stage of prosecution—after the applicants canceled the original claims, presented new claims, and made amendments to those new claims—the Examiner rejected the amended claims as obvious over a combination including Dörschug, but not Massey and/or Hirai. *Id.* at 187, 190–191.

Further, although Patent Owner cites to Dörschug's disclosure of a plasmid for the preparation of insulin glargine and components in aqueous solution, we are not aware of any rejection in which the Examiner relied on Dörschug as teaching insulin glargine in a formulation with particular excipients (i.e., the arguments Petitioner asserts with respect to Lantus Label and Owens). Rather, the Examiner relied on Dörschug as teaching insulin glargine in weakly acidic solution. *See, e.g.*, Ex. 1001A, 55, 191. For these reasons, we decline to exercise our discretion to deny institution under § 325(d).

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. 14 (citing Ex. 1003 ¶¶ 31–34). As an example, Petitioner notes 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. 14–15; *see* Ex. 1003 ¶ 34.

At this stage of the proceeding, Patent Owner does not dispute Petitioner's proposed level of ordinary skill, which we adopt for purposes of this decision. *See* Prelim. Resp. 11. We also find, for purposes of this decision, that the prior art itself is sufficient to demonstrate the level of ordinary skill in the art at the time of the invention. *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 Dr. Yalkowsky's statement of qualifications and curriculum vitae, for the purposes of this decision, we find that he is qualified to opine from the perspective of a person of ordinary skill in the art at the time of the invention. *See* Ex. 1003 ¶¶ 2–16 (Dr. Yalkowsky's statement of qualifications); *id.* at Exhibit A (Dr. Yalkowsky'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); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (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).

Petitioner proposes that we construe several claim limitations, including the phrase "a pharmaceutical formulation," and the terms "polysorbate," "poloxamer," "polysorbate 20," and "polysorbate 80." Pet. 15–17. Although Patent Owner does not dispute Petitioner's proposed constructions at this stage of the proceeding (*see* Prelim. Resp. 11), neither party identifies a dispute that turns on the meaning of the limitations Petitioner proposes we construe. Thus, we determine that no claim term requires construction for purposes of this decision. *See Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) ("only those terms need be construed that are in controversy, and only to the extent necessary to resolve the controversy").

D. Redundancy of the Asserted Grounds of Unpatentability

Patent Owner argues that we should deny Grounds 4–6 because they are redundant to Grounds 1–3, and Petitioner has made no meaningful distinction between the sets of grounds. Prelim. Resp. 14–15. We decline to exercise our discretion to deny Grounds 4–6 based on Patent Owner's argument. Instead, we address each ground on the merits.

E. Pleading Requirements

Patent Owner argues that we should deny Grounds 2–4 because Petitioner fails to identify with particularity the evidence Petitioner relies upon in those grounds. Prelim. Resp. 49–50. More specifically, Patent Owner argues that the Petition fails:

> "(1) to identify clearly the grounds and references on which Petitioner is relying to assert that the challenged claims are not patentable; (2) to specify where the limitations of the challenged claims are taught or suggested by the cited references; and (3) to provide a sufficiently detailed explanation of the significance of the citations. . . ."

Id. at 48 (quoting *Whole Space Indus. Ltd. v. Zipshade Indus. (B.V.I.) Corp.*, Case IPR2015-00048, slip op. 18 (Paper 14) (PTAB July 24, 2015) and citing 35 U.S.C. § 312(a)(3); 37 C.F.R. §§ 42.22(a)(2), 42.104(b)(2), 42.104(b)(4), 42.104(b)(5)).

With respect to Ground 2, Patent Owner argues that "Petitioner switches between [Lantus Label] and Owens" in presenting its arguments. *Id.* at 49 (citing Pet. 41–43). For Ground 3, Patent Owner argues that Petitioner "obfuscates the nature of its challenge . . . by initially styling that ground as alleging that claims 7 and 24 are obvious over a combination of [Lantus Label] and Grau," but then citing to FASS in the concluding sentence of the argument. *Id.* at 50 (citing Pet. 43). And for Ground 4, Patent Owner argues that although presented as based on the combination of Owens and Lougheed, Petitioner "injects [Lantus Label]" into the ground "as the basis for adding polysorbate 20 and polysorbate 80 to the Owens formulation." *Id.* (citing Pet. 46).

With respect to Grounds 2 and 3, we find that the Petition sets forth (1) each of the references upon which Petitioner relies, (2) where each reference discloses each limitation of the challenged claims (i.e., claims 7 and 24), and (3) why a person of ordinary skill in the art would have been prompted to combine the

teachings of the references, with a reasonable expectation of success in arriving at the claimed invention. *See* Pet. 41–42 (Lantus Label and FASS), 43–45 (Lantus Label and Grau). Rather than an attempt to obfuscate the nature of its challenges, it appears to us that Petitioner's reference to Owens in the concluding sentences of Ground 2 and to FASS in the concluding sentence of Ground 3 are typographical errors. Thus, we treat them as such and do not deny those grounds on that basis.

Regarding Ground 4, it appears that Petitioner's cite to Lantus Label is not a typographical error, or an attempt to include the Lantus Label in the ground. Rather, we consider Petitioner's reference to the Lantus Label as demonstrating common knowledge in the art that would have prompted an ordinary artisan to modify Owens' insulin glargine formulation. *See* Pet. 46; *see also Dystar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 1361 (Fed. Cir. 2006) (rationale for modifying the prior art "may be found in any number of sources, including common knowledge, the prior art as a whole, or the nature of the problem itself"). Thus, we do not agree with Patent Owner's assertion that it "is unclear whether Ground 4 is the combination of Owens and Lougheed, or the combination of Owens, Lougheed, and [Lantus Label]." Prelim. Resp. 50. Accordingly, we do not deny Grounds 2–4 for failing to meet the pleading requirements.

F. Asserted References

Before turning to Petitioner's asserted grounds, we provide a brief summary of the asserted references.[10] First, however, we address a preliminary argument

[10] 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.

Patent Owner raises with respect to whether Lantus Label is prior art to the '652 patent.

1. Whether Lantus Label is Prior Art

Patent Owner argues in the Preliminary Response that Petitioner fails to present evidence that Lantus Label is prior art to the '652 patent because the Declaration of Ms. Van Skaik (Ex. 1004A), which Petitioner provides to support the public accessibility of Lantus Label, refers to a version of Exhibit 1004 that is not of record in either proceeding, and the version of Exhibit 1004 that is part of the record does not bear sufficient indicia of public availability. Prelim. Resp. 41–42. With our authorization, Petitioner filed a corrected version of Exhibit 1004 that appears to be the version of the exhibit referenced in Ms. Van Skaik's Declaration. *See* Paper 9, 3–4; corrected Ex. 1004; Ex. 1004A ¶ 5. Petitioner also submitted a Declaration from its counsel (Paper 11) explaining that the version of Exhibit 1004 accompanying the Petition in each proceeding was a working version of the document that counsel inadvertently filed as Exhibit 1004. Thus, Patent Owner's argument appears to be moot.

In any event, Ms. Van Skaik, Executive Director of the Lloyd Library and Museum, testifies that the Lloyd Library and Museum received the Physician's Desk Reference ("PDR") publication containing Lantus Label on December 1, 2000—the same date stamped on the cover page of corrected Exhibit 1004. Ex. 1004A ¶ 5. Ms. Van Skaik further testifies that the PDR publication containing Lantus Label would have been available to the public on December 1, 2000, or shortly thereafter. *Id.* On this record, we find Petitioner shows sufficiently that Lantus Label has been "disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art exercising reasonable diligence[] can locate it." *Kyocera Wireless Corp. v.*

ITC, 545 F.3d 1340, 1350 (Fed. Cir. 2008). Thus, for purposes of this decision, Petitioner provides adequate evidence to make a threshold showing of public availability such that Lantus Label qualifies as a "printed publication" within the meaning of 35 U.S.C. § 314(a).

2. 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) for injection that "consists of insulin glargine dissolved in a clear aqueous fluid." Ex. 1004, 3. 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.").

3. 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 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.

4. 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, $CH_3(CH_2)_N$, with 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").

5. 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.

6. 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 formulations containing Genapol 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.

G. Ground 1: Asserted Obviousness over the Combination of Lantus Label and Lougheed

Petitioner asserts that claims 1–25 of the '652 patent are unpatentable under 35 U.S.C. § 103(a) because the subject matter of those claims would have been obvious over the combination of Lantus Label and Lougheed. Pet. 25–41. Patent Owner opposes. Prelim. Resp. 15–41. Having considered the arguments and evidence before us, for the reasons set forth below, we find that the record establishes a reasonable likelihood that Petitioner will prevail on its asserted ground.

1. Limitations of the Challenged Claims

Petitioner asserts that Lantus Label teaches every limitation of independent claims 1, 7, and 24, except that Lantus Label does not teach "at least one chemical entity chosen from polysorbate 20 and polysorbate 80," as recited in claim 1, or "at least one chemical entity chosen from polysorbate and poloxamers," as recited in claims 7 and 24. *Id.* at 25–26, 29–30 (citing Ex. 1001, 4:27–28; Ex. 1003 ¶¶ 98–102, 129, 160–162, 175–180; Ex. 1004, 3). For those limitations, Petitioner points to Lougheed's teaching of adding polysorbate 20 (Tween 20) or polysorbate 80 (Tween 80) to insulin formulations. *Id.* at 26, 30 (citing Ex. 1003 ¶¶ 163–169, 175–180; Ex. 1006, 4, 7, Table 3). Petitioner makes similar assertions regarding the limitations of the dependent claims, relying on the disclosure of either Lantus Label or Lougheed for teaching the additional limitations of those claims. *See id.* at 31–33, 37–39 (relying on Lougheed for teaching the additional limitations of claims 2, 8, 13, 14, 17–19, 21, and 22); *id.* at 33–36, 39–41 (relying on Lantus Label for teaching the additional limitations of claims 3–6, 9–12, 15, 16, 20, 23, and 25).

At this stage of the proceeding, Patent Owner does not contest Petitioner's arguments or evidence that Lantus Label and Lougheed teach or suggest each limitation of claims 1–25. *See generally* Prelim. Response. On the current record, we find Petitioner shows sufficiently that Lantus Label and Lougheed disclose each limitation of those claims.

The nub of the parties' dispute centers on whether Petitioner shows sufficiently that one of ordinary skill in the art would have had a reason to modify insulin glargine formulations to include Lougheed's disclosed nonionic surfactants, e.g., polysorbate 20 and/or polysorbate 80, and whether the ordinary artisan would have reasonably expected success in achieving the claimed pharmaceutical formulations. We address those issues below.

2. Reason to Modify Lantus Label's Insulin Glargine Formulation

With respect to a reason to modify Lantus Label's insulin glargine formulation, Petitioner asserts it was well-known in the art that insulin had a tendency to aggregate upon storage and delivery. Pet. 26–28 (citing Ex. 1001, 3:2–6; Ex. 1003 ¶¶ 163–169; 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. 26. Petitioner also directs us to portions of Dr. Yalkowsky's Declaration and the studies he discusses therein. *See id.* at 6–7 (citing Ex. 1003 ¶¶ 105–123, 126). Dr. Yalkowsky testifies that insulin glargine would have been expected to aggregate due to the presence of monomers and its acidic pH environment. Ex. 1003 ¶¶ 105–108, 126 (citing Ex. 1014, 9; Ex. 1015, 3–4, 6; Ex. 1018, 1, 8 Ex. 1031, 1). Additionally, Petitioner asserts that Lantus Label explicitly warns patients not to use the product if aggregation occurs

(i.e., Lantus Label also provides a reason to modify the insulin glargine formulation). Pet. 27 (citing Ex. 1004, 5–6).

Patent Owner responds that Petitioner fails to provide: (1) a prior art disclosure of a glargine aggregation problem; and (2) evidence that a person of ordinary skill in the art would have expected the same aggregation problem for glargine, as was known for human or animal insulin formulations. Prelim. Resp. 16–26. Specifically, Patent Owner argues that Lantus Label describes its solution as "*completely soluble*," and that neither Petitioner nor Dr. Yalkowsky explains why a person of ordinary skill in the art would have understood the "use-only-when-clear" patient instructions in Lantus Label as conveying an aggregation problem. *Id.* at 17 (citing 1004, 3); *see also id.* (explaining that Owens states glargine is a "*clear* acidic solution" with "*stabilization* of the [Glargine] molecule"). Patent Owner also directs us to a number of other parenteral drug products in the PDR that carry the same instruction. *Id.* at 17–18, n.3.

As to insulin glargine and human or animal insulin, Patent Owner contends that Petitioner "conflates Glargine and non-Glargine insulin," even though Petitioner admits that glargine and human insulin are different molecules with different structures, chemical properties, and biological properties. *Id.* at 20–21; *see id.* at 25–26 (citing Ex. 1014, 10, 28). According to Patent Owner, Petitioner's failure to address the differences between glargine and non-glargine insulins renders Petitioner's arguments regarding insulin glargine aggregation "nothing more than . . . conclusory." *Id.* at 22–24.

Patent Owner's argument regarding Lantus Label's patient warning has merit, but Petitioner provides us with additional evidence to support its argument that insulin glargine would have been expected to aggregate. As explained above, Petitioner relies on Lougheed's disclosure that aggregation was a known obstacle

to insulin formulations. *See* Ex. 1006, 1 ("Unfortunately, the tendency of insulin to aggregate during storage in and delivery from . . . devices remains one of the fundamental obstacles to their prolonged clinical use."). Petitioner also cites to the background of the '652 patent, which discusses properties of insulins generally, including insulin glargine and human or animal insulin, without distinguishing between different types of insulin. Ex. 1001, 3:2–6 ("Especially 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)." (emphasis added)). Further, Petitioner relies on Dr. Yalkowsky's testimony regarding factors that contribute to insulin aggregation, including acidic pH. Pet. 6–7 (citing Ex. 1003 ¶¶ 103–108, 126). Dr. Yalkowsky's testimony in that regard appears to be supported by objective evidence. *See* Ex. 1003 ¶¶ 103–108 (citing studies of insulin reported in Ex. 1014, 8–9; Ex. 1015, 3–4, 6–7; Ex. 1018, 1, 8; Ex. 1031, 1). At this stage of the proceeding, and based on the current record, we find that Petitioner establishes sufficiently that a person of ordinary skill in the art would have expected insulin glargine to aggregate and, therefore, would have had a reason to modify Lantus Label's insulin glargine formulation.

3. Adding nonionic excipients, such as polysorbate 20 and polysorbate 80, to an insulin glargine formulation

Petitioner asserts that a person of ordinary skill in the art would have modified Lantus Label's formulation by adding nonionic surfactants, such as polysorbate 20 and/or polysorbate 80, because Lougheed expressly discloses that such surfactants enhance the stability of insulin formulations and decrease insulin aggregation. Pet. 26. In that regard, Petitioner directs us to Lougheed's experiments with insulin formulations that include different nonionic surfactants,

e.g., polysorbate 20 and polysorbate 80, in extreme storage conditions. *Id.* (citing Ex. 1006, 1). According to Petitioner, Lougheed's results show that using polysorbate 20 and polysorbate 80 as excipients in insulin formulations enhances stability and decreases aggregate formation. *Id.* (citing Ex. 1003 ¶¶ 163–169; Ex. 1006, 4, 7, Table 3).

Petitioner further asserts that Lougheed's choice of polysorbate 20 and polysorbate 80 as excipients is "not surprising" because 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 26–27 (citing Ex. 1003 ¶¶ 163–169, 172; 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 and/or polysorbate 80 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 27.

In response, Patent Owner first argues that Petitioner fails to show sufficiently that the ordinary artisan would have turned to Lougheed (or any other non-glargine asserted reference). Prelim. Resp. 27. Specifically, Patent Owner asserts that Petitioner fails to address the differences between the glargine formulation Lantus Label describes and the porcine insulin formulations that Lougheed describes. *Id.* at 28. Patent Owner explains that, in addition to protein type, those differences include formulation pH (acidic for Lantus Label vs. neutral/basic for Lougheed and Grau or none specified for FASS) and formulation delivery type (injection for Lantus Label vs. pump for Lougheed, FASS, and Grau). *Id.* Patent Owner contends that such differences matter, and that Petitioner's failure to address them is a "significant deficiency." *Id.* at 29.

With respect to protein type, Patent Owner asserts the prior art of record indicates that "differences in the amino acid chains of human and animal insulins can result in large differences in aggregation tendencies, in unpredictable ways." *Id.* (citing Ex. 1014, 2; Ex. 1015, 2). As explained above, however, the '652 patent specification refers to what was known about insulins generally, without distinguishing between glargine (i.e., modified insulin), human, and animal insulin. *See* Ex. 1001, 3:2–4 ("Especially at acidic pH, insulins . . . show a decreased stability and an increased proneness to aggregation"), 3:32–34 ("The present invention was thus based on the object of finding preparations for acid-soluble insulins containing surfactants"), 3:41–43 ("It has now surprisingly been found that the addition of surfactants can greatly increase the stability of acidic insulin preparations. . . ."); *see also* Ex. 1001A, 2817 (original claim 1 of the application that matured into the '652 patent reciting a pharmaceutical formulation with an acidic pH comprising "a polypeptide selected from the group consisting of bovine, porcine, or human insulin, an insulin analogue, an insulin derivative, an active insulin metabolite and combinations thereof").

As to pH, Patent Owner contends that none of the cited references addresses stabilizing a protein in an acidic solution, and that Petitioner fails to explain why a person of ordinary skill in the art would have been prompted to combine glargine formulations at acidic pH with Lougheed's animal insulin formulations at neutral/basic pH. *Id.* at 29–30. Petitioner, however, does not argue that one of ordinary skill in the art would have modified Lantus Label's insulin glargine formulation with neutral/basic pH non-glargine insulin formulations.

Rather, Petitioner argues that the ordinary artisan would have been prompted to modify the insulin glargine formulation to include polysorbate 20 and/or polysorbate 80 as excipients, given the prior art teachings that such excipients were

known to stabilize insulin formulations against aggregation and that acidic pH was known to contribute to aggregation. *See* Pet. 6–7 (citing Ex. 1003 ¶¶ 103–108, 126), 27–28; Ex. 1006, 3 (explaining that observed FSR values for insulin formulations including Tween 20 (i.e., polysorbate 20) and Tween 80 (i.e., polysorbate 80) are 68 days and 48 days, respectively, as compared with 10 days for insulin controls (i.e., formulations that lacked surfactant additives), 7 ("With respect to the stabilizers employed, it is apparent that all the anionic and nonionic detergent additives [i.e., surfactants], with the exception of Tween 60, markedly increased the stability of their respective formulations when these were subjected to continuous rotation at 37°C."), Table 3. Further, in making its argument, Patent Owner does not direct us to any evidence in the record suggesting that the pH of the formulation would have had an effect on the ability of polysorbate 20 and polysorbate 80 to stabilize an insulin glargine formulation.

Regarding route of administration, Patent Owner argues that Petitioner fails to explain why a person of ordinary skill in the art "would have looked to formulations tested under the mechanical stresses and materials used in insulin pumps for continuous infusion, and have combined these components with those from the once-daily subcutaneous injection Glargine." Prelim. Resp. 31. In making its argument, however, Patent Owner does not direct us to evidence in the record suggesting why differences between pump materials and injectable materials would have mattered to the ordinary artisan. To the contrary, the '652 patent and prior art appear to suggest that air-insulin interfaces and interactions with hydrophobic surfaces promote insulin aggregation, not the type of material used to deliver the insulin formulation. *See, e.g.*, Ex. 1001, 3:8–17; Ex. 1006, 2.

4. Teaching Away and Other Negative Consequences

Patent Owner also argues that Petitioner fails to account for disclosures in the prior art that support nonobviousness. Specifically, Patent Owner argues that Lougheed teaches away from selecting a nonionic surfactant (Prelim. Resp. 35–38), and that Petitioner fails to account for the disclosure of negative consequences in other prior art of record (*id.* at 38–40). With respect to teaching away, Petitioner argues that Lougheed would have directed a person of ordinary skill in the art to use anionic surfactants, specifically sodium dodecyl sulfate (SDS), and away from nonionic surfactants, such as polysorbate 20 and polysorbate 80. *Id.* at 35. This is so, argues Patent Owner, because (1) Lougheed reports achieving better stability results with SDS than with the polysorbate additives, and (2) Lougheed hypothesizes that anionic surfactants stabilize the monomeric form of insulin (i.e., the form of insulin Petitioner argues is prevalent in insulin glargine), whereas nonionic surfactants stabilize dimers and higher order structures. *Id.* at 35–38.

At this stage of the proceeding, we are not persuaded that Lougheed teaches away from adding polysorbate 20 and/or polysorbate 80 to Lantus Label's insulin glargine formulation. Even assuming that Lougheed discloses a preference for using SDS as an excipient, that preference does not control the obviousness inquiry. Rather, we must consider all disclosures, even unpreferred embodiments, in an obviousness analysis. *Merck & Co. v. Biocraft Labs, Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989). And, as Petitioner explains, Lougheed expressly discloses that adding nonionic surfactants, such as polysorbate 20 and polysorbate 80, to an insulin formulation enhances stability and decreases aggregate formation. Pet. 26 (citing Ex. 1006, 4, 7, Table 3); Ex. 1006, 7 ("all the anionic and nonionic detergent additives, with the exception of Tween 60, markedly increased the stability of their respective formulations when the[y] were subjected to continuous

rotation at 37°C."); *see id.* at 3 ("As is evident from the FS values, aggregate formulation was inhibited by the nonionics . . . Tween 20 . . . [and] Tween 80. . . . FSR values for these solutions were respectively . . . 68 [and] 48 . . . as compared with 10 days for the insulin controls.").

Further, we find that Patent Owner's argument regarding Lougheed's "hypothesis" that nonionic surfactants stabilize dimer or higher polymers raises a factual dispute as to whether one of skill in the art would have been discouraged from including polysorbate 20 and/or polysorbate 80 as excipients in an insulin glargine formulation. *See In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004). That dispute is best resolved on the full trial record, and we invite the parties to address the issue further in the Response and Reply.

With respect to the negative consequences of certain formulation excipients, Patent Owner directs us to portions of the 1994 Handbook of Pharmaceutical Excipients ("Handbook")[11] teaching that polysorbates were known to undergo hydrolysis in an acidic environment, and that using polysorbates in a formulation that contains phenol can result in discoloration and/or precipitation. Prelim. Resp. 39–40. Patent Owner also directs us to the Handbook entry for cresol, which states that its "[a]ntimicrobial activity is reduced in the presence of nonionic surfactants." Ex. 1019, 5; Prelim. Resp. 40.

Patent Owner's arguments are not without merit. We find, however, that they raise factual disputes as to whether one of skill in the art would have been discouraged from including polysorbate 20 and/or polysorbate 80 as excipients in

[11] HANDBOOK OF PHARMACEUTICAL EXCIPIENTS 139, 377 (Ainley Wade & Paul J. Weller eds., 2d ed. 1994) (Ex. 1019). Although we refer to the original pagination in this citation, like Patent Owner, we refer in our discussion to the pagination Petitioner added to the exhibit.

the Lantus Label insulin glargine formulation, which is acidic and includes m-cresol as an excipient. For example, although Patent Owner points to the Handbook's disclosure that "gradual saponification [of polysorbates] occurs with strong acids," it is not clear from the current record what the person of ordinary skill in the art would have understood from such teaching. Nor is it apparent from the current record that one of ordinary skill in the art would have been discouraged from using polysorbates as excipients with phenol or cresol in light of the Handbook's teachings regarding discoloration and antimicrobial activity. As our reviewing court has explained, "a given course of action often has simultaneous advantages and disadvantages, and this does not necessarily obviate motivation to combine." *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006). We invite the parties to address these issues further in the Response and Reply.

In sum, on the present record, we find that Petitioner establishes a reasonable likelihood of prevailing in showing that a person of ordinary skill in the art would have been prompted to add polysorbate 20 and/or polysorbate 80 as excipients to an insulin glargine formulation, with a reasonable expectation of success in achieving the claimed pharmaceutical formulations.

H. Grounds 2 and 3: Asserted Obviousness over the Combination of Lantus Label and FASS or Lantus Label and Grau

Petitioner asserts that claims 7 and 24 of the '652 patent are unpatentable under 35 U.S.C. § 103(a) because the subject matter of those claims would have been obvious over the combination of Lantus Label and FASS or Grau. Pet. 41–45. Patent Owner opposes. Prelim. Resp. 15–41. Having considered the arguments and evidence before us, for the reasons set forth below, we find that the record establishes a reasonable likelihood that Petitioner will prevail on its asserted grounds.

Petitioner's arguments are substantially the same as those for claims 7 and 24 in Ground 1, except that Petitioner cites FASS or Grau instead of Lougheed. Petitioner argues that Lantus Label teaches all of the elements of claims 7 and 24, except that Lantus Label does not teach "at least one chemical entity chosen from polysorbate and poloxamers," as recited in both claims. Pet. 41–42 (Lantus Label and FASS), 43 (Lantus Label and Grau). For that limitation in Ground 2, Petitioner directs us to FASS' teaching that adding the stabilizer poly(oxyethylene, oxypropylene)glycol (i.e., a poloxamer) to an insulin formulation "prevents precipitation and flocculation of the insulin," which makes the formulation "particularly suited for use in insulin pumps." *Id.* at 42 (quoting Ex. 1007A, 7); *see id.* (citing Ex. 1033A, 6). 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 43–44 (citing Ex. 1008, 2–6).

As with Ground 1, Petitioner argues that a person of ordinary skill in the art would have been prompted to modify Lantus Label's insulin glargine formulation to include poloxamers, such as those disclosed in FASS and Grau, in view of the well-known tendency for insulin to aggregate upon storage and delivery—a recognized obstacle to formulating insulins. *Id.* at 42, 44–45. And, like Ground 1, Petitioner supports its assertions with citations to the prior art, as well as Dr. Yalkowsky's testimony. *Id.* (citing Ex. 1006, 1; Ex. 1003 ¶¶ 223–229, 231–237); *see* Ex. 1008, 1 (describing insulin's tendency to precipitate and aggregate). Likewise, Petitioner argues that a person of ordinary skill in the art would have reasonably expected success in achieving the claimed pharmaceutical formulations. Pet. 42, 44–45.

Patent Owner does not provide separate arguments for Grounds 2 and 3 to address Petitioner's assertions that a person of ordinary skill in the art would have been prompted to modify Lantus Label's insulin glargine formulation to include poloxamers as excipients, with a reasonable expectation of success in achieving the claimed pharmaceutical formulations. Rather, Patent Owner's arguments in that regard address Grounds 1–6 collectively. *See, e.g.*, Prelim. Resp. 15 (addressing all six of Petitioner's asserted grounds together), 27 (same), 33 (same).

As explained above with respect to Ground 1, we find that Patent Owner's arguments raise disputed issues of material fact that are best resolved on a full trial record. *See supra* §§ III.G.2–III.G.4. Accordingly, for substantially the same reasons set forth above, we find that Petitioner demonstrates a reasonable likelihood that the combined teachings of Lantus Label and FASS (Ground 2) or Lantus Label and Grau (Ground 3) disclose each limitation of claims 7 and 24, and that one of ordinary skill in the art would have modified Lantus Label's insulin glargine formulation to include poloxamers as excipients, with a reasonable expectation of success in achieving the claimed pharmaceutical formulations.

I. Ground 4: Asserted Obviousness over the Combination of Owens and Lougheed

Petitioner asserts that claims 1–25 of the '652 patent are unpatentable under 35 U.S.C. § 103(a) because the subject matter of those claims would have been obvious over the combination of Owens and Lougheed. Pet. 25–41. Patent Owner opposes. Prelim. Resp. 15–41. Having considered the arguments and evidence before us, for the reasons set forth below, we find that the record establishes a reasonable likelihood that Petitioner will prevail on its asserted ground.

Petitioner's arguments are substantially the same as those for Ground 1, except that Petitioner cites Owens instead of Lantus Label. As with Lantus Label,

Petitioner argues that Owens teaches all of the elements of independent claims 1, 7, and 24, except that Owens does not teach "at least one chemical entity chosen from polysorbate 20 and polysorbate 80," as recited in claim 1, or "at least one chemical entity chosen from polysorbate and poloxamers," as recited in claims 7 and 24. Pet. 45–48 (citing Ex. 1001, 4:27–28; Ex. 1003 ¶¶ 98–102, 239; Ex. 1005, 3–4). For those limitations, Petitioner points to Lougheed's teaching of adding polysorbate 20 (Tween 20) or polysorbate 80 (Tween 80) to insulin formulations. *Id.* at 26, 30 (citing Ex. 1003 ¶¶ 126, 239–246, 249–253; Ex. 1006, 427, 430, Table 3). Petitioner makes similar assertions regarding the limitations of the dependent claims, relying on the disclosure of either Owens or Lougheed for teaching the additional limitations of those claims. *See id.* at 48–50, 52–54, 55–56 (relying on Lougheed for teaching the additional limitations of claims 2, 8, 13, 14, 17–19, 21, 22, and 25); *id.* at 50–52, 54–55 (relying on Owens for teaching the additional limitations of claims 3–6, 9–12, 15, 16, 20, and 23).

As with Ground 1, Petitioner argues that a person of ordinary skill in the art would have been prompted to modify Owens' insulin glargine formulation to include polysorbate 20 and polysorbate 80, in view of the well-known tendency for insulin to aggregate upon storage and delivery. Pet. 45–48. And, like Ground 1, Petitioner supports its assertions with citations to Lougheed and Dr. Yalkowsky's testimony. *Id.* (citing Ex. 1003 ¶¶ 126, 239–246, 249–253; Ex. 1006, 4, 7, Table 3). Likewise, Petitioner argues that a person of ordinary skill in the art would have reasonably expected success in achieving the claimed pharmaceutical formulations. *Id.*

Patent Owner does not provide separate arguments for Ground 4 to address Petitioner's assertions that a person of ordinary skill in the art would have been prompted to modify Owens' insulin glargine formulation to include polysorbate 20

and/or polysorbate 80 as excipients, with a reasonable expectation of success in achieving the claimed pharmaceutical formulations. Rather, Patent Owner's arguments in that regard address Grounds 1–6 collectively. *See, e.g.*, Prelim. Resp. 15 (addressing all six of Petitioner's asserted grounds together), 27 (same), 33 (same).

As explained above with respect to Ground 1, we find that Patent Owner's arguments raise disputed issues of material fact that are best resolved on a full trial record. *See supra* §§ III.G.2–III.G.4. Accordingly, for substantially the same reasons set forth above, we find that Petitioner demonstrates a reasonable likelihood that the combined teachings of Owens and Lougheed disclose each limitation of claims 1–25, and that one of ordinary skill in the art would have modified Owens' insulin glargine formulation to include polysorbate 20 and/or polysorbate 80 as excipients, with a reasonable expectation of success in achieving the claimed pharmaceutical formulations.

J. Grounds 5 and 6: Asserted Obviousness over the Combination of Owens and FASS or Owens and Grau

Petitioner asserts that claims 7 and 24 of the '652 patent are unpatentable under 35 U.S.C. § 103(a) because the subject matter of those claims would have been obvious over the combination of Owens and FASS or Grau. Pet. 56–60. Patent Owner opposes. Prelim. Resp. 15–41. Having considered the arguments and evidence before us, for the reasons set forth below, we find that the record establishes a reasonable likelihood that Petitioner will prevail on its asserted grounds.

Petitioner's arguments are substantially the same as those for claims 7 and 24 in Grounds 1–4, except that Petitioner cites FASS or Grau instead of Lougheed, and Owens instead of Lantus Label. Petitioner argues that Owens teaches all of the

elements of claims 7 and 24, except that Owens does not teach "at least one chemical entity chosen from polysorbate and poloxamers," as recited in both claims. Pet. 56–57 (Owens and FASS), 58–59 (Owens and Grau). For that limitation in Ground 5, Petitioner directs us to FASS' teaching that adding the stabilizer poly(oxyethylene, oxypropylene)glycol (i.e., a poloxamer) to an insulin formulation "prevents precipitation and flocculation of the insulin," which makes the formulation "particularly suited for use in insulin pumps." *Id.* at 57 (quoting Ex. 1007A, 7); *see id.* (citing Ex. 1033A, 6). For that limitation in Ground 6, 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 58–59 (citing Ex. 1008, 2–6).

As with Grounds 1–4, Petitioner argues that a person of ordinary skill in the art would have been prompted to modify Owens' insulin glargine formulation to include poloxamers, such as those disclosed in FASS and Grau, in view of the well-known tendency for insulin to aggregate upon storage and delivery—a recognized obstacle to insulin formulating. Pet. 57–59. And, like Grounds 1–4, Petitioner supports its assertions with citations to the prior art, as well as Dr. Yalkowsky's testimony. *Id.* (citing Ex. 1006, 1; Ex. 1003 ¶¶ 297–300, 302–306); *see also* Ex. 1008, 1 (describing insulin's tendency to precipitate and aggregate as an impediment to developing delivery devices for treating diabetes). Likewise, Petitioner argues that a person of ordinary skill in the art would have reasonably expected success in achieving the claimed pharmaceutical formulations. Pet. 57–60.

Patent Owner does not provide separate arguments for Grounds 5 and 6 to address Petitioner's assertions that a person of ordinary skill in the art would have been prompted to modify Owens' insulin glargine formulation to include

poloxamers as excipients, with a reasonable expectation of success in achieving the claimed pharmaceutical formulations. Rather, Patent Owner's arguments in that regard address Grounds 1–6 collectively. *See, e.g.*, Prelim. Resp. 15 (addressing all six of Petitioner's asserted grounds together), 27 (same), 33 (same).

As explained above with respect to Ground 1, we find that Patent Owner's arguments raise disputed issues of material fact that are best resolved on a full trial record. *See supra* §§ III.G.2–III.G.4. Accordingly, for substantially the same reasons set forth above, we find that Petitioner demonstrates a reasonable likelihood that the combined teachings of Owens and FASS (Ground 5) or Owens and Grau (Ground 6) disclose each limitation of claims 7 and 24, and that one of ordinary skill in the art would have modified Owens' insulin glargine formulation to include poloxamers as excipients, with a reasonable expectation of success in achieving the claimed pharmaceutical formulations.

IV. CONCLUSION

Petitioner establishes a reasonable likelihood of prevailing in challenging claims 1–25 of the '652 patent, and Patent Owner's arguments and evidence in the Preliminary Response do not persuade us otherwise. Although many of Patent Owner's arguments raise genuine issues of material fact, the parties will have the opportunity to further develop these facts during trial, and the Board will evaluate the fully-developed record at the close of the evidence.

Accordingly, taking account of the information presented in the Petition and the Preliminary Response, and the evidence of record, we determine that Petitioner establishes a reasonable likelihood that it will prevail in showing that claims 1–25 of the '652 patent are unpatentable. Our findings and conclusions are not final and may change upon consideration of the full record developed during trial.

V. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that the Petition is granted and an *inter partes* review is instituted as to:

Claims 1–25 of the ’652 patent under 35 U.S.C. § 103 over the combination of Lantus Label and Lougheed;

Claims 7 and 24 of the ’652 patent under 35 U.S.C. § 103 over the combination of Lantus Label and FASS;

Claims 7 and 24 of the ’652 patent under 35 U.S.C. § 103 over the combination of Lantus Label and Grau;

Claims 1–25 of the ’652 patent under 35 U.S.C. § 103 over the combination of Owens and Lougheed;

Claims 7 and 24 of the ’652 patent under 35 U.S.C. § 103 over the combination of Owens and FASS; and

Claims 7 and 24 of the ’652 patent under 35 U.S.C. § 103 over the combination of Owens and Grau;

FURTHER ORDERED that no other ground of unpatentability is authorized;

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

FURTHER ORDERED that Petitioner shall update its mandatory notices, within three days of the entry of this Decision, to include as related matters the pending and concluded litigation that Patent Owner identifies and IPR2017-01528.

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