No. _____

In the Supreme Court of the United States

SANOFI-AVENTIS DEUTSCHLAND GMBH,

Applicants,

v.

MYLAN PHARMACEUTICALS INC.,

Respondents.

On Application to Stay or Recall the Mandate of the U.S. Court of Appeals for the Federal Circuit

APPLICATION TO STAY OR RECALL THE FEDERAL CIRCUIT'S MANDATE PENDING THE FILING AND DISPOSITION OF A WRIT OF CERTIORARI

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CORPORATE DISCLOSURE STATEMENT

Per Supreme Court Rule 29.6, Applicant Sanofi-Aventis Deutschland GmbH's parent corporation is Hoechst GmbH, which in turn is owned by Sanofi Foreign Participations B.V. Sanofi holds a 10% or greater ownership interest in Sanofi Foreign Participations B.V.

To the HONORABLE JOHN G. ROBERTS, JR., Chief Justice of the United States Supreme Court and Circuit Justice for the Federal Circuit Court of Appeals:

INTRODUCTION

Pursuant to 28 U.S.C. § 2101(f) and Supreme Court Rule 23, Sanofi applies to stay, or in the alternative, recall the mandate of the United States Court of Appeals for the Federal Circuit pending the disposition of Sanofi's forthcoming petition for a writ of certiorari.

This case presents a question of exceptional importance concerning a party's right to have its case adjudicated according to the law as it exists at the time its case is decided. On October 31, the Federal Circuit significantly changed the law while deciding an important structural constitutional question implicating foundational concerns about the separation of powers. In *Arthrex, Inc. v. Smith & Nephew, Inc.*, 941 F.3d 1320 (Fed. Cir. 2019), the Federal Circuit declared that the Administrative Patent Judges ("APJs") who adjudicate private patent rights on the Patent Trial and Appeals Board ("PTAB") are unconstitutionally appointed. The Federal Circuit accordingly held that the Final Written Decisions ("FWDs") issued by APJs before *Arthrex*

issued—like the underlying decision here—were the result of an *ultra vires* exercise of authority and thus invalid.

A divided panel of the Federal Circuit, however, departing from this Court's longstanding precedent, declined to apply this newly established law to Sanofi's ongoing appeal. The majority held that "failure to raise the *Arthrex* Appointments Clause issue in the opening brief forfeits the challenge." A024 n.4. This holding conflicts with this Court's established cases recognizing that the fundamental structural interests protected by the Appointments Clause warrant excusing ordinary waiver principles and instead recognize that a significant change of law should apply to pending appeals, regardless of waiver. At the very least, there is a reasonable likelihood that this Court will decide to hear the case and reaffirm these principles as they apply to the important separation-of-powers questions decided in *Arthrex*.

Granting a stay will allow this Court to consider these issues without further threatening Sanofi's patent rights. The underlying patents at issue here claim a formulation of insulin glargine, a breakthrough insulin analog that, as the result of Sanofi's significant investment in research and development, vastly improved the life of

diabetic patients. The rights extended by the patents have allowed Sanofi to continue to invest in research and development of other life-changing treatments. Absent a stay, Sanofi might lose these valuable patent rights before this Court has a chance to weigh in.

By contrast, any harm to Mylan from a stay of the mandate will be minimal at best. In addition to seeking *inter partes* review before the PTAB, Mylan filed a section 505(b)(2), 21 U.S.C. § 355(b)(2), new drug application ("NDA") seeking to market a glargine follow-on biologic. By virtue of an infringement suit Sanofi filed in the District of New Jersey under the Hatch-Waxman Act, a 30-month stay of FDA approval of Mylan's NDA is in effect until March 18, 2020, absent any earlier order from the District Court. *See Sanofi-Aventis U.S. LLC, et al. v. Mylan GmbH, et al.*, No. 17-cv-09105, ECF 285 (D.N.J. Mar. 18, 2019). Mylan does not yet have tentative FDA approval for its proposed glargine product, and it likely will not receive such approval before the 30-month stay of FDA approval expires. Indeed, Mylan has represented that the FDA has set a mid-2020 "goal" for resolving its application, well after the expiration of the 30-month stay. Because a stay of the Federal Circuit's mandate will not extend the 30-month stay, a stay of the mandate

pending Sanofi's certiorari petition will not delay FDA approval of Mylan's proposed product. It will, however, have the effect of maintaining the status quo of any litigation on the '652 patent until the appellate process has terminated. This Court should stay issuance of the Federal Circuit's mandate until this Court has an opportunity to resolve Sanofi's forthcoming petition for certiorari, in which Sanofi intends to challenge not only the waiver issues described herein, but also the Federal Circuit's affirmance of the PTAB's obviousness determination.

BACKGROUND

This appeal concerns two Sanofi patents claiming a reformulation of insulin glargine, a long-acting insulin analog—marketed under the tradename Lantus®—that achieved a major breakthrough in diabetes therapy by allowing a once-daily administration of medication. Sanofi developed the reformulation to address unexpected aggregation problems with the original glargine formulation it discovered after Lantus® launched. Lantus®, as reformulated, has achieved considerable commercial success, becoming the most-prescribed long-acting insulin on the market. This success has in turn enabled Sanofi to continue to invest in research and development of other life-saving treatments.

In 2017, Mylan filed for *inter partes* review of two Sanofi patents, U.S. Patents Nos. 7,476,652 and 7,713,930, which protect Sanofi's glargine reformulation. The PTAB instituted review and found the patents invalid as obvious. Sanofi appealed. Concurrently with the PTAB proceedings, Sanofi brought an infringement action against Mylan in the District Court of New Jersey on the '652 and '930 patents at issue here, as well as several other unrelated patents. Pursuant to the Hatch-Waxman Act, the District Court entered a 30-month stay of FDA approval of Mylan's pending NDA while the infringement action is pending.

After briefing and oral argument in Sanofi's appeal, the Federal Circuit decided *Arthrex*, holding that the PTAB's APJs were appointed in violation of the Appointments Clause. 941 F.3d 1320. Rejecting the argument that Arthrex waived its Appointments Clause challenge by failing to raise the issue below, the Federal Circuit recognized that Appointments Clause challenges raise "important structural interests and separation of powers concerns" that should be "incentivized at the appellate level." *Id.* at 1340.

To remedy the Appointments Clause issue going forward, the Federal Circuit severed the portion of the Patent Act protecting APJs from for-cause removal. *Id.* at 1337. However, because the APJs were not constitutionally appointed when they issued the final written decision below in *Arthrex*, the Federal Circuit vacated the PTAB's decision and ordered that a new panel of constitutionally appointed APJs consider the matter on remand. *Id.* at 1340 ("[W]here the final decision was rendered by a panel of APJs who were not constitutionally appointed and where the parties presented an Appointments Clause challenge on appeal, [this case] must be vacated and remanded."). The *Arthrex* opinion limited itself to "cases where final written decisions were issued and where litigants present an Appointments Clause challenge on appeal." *Id.*

The next day, without the benefit of briefing or argument on the question, a panel of the Federal Circuit went further and held that a party who did not raise an Appointments Clause challenge in its opening brief had forfeited its *Arthrex* argument. *Customedia Techs., LLC v. Dish Network Corp.*, 941 F.3d 1173 (Fed. Cir. 2019). Both the *Arthrex* and *Customedia* decisions remain contested, with parties pursuing *en banc* review and the Federal Circuit requesting responses in each case.

On November 5, 2019, days after *Arthrex* was decided, Sanofi filed a Rule 28(j) letter alerting the Federal Circuit panel to the newly controlling law. ECF 52. Sanofi acknowledged that it had not raised an Appointments Clause challenge in its opening brief, but it requested supplemental briefing on the effect of *Arthrex*, including whether any of the well-established exceptions to waiver applied. *Id.* at 2. Two weeks later, a divided panel affirmed the PTAB's orders. The majority construed Sanofi's Rule 28(j) letter as a request to vacate and remand the PTAB's decision and, following *Customedia*, held that Sanofi had forfeited the argument because it did not raise an Appointments Clause challenge in its opening brief. A024 n.4.

Judge Newman dissented, disagreeing with the panel majority's holding that *Arthrex* should not apply. A031. She noted that "at the time these appeals were filed, there was no holding of illegality of appointments of the PTAB's [APJs]." A030. *Arthrex* reflected a change in the law and "[i]t is well established that when the law changes while a case is on appeal, the changed law applies." *Id.* Thus, "Sanofi is entitled to the same benefit of the *Arthrex* decision as are the *Arthrex* parties"—that is, to vacate and remand for a new hearing. A031. After the Federal

Circuit's affirmance of the PTAB's finding of invalidity, the District Court stayed the infringement action as to the '652 patent.[1] The case remains stayed, with the 30-month statutory stay of FDA approval of Mylan's pending NDA set to expire on March 18, 2020, absent any earlier action of the District Court.

Sanofi filed a petition for rehearing *en banc* on December 19, 2019, asking the full Federal Circuit to reconsider the panel's waiver ruling. In addition, each of the three parties to *Arthrex* filed *en banc* petitions asking the full Court to consider a range of issues implicated by the opinion, some arguing that *Arthrex* went too far in finding an Appointments Clause violation and remanding the FWDs; some arguing that *Arthrex* did not go far enough. At the Federal Circuit's invitation, each of the *Arthrex* parties filed responses to the petitions on January 17, 2020. The Federal Circuit similarly requested a response to *Customedia*'s petition for *en banc* rehearing, which parroted Sanofi's arguments in substantially similar form. These petitions remain pending.

[1] Sanofi no longer asserts the '930 patent against Mylan in the New Jersey action.

On January 28, 2020, the Federal Circuit denied Sanofi's petition for rehearing *en banc*. On February 6, 2020, the Federal Circuit denied Sanofi's motion to stay the mandate pending Sanofi's petition to this Court for certiorari. Absent a stay from this Court, the Federal Circuit will issue its mandate. A003.

ARGUMENT

I. THIS COURT SHOULD STAY THE MANDATE PENDING SANOFI'S PETITION FOR CERTIORARI

Pursuant to Supreme Court Rule 23(2) and 28 U.S.C. § 2112(f), this Court may stay the mandate of the Federal Circuit pending the disposition of Sanofi's forthcoming petition for a writ of certiorari. In reviewing an application to stay the mandate, this Court considers whether there is "a reasonable probability that certiorari will be granted" and "a significant possibility that the judgment below will be reversed," as well as "a likelihood of irreparable harm (assuming the correctness of the applicant's position) if the judgment is not stayed." *Barnes v. E-Sys., Inc. Grp. Hosp. Med. & Surgical Ins. Plan*, 501 U.S. 1301, 1302 (1991) (Scalia, J., in chambers). When these factors are present, the Court also balances "the equities," including "the relative harms to applicant and

respondent, as well as the interests of the public at large." *Id.* at 1304–05 (citation omitted). This case satisfies each of these factors.

First, this application presents a compelling case for certiorari. The Federal Circuit issued an erroneous decision on an indisputably important question of patent law. The decision sanctions the termination of valuable patent rights by APJs acting clearly beyond their constitutional authority—a fundamental separation-of-powers principle that this Court has frequently intervened to police, including only a couple of terms ago. *Lucia v. S.E.C.*, 138 S. Ct. 2044 (2018). Moreover, the Federal Circuit's decision does so while ignoring this Court's well-established precedent holding that a significant change in law applies to all cases pending on review, regardless of waiver. Given the fundamental importance of the issue and the Court's precedent on waiver in these circumstances, there is a reasonable probability that the Court will grant Sanofi's petition and reverse.[2]

Second, there is good cause for a stay. The Court may also "'balance the equities'—to explore the relative harms to applicant and respondent,

[2] Sanofi additionally intends to challenge the Federal Circuit's obviousness determination in its forthcoming petition for certiorari.

as well as the interests of the public at large." *Rostker v. Goldberg*, 448 U.S. 1306, 1308 (1980) (Brennan, J., in chambers). "The likelihood that denying the stay will permit irreparable harm to the applicant may not clearly exceed the likelihood that granting it will cause irreparable harm to others." *Barnes*, 501 U.S. at 1305. Again, these elements are satisfied here. Absent a stay, Sanofi may lose its valuable patent rights by virtue of a decision rendered by administrative judges who were unconstitutionally appointed and acting *ultra vires*, as the Federal Circuit already found. The consequences of the loss of any patent rights would cause irreparable harm to Sanofi, while resulting in no harm to Mylan, given that regardless of when the mandate issues, Mylan will be able to market its follow-on biologic once the 30-month stay expires, absent an earlier ruling from the District of New Jersey (provided Mylan has regulatory approval). Thus, the balance of equities and the public interest also weigh in Sanofi's favor and in favor of maintaining the status quo. Among other things, although the harm to Sanofi absent a stay could be substantial, Mylan cannot articulate any similar harm—it did not articulate any in its response to Sanofi's motion to stay the mandate in the Federal Circuit. ECF 73 at 12. Indeed, Mylan does not

yet even have tentative FDA approval to market its competing insulin glargine product.[3] To avoid this inequitable result, this Court should stay the mandate pending Sanofi's petition for certiorari.

A. There Is a Reasonable Possibility That The Supreme Court Will Grant Certiorari

Sanofi's petition presents a certworthy issue: an "important federal question" that the Federal Circuit has decided "in a way that conflicts with relevant decisions of this Court." Sup. Ct. R. 10(c). The underlying *Arthrex* issue implicates a serious constitutional question going to the authority of APJs to decide critical issues of patent rights, and the Federal Circuit's decision to impose a waiver rule respecting the adjudication of those rights conflicts with this Court's long-standing precedent.

In *Arthrex*, the Federal Circuit held that the statutory scheme whereby the Secretary of Commerce appoints APJs violated the Appointments Clause of the Constitution. 941 F.3d 1320. Because no

[3] As explained above, the 30-month stay under the Hatch-Waxman Act for Mylan's insulin glargine vial product expires on March 18, 2020, absent an earlier order of the District of New Jersey. Although Sanofi's petition for certiorari will not be decided by then, Sanofi is not seeking to extend the 30-month stay beyond March 18, 2020.

presidentially-appointed officer can review, vacate, or correct APJ decisions, and because removal power over APJs is limited—*i.e.*, APJs can be removed only for cause—*Arthrex* held that APJs are principal officers under the statute. *Id.* at 1335. Therefore, they "must be appointed by the President and confirmed by the Senate; because they are not, the current structure of the Board violates the Appointments Clause." *Id.*

Structural constitutional challenges, like those posed by the Appointments Clause, implicate important separation of powers concerns that excuse waiver. *Freytag v. C.I.R.*, 501 U.S. 868, 879 (1991) (court may exercise discretion to "hear petitioners' challenge to the constitutional authority" of tax judges over claims of waiver); *cf. Commodity Futures Trading Comm'n v. Schor*, 478 U.S. 833, 850–51 (1986) ("To the extent that this structural principle is implicated in a given case, the parties cannot by consent cure the constitutional difficulty."). "The Clause is a bulwark against one branch aggrandizing its power at the expense of another branch, but it is more: it 'preserves another aspect of the Constitution's structural integrity by preventing the diffusion of the appointment power.'" *Ryder v. United States*, 515 U.S. 177, 182 (1995) (quoting *Freytag*, 501 U.S. at 878). Thus, "the strong interest of the

federal judiciary in maintaining the constitutional plan of separation of powers" overcomes the usual rule of entertaining only preserved issues on appeal. *Freytag*, 501 U.S. at 879 (citing *Glidden Co. v. Zdanok*, 370 U.S. 530, 536 (1962)). Indeed, the concern over whether officers exercising executive power are constitutionally appointed is so important that in *Freytag*, for example, this Court disregarded waiver arguments and allowed an Appointments Clause challenge. This Court has even allowed an Appointments Clause challenge where, as here, the party first raised the issue in "a supplemental brief upon a second request for review." *Glidden*, 370 at 536 (citing *Lamar v. United States*, 241 U.S. 103, 117 (1916)) (Appointments Clause challenge may be raised for the first time before this Court)).

The Appointments Clause and separation of powers issues are no less important here than they are in *Arthrex* or any other Appointments Clause case, including those that this Court has reviewed in recent years. *See Lucia*, 138 S. Ct. 2044. Indeed, this Court routinely grants review in cases presenting significant separation of powers issues even absent a conflict between the courts of appeals. *See, e.g.*, *Free Enter. Fund v. Public Co. Accounting Oversight Bd.*, 561 U.S. 477 (2010); *Clinton v. New York*,

524 U.S. 417 (1998); *Edmond v. United States*, 520 U.S. 651 (1997); *Morrison v. Olsen*, 487 U.S. 654 (1988). The Federal Circuit in *Arthrex* established that APJs were adjudicating private property rights that, by definition, have been decided by officials who were unconstitutionally appointed and thus acting *ultra vires*. *Arthrex*, 941 F.3d at 1327. Thus, Sanofi's patents were invalidated by APJs without the lawful authority to decide important questions of private property rights.

The Federal Circuit's failure to apply a change in law consistently is itself concerning given these important, foundational concerns and this Court's clear precedent that excuses waiver when a party promptly raises an issue following a significant change of law. *E.g.*, *Hormel v. Helvering*, 312 U.S. 552, 558–59 (1941) (waiver does not apply in "those [cases] in which there have been judicial interpretations of existing law after decision below and pending appeal—interpretations which if applied might have materially altered the result"). This Court has long held that when the law changes while a case is pending on appeal, "an appellate court must apply the law in effect at the time it renders its decision." *Thorpe v. Hous. Auth. of Durham*, 393 U.S. 268, 281 (1969); *Harper v. Va. Dep't of Taxation*, 509 U.S. 86, 97 (1993); *Griffith v. Kentucky*, 479 U.S.

314, 323 (1987). This Court's refusal to do so ignores this fundamental rule of law. *James B. Beam Distilling Co. v. Georgia*, 501 U.S. 529, 537 (1991) ("[T]he principle that litigants in similar situations should be treated the same [is] a fundamental component of *stare decisis* and the rule of law.").

Arthrex ushered in a "significant change of law" that was not indicated by prior precedent. Before *Arthrex*, both this Court and the Federal Circuit reviewed numerous appeals arising from PTAB adjudications, without questioning whether the APJs adjudicating the parties' patent rights were acting *ultra vires*. In 2019 alone, the Federal Circuit *twice* rejected—under Rule 36[4]—precisely the same Appointments Clause challenge that ultimately was successful in *Arthrex*. *See Trading Techs. Int'l, Inc. v. IBG LLC*, 771 F. App'x 493 (Fed. Cir. 2019); *Bedgear, LLC v. Fredman Bros. Furniture Co.*, 779 F. App'x 748 (Fed. Cir. 2019). This Court, too, saw no reason to weigh in on the argument that APJs are unconstitutionally-appointed principal officers,

[4] The Federal Circuit issues such Federal Circuit Rule 36 judgments only when the issues of fact or law are so clear that no opinion—even a non-precedential one—is warranted.

denying certiorari in *Smartflash LLC v. Samsung Electronics America, Inc.* in 2018. 139 S. Ct. 276 (2018); Petition for Writ of Certiorari at 18, *Smartflash LLC*, 2018 WL 3913634 (Aug. 9, 2018) (No. 18-189). And this Court recently upheld the constitutionality of the IPR proceedings, including against a challenge that the PTAB judges exercised powers beyond their authority as non-Article III judges. *Oil States Energy Servs. v. Greene's Energy Grp.*, 138 S. Ct. 1365 (2018). Prior decisions of the Federal Circuit—as well this Court's denial of certiorari—too, supported Sanofi's reasonable reliance on the presumption that the appointment of APJs was constitutional. *E.g.*, *In re DBC*, 545 F.3d 1373, 1380 (Fed. Cir. 2008), *cert. denied*, 558 U.S. 816 (2009) (holding Congress's 2008 re-delegation of the appointment of APJs to the Secretary of Commerce "eliminate[ed] the issue of unconstitutional appointments going forward"); *In re Alappat*, 33 F.3d 1526, 1533–35 (Fed. Cir. 1994) (en banc) (*abrogated on other grounds*) (under predecessor *inter partes* reexamination regime, holding then-Commissioner's ability to "determine the composition of Board panels" provided the necessary officer oversight). Indeed, just a few years ago in *Ethicon Endo Surgery, Inc. v. Covidien LP*, the Federal Circuit *upheld* the Director's delegation

of authority to institute IPR review to APJs, deeming them "subordinate officers." 812 F.3d 1023, 1031 (Fed. Cir. 2016), *en banc reh'g denied*, 826 F.3d 1366, *cert. denied*, 137 S. Ct. 625 (2017). *Arthrex*'s holding that APJs were in fact principal officers, and therefore subject to presidential appointment and senate confirmation under the Appointments Clause, is a departure from the Federal Circuit's prior law articulated in *Ethicon* that APJs were subordinate, thus not implicating any Appointments Clause issue.[5]

Indeed, reflecting the importance of the underlying constitutional issues involved, the ultimate result and reach of *Arthrex* itself remains unsettled. Recognizing the exceptional importance of this issue, all parties to the *Arthrex* appeal have filed petitions for rehearing *en banc*, and the Federal Circuit, recognizing the significance of the issues, has called for responses to each. These petitions, along with other petitions raising the exact same waiver issues in this case, remain pending before the Federal Circuit.

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[5] The reviewability of the institution decision itself was considered by this Court in 2016, raising no concerns about the exercise of the APJ's authority for those decisions. *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131 (2016).

Likewise, the Federal Circuit has called for a response to *en banc* petitions (including in *Customedia*) raising the related issue whether the PTAB's pre-*Arthrex* institution decisions are suspect if, as *Arthrex* held, APJs were not acting as "subordinate officers" as *Ethicon* had previously established. If *en banc* rehearing is granted in the *Arthrex* appeal or in *Customedia*, what the full Federal Circuit has to say could very well affect the proper resolution of this appeal. Indeed, if the Federal Circuit were to determine that, contrary to *Arthrex*'s and *Ethicon*'s express holding, *see Arthrex*, 914 F.3d at 1335, the finding that APJs had been acting as principal officers invalidates previous institution decisions, that ruling would likewise be another fundamental change of law applicable to pending cases, and unfairly denied by the Federal Circuit's refusal to stay the mandate.

Because the issues here are inextricably bound up with *Arthrex*, it is all the more prudent to hold the mandate.

B. There Is a Fair Prospect That This Court Will Reverse the Federal Circuit

Given the important, foundational concerns here, Sanofi's petition is certworthy, and there is a fair prospect that a majority of this Court will reverse the Federal Circuit's decision. Failure to apply a change of

law is compounded here by the fact that *Arthrex* and its application are in flux. There is a good chance that the Federal Circuit will not have the final say on the Appointments Clause questions—this Court may well review the *Arthrex* decision itself, just as it reviewed another Appointments Clause challenge a couple of terms ago. *See Lucia*, 138 S. Ct. 2044. If that is the case, this Court would likely hold this petition and grant the case, vacate, and remand based on the Court's decision in *Arthrex*. Again, there is all the more reason to hold the mandate pending review in this Court.

Enforcing the separation of powers issues here, too, is especially important to a majority of this Court. *Oil States*, 138 S. Ct. at 1386 (Gorsuch, J., dissenting joined by Roberts, C.J.) (arguing that the PTAB's statutory scheme "represents a retreat from the promise of judicial independence" due to political control); *Wellness Int'l Network, Ltd. v. Sharif*, 575 U.S. 665 (2015) (Roberts, C.J., dissenting, joined by Thomas, J.) (emphasizing that the "structural separation of powers" are too important to allow parties to override such barriers by consent). *Arthrex*, like this Court's decision in *Lucia*, aims to vindicate the Appointments Clause's separation of powers principles, ensuring that the different

branches of government do not overreach and aggrandize power. But limiting *Arthrex*'s application to only a subset of cases undermines these principles. Such a practice effectively revives this Court's former—and overruled—practice of denying backward-looking relief in constitutional cases abandoned in *Harper*. It is fundamental that the judiciary's role is to say what the law is, leaving for the legislature to enact forward-looking laws. Core to that role is the understanding that the judiciary's pronouncements operate retrospectively. *See Harper*, 509 U.S. at 97. Prospective decisionmaking violates "basic norms of constitutional adjudication," *id.*, and selective application of a new rule of law reduces legal change to the kind of prospective application "smacking of the legislative process." *Id.* at 108 (Scalia, J., concurring).

Affirming the Federal Circuit's decision below would mean approving of a practice that works *against* judicial efficiency in an already overcrowded legal system. But "economy supplies no license for ignoring these—often vitally inefficient [constitutional]—protections." *Oil States*, 138 S. Ct. at 1380 (Gorsuch, J., dissenting). Following a change of law, "the failure to raise the claim in an opening brief reflects not a lack of diligence, but merely a want of clairvoyance." *Joseph v.*

United States, 574 U.S. 1038 (table) (2014) (Kagan, J., dissenting from denial of certiorari). Faulting litigants for their "misprediction alone to deny relief" to a similarly-situated litigant violates the fundamental rule that rules apply retroactively to all cases on review. *Id.* The result is untenable: "insisting on preservation of claims in this context forces every appellant to raise 'claims that are squarely foreclosed by circuit and [even] Supreme Court precedent on the off chance that [a new] decision will make them suddenly viable.'" *Id.* (internal citation omitted).

For these reasons, there is—at a minimum—a "reasonable probability" that this Court will grant certiorari and a "fair prospect" that it will reverse. *Conkright v. Frommert*, 556 U.S. 1401, 1402 (2009) (Ginsburg, J., in chambers).

C. Absent a Stay, Sanofi Will Suffer Irreparable Harm

Absent a stay from this Court, the Federal Circuit's erroneous decision will take effect and Sanofi will suffer irreparable harm. Sanofi could lose its patent rights, unable to take advantage of any changes in the law from this Court, and the *ultra vires* acts of APJs over valuable property rights will be permanent and isolated from judicial review. Uncertain and thorny legal issues remain, and until they are definitively

resolved, the Federal Circuit's mandate should be held. Sanofi seeks only a delay of the mandate until the unsettled legal issues at play have been finally decided and the appeal has terminated. To do otherwise would subject Sanofi to harm for which it could not be adequately compensated if Sanofi ultimately prevails at this Court. *See, e.g.*, *Kearns v. Chrysler Corp.*, 32 F.3d 1541, 1549–50 (Fed. Cir. 1994) ("In view of the fact that the principal right afforded by a patent is the 'right to exclude' . . . the nature of the patent grant weighs against holding that monetary damages always suffice to make the patentee whole.") (internal citation omitted).

Even though, as discussed more fully below, staying the mandate will not prohibit Mylan from coming to market after it receives final FDA approval, a stay protects Sanofi from other companies appropriating Sanofi's valuable intellectual property. *See, e.g.*, *Abbott Labs. v. Sandoz, Inc.*, 544 F.3d 1341, 1362 (Fed. Cir. 2008); *Sanofi-Synthelabo v. Apotex, Inc.*, 470 F.3d 1368, 1382–83 (Fed. Cir. 2006). Sanofi's patents reflect Sanofi's investment of "enormous costs in terms of time, research, and development" involved in the reformulation of glargine. *Kewanee Oil Co. v. Bicron Corp.*, 416 U.S. 470, 480 (1974). Sanofi has used its success with

that reformulation, among others, to support its continuing research and development activities. Loss of Sanofi's patents could endanger that work. Sanofi Form 20-F, at 12 (2018); *Bio-Tech. Gen. Corp. v. Genentech, Inc.*, 80 F.3d 1553, 1566 (Fed. Cir. 1996).

D. The Equities Favor a Stay

The equities, too, weigh heavily in favor of a stay. This Court must "balance the equities" and "explore the relative harms to applicant and respondent, as well as the interests of the public at large." *Barnes*, 501 U.S. at 1305. But this balancing is "quite easy" where, as here, there is "no irreparable harm that granting the stay would produce." *Id.*

Mylan can point to no harm that results from a stay. Indeed, Mylan's development partner Biocon recently informed investors that it does not expect to have FDA approval to market its planned glargine follow-on biologic until mid-2020. Q3 2020 Biocon Ltd. Earnings Call (Jan, 24, 2020). Moreover, the 30-month stay under the Hatch-Waxman Act will expire on its own force in less than two months, absent an earlier ruling from the District of New Jersey. A stay of this Court's mandate will not further extend the 30-month stay. Once the 30-month stay has expired (and assuming Mylan receives final regulatory approval), Mylan

will be able to market its follow-on biologic. Thus, there is no harm to Mylan, which cannot proceed without final FDA approval in the first place, in waiting at least until the 30-month stay expires, and no countervailing reason to issue the mandate before Sanofi has exercised all of its rights to seek a fulsome review. Maintaining the status quo here promotes judicial economy and efficiency.

The public interest also favors a stay. This Court recognizes the "patent system's desirable stimulus to invention," *Blonder-Tongue Labs., Inc. v. Univ. of Ill. Found.*, 402 U.S. 313, 343 (1971), offering "reward for inventions," *Kewanee Oil*, 416 U.S. at 480. At bottom, the "productive effort" patent rights foster "will have a positive effect on society through the introduction of new products and processes." *Id*. Here, patent rights incent "innovative drug companies to continue costly development efforts." *Sanofi-Synthelabo*, 470 F.3d at 1383; *Abbott Labs.*, 544 F.3d at 1362–63. It is in the public interest for Sanofi to continue to develop treatments for life-threatening conditions.

CONCLUSION

For the foregoing reasons, Sanofi respectfully requests that the Court stay the issuance of the Federal Circuit's mandate, or, if the

mandate has been issued, direct that the mandate be recalled and stayed, pending the disposition of Sanofi's petition for a writ of certiorari.

Dated: February 7, 2020

Respectfully submitted,

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APPENDIX

APPENDIX CONTENTS

NOTE: This order is nonprecedential.

United States Court of Appeals for the Federal Circuit

SANOFI-AVENTIS DEUTSCHLAND GMBH,
Appellant

v.

MYLAN PHARMACEUTICALS INC.,
Appellee

2019-1368, 2019-1369

Appeals from the United States Patent and Trademark Office, Patent Trial and Appeal Board in Nos. IPR2017-01526, IPR2017-01528.

ON MOTION

Before NEWMAN, TARANTO, and CHEN, *Circuit Judges.*

PER CURIAM.

O R D E R

Appellant Sanofi-Aventis Deutschland GmbH moves to stay the issuance of this court's mandate pending the consideration of a petition for a writ of certiorari in the Supreme Court of the United States. Appellee Mylan Pharmaceuticals Inc. opposes the motion.

Upon consideration thereof,

IT IS ORDERED THAT:

The motion is denied.

FOR THE COURT

February 6, 2020
Date

/s/ Peter R. Marksteiner
Peter R. Marksteiner
Clerk of Court

NOTE: This order is nonprecedential.

United States Court of Appeals for the Federal Circuit

SANOFI-AVENTIS DEUTSCHLAND GMBH,
Appellant

v.

MYLAN PHARMACEUTICALS INC.,
Appellee

2019-1368, 2019-1369

Appeals from the United States Patent and Trademark Office, Patent Trial and Appeal Board in Nos. IPR2017-01526, IPR2017-01528.

ON PETITIONS FOR PANEL REHEARING AND REHEARING EN BANC

Before PROST, *Chief Judge*, NEWMAN, LOURIE, DYK, MOORE, O'MALLEY, REYNA, WALLACH, TARANTO, CHEN, HUGHES, and STOLL, *Circuit Judges*.

PER CURIAM.

O R D E R

Appellee Mylan Pharmaceuticals Inc. filed a petition for panel rehearing. Appellant Sanofi-Aventis

Deutschland GmbH separately filed a combined petition for panel rehearing and rehearing en banc. The petitions were referred to the panel that heard the appeal, and thereafter the petition for rehearing en banc was referred to the circuit judges who are in regular active service.

Upon consideration thereof,

IT IS ORDERED THAT:

The petitions for panel rehearing are denied.

The petition for rehearing en banc is denied.

The mandate of the court will issue on February 4, 2020.

FOR THE COURT

January 28, 2020
Date

/s/ Peter R. Marksteiner
Peter R. Marksteiner
Clerk of Court

NOTE: This disposition is nonprecedential.

United States Court of Appeals for the Federal Circuit

SANOFI-AVENTIS DEUTSCHLAND GMBH,
Appellant

v.

MYLAN PHARMACEUTICALS INC.,
Appellee

2019-1368, 2019-1369

Appeals from the United States Patent and Trademark Office, Patent Trial and Appeal Board in Nos. IPR2017-01526, IPR2017-01528.

Decided: November 19, 2019

ADAM BANKS, Weil, Gotshal & Manges LLP, New York, NY, argued for appellant. Also represented by ELIZABETH WEISWASSER, ANISH R. DESAI, ANDREW GESIOR, AARON L. J. PEREIRA; ROBERT T. VLASIS, III, Washington, DC.

DOUGLAS H. CARSTEN, Wilson, Sonsini, Goodrich & Rosati, PC, San Diego, CA, argued for appellee. Also represented by JEFFREY WILLIAM GUISE, ALINA LEONIDOVNA LITOSHYK, ELHAM FIROUZI STEINER, LORELEI WESTIN; NICOLE W. STAFFORD, Austin, TX; WENDY L. DEVINE, San

Francisco, CA; ADAM WILLIAM BURROWBRIDGE, LORA MARIE GREEN, RICHARD TORCZON, Washington, DC.

Before NEWMAN, TARANTO, and CHEN, *Circuit Judges.*

Opinion for the court filed by *Circuit Judge* TARANTO.

Dissenting opinion filed by *Circuit Judge* NEWMAN.

TARANTO, *Circuit Judge.*

Sanofi-Aventis Deutschland GMBH's owns U.S. Patent Nos. 7,476,652 and 7,713,930, which describe and claim certain formulations of a particular kind of insulin. Mylan Pharmaceuticals Inc. sought and obtained from the Patent and Trademark Office (PTO) inter partes reviews of all claims of those patents under 35 U.S.C. §§ 311–319. In those reviews, the PTO's Patent Trial and Appeal Board agreed with Mylan that the subject matter of the claims is unpatentable for obviousness. Sanofi appeals, challenging the Board's findings that a relevant artisan would have had a motivation to combine prior-art references to arrive at the claimed inventions with a reasonable expectation of success, and also challenging the Board's evaluation of Sanofi's evidence of commercial success. We reject Sanofi's challenges and affirm the Board's decisions.

I

The '930 patent issued from a continuation of the application that issued as the '652 patent, and the two share a specification. The patents involve a genetically engineered form of insulin—insulin glargine (sometimes called simply "glargine")—identified in the patent as "Gly(A21)-Arg(B31)-Arg(B32)-human insulin." '652 patent, col. 2, lines 56–57. The patents describe and claim formulations of glargine that include a nonionic surfactant—polysorbates or poloxamers in the '652 patent, esters and ethers of

polyhydric alcohols in the '930 patent. Claim 7 of the '652 patent is illustrative for present purposes:

> 7. A pharmaceutical formulation comprising Gly(A21), Arg(B31), Arg(B32)-human insulin,
>
> at least one chemical entity chosen from polysorbate and poloxamers;
>
> at least one preservative; and
>
> water,
>
> wherein the pharmaceutical formulation has a pH in the acidic range from 1 to 6.8.

'652 patent, col. 11, lines 21–28.

The parties accept that certain background facts were publicly known at the 2002 priority date for these patents. Glargine is a modified version of human insulin that, when injected as part of an acidic solution, acts for longer in a subject than does natural human insulin. Glargine stays in solution at relatively acidic pH levels, and in the prior-art glargine product (which lacked the surfactants claimed in the patents now at issue), it was injected into a patient as part of an acidic solution. Once the glargine-containing solution is in tissue under the skin, the higher, substantially neutral pH of the tissue causes glargine to precipitate out of solution and to aggregate into hexamers, which then act as a reservoir of glargine that is slowly released into the patient's blood over twenty-four hours. Natural human insulin is more soluble than glargine at the neutral pH level of human tissue below an injection site. Natural human insulin is generally injected in a solution of comparably neutral pH; and when injected, it rapidly dissociates into monomers—the physiologically active form of insulin. Such rapid disassociation allows for faster processing by the body but also necessitates more frequent injections.

Sanofi first commercially sold glargine in the U.S. in May 2001, under the trade name Lantus®, whose product

label identifies, among other things, a pH of 4 and the inclusion of some zinc. Physician's Desk Reference at 709 (55th ed. 2001) (Lantus® Label); J.A. 6690. Some patients soon began reporting problems with turbidity in the vials, *i.e.*, before injection. Sanofi determined that the turbidity was caused by undesirable "non-native" aggregation of the glargine protein while still in solution. Non-native aggregation denatures the insulin protein and is substantially irreversible. By contrast, "native" aggregation preserves the structure of the insulin protein and is reversible. Glargine's mechanism of action requires some amount of desirable native aggregation after injection under the skin for its slow-release property to take effect. Sanofi resolved the vial-turbidity problem by adding a nonionic surfactant to the glargine formulation to prevent non-native aggregation.

Mylan petitioned the PTO for inter partes reviews of all claims of the '652 and '930 patents, arguing unpatentability for obviousness based on combining either the Lantus® Label or an article by Owens[1] with one or more of three secondary references.[2] The parties do not dispute that, for each claim, the asserted combinations of

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[1] 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 (2000) (Owens).

[2] The three secondary references are: W.D. Lougheed, et al., *Physical Stability of Insulin Formulations*, 32 DIABETES 424 (1983) (Lougheed); Farmaceutiska Specialiteter I Sverige, Summary of Product Characteristics Entry for Insuman Infusat (2000) (FASS); and Ulrich Grau & Christopher D. Saudek, *Stable Insulin Preparation for Implanted Insulin Pumps: Laboratory & Animal Trials*, 36 DIABETES 1453 (1987) (Grau).

references teach every claim limitation. The main dispute is whether a relevant artisan would have been motivated to combine these references in the way claimed in the two patents at issue, with a reasonable expectation of success.

On December 13, 2017, the Board, acting as delegee of the PTO's Director, 37 C.F.R. §§ 42.4, 42.108, instituted the two requested reviews. *Mylan Pharm. Inc. v. Sanofi-Aventis Deutschland GmbH*, IPR2017-01526, 2017 WL 6403855 (P.T.A.B. Dec. 13, 2017) (covering the '652 patent); *Mylan Pharm. Inc. v. Sanofi-Aventis Deutschland GmbH*, No. IPR2017-01528, 2017 WL 6403082 (P.T.A.B. Dec. 13, 2017) (covering the '930 patent). On December 12, 2018, the Board issued final written decisions in both proceedings, determining that all claims in both patents are unpatentable for obviousness based on combinations of Lantus® Label or Owens with Lougheed, FASS, and/or Grau. *Mylan Pharm. Inc. v. Sanofi-Aventis Deutschland GmbH*, IPR2017-01526, 2018 WL 6584915 (P.T.A.B. Dec. 12, 2018) (*Decision*); *Mylan Pharm. Inc. v. Sanofi-Aventis Deutschland GmbH*, IPR2017-01528, 2018 WL 6584640 (P.T.A.B. Dec. 12, 2018).[3] The Board found that a relevant artisan would have been motivated to make the required combination based on a recognition that insulins had an aggregation problem in vials with air space and that surfactants (like the standard ones claimed here) offered a solution. *Decision* at *12–18. The Board also determined that, given the prior-art analysis, Sanofi's evidence of commercial success was too weak to support a conclusion of nonobviousness. *Id.* at *18–20.

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[3] The Board's final written decisions are substantively identical for present purposes. In its appeal to this court, Sanofi has not made separate arguments regarding the two decisions. Accordingly, we hereafter discuss and cite only the decision in IPR2017-01526 (*Decision*), but our analysis applies equally to IPR2017-01528.

Sanofi timely appealed under 35 U.S.C. §§ 141(c), 319. We have jurisdiction under 28 U.S.C. § 1295(a)(4)(A).

II

We review the Board's compliance with legal standards de novo, *Pride Mobility Products Corp. v. Permobil, Inc.*, 818 F.3d 1307, 1314 (Fed. Cir. 2016), and its underlying factual determinations for substantial evidence, *Personal Web Technologies, LLC v. Apple, Inc.*, 848 F.3d 987, 991 (Fed. Cir. 2017). Among the factual determinations in an obviousness analysis are "findings as to . . . the presence or absence of a motivation to combine or modify with a reasonable expectation of success[] and objective indicia of non-obviousness." *Ariosa Diagnostics v. Verinata Health, Inc.*, 805 F.3d 1359, 1364 (Fed. Cir. 2015).

A

Sanofi challenges the Board's finding of a motivation to combine the prior-art references to arrive at the claimed glargine formulation with certain surfactants. Sanofi argues that (1) *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398 (2007), required the Board to find that the prior art disclosed an aggregation problem for glargine specifically (not just insulins in general); (2) the Board improperly relied on each patent's own (shared) specification in finding a motivation to combine; and (3) substantial evidence does not support the Board's finding because key evidence cited by the Board concerned insulins in general rather than glargine specifically. The first two contentions assert legal errors, the third evidentiary insufficiency. We address the contentions in turn. We find each one unpersuasive.

1

Sanofi argues that the Board was required, under *KSR*, to find in the prior art a recognition of an aggregation problem for glargine specifically, not just for insulins generally. In Sanofi's view, *KSR* demands more than a factually supported finding that recognition of an aggregation risk for

insulins generally would have motivated a relevant artisan to address aggregation for this particular insulin. We reject Sanofi's view of *KSR*.

The Supreme Court in *KSR* explained that, "because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known," "it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *Id.* at 418–19. But *KSR* stressed flexibility and realism over rigidity and formalism in assessing what such reasons might be:

> In *KSR,* the Supreme Court criticized a rigid approach to determining obviousness based on the disclosures of individual prior-art references, with little recourse to the knowledge, creativity, and common sense that an ordinarily skilled artisan would have brought to bear when considering combinations or modifications. *KSR*, 550 U.S. at 415–22. Rejecting a blinkered focus on individual documents, the Court required an analysis that reads the prior art in context, taking account of "demands known to the design community," "the background knowledge possessed by a person having ordinary skill in the art," and "the inferences and creative steps that a person of ordinary skill in the art would employ." *Id.* at 418. This "expansive and flexible approach," *id.* at 415, is consistent with our own pre-*KSR* decisions acknowledging that the inquiry "not only permits, but *requires,* consideration of common knowledge and common sense." *DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.,* 464 F.3d 1356, 1367 (Fed. Cir. 2006).

Randall Mfg. v. Rea, 733 F.3d 1355, 1362 (Fed. Cir. 2013); *see also Arctic Cat Inc. v. Bombardier Recreational Prod.*

Inc., 876 F.3d 1350, 1359 (Fed. Cir. 2017) ("The court should consider a range of real-world facts to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue.") (citation and internal quotation marks omitted).

The Board did not depart from *KSR* when it made, and relied on, findings that a relevant artisan would have recognized a potential aggregation-in-the-vial problem with glargine as part of the general recognition of aggregation problems with insulins. Nothing in *KSR* demands the kind of prior-art identifications of a problem at the level of specificity that Sanofi urges. The Board thus properly examined the evidence in this particular case to determine whether a relevant artisan would have recognized an insulin aggregation problem in the prior art and expected glargine to share that problem. *Decision* at *14–16. Whether the Board was correct is a case-specific matter of evidentiary sufficiency—a matter we discuss more fully infra.

2

We also reject Sanofi's contention that the Board committed legal error when it cited the shared patent specification. The "background of the invention" portion of the specification includes the following passage:

> The specific preparation of insulin glargine, which leads to the prolonged duration of action, is characterized, in contrast to previously described preparations, by a clear solution having an acidic pH. Especially at acidic pH, insulins, however, 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)).

> The proneness to aggregation can additionally be promoted by hydrophobic surfaces which are in contact with the solution (Sluzky et al., Proc. Natl. Acad. Sci. 88:9377-9381 (1991). Surfaces which can be considered as hydrophobic are the glass vessels of the preparations, the stopper material of the sealing caps or the boundary surface of the solution with the air supernatant. In addition, very fine silicone oil 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.

'652 patent, col. 2, line 66 through col. 3, line 17. The Board cited this material in finding that insulin was known to aggregate on hydrophobic surfaces, at the air/water interface of a container, and in acidic solutions. *Decision* at *14–15.

Sanofi challenges the Board's reliance on this material as legally improper, invoking our longstanding recognition that a tribunal should not "look[] to knowledge taught by the inventor . . . and then use[] that knowledge against its teacher." *Panduit Corp. v. Dennison Mfg. Co.*, 774 F.2d 1082, 1092 (Fed. Cir. 1985), *vacated on other grounds*, 475 U.S. 809 (1986); *see also InTouch Techs., Inc. v. VGO Commc'ns, Inc.*, 751 F.3d 1327, 1351 (Fed. Cir. 2014). But the Board did not violate that principle, because it did not use the specification for its teachings about the inventor's discovery. Rather, it used the specification for its teachings about prior-art knowledge, and that use of a specification is not just common, given patent drafters' standard practice of reciting prior art in setting out the background of the invention, but permissible. *E.g.*, *Smith & Nephew, Inc. v. Rea*, 721 F.3d 1371, 1378–79 (Fed. Cir. 2013); *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1362 (Fed. Cir. 2007); *cf. WesternGeco LLC v. ION Geophysical Corp.*, 889 F.3d 1308, 1329–30 (Fed. Cir. 2018) (specification confirmed Board's understanding of prior art in anticipation context).

The Board understood the patent specification, on this issue, to be addressing what was already known—a reading that is reasonable given the language used and citations to prior art. Moreover, the Board used the cited material not as the sole support for any finding but in conjunction with support from other sources. The Board found evidence of insulin aggregation on hydrophobic surfaces and at air/water interfaces in a handful of other prior-art references. *Decision* at *14–15. The Board cited four additional references to support the finding that insulin was known to aggregate in acidic solutions. *Id.* at *15. The Board's use of the patent specification, we conclude, did not rest on legal error.

3

We further conclude that the Board's finding of a motivation to combine is supported by substantial evidence. While the Board must provide "a reasoned basis" for its actions, "'we will uphold a decision of less than ideal clarity if the agency's path may reasonably be discerned.'" *In re NuVasive, Inc.*, 842 F.3d 1376, 1383 (Fed. Cir. 2016) (quoting *Bowman Transp., Inc. v. Ark.–Best Freight System, Inc.*, 419 U.S. 281, 285, 286 (1974)). The Board "must articulate a *reason why* a [relevant artisan] would combine the prior art references." *Id.* at 1382. And the finding of such a reason must be supported by substantial evidence, which is "such relevant evidence as a reasonable mind might accept as adequate to support a conclusion." *Id.* at 1380 (citation and internal quotation marks omitted); *see also Intelligent Bio-Systems, Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1366 (Fed. Cir. 2016) (explaining that review for substantial evidence "requires examination of the record as a whole, taking into account evidence that both justifies and detracts from an agency's decision") (citation and internal quotation marks omitted).

The Board's findings with respect to the motivation to combine are detailed and well supported. The Board found

that insulins "had a known tendency to aggregate in the presence of hydrophobic surfaces" and at air-water interfaces and that a relevant artisan would have expected glargine to behave similarly to other insulins when in contact with hydrophobic surfaces and at air-water interfaces. *Decision* at *14. The Board also found that nonionic surfactants, including the claimed ones, were well known and had been used successfully to stabilize insulin formulations, and so would have been looked to by a relevant artisan concerned about aggregation in glargine. *Id.* at *11–12, *17. The record contains substantial evidence to support those findings.

Two references by Brange disclose that insulins with a variety of amino acid structures each display some degree of aggregation. J.A. 6762; J.A. 6797. Likewise, as already discussed, the shared specification of the '652 and '930 patents itself indicates, in a discussion introduced by discussing glargine, that insulins tend to aggregate on hydrophobic surfaces (like the glass of vials), especially in acidic solutions like those used for glargine. *See* '652 patent, col. 2, line 66 through col. 3, line 17. Mylan's expert explained, with citations to prior art, that "insulin aggregation is a well-established problem in the field and described in detail by numerous references." J.A. 6475.

Sanofi argued that the prior art discloses aggregation only in insulin pumps, but the Board disagreed, finding instead 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." *Decision* at *15. Prior art supports the Board's determination. *See*, *e.g.*, J.A. 6796 (noting that insulin has a tendency to aggregate on hydrophobic surfaces); J.A. 14535 ("It has been suggested that insulin is destabilized by adsorption at hydrophobic interfaces (air-water or water-pump materials). . . ."); J.A. 6906; J.A. 6951. The Board also reasonably understood Mylan's expert to testify that aggregation "was known in the art not to be unique to

[insulin] pumps," J.A. 12246 (quoted in *Decision* at *15), and found that Sanofi's expert, in suggesting otherwise, relied on evidence that went no further than indicating that insulin pumps showed a greater tendency for aggregation than other container types, *Decision* at *15.

Other evidence reasonably supports the Board's finding that a relevant artisan would have understood glargine to come within the general recognition of an aggregation problem for insulins. The Lantus® Label discloses glargine formulated as a solution with an acidic pH, J.A. 6690, and both the Lantus® Label and Owens teach glargine formulations in vials known to contain hydrophobic surfaces and an air-water interface, J.A. 6693; J.A. 6699–700. There was evidence, too, that, while insulin exists in equilibrium as monomers, dimers, and hexamers, an acidic environment shifts the equilibrium toward monomers, which are more susceptible to aggregation. J.A. 6769–70; J.A. 6798–99; J.A. 6830; J.A. 14535. And relatedly, although Lantus® contains zinc, which can affect rates of aggregation, the evidence supports the Board's findings, *Decision* at *15, that zinc does not bind to insulin in an acidic solution, like the Lantus® solution, J.A. 13741, and, more generally, that zinc in the Lantus® solution would not have led a relevant artisan to see glargine as immune from the general problem of insulin aggregation in vials.

The evidence also supports the Board's finding that the prior art taught use of nonionic surfactants like those claimed in the present patents to address the aggregation problem. For example, Lougheed teaches the addition of polysorbate 20 or polysorbate 80 to insulin formulations to reduce aggregation. J.A. 6706 ("[A]ggregate formation [in insulin formulations] was inhibited by the nonionics . . . Tween 20, [and] Tween 80."). Both FASS and Grau teach the use of a poloxamer to stabilize an insulin formulation. J.A. 6725 ("Addition of a stabilizer poly(oxyethylene, oxypropylene), glycol, prevents precipitation and flocculation of the insulin."); J.A. 6732 ("Genapol, a surface-active

polyethylene-polypropylene glycol, effectively prevents adsorption of insulin to hydrophobic surfaces."). Mylan's expert declaration provides further support when it points, with citations to prior art, to "the routine use of polysorbates and poloxamers in insulin formulations for inhibiting protein aggregation." J.A. 6475–76.

Sanofi points to our non-precedential decision in *Novartis Pharmaceuticals Corp. v. Watson Laboratories, Inc.*, 611 F. App'x 988 (Fed. Cir. 2015), but that decision does not undermine the Board's finding here. In *Novartis*, we affirmed a district court's determination of non-obviousness where the prior art teaching was reasonably found to differ significantly from the claimed invention. *Id.* at 995–96 (concluding that it would not be obvious to modify rivastigmine in the way claimed to solve the well-known problem of oxidative degradation with physostigmine, because the prior art taught that rivastigmine had "greater chemical stability" than physostigmine). That ruling does not help Sanofi in challenging the Board's determination of obviousness based on findings that the glargine compound is similar to other insulins in the respects relevant to the obviousness analysis.

B

Sanofi also challenges the Board's finding that a relevant artisan would have had a reasonable expectation of success in adding the claimed surfactants to the existing glargine preparation in the way claimed in the patents at issue here. Its focus on this issue, as on the related motivation-to-combine issue, is the contention that the Board looked at insulins generally and did not make adequately supported findings about glargine specifically. We reject Sanofi's challenge.

1

As a preliminary matter, we address Sanofi's argument that the Board improperly relied, in its reasonable-

expectation-of-success analysis, on evidence submitted by Mylan in reply to Sanofi's patent owner's response. We review the Board's decisions regarding the scope of proper reply material for an abuse of discretion. *Ericsson Inc. v. Intellectual Ventures I LLC*, 901 F.3d 1374, 1379 (Fed. Cir. 2018). We see no abuse of discretion in the present IPRs.

Under the governing IPR rules, there is no impropriety when the Board considers reply evidence to the extent that the evidence is offered to show why a patent owner's response is wrong in its criticisms of the sufficiency of the petition's case for unpatentability, including where the patent owner's response introduces what amounts to a new defense to an otherwise-sufficient case of unpatentability in the petition. *See*, *e.g.*, *Idemitsu Kosan Co. v. SFC Co.*, 870 F.3d 1376, 1381 (Fed. Cir. 2017) (reply evidence may respond to teaching-away contention in patent owner's response). Here, Mylan's petitions made its case for finding a reasonable expectation of success, *see*, *e.g.*, J.A. 384; J.A. 457, and after Sanofi made arguments against such a finding in its patent owner's response, Mylan's reply included rebuttal argument and evidence addressing Sanofi's points, J.A. 1819–37; J.A. 12231–91 (excerpts of reply expert declaration); *see* J.A. 2414–18 (excerpts of Sanofi's specification of objected-to passages). The Board allowed Sanofi to file at least one sur-reply on the issue of reasonable expectation of success, as well as several motions to exclude, but the Board found all of Sanofi's objections either unpersuasive, because Mylan's reply evidence was proper rebuttal evidence, or moot, because the Board had not relied on particular objected-to evidence. *See Decision* at *5–6; J.A. 15304–06. We see no abuse of discretion in the Board's rulings in this regard.

2

On the merits, Sanofi argued to the Board that, although surfactants were known to stabilize insulins generally, a relevant artisan would not have expected the same

result for glargine specifically because its mechanism of action depends on some favorable native aggregation. To the extent that Sanofi contends that the Board did not consider this argument, Sanofi is incorrect. The Board thoroughly considered Sanofi's argument but found it unpersuasive. To the extent that Sanofi contends that there is no substantial evidence to support a finding of reasonable expectation of success for glargine specifically, we conclude that Sanofi is incorrect in that contention as well.

The Board began its reasonable expectation of success analysis by finding that a number of nonionic surfactants—including the claimed nonionic surfactants—were shown in the prior art to have been successfully used to prevent aggregation of various types of insulins and other peptides. *Decision* at *17. The prior art supports this determination. *See*, *e.g.*, J.A. 6706–07 ("[A]ggregate formation [in insulin formulations] was inhibited by the nonionic[] [surfactants]," including polysorbate 20 and polysorbate 80.); J.A. 6725 ("Addition of a stabilizer poly(oxyethylene, oxypropylene), glycol," a poloxamer, "prevents precipitation and flocculation of the insulin."). Mylan's expert declared that a relevant artisan, when considering which nonionic surfactants to use in a glargine formulation, would look to nonionic surfactants (such as polysorbates) approved by the Food and Drug Administration (FDA) for use in other protein formulations, and the Board, after its prior-art recitation, credited that statement. *Decision* at *17.

The Board found "unpersuasive [Sanofi's] arguments that an ordinarily skilled artisan would not have reasonably expected success when adding a nonionic surfactant to insulin glargine in view [of] their success stabilizing other insulins and proteins." *Id.* For example, Sanofi contended that adding a nonionic surfactant to a strong acid had the potential to cause undesirable hydrolysis or saponification. But the Board explained that Sanofi did not put forth any evidence that the prior-art glargine compounds existed in a strong acid, and it pointed to evidence that polysorbates

had in fact been used in pharmaceutical formulations at acidic pH (3.0 to 4.0). *Id.* at *18 (citing J.A. 7450–51; J.A. 12907).

The Board also credited Mylan's evidence that the presence of phenols in a glargine formulation would not have dissuaded a relevant artisan from expecting success in using nonionic surfactants. *Id.* The Board reasonably did so. The Board noted that other pharmaceutical formulations include both nonionic surfactants and phenols. *Decision* at *18 (citing, *e.g.*, J.A. 12911). There also was evidence, including from Sanofi's expert, that phenols in insulin formulations stabilize hexamers, whereas surfactants prevent irreversible denaturation of monomers but do not prevent hexamer formation. J.A. 14249–53; J.A. 14387; *see* J.A. 6732; J.A. 6910. Moreover, the testimony of Sanofi's expert about a problem was carefully limited, stating only that nonionic surfactants in a glargine formulation "could" disrupt the native aggregation that phenols promote. J.A. 14307–09. Mylan's expert, in contrast, stated unequivocally that a nonionic surfactant's potential interference with phenols would not dissuade a relevant artisan from using both in a formulation. J.A. 12298.

The Board did not expressly address Sanofi's arguments about the potential for discoloration or peroxide formation. But the Board rejected them implicitly as bases for finding no reasonable expectation of success: those arguments were within the pages of the patent owner's response that recited various potential negative consequences that the Board addressed collectively, finding Sanofi's arguments in those pages unpersuasive whether considered with respect to motivation to combine or reasonable expectation of success. *Decision* at *18. The Board is not required to "expressly discuss each and every negative and positive piece of evidence lurking in the record." *Novartis AG v. Torrent Pharm. Ltd.*, 853 F.3d 1316, 1328 (Fed. Cir. 2017). Sanofi has not shown that its evidence on these two particular potential consequences

undermines the Board's finding that, considering all relevant factors, an ordinary artisan would have had a reasonable expectation of success in adding a nonionic surfactant to a glargine formulation. *Decision* at *18. We conclude that the Board's finding is supported by substantial evidence.

C

Lastly, Sanofi challenges the Board's analysis of commercial success. The Board accepted that Sanofi's product was a commercial success. *Decision* at *19. The Board found that Sanofi's commercial success evidence was ultimately "weak" so as not to warrant an ultimate conclusion on obviousness different from the one strongly indicated by the motivation-to-combine and reasonable-expectation-of-success analysis. *Decision* at *19 n.14, *20. We reject Sanofi's challenge to the Board's reasoning—whether it is viewed as a factual finding of only a weak nexus of commercial success to the claimed invention or as part of the ultimate legal weighing to determine obviousness. *See Intercontinental Great Brands LLC v. Kellogg N. America Co.*, 869 F.3d 1336, 1347 (Fed. Cir. 2017).

Certain facts are not in dispute. Sanofi enjoyed commercial success with Lantus®, but that success began with the original glargine formulation, which lacked the surfactant claimed in the '652 and '930 patents. *Decision* at *19. Recognizing that, standing alone, that fact would suggest that the success is not traceable to the new glargine-surfactant combination, Sanofi asserted to the Board that, had it not reformulated the Lantus® product to include a nonionic surfactant, it "'could have'" suffered potential regulatory action and a loss of sales. *Id.* (quoting Sanofi's patent owner's response). That assertion on its face is only about what "'could have occurred.'" *Id.* And the evidence offered by Sanofi in support, which the Board cited but did not expressly discuss, plainly goes no further. Sanofi's evidence consists only of its experts' hypothetical conjectures

about what "could have" happened to future Lantus® sales in the absence of reformulation with a nonionic surfactant. J.A. 15045–47; J.A. 14319–22. Moreover, Sanofi in fact continued to sell its original Lantus® product, without a nonionic surfactant, even after FDA approval of its reformulated product. J.A. 7495.

It is against this background that the Board relied on another fact in deeming Sanofi's evidence of commercial success "weak" as a factor in the obviousness analysis. It explained that Sanofi owned two so-called "blocking patents" giving Sanofi exclusive rights to the glargine compound itself—the last of which expired in 2014, many years after the 2002 priority date—which gave Sanofi control over another's commercial domestic entry into the market with the improvement claimed in the '652 and '930 patents. *Decision* at *19. Relying on our decisions in *Galderma Laboratories, L.P. v. Tolmar, Inc.*, 737 F.3d 731, 740 (Fed. Cir. 2013), and *Acorda Therapeutics, Inc. v. Roxane Laboratories, Inc.*, 903 F.3d 1310, 1337 (Fed. Cir. 2018), the Board determined that Sanofi's blocking patents made Sanofi's commercial success with the modified Lantus® product—following its commercial success with the original Lantus® product—"weak" as evidence of obviousness. *Id.* at *19–20.

We see no reversible error in that ruling. We have explained that the existence of a blocking patent in circumstances like those present here "may deter non-owners and non-licensees [of that patent] from investing the resources needed to make, develop, and market such a later, 'blocked' invention, because of the risk of infringement liability and associated monetary or injunctive remedies," *Acorda*, 903 F.3d at 1337, and thus, depending on the record made in a particular case, justify discounting evidence of commercial success because the blocking patent can help explain why, for reasons other than non-obviousness, no one else arrived at the later patent's improvement despite a potential economic benefit from meeting a market demand (as evidenced by commercial success), *id.* at 1339. In this case,

the existing glargine compound patents were listed in the FDA's *Approved Drugs with Therapeutic Equivalence Evaluations* (27th ed. 2007) for the original Lantus® product. J.A. 9787. Although Sanofi's expert knew of those patents, he did not consider them in his commercial-success analysis. *See Decision* at *19. On the other hand, Mylan's expert testified that the existing patents "'would have blocked competitors from commercializing a product that embodied'" the claimed glargine formulations and "'provided strong disincentives for others to develop and commercialize'" the claimed glargine formulations. *Id.* (quoting J.A. 13787). Sanofi did not present arguments and evidence that would allow us to find reversible error in the Board's analysis.

Sanofi argues that the Board's blocking-patent analysis was flawed because the glargine compound patents did not block all long-acting insulins from entering the market. That objection is misplaced. The specific question at issue, the Board properly recognized, is obviousness of *the claimed invention*, not of other products that might address a similar need. Sanofi itself has insisted throughout the present proceedings that the issue is the obviousness of the claimed glargine-surfactant combination, not the obviousness of the insulin-surfactant combinations, much less of other insulin products. We see no error in the Board's consideration of the relevance of blocking patents to the potential discouragement of others from coming up with the specific invention at issue.

For at least those reasons, and in light of the strength of the motivation-to-combine and reasonable-expectation-of-success part of the obviousness analysis, we reject Sanofi's argument that its commercial-success evidence undermines the Board's determination of obviousness.

III

For the foregoing reasons, we affirm the Board's decisions that all claims of the '652 and '930 patents are unpatentable for obviousness.[4]

AFFIRMED

[4] On November 5, 2019, Sanofi filed a letter with the court asking the court to vacate the Board's decision and remand for reconsideration by a different Board panel under this court's decision regarding the Appointments Clause in *Arthrex, Inc. v. Smith & Nephew, Inc.*, No. 2018-2140, —— F.3d ——, 2019 WL 5616010 (Fed. Cir. Oct. 31, 2019). We reject the request. Sanofi did not raise an Appointments Clause issue in its opening brief in this court (or its reply brief). Our precedent holds that failure to raise the *Arthrex* Appointments Clause issue in the opening brief forfeits the challenge. *Customedia Technologies, LLC v. Dish Network Corp.*, Nos. 2018-2239, -2240, -2310, 2019-1000, -1002, -1003, -1027, -1029, —— F.3d ——, 2019 WL 5677703 (Fed. Cir. Nov. 1, 2019); *Customedia Technologies, LLC v. Dish Network Corp.*, No. 2019-1001, —— F.3d ——, 2019 WL 5677704 (Fed. Cir. Nov. 1, 2019).

NOTE: This disposition is nonprecedential.

United States Court of Appeals for the Federal Circuit

SANOFI-AVENTIS DEUTSCHLAND GMBH,
Appellant

v.

MYLAN PHARMACEUTICALS INC.,
Appellee

2019-1368, 2019-1369

Appeals from the United States Patent and Trademark Office, Patent Trial and Appeal Board in Nos. IPR2017-01526, IPR2017-01528.

NEWMAN, *Circuit Judge,* dissenting.

The court today rules that it was obvious to create this new formulation to remedy the unforeseen deterioration of glargine insulin when stored in glass ampoules with an air space. The court reasons that the "background knowledge" of insulin science renders these new compositions obvious—although neither the problem nor its remedy is shown in the prior art.

The court today enlarges the criteria of invalidity, to include hindsight analysis of foreseeability of the problem and its solution, citing information in the inventor's patent

specification as prior art against the invention. The court thus adds to the unpredictability of judicial assessment of "obviousness." I respectfully dissent.

Sanofi's inventors discovered the cause of the instability on storage, and devised a solution, none of which is in the prior art

It was of critical importance to preserve glargine's property of insulin activity and extended release after injection into the body, while finding a remedy for the instability that was observed during prolonged storage. The law of obviousness for medicinal products requires pragmatic, as well as wise application, for physiological properties and bodily responses to new products cannot be reliably known without experimental evaluation.

The panel majority discards Sanofi's testimony concerning the complex molecule that is glargine insulin and its extended release properties after injection under the skin. The majority ignores the known uncertainties of insulin formulation instability. Instead, the PTAB and now the panel majority look for and find the various components of Sanofi's new composition in the scientific literature, and rule that this stabilized new glargine formulation could obviously be made and would obviously be successful in preserving extended-release properties and full insulin activity without adverse physiologic response, while avoiding the observed deterioration in ampoules.

The PTAB found that a person of skill would have recognized a potential aggregation problem in the vial, a finding contrary to the fact that the potential aggregation was not recognized. A cited reference to Chawla states that "[u]nder normal use by the patient, aggregation of insulin does not appear to be a significant problem in the commercially available syringes and infusion test sets." J.A.6953. Nonetheless, the PTAB, and now my colleagues, plug that gap with retrospective judicial prescience.

Sanofi's inventors discovered that the turbidity appearing in some vials was not a simple "aggregation in the vial." Unlike insulin, which was known to undergo reversible aggregation, the glargine turbidity was found to be an irreversible chemical reaction. This reaction of glargine was not reported in the prior art. Nor does the prior art suggest how such a product would behave upon entering the human body.

Although there was no evidence or suggestion for the inactivation of glargine when stored in glass ampoules, my colleagues hold that a person of ordinary skill would have foreseen this problem and known its solution. That Sanofi's inventors knew of the tendency of insulin to aggregate, as so stated in their specification, is evidence not of obviousness, but of nonobviousness, for glargine had undergone clinical development without this problem being apparent. Sanofi explained the uncertainties in insulin reactivity, citing the known potential for discoloration and peroxide formation, and that such reactions cannot be predicted. The PTAB brushed off these uncertainties as "unpersuasive" without any analysis, as do my colleagues. Maj. Op. at 16–17, 20. However, the behavior of a new composition inside the body requires experimentation and evidence, not speculation and hindsight.

As reiterated in *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1079 (Fed. Cir. 2012), "[t]he objective considerations, when considered with the balance of the obviousness evidence in the record, guard as a check against hindsight bias"). In *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983), this court observed that objective indicia may be the most important evidence of nonobviousness—yet the court here discards this evidence entirely. *Id.* ("It is jurisprudentially inappropriate to disregard any relevant evidence on any issue in any case, patent cases included. Thus evidence rising out of the so-called 'secondary considerations' must always when present be considered en route to

a determination of obviousness. Indeed, evidence of secondary considerations may often be the most probative and cogent evidence in the record." (internal citations omitted)).

Nonetheless, my colleagues find that this problem and its solution were obvious, drawing on "the knowledge taught by the inventor . . . and then use[ing] that knowledge against its teacher." *Panduit Corp. v. Dennison Mfg. Co.*, 774 F.2d 1082, 1092 (1986). *See Innogenetics, N.V. v. Abbott Labs.,* 512 F.3d 1363, 1373–74 (Fed.Cir.2008) (cautioning against "the pitfalls of hindsight that belie a determination of obviousness."). The objective considerations of nonobviousness cannot be ignored.

The court states that the commercial success of Sanofi's product is "too weak to support a conclusion of nonobviousness." Maj. Op. at 5. Mylan argues that the commercial success of this product cannot be considered, on the theory that Sanofi's "blocking patents" prevented others from entering this field. The record states that the last of the glargine basic patents expired in 2014. Mylan offered no evidence of development of competitive formulations, although the Hatch-Waxman Act insulates such development from infringement. My colleagues err in viewing this theory as negating nonobviousness, for by statute medicinal product development cannot be blocked.

Here, the glargine was reformulated to preserve its stability, and achieved marked commercial success. On the correct law, obviousness was not established.

The patent specification is not prior art

The court holds that "The Board's use of the patent specification, we conclude, did not rest on legal error." Maj. Op. at 10. This is incorrect. The court's ratification of reliance on the inventor's specification to invalidate the invention disclosed therein, is plain error. A patent specification may be edifying and must be descriptive and enabling, but it is not prior art. *See Graham v. John Deere*

Co., 383 U.S. 1, 36 (1966) (avoid the "temptation to read into the prior art the teachings of the invention at issue.").

The law of innovation and obviousness

Innovation requires stable laws and consistent application of those stable laws. My colleagues state that an "expansive and flexible approach" must be applied to the question of obviousness, and that "creative steps" may be obvious, citing *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 415 (2007). Maj. Op. at 7. However, *KSR's* guidance is in the context of the statute. The statutory standards of novelty and nonobviousness require objectivity, consistency, and predictability.

An effective patent system requires providing patentees with reasonable reliance on their patents as granted by the government, lest the incentive for innovation be diminished.[1] Stability of legal rules is the foundation of commercial activity. The courts and the PTAB must apply the same law as did the examiner on granting the patent. Here, the PTAB and now this court place a fresh spin on the law, to the detriment of consistency and reliability.

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[1] In recent legislative hearings, witnesses explained the disincentive flowing from inconsistent and unpredictable judicial rulings—to the detriment of inventors, industry, the public, and the nation's economic and competitive vigor. *See* The State of Patent Eligibility in America: *Hearings Before the S. Comm. on Intellectual Property*, 116th Cong. (2019), https://www.judiciary.senate.gov/meetings/the-state-of-patent-eligibility-in-america-part-i; https://www.judiciary.senate.gov/meetings/the-state-of-patent-eligibility-in-america-part-ii; https://www.judiciary.senate.gov/meetings/the-state-of-patent-eligibility-in-america-part-iii.

On application of correct law, the patentability of these new and improved formulations of glargine should be sustained.

The recent ruling on the Appointments Clause of the Constitution

Promptly after this court's holding in *Arthrex, Inc. v. Smith & Nephew, Inc.,* No. 2015-2140, ___ F.3d ____, 2019 WL 5616010 (Fed. Cir. Oct. 31, 2019) that the method of appointment of administrative patent judges violates the Appointments Clause, Sanofi moved to brief the application of this ruling to the PTAB decisions here on appeal. *See* Sanofi Letter under Rule28(j) ("Sanofi requests that the Court allow briefing to address whether factors, including the 'exceptional importance' of the issue and the 'significant change in law' *Arthrex* reflects, warrant an exception to any waiver here." (citing *Arthrex*, 2019 WL 5616010 at *6)). Sanofi pointed out that "these issues were not addressed in *Customedia*," and that "[w]aiver is 'exercised on the facts of individual cases.'" *Id.*

My colleagues deny the motion, ruling that our recent *Customedia* rulings establish that the *Arthrex* ruling cannot be applied to pending appeals, unless the appellant had raised an Appointments Clause challenge in its principal brief on appeal. Maj. Op. at 20 n.4. However, at the time these appeals were filed, there was no holding of illegality of appointments of the PTAB's Administrative Patent Judges. It is well established that when the law changes while a case is on appeal, the changed law applies. *Thorpe v. Hous. Auth. of Durham*, 393 U.S. 268, 282 (1969). "[I]n great national concerns . . . the court must decide according to existing laws, and if it be necessary to set aside a judgment, rightful when rendered, but which cannot be affirmed but in violation of law, the judgment must be set aside." *United States v. Schooner Peggy*, 1 Cranch 103, 110 (1801).

While the law of the case doctrine stands for the idea that when a court decides a matter of law or fact, its decision controls those same issues in subsequent stages of the same case, *Christianson v. Colt Indus. Operating Corp.*, 486 U.S. 800, 815–16 (1988), here an administrative ruling is on appeal to the court. As this court observed in *Dow Chem. Co. v. Nova Chems. Corp. (Can.)*, 803 F.3d 620, 629 (Fed. Cir. 2015), a change in governing law applies to the pending appeal when the change occurs while the case is on appeal.

Thus, Sanofi is entitled to the same benefit of the *Arthrex* decision as are the *Arthrex* parties. The foundation of a nation ruled by law is that the same rules, as well as the same law, will be applied in the same way to parties in pending litigation.

The majority errs in denying Sanofi's motion.

United States Court of Appeals for the Federal Circuit

November 20, 2019

ERRATA

Appeal Nos. 2019-1368, 2019-1369

SANOFI-AVENTIS DEUTSCHLAND GMBH,
Appellant

v.

MYLAN PHARMACEUTICALS INC.,
Appellee

Decided: November 19, 2019
Non-Precedential Opinion

Please make the following change:

On page 20, footnote 4, line 2, "decision" is changed to "decisions"

Trials@uspto.gov
571-272-7822

Paper No. 89
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 IPR2017-01526
Patent 7,476,652 B2

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

ANKENBRAND, *Administrative Patent Judge*.

FINAL WRITTEN DECISION

Finding Claims 1–25 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)

Granting Petitioner's First Motion to Seal, Denying 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 1–25 (collectively, the "challenged claims") of U.S. Patent No. 7,476,652 B2 (Ex. 1001, "the '652 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 1–25 of the '652 patent are unpatentable under 35 U.S.C. § 103 as obvious over the combination of Lantus Label[1] and Lougheed[2];
2. Claims 7 and 24 of the '652 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 709–13 (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 424–32 (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 7 and 24 of the '652 patent are unpatentable under 35 U.S.C. § 103 as obvious over the combination of Lantus Label and Grau[4];
4. Claims 1–25 of the '652 patent are unpatentable under 35 U.S.C. § 103 as obvious over the combination of Owens[5] and Lougheed;
5. Claims 7 and 24 of the '652 patent are unpatentable under 35 U.S.C. § 103 as obvious over the combination of Owens and FASS; and
6. Claims 7 and 24 of the '652 patent are unpatentable under 35 U.S.C. § 103 as obvious over the combination of Owens and Grau.

Paper 13 ("Institution Decision" or "Inst. Dec.").

Following institution, Sanofi-Aventis Deutschland GmbH ("Patent Owner") filed a Response (Paper 27, "Resp.") and supporting declarations from Bernhardt Trout, Ph.D. (Ex. 2006) and Laurence C. Baker, Ph.D. (Ex. 2039). Petitioner filed a Reply (Paper 43, "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 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 46) and a Motion to Strike (Paper 47, "Mot. to Strike"). Petitioner

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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 813–19 (2000) (Ex. 1005).

filed an opposition to Patent Owner's Motion to Strike (Paper 52, "Mot. to Strike Opp.").

Petitioner and Patent Owner also filed several motions to seal certain briefs and exhibits. Paper 41 (Petitioner's Motion to Seal and for Entry of Proposed Protective Order), Paper 45 (Patent Owner's Supplemental Motion to Seal), Paper 78 (Patent Owner's Motion to Seal), Paper 87 (Petitioner's Motion to Seal). Both parties also filed motions to exclude, which have been fully briefed. *See* Papers 57, 64, 79 (briefing related to Petitioner's Motion to Exclude); Papers 61, 67, 71 (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 60, 68. The record further includes a transcript of the final oral hearing conducted on September 27, 2018. Paper 77 ("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 79 (confidential version), 80 (public version)), and Petitioner filed the Sur-sur-reply (Papers 86 (confidential version), 88 (public version)).

B. *Related Matters*

The parties identify 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 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 7, 2; Paper 14, 1–2. The parties also identify 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.). Paper 7, 2; Paper 14, 1.

And the parties identify as related Case IPR2017-01528— an *inter partes* review involving claims 1–20 of U.S. Patent No. 7,713,930 (Ex. 1002), which issued from a continuation application to the application that issued as the '652 patent. Paper 7, 2; Paper 14, 2. Concurrent with this decision, we issue a Final Written Decision in Case IPR2017-01528.

C. *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 during storage and

administration, including those on glass storage vessels, solution/air boundary layers, sealing cap stopper materials, and siliconized insulin syringes. *Id.* at 3:8–17.

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).

D. *Illustrative Claim*

We instituted an *inter partes* review of claims 1–25 of the '652 patent, of which claims 1, 7, and 24 are 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 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.

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]

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

[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 79; Exs. 2060–2069. And Petitioner filed a sur-sur-reply in response to Patent Owner's sur-reply on this issue. Paper 86.

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. 49, 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 46, 79. 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.

B. *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 57 ("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 64.

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 61 ("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 67, 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 67, 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 67, 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 67, 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.

C. *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.

D. *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 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. 14–15; *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. 19–21. 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.* at 19–20.

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).

E. *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 (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

[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).

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. 9. Neither party contests our decision not to expressly construe claim terms. *See* Resp. 18–19; *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").

F. *Summary of Asserted References*

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

1. 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 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

[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.

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.").

2. 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.

3. 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").

4. 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.

5. 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.

G. *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. 25–60. 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 4: Lantus Label or Owens and Lougheed collectively teach or suggest each limitation of claims 1–25

Petitioner asserts that Lantus Label or Owens teaches every limitation of independent claims 1, 7, and 24, except for "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. 25–26, 29–30 (discussing Lantus Label and citing Ex. 1001, 4:27–28; Ex. 1003 ¶¶ 98–102, 129, 160–162, 175–180; Ex. 1004, 3), 45–48 (discussing Owens and 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, 45–47 (citing Ex. 1003 ¶¶ 163–169, 175–180, 242, 251–252; Ex. 1006, 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 4) or Lougheed (Grounds 1 and 4) for teaching the additional limitations of those claims. *See id.* at 31–33, 37–39, 48–50, 52–54, 55–56 (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); *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).

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 1–25. *See generally* Resp.[10]

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

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 claims 1, 7, and 24, except for the limitation of "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. Ex. 1004, 3; Ex. 1005, 3–4; *see* Ex. 1003 ¶¶ 129–131 160–62, 175–80, 239. 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) or polysorbate 80 (Tween 80) to insulin formulations. Ex. 1006, 4, 7, Table 3; Ex. 1003 ¶¶ 163–169, 175–180. And we find that Lantus Label (Ground 1), Owens (Ground 4) or Lougheed (Grounds 1 and 4) teach or suggest the additional limitations of dependent claims 2–6, 8–23, and 25. *See* Pet. 31–41, 45–56; Ex. 1003 ¶¶ 182–184, 197, 204, 208–209, 212, 216, 220, 260, 255–257, 264–265, 268–269, 273–275, 277–278, 285–287, 289–292, 294–295; Ex. 1004, 3; Ex. 1005, 3–4; Ex. 1006, 4–7, Tables 3–6. 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 1–25.

b. Grounds 2, 3, 5, and 6: Lantus Label and FASS or Grau, and Owens and FASS or Grau collectively teach each limitation of claims 7 and 24

Petitioner asserts that Lantus Label and FASS (Ground 2) or Grau (Ground 3) collectively teach each limitation of claims 7 and 24. Pet. 41–45. Petitioner further asserts that Owens and FASS (Ground 5) or Grau (Ground 6) collectively teach each limitation of claims 7 and 24. Pet. 56–60. Petitioner's arguments as to how the references collectively teach each limitation are substantially the same as those for claims 7 and 24 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 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).

For Grounds 5 and 6, Petitioner argues that Owens teaches all of the limitations 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).

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 1–25. *See generally* Resp.[11]

As explained above, based on the full trial record, we find that Lantus Label or Owens teaches every limitation of claims 7 and 24, 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* Ex. 1003 ¶¶ 129, 160–162, 175–180, 223, 239 (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 claims 7 and 24.

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

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 a surfactant, such as the polysorbates 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. 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 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, 13 (citing Ex. 1001, 3:2–14; 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 '652 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 and polysorbate 80 enhance the stability of insulin formulations and decrease insulin aggregation. *Id.* at 26 (citing Ex. 1003 ¶¶ 163–169; 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. *Id.* at 57–59 (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 27 (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 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, polysorbate 80, and/or a poloxamer 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; *see, e.g.*, *id.* at 58–60 (citing Ex. 1003 ¶¶ 297–300, 302–306; Ex. 1005, 3; Ex. 1007A).

b. Patent Owner's assertions

Patent Owner responds that Petitioner fails to provide prior art evidence that glargine had a tendency to aggregate. Resp. 29–32. 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 30–31 (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 31 (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. 32–44. 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 33–38 (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 38–40 (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 40–42. 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 42–44 (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 '652 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 44–46.

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. 46–47. 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 52–56. 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. 29–32. 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, 24, 27–28. 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 ’652 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. 1001, 3:8–14. The ’652 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 ’652 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 ’652 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 ’652 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 ’652 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 '652 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 '652 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 '652 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[12] 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. 38–39. First, Patent Owner contends that Jones's statement is erroneous and based on a misreading of another reference that it cites—Hoogwerf.[13] Resp. 38–39. 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.

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[12] 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.

[13] 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).

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 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 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). 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 and polysorbate 80); 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 52–56. 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. 52–53 (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 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).

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 1–12, 15–21, and 23–25 of the '652 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 57–58 (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 '652 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 59 (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[14] covering the insulin glargine compound. *See* Resp. 57–60; Ex. 1055, 18:–20:3 (Dr. Baker's testimony that he generally understands what "blocking patents" are, but did not investigate whether there was a blocking patent).

[14] 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).

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 '652 patent. Ex. 1169 ¶ 32. We credit Dr. McDuff's testimony and find, on the record before us, that Patent Owner's insulin glargine 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 '652 patent. *Acorda Therapeutics, Inc. v. Roxane Labs., Inc.*, 903 F.3d 1310, 1339 (Fed. Cir. 2018); *see Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 740 (Fed. Cir. 2013) ("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 1–25 of the '652 patent would have been obvious over the combination Lantus Label and Lougheed; (2) claims 7 and 24 of the '652 patent would have been obvious over the combination of Lantus Label and FASS; (3) claims 7 and 24 of the '652 patent would have been obvious over the combination of Lantus Label and Grau; (4) claims 1–25 of the '652 patent would have been obvious over the combination Owens and Lougheed; (5) claims 7 and 24 of the '652 patent would have been obvious over the combination of Owens and FASS; and (6) claims 7 and 24 of the '652 patent would have been obvious over the combination of Owens and Grau.

IV. MOTIONS TO SEAL

Patent Owner and Petitioner each filed unopposed Motions to Seal portions of certain papers and exhibits. Papers 41, 45, 78, 87. Accompanying Petitioner's first motion is a request to enter an agreed upon protective order. Paper 41, Attachment.

Patent Owner seeks to seal Exhibits 1144–1161 and the portions of Petitioner's Reply (Paper 43) and Dr. Langer's declaration (Ex. 1111) that reference Exhibits 1144–1161 or the information contained in those exhibits. Paper 45 (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 79) that reference those exhibits. Paper 78. 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 45, 2–15.

Petitioner seeks to seal Exhibit 1086 and the portions of its sur-sur-reply (Paper 86) that reference Exhibits 2065–2068. Papers 41, 87. 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 41, 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.* 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 87, 1.

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 80) and proposed redacted public versions of Petitioner's Reply and Dr. Langer's declaration (Paper 45, Attachments 1–2). Petitioner filed a public version of its sur-sur-reply. Paper 88.

"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.[15]

[15] 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.

As to Petitioner's motion to seal the sur-sur-reply (Paper 87), 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 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 1–25 of the '652 patent are unpatentable;

FURTHER ORDERED that Patent Owner's Motion to Strike (Paper 47) is denied-in-part and dismissed-in-part as moot;

FURTHER ORDERED that Petitioner's Motion to Exclude (Paper 57) is dismissed as moot;

FURTHER ORDERED that Patent Owner's Motion to Exclude (Paper 61) is denied-in-part and dismissed-in-part as moot;

FURTHER ORDERED that the parties' proposed protective order (Paper 41, 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 41) is granted;

FURTHER ORDERED that Petitioner's second Motion to Seal (Paper 87) is denied without prejudice;

FURTHER ORDERED that Patent Owner's Supplemental Motion to Seal (Paper 45) and Patent Owner's Motion to Seal (Paper 78) 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 86), 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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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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