No. 19-____

IN THE

Supreme Court of the United States

SANOFI-AVENTIS DEUTSCHLAND GMBH,

Petitioner,

v.

MYLAN PHARMACEUTICALS INC.,

Respondent.

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

PETITION FOR A WRIT OF CERTIORARI

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QUESTIONS PRESENTED

While Sanofi's appeal was pending before the Federal Circuit, the court decided *Arthrex, Inc.* v. *Smith & Nephew, Inc.*, 941 F.3d 1320 (Fed. Cir. 2019), holding that Administrative Patent Judges (APJs) on the Patent Trial and Appeals Board (PTAB) were appointed in violation of the Appointments Clause, and vacated and remanded the APJs' final written decision for redetermination by properly appointed APJs. But the Federal Circuit subsequently held that this change in law applies only to parties who raised an Appointments Clause challenge in their opening appellate brief, and refused to apply its new law to all other parties whose appeals were pending when *Arthrex* was decided. Thus, in the decision below, the Federal Circuit refused to vacate and remand the PTAB's decisions—issued by unconstitutionally-appointed judges—because Sanofi had not raised such a challenge in its opening brief, and affirmed the PTAB's finding that the challenged patents were invalid as obvious.

The questions presented are:

1. Whether, in a pending case, a court can refuse to entertain a constitutional, separation-of-powers challenge based on an intervening change of law on the grounds of forfeiture.

2. Whether the Federal Circuit's obviousness holding is an unwarranted expansion of this Court's decision in *KSR International Co.* v. *Teleflex, Inc.*, 550 U.S. 398 (2007), and is inconsistent with the Patent Act.

RELATED PROCEEDINGS

The following proceedings are directly related to the case:

Mylan Pharms. Inc. v. *Sanofi-Aventis Deutschland GMBH*, IPR2017-01526 (P.T.A.B.), final written decision entered December 12, 2018.

Mylan Pharms. Inc. v. *Sanofi-Aventis Deutschland GMBH*, IPR2017-01528 (P.T.A.B.), final written decision entered December 12, 2018.

Sanofi-Aventis Deutschland GMBH v. *Mylan Pharms. Inc.*, Nos. 2019-1368, 2019-1369 (Fed Cir.), judgment entered on November 19, 2019.

PARTIES TO THE PROCEEDING

Petitioner Sanofi-Aventis Deutschland GmbH was appellant in the court of appeals.

Respondent Mylan Pharmaceuticals Inc. was appellee in the court of appeals.

RULE 29.6 STATEMENT

Petitioner 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.

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OPINIONS BELOW

The Federal Circuit's opinion (App. 1a–29a) is unreported, but is available at 791 F. App'x 916 (Fed Cir. 2019). The PTAB's final written decisions (App. 30a–83a; App. 84a–140a) are unreported, but are available at 2018 WL 6584915 and 2018 WL 6584640.

JURISDICTION

The judgment of the court of appeals was entered on November 19, 2019. App. 1a. The court of appeals denied a timely petition for rehearing *en banc* on

January 28, 2020. App. 141a–142a. On March 19, 2020, the Court issued an order extending the time for filing a petition for a writ of certiorari to 150 days from the date of the lower court's denial of a timely petition for rehearing, thus to and including June 26, 2020. The jurisdiction of this Court is invoked under 28 U.S.C. § 1254(1).

CONSTITUTIONAL AND STATUTORY PROVISIONS INVOLVED

The Appointments Clause of the U.S. Constitution and section 103 of the Patent Act, 35 U.S.C. § 103, are reproduced in the Appendix. App. 143a–144a.

INTRODUCTION

For nearly a decade, the Administrative Patent Judges (APJs) appointed to the Patent Trials and Appeals Board (PTAB) have presided over thousands of *inter partes* review proceedings adjudicating significant patent rights. Throughout that time, there was no suggestion of any constitutional infirmity in how the APJs were appointed or in their authority to render decisions. Indeed, the Federal Circuit had rebuffed claims that the APJs were appointed in violation of the Appointments Clause, as well as the underpinnings of any such challenge, including by holding that APJs were "subordinate officers"—and not principal ones.

Arthrex, Inc. v. *Smith & Nephew, Inc.*, 941 F.3d 1320 (Fed. Cir. 2019) changed all of that. *Arthrex* held that APJs *are* in fact principal officers, so they must be appointed by the president and confirmed by the Senate. Because APJs are appointed by the secretary of commerce, however, their appointments violate the Appointments Clause, and their decisions are therefore invalid. As the Federal Circuit made clear

in *Arthrex*, the Appointments Clause violation it uncovered was not trivial: The Appointments Clause implicates "important structural interests and separation of powers concerns" and is "'a fundamental constitutional safeguard' and an 'exceptionally important' consideration in the context of *inter partes* review proceedings." *Id*. at 1326–27 (citation omitted).

But the Federal Circuit held that these "exceptionally important" protections did not extend to every litigant that had its patent rights extinguished by unconstitutionally-appointed APJs. Rather, the Federal Circuit held that only those litigants with the clairvoyance to raise an Appointments Clause challenge in their opening brief deserved the protection of the new rule. In so doing, the Federal Circuit departed from longstanding precedent permitting courts to entertain new arguments based on an intervening change of law—particularly when the change concerns significant structural constitutional principles, like the separation of powers principles protected by the Appointments Clause. The Court should grant certiorari to uphold the robust enforcement of the Appointments Clause and the separation of powers principles the Clause protects, as well as to protect the fundamental rule of law that treats similarly-situated litigants consistently.

This Court's review is also warranted to consider the Federal Circuit's holding that the patent claims at issue were obvious. This Court last visited the question of obviousness in *KSR International Co.* v. *Teleflex, Inc.*, 550 U.S. 398 (2007), where it held that the Federal Circuit had applied an obviousness test that was too "rigid" and at odds with the flexibility and real-world considerations that the statute and this Court's precedents demand. But in the decision below,

as in other cases in the years since *KSR*, the Federal Circuit expanded *KSR*'s admonition for "flexibility" too far in the other direction—eschewing the safeguards *KSR* established to prevent hindsight bias, and leaving the obviousness analysis far short of the reliability and predictability required.

Thus, the Federal Circuit's unwarranted expansion of *KSR* here resulted in the court finding obviousness without identifying a "known problem" in the art addressed and solved by the claimed invention. Instead, the Federal Circuit held that it could rely on evidence of a different problem, not addressed or solved by the claimed invention. App. 7a–9a. Moreover, the Federal Circuit engaged in impermissible hindsight, sanctioning the PTAB's reliance on insights contributed by the patent specification itself to find obviousness. *Id.* at 9a–11a. It has been more than a decade since this Court last considered the question of obviousness and this Court's review is warranted to recalibrate the Federal Circuit's approach developed in the intervening years.

STATEMENT

1. Sanofi's insulin glargine was a breakthrough in diabetes therapy. By making various modifications to human insulin at the molecular level, Sanofi scientists dramatically changed insulin's properties to create a pharmaceutical that allows for once-daily drug administration—a long sought-after goal of diabetes therapy. *Id*. at 3a–4a, 50a, 104a. Several fundamental changes from human insulin give glargine its long-acting profile. Importantly, although glargine is dissolved in a clear solution when stored in a vial, upon injection it precipitates out of solution, aggregating to form a solid reservoir under the skin. *Id.* at 3a–4a. This reservoir slowly dissociates throughout the day, delivering

a steady stream of medicament to patients. Such *desirable* aggregation—a core feature distinguishing glargine from other insulins—is critical to its unique mechanism of action. *Id.*

In May 2001, Sanofi began selling glargine commercially in the United States under the trade name Lantus. *Id.* at 4a. Throughout the development, testing and regulatory approval for glargine, there was no detection of any problem of *undesirable* glargine aggregation in the storage vials. C.A. App. 14275, 14284. Rather, the Lantus label described glargine as "soluble" and "clear" in its storage environment. *Id.* at 6690, 6693.

Shortly after the U.S. launch, however, Sanofi received a small number of confidential reports that some Lantus vials were turning turbid (cloudy). App. 4a. This turbidity was unexpected and unexplained. No turbidity was discovered in the testing and approval of glargine. Nor, more generally, was instability of any insulin formulation an issue in any prior commercialized product. Rather, the prior art described insulins stored and sold in vials as "uniformly stable" and found that "aggregation of insulin does *not* appear to be a significant problem in commercially available syringes." App. 24a (quoting C.A. App. 6953) (emphasis added); C.A. App. 6732.

Following extensive analysis, Sanofi scientists discovered that adding nonionic surfactants stabilized the formulation. That surfactants could work successfully with glargine was surprising. Surfactants were known in the art to impede—or even prevent—aggregation and it was thought that such properties could disrupt glargine's unique mechanism of action that depends on desirable aggregation to work. C.A. App. 14375–14377.

Sanofi applied for and received two patents relating to this discovery, U.S. Patent Nos. 7,476,652 and 7,713,930.[1] Sanofi reformulated its Lantus vial product to embody the patented invention, which was later approved by the FDA. App. 19a–20a.

2. More than fifteen years after Sanofi obtained its patents and after a decade of success and positive patient outcomes, Mylan petitioned for *inter partes* reviews of the two reformulation patents.[2] Mylan asserted that the patents were invalid as obvious over a combination of the original glargine formulation (which Mylan's expert admitted disclosed that glargine was "soluble and stable" in its storage vial) with several secondary references concerning other insulins. C.A. App. 6540. None of the references suggested that aggregation of insulin of any sort was a problem in commercialized storage vials. Indeed, to the extent the secondary references concerned insulin aggregation at all, they discussed aggregation that occurred in laboratory conditions specifically designed to provoke aggregation for study and analysis, typically in the unique context of continuous pump infusion systems. *See, e.g.*, *id.* at 6704, 6727, 6723.

On December 12, 2018, the PTAB issued its final written decisions finding the two patents obvious. App. 30a–83a; App. 84a–140a. As relevant here, the PTAB held that, as a matter of law, Mylan did not need to show that there was a prior art recognition of

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[1] The patents share a single specification. *See* App. 2a. Because the relevant analysis as to both patents is the same, the petition refers generally to the proceedings for the '652 patent, although the analysis applies equally to both.

[2] The '652 patent is also asserted in a pending action in the District of New Jersey. *Sanofi-Aventis U.S. LLC* v. *Mylan GmbH*, No. 17-cv-9105-SRC (D.N.J.).

the problem that the claimed invention identified and solved—that "insulin glargine had a tendency to aggregate." App. 64a, 120a. Instead, the PTAB found it sufficient to identify a different problem, not addressed by the challenged claims—that other insulins, with different characteristics and mechanisms of action from glargine, had aggregation problems under certain conditions. *Id.* at 64a, 120a.

3. a. Sanofi timely appealed. After briefing and oral argument, but while Sanofi's appeal was pending, the Federal Circuit held in another case that the PTAB's APJs—including those who adjudicated Sanofi's IPR proceeding and invalidated Sanofi's patents—were appointed in violation of the Appointments Clause. *Arthrex*, 941 F.3d 1320. The Federal Circuit held that APJs are principal officers because they wield significant power, render decisions not subject to review by a principal officer, and have tenure protections that prohibit a principal officer from removing them at will. *Id.* at 1331–35. Principal officers must be appointed by the president with the advice and consent of the Senate. U.S. Const. art. II, § 2, cl. 2. APJs, however, are appointed by the secretary of commerce. Accordingly, the Federal Circuit held, the APJs' adjudication of patent rights was an *ultra vires* exercise of their authority. *Arthrex*, 941 F.3d at 1335.

To remedy the Appointments Clause violation, the Federal Circuit severed the removal protections for APJs, rendering them inferior officers no longer subject to the requirement of presidential appointment. *Id.* at 1338. The Federal Circuit held that final written decisions issued by unconstitutionally-appointed APJs must be vacated and, on remand, assigned to a different panel of properly-appointed APJs. *Id.* at 1340.

But the Federal Circuit subsequently limited the reach of *Arthrex* to only some parties who had their cases adjudicated by unconstitutionally-appointed APJs. Specifically, the day following its decision in *Arthrex*—and without the benefit of briefing or oral argument on the issue—the Federal Circuit issued a precedential opinion holding that a patent owner who did not raise an Appointments Clause challenge in its opening appellate brief had forfeited its *Arthrex* argument. *Customedia Techs., LLC* v. *Dish Network Corp.*, 941 F.3d 1173 (Fed. Cir. 2019).

b. Later that week, while Sanofi's appeal remained pending, Sanofi filed a Fed. R. App. P. 28(j) supplemental authority letter citing *Arthrex*. Sanofi acknowledged that it had not raised an Appointments Clause challenge in its opening brief, but requested supplemental briefing on whether any of the well-established exceptions to forfeiture—including an intervening change in law—permitted the application of *Arthrex* here while the appeal remained pending.

4. A divided panel of the Federal Circuit affirmed the PTAB's final written decisions. The majority construed Sanofi's Rule 28(j) letter as a request to vacate and remand under *Arthrex*, and held that, under *Customedia*, Sanofi had forfeited the argument because it did not raise an Appointments Clause challenge in its opening brief. App. 22a n.4. As in *Customedia*, the court did not expressly consider—and provided no explanation as to why—an exception for an argument based on an intervening change of law did not apply.

The majority also affirmed the PTAB's obviousness finding. The majority held that the PTAB did not need to find that there was a prior art recognition of a problem of glargine aggregation—the problem identified and solved by the claimed invention. *Id.* at 7a–9a.

Instead, the majority held that it would suffice to show an aggregation problem with other insulins—formulations that not only are not encompassed within the claimed invention, but operate in fundamentally different ways from glargine. *Ibid*. The majority also held that it was proper for the PTAB to have relied on the patents' specification to disclose the key insight that glargine aggregated during storage, when that was not disclosed anywhere in the prior art. *Id.* at 9a–11a.

Judge Newman dissented, disagreeing with both holdings of the panel majority. She noted that "at the time these appeals were filed, there was no holding of illegality of appointments of the PTAB's Administrative Patent Judges." *Id*. 29a (Newman, J. dissenting). *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." *Ibid*. (citing *Thorpe* v. *Hous. Auth. of Durham*, 393 U.S. 268, 282 (1969)). Thus, "Sanofi is entitled to the same benefit of the *Arthrex* decision as are the *Arthrex* parties." *Ibid.*

On the obviousness question, Judge Newman found that the majority impermissibly "enlarge[d] 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." *Id*. at 23a. Judge Newman acknowledged that neither a glargine aggregation problem, nor its solution, were shown in the prior art. *Ibid.* Thus, "[t]hat Sanofi's inventors knew of the tendency of insulin to aggregate, as so stated in their specification, is evidence not of obviousness, but of non-obviousness, for glargine had undergone clinical development without this problem being apparent." *Id.* at 25a. The PTAB's use of the patents' specification to find

obviousness was therefore "plain error": "A patent specification may be edifying and must be descriptive and enabling, but it is not prior art." *Id.* at 27a.

The Federal Circuit subsequently denied Sanofi's timely petition for rehearing *en banc*. *Id*. at 141a–142a.

REASONS FOR GRANTING THE PETITION

This Court should grant certiorari to review the important and recurring question whether, in a pending case, a court may refuse on the grounds of forfeiture to consider a structural constitutional challenge based on an intervening change of law. A core rule of law principle is that courts decide cases based on the law as it stands at the time of their decision. That principle leads to a vital exception to the ordinary forfeiture rule that allows litigants to pursue claims based on intervening changes of law, regardless of whether they were otherwise timely raised. That exception takes on even more significance when the change of law concerns structural constitutional protections, like the separation of powers concerns animating the Appointments Clause—concerns that go to the APJs' basic authority to adjudicate patent rights at all.

The Federal Circuit did not attend to these concerns here; indeed, it did not even *consider* whether the change in law wrought by *Arthrex*—a decision which the Federal Circuit itself characterized as vindicating "exceptionally important" interests—warranted entertaining Sanofi's Appointments Clause challenge. In so doing, the Federal Circuit added to the lack of uniformity among the lower courts in applying this change-of-law exception in constitutional cases. This question will recur, both with respect to the *Arthrex* decision itself, and with respect to how courts handle other changes of law that occur while a case is pending.

This Court's review is warranted to emphasize the significance of the change-of-law exception in constitutional cases raising structural concerns.

The petition also presents important questions concerning the Federal Circuit's approach to the obviousness analysis as it has evolved since *KSR*. In *KSR*, the Court recognized the need to balance flexibility in the obviousness analysis with the "uniformity and definiteness" the Patent Act demands. The Federal Circuit here upset that balance. It failed to adhere to critical guidelines *KSR* established, including those set forth to guard against improper hindsight bias. The Federal Circuit thus created more uncertainty and less reliability in the obviousness analysis. This Court's review is warranted to reset that balance.

I. The Application Of *Arthrex* To Pending Cases Raises An Important And Recurring Issue Of Federal Law

A. This Court Has Long Recognized That Intervening Changes Of Law Apply To Pending Cases, Regardless Of Forfeiture

1. This Court has long held that "when the law changes while a case is on appeal, the changed law applies." App. 29a (Newman, J., dissenting) (citing *Thorpe,* 393 U.S. at 281). It is the responsibility of each court, at every level, to "decide according to existing laws." *Plaut* v. *Spendthrift Farm, Inc.*, 514 U.S. 211, 227 (1995) (quoting *United States* v. *Schooner Peggy*, 5 U.S. (1 Cranch) 103, 110 (1801)). Thus, when a new rule is announced, courts are to "apply that rule to all similar cases pending on direct review." *Griffith* v. *Kentucky*, 479 U.S. 314, 323 (1987). Because federal courts must apply the newly "controlling interpretation of federal law,"

they have no "constitutional authority" to "disregard current law or to treat similarly situated litigants differently." *Harper* v. *Va. Dep't of Taxation*, 509 U.S. 86, 97 (1993).

The reason for this, as Judge Newman's dissent below recognized, is that "[t]he 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." App. 29a. When courts refuse to give effect to new or changed law in pending cases, the "integrity of judicial review" is compromised—particularly in the case of a constitutional challenge. *Griffith*, 479 U.S. at 323. Indeed, the failure to apply new law in pending cases unjustly results in "[s]imply fishing one case from the stream of appellate review, using it as a vehicle for pronouncing new constitutional standards, and then permitting a stream of similar cases subsequently to flow by unaffected by that new rule." *Id.* (quoting *Williams* v. *United States*, 401 U.S. 667, 679 (1971) (Harlan, J., concurring in the judgment)).

2. For this reason, this Court has recognized an important exception to the ordinary rule that arguments not raised in an opening brief are forfeited.[3] Forfeiture does not apply in "those [exceptional 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." *Hormel* v. *Helvering*, 312 U.S. 552, 558–59 (1941). Thus, when the law changes while a case is pending on appeal, the "rigid and undeviating judicially declared practice" to enforce forfeiture of unpreserved issues must yield. *Id.* at 557; App. 29a (Newman, J.,

[3] This exception, applying only to still-pending cases, does not implicate finality concerns.

dissenting) ("a change in governing law applies to the pending appeal when the change occurs while the case is on appeal").

This exception rests on several core principles. For one thing, a party cannot forfeit an argument or a constitutional claim that has not yet been recognized. *See, e.g.*, *Johnson* v. *Zerbst*, 304 U.S. 458, 464 (1938) (effective waiver must be one of a "known right or privilege").[4] Thus, in *Curtis Publishing Co.* v. *Butts*, 388 U.S. 130 (1967), for example, the petitioner had not waived its right to assert a constitutional defense based on *New York Times Co.* v. *Sullivan*, 376 U.S. 254 (1964) because *Sullivan*—and therefore the defense it established—had not been decided until after trial. As the Court recognized, "[t]he mere failure to interpose a [constitutional] defense prior to the announcement of a decision which might support it cannot prevent a litigant from later invoking such a ground." *Curtis Publ'g Co.*, 388 U.S. at 143; *see also Holzsager* v. *Valley Hosp.*, 646 F.2d 792, 796 (2d Cir. 1981) ("[A] party cannot be deemed to have waived objections or defenses which were not known to be available at the time they could first have been made, especially when it does raise the objections as soon as their cognizability is made apparent."); *Spiegla* v. *Hull*, 481 F.3d 961, 964 (7th Cir. 2007) ("A party cannot . . . waive an argument that did not exist when he submitted his brief.").

This exception also promotes judicial efficiency. To be sure, a fundamental purpose behind forfeiture is to prevent parties from unfairly prejudicing opponents

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[4] Although waiver and forfeiture are "not really the same," courts have "so often used them interchangeably that it may be too late to introduce precision." *Freytag* v. *C.I.R.*, 501 U.S. 868, 894 n.2 (1991) (Scalia, J., concurring).

and incentivize the presentation of claims at the proper time and place. "Insisting on preservation of claims" when a new claim is based on a change of law, however, "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.'" *Joseph*, 135 S. Ct. at 706 (Kagan, J., respecting denial of certiorari) (citation omitted). Thus, a rigid application of forfeiture in the face of an intervening change in law—especially where that change implicates structural constitutional issues—works against this purpose, compelling litigants to "clog the judicial pipes . . . on pain of forfeiting all right to benefit from future changes in the law, to include challenges to settled law." *In re Davenport*, 147 F.3d 605, 610 (7th Cir. 1998) (Posner, J.).

Moreover, where the underlying issue involves a "pure question of law" for which the "proper resolution of the issue is beyond any doubt," no undue prejudice results from excusing forfeiture. *Automated Merch. Sys., Inc.* v. *Lee*, 782 F.3d 1376, 1379–80 (Fed. Cir. 2015). In the case of an intervening change of law where "the issue is purely one of law important in the administration of federal justice . . . resolution of the issue does not depend on any additional facts not considered by the district court." *Roosevelt* v. *E.I. Du Pont de Nemours & Co.*, 958 F.2d 416, 419 n.5 (D.C. Cir. 1992) (Ginsberg, J.) (entertaining a new argument on appeal). Moreover, no prejudice results from the lack of further briefing on the underlying issue; all the court must consider is whether to apply the changed law.

In the end, failing to raise a claim that is later endorsed by a change of law reflects "not a lack of diligence, but merely a want of clairvoyance." *Joseph*, 135

S.Ct. at 706 (Kagan, J., respecting denial of certiorari); *Hawknet, Ltd.* v. *Overseas Shipping Agencies*, 590 F.3d 87, 92 (2d Cir. 2009) ("[T]he doctrine of waiver demands conscientiousness, not clairvoyance, from parties.").

3. This Court has further acknowledged that it is particularly warranted for courts to consider arguments based on changes of law concerning structural constitutional claims under the Appointments Clause—claims that relate to judicial officers' fundamental authority to adjudicate individual rights—regardless of when they are raised in the course of a pending case. The Appointments Clause is integral to the Constitution's careful separation of powers, "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* v. *C.I.R.*, 501 U.S. 868, 878 (1991)). "The roots of the separation-of-powers concepts embedded in the Appointments Clause are structural and political." *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. *Id*. at 879 (citing *Glidden Co.* v. *Zdanok*, 370 U.S. 530, 536 (1962)).

These structural protections are so important that "notions of consent and waiver cannot be dispositive because the limitations serve institutional interests that the parties cannot be expected to protect." *Commodity Future Trading Comm'n* v. *Schor*, 478 U.S. 833, 851 (1986); *see also Wellness Int'l Network Ltd.* v. *Sharif*, 135 S. Ct. 1932, 1950 (2015) (Roberts, C.J., dissenting with Thomas, J.) (emphasizing that "structural sepa-

ration of powers" are too important to allow parties to override such barriers by consent or waiver). While a private litigant may waive personal constitutional rights, the "values of liberty and accountability protected by the separation of powers belong not to any branch of the Government but to the Nation as a whole." *Id*. at 1955 (Roberts, C.J., dissenting).[5] Accordingly, the judiciary cannot wholly depend on individuals to assert institutional interests to enforce the separation of powers. *Schor*, 478 U.S. at 851.

Indeed, that is why courts have often overlooked forfeiture to decide structural constitutional challenges—including Appointments Clause challenges—that were not timely raised.[6] In *Freytag*, for example, this Court disregarded forfeiture arguments and heard an Appointments Clause challenge, noting that it was permissible to hear a challenge first raised in "a supplemental brief upon a second request for review." 501 U.S. at 879 (quoting *Glidden*, 370 U.S. at 536 (citing *Lamar* v.

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[5] *See also PHH Corp.* v. *Consumer Fin. Protection Bureau*, 839 F.3d 1 (D.C. Cir. 2016), *rev'd en banc*, 881 F.3d 75 (D.C. Cir. 2018) (Kavanaugh, J.) (permitting an Appointments Clause challenge despite claims of waiver); *Bahlul* v. *United States*, 840 F.3d 757, 760 n.1 (D.C. Cir. 2016) (*en banc*) (Kavanaugh, J., concurring) (recognizing a structural constitutional claim as an "extraordinarily important case" that permits courts to hear forfeited structural constitutional claims).

[6] By contrast, courts that have held a party forfeited an Appointments Clause challenge have done so because there was no intervening change of law. *See, e.g.*, *David Stanley Consultants* v. *Dir., Office of Workers' Compensation Programs*, 800 F. App'x 123, 127–28 (3d Cir. 2020) (refusing to hear Appointments Clause Challenge because no "extraordinary circumstances" justified review); *N.L.R.B.* v. *RELCO Locomotives, Inc.*, 734 F.3d 764, 796–97 (8th Cir. 2013) (refusing to permit Appointments Clause challenge because "[t]here was no change in facts or law which altered the availability of RELCO's appointments clause challenge.").

United States, 241 U.S. 103, 117 (1916))); *see also Nguyen* v. *United States*, 539 U.S. 69, 73–74 (2003); *Samuels, Kramer & Co.* v. *C.I.R*, 930 F.2d 975, 984 (2d Cir. 1991); *Jones Bros., Inc.* v. *Sec'y of Labor*, 898 F.3d 669, 677–78 (6th Cir. 2018).

The important interests protected here by the Appointments Clause are no different. Indeed, in *Arthrex* itself, the Federal Circuit excused at least one level of forfeiture to reach the Appointments Clause issue, given that Arthrex raised the issue in the Federal Circuit for the first time on appeal. 941 F.3d at 1327. The Federal Circuit recognized that the Appointments Clause issue raised "exceptionally important" questions, including whether valuable private property rights were properly adjudicated by officers acting *ultra vires*, which justified hearing the issue over a challenge of waiver. *Id.*

Those separation of powers interests remain just as weighty here. At its core, the "[s]eparation of powers is 'a fundamental constitutional safeguard,'" *id.* at 1326–27, and the effect of *ultra vires* acts by unconstitutionally-appointed and unaccountable officers persists regardless of any failure to raise the issue in an opening brief.

B. Federal Courts Have Applied The Change-In-Law Exception Inconsistently

The courts of appeals, however, have applied the change-in-law exception to forfeiture inconsistently. On the one hand, courts have repeatedly held that a court should entertain an argument based on an intervening change of law announced while a case is pending on appeal regardless of when the party raised it. *See, e.g.*, *Gucci Am., Inc.* v. *Weixing Li*, 768 F.3d 122, 135–36 (2d Cir. 2014) (holding a party "does not waive" an argument that "would have been directly contrary

to controlling precedent" at the time); *Wang* v. *Chinese Daily News, Inc.*, 737 F.3d 538, 543 (9th Cir. 2013) (entertaining claims based on a change of law announced in *Wal-Mart Stores, Inc.* v. *Dukes*, 564 U.S. 338 (2011)); *DSC Commc'ns Corp.* v. *Next Level Commc'ns*, 107 F.3d 322, 326 n.2 (5th Cir. 1997) (entertaining claims based on an "important clarification of the law" issued "after briefing and oral argument").[7]

Indeed, the Federal Circuit has at times entertained arguments raised for the first time on appeal (or after the filing of an opening brief) based on intervening changes of law. *See, e.g.*, *BioDelivery Scis. Int'l, Inc.* v. *Aquestive Therapeutics, Inc.*, 898 F.3d 1205, 1210 (Fed. Cir. 2018) (entertaining arguments based on the change of law articulated in *SAS Inst., Inc.* v. *Iancu*, 138 S. Ct. 1348 (2018)); *In re Micron Tech., Inc.*, 875 F.3d 1091, 1095–96 (Fed. Cir. 2017) (entertaining arguments based on change of law articulated in *TC Heartland LLC* v. *Kraft Food Grp. Brands LLC*, 137 S. Ct. 1514 (2017)).

By contrast, the Federal Circuit below refused to apply the change-of-law exception to forfeiture here. Indeed, the Federal Circuit refused even to *consider* whether the exception applied to Sanofi's Appointments Clause challenge under *Arthrex*. Instead, without the benefit of briefing or argument on the question, the Federal Circuit mechanically applied its precedential opinion in *Customedia*—a case decided the day after

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[7] *See also, e.g.*, *Roosevelt*, 958 F.2d at 419 n.5 (Ginsberg, J.) (entertaining an argument based on "an intervening change in the law" constituting a "qualifying circumstance[]" that permits "consideration of issues not raised earlier"); *Big Horn Cty. Elec. Co-op., Inc.* v. *Adams*, 219 F.3d 944, 954 (9th Cir. 2000) (finding "waiver argument fails" where "an intervening change in the law . . . altered [Plaintiff's] stance").

Arthrex—holding that *Arthrex* arguments not raised in an opening brief are forfeited. *Customedia*, for its part, likewise was decided without the benefit of any briefing or argument on that question, and failed to consider whether the change-in-law exception applies to Appointments Clause challenges under *Arthrex*.

Further inconsistency is found in other federal courts as well, failing to entertain new arguments based on intervening changes of constitutional law. In *Martinez* v. *Tex. Dep't of Criminal Justice*, 300 F.3d 567, 574–75 (5th Cir. 2002), for example, the court refused to consider a sovereign immunity argument raised for the first time on appeal, notwithstanding a change of law. *See also, e.g.*, *United States* v. *Nealy*, 232 F.3d 825, 830–31 (11th Cir. 2000) (refusing to entertain an argument raised for the first time in supplemental briefing in a criminal case where "the issues arise based on the intervening decisions or new developments cited in the supplemental authority"). Indeed, the federal courts' haphazard approach to forfeiture in the context of intervening changes of law leaves behind a confusing array of decisions, including reaching different conclusions based on the same underlying change in law. *Compare Carroll* v. *Gen. Accident Ins. Co.*, 891 F.2d 1174, 1175 n.1 (5th Cir. 1990) (entertaining claims based on *Patterson* v. *McLean Credit Union*, 491 U.S. 164 (1989) because it was an intervening change of law), *with McGinnis* v. *Ingram Equip. Co., Inc.*, 918 F.2d 1491, 1495–96 (11th Cir. 1990) (declining to address arguments based on *Patterson* that were not presented below).

This is a recurring issue. Several filed and anticipated petitions will raise precisely the same question, whether, due to forfeiture, courts may refuse to consider arguments based on the change in law reflected

in *Arthrex*. *See* Petition for Writ of Certiorari, Petition for Writ of Certiorari, *Arthrex, Inc. v. Smith & Nephew, Inc.* (Apr. 6, 2020) (No. 19-1254) [hereinafter *Arthrex '541* Petition]; *see also Customedia*, 941 F.3d 1173 (Fed. Cir. 2019); *Bos. Sci. Neuromodulation Corp.* v. *Nevro Corp.*, 2020 WL 2787715 (Fed. Cir. May 29, 2020).

Moreover, absent the Court's guidance, the issue will continue to recur elsewhere when an intervening change of law implicates other structural constitutional issues. Indeed, in recent years, this Court has expressly overruled its precedent numerous times in the context of structural constitutional changes, leaving lower courts to figure out how to apply the intervening changes of law in pending cases. *See, e.g.*, *Franchise Tax Bd. of Cal.* v. *Hyatt*, 139 S. Ct. 1485, 1492 (2019) ("We therefore overrule [*Nevada* v.] *Hall*, [440 U.S. 410 (1979)]"); *Rucho* v. *Common Cause*, 139 S. Ct. 2484 (2019) (overruling *Davis* v. *Bandemer*, 478 U.S. 109 (1986)); *South Dakota* v. *Wayfair, Inc.*, 138 S. Ct. 2080 (2018) (overruling *Quill Corp.* v. *North Dakota*, 504 U.S. 298 (1992)). The Court should clarify the applicable standard and insist that it be applied uniformly. And, if the change-in-law exception is not routinely and predictably available, it is all the more necessary that parties know the standard to preserve potential arguments.

C. The Federal Circuit Improperly Refused To Apply An Intervening Change Of Law Implicating A Structural Constitutional Challenge

1. Had the Federal Circuit considered and applied the change-of-law exception, it would have entertained Sanofi's Appointments Clause argument because *Arthrex* represented a significant and intervening change of law. At the time Sanofi filed its opening brief, "strong

precedent" indicated that the appointment of APJs carried no constitutional infirmity. *Curtis*, 388 U.S. at 143–44. As the dissent below recognized, "there was no holding of illegality of appointments of the PTAB's Administrative Patent Judges" prior to *Arthrex*. App. 29a (Newman, J., dissenting). To the contrary, a prior Appointments Clause challenge to APJs under the AIA-predecessor statute held that when Congress re-delegated appointment of APJs to the secretary of commerce, it "*eliminate[d]* the issue of unconstitutional appointments going forward." *In re DBC*, 545 F.3d 1373, 1380 (Fed. Cir. 2008) (emphasis added). Likewise, in upholding the delegation of authority to institute *inter partes* review to APJs, the Federal Circuit found that APJs were "subordinate officers" who report to the Director—not principal officers, as *Arthrex* later found. *Ethicon Endo-Surgery, Inc.* v. *Covidien LP*, 812 F.3d 1023, 1031–33 (Fed. Cir. 2016), *cert. denied*, 137 S. Ct. 625 (2017); *see also In re Alappat*, 33 F.3d 1526, 1535–36 (Fed. Cir. 1994), *abrogated on other grounds by In re Bilski*, 545 F.3d 943 (Fed. Cir. 2008) (under predecessor *inter partes* reexamination regime, holding then-Commissioner's ability to "determine the composition of Board panels" provided necessary officer oversight).

Moreover, prior to *Arthrex*, the Federal Circuit had reviewed hundreds of IPR appeals without ever questioning the constitutionality of the appointment of APJs or the *ultra vires* actions of the PTAB—including in cases that raised the argument in an opening brief. Indeed, the law was so well settled that the Federal Circuit at least twice summarily rejected the *same* challenge to the appointment of APJs that ultimately was successful in *Arthrex*. *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), *rehearing granted & judgment vacated*, 803 F. App'x 407 (Fed. Cir. 2020). This Court, too, had upheld the constitutionality of IPR proceedings, including against a challenge that APJs exercised powers beyond their authority as non-Article III judges. *Oil States Energy Servs., LLC* v. *Greene's Energy Grp., LLC*, 138 S. Ct. 1365 (2018).[8]

2. Furthermore, the thrust of the intervening authority—a structural constitutional challenge—renders the Federal Circuit's refusal to apply *Arthrex* even more egregious. *Arthrex* aims to vindicate separation of powers principles, ensuring that the executive branch does not aggrandize power and diffuse its accountability by permitting unconstitutionally-appointed judges to adjudicate private property rights. The Executive Branch's delegation of power to APJs who "lack[] authority to exercise those functions . . . . threaten[s] liberty and thwart[s] accountability by empowering entities that lack the structural protections the Framers carefully devised." *Wellness*, 135 S. Ct. at 1957–58. But insulated from the president's constitutionally-mandated oversight role, the Appointments Clause's requirements are rendered null and void.

Limiting *Arthrex*'s application to only a subset of cases undermines these principles, effectively reviving this Court's former—and overruled—practice of denying backward-looking relief in constitutional cases.

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[8] The "strong precedent" indicating APJs posed no constitutional infirmity distinguishes *Arthrex* from this Court's decision in *Lucia* v. *S.E.C.*, 138 S. Ct. 2044 (2018), which recognized that "*Freytag* says everything necessary to decide this case." *Id.* at 2053; *see also, e.g.*, *Island Creek Coal Co.* v. *Wilkerson*, 910 F.3d 254, 257 (6th Cir. 2018) (refusing to entertain a *Lucia* claim because it was not an intervening change in law); *Turner Bros., Inc.* v. *Conley*, 757 F. App'x 697, 699–700 (10th Cir. 2018).

See Harper, 509 U.S. at 97. In failing to apply its own decision in *Arthrex* here, the Federal Circuit left past violations to stand. Yet even "[s]light encroachments create new boundaries from which legions of power can seek new territory to capture." *Stern* v. *Marshall*, 564 U.S. 462, 503 (2011). The Appointments Clause and separation of powers issues are no less important here than they are in *Arthrex* or any other Appointments Clause case.

3. Finally, this case presents a clear vehicle to visit this important issue and provide much-needed guidance to the lower courts grappling with it. The importance of the separation of powers is at its zenith when the *ultra vires* actions of an unconstitutionally-appointed officer, left unchecked, extinguishes valuable property interests. *Cf. Thryv, Inc.* v. *Click-To-Call Techs., LP*, 140 S. Ct. 1367, 1380 (2020) (Gorsuch, J., dissenting) ("Inventors . . . just have to hope that the bureaucracy revoking their property rights will take the extra trouble of doing so in accordance with law.").

At the least, the Court should hold Sanofi's petition for forthcoming petitions raising similar forfeiture issues, *see supra*, or the petition in *Arthrex* itself. *See Arthrex '541* Petition at 29 ("Arthrex ['907] plans to seek this Court's review."). The petition in *Arthrex* will raise the underlying question whether the Federal Circuit correctly held APJs are unconstitutionally-appointed principal officers, as well as whether the Federal Circuit's remedy—severing of removal protections—successfully rendered APJs inferior officers. And, because the Federal Circuit reached the Appointments Clause challenge for the first time on appeal, *see Arthrex*, 941 F.3d at 1326, the Court may need to resolve an embedded forfeiture question. If this Court grants certiorari in *Arthrex*, its decision may have significant implications

for the question presented here, including as to the proper forfeiture analysis in Appointments Clause cases. This Court, therefore, should at a minimum consider holding Sanofi's petition or hearing this petition together with *Arthrex*.

II. The Federal Circuit's Obviousness Analysis Goes Beyond *KSR* And The Patent Act

In *KSR International Co.* v. *Teleflex Inc.*, 550 U.S. 398, 415 (2007), the last time this Court addressed the obviousness question, the Court found that the Federal Circuit had applied an overly "rigid approach" that was inconsistent with the "expansive and flexible" analysis established in this Court's precedents. The Court held that the Federal Circuit's obviousness analysis incorrectly reduced the inquiry to "rigid and mandatory formulas" and insisted that courts should instead look to a variety of factors in conducting the obviousness inquiry. *Id.* at 419. Still, the Court did not sanction an open-ended inquiry. In particular, as a bulwark against relying on impermissible hindsight, the Court cautioned that the inquiry should focus on whether "there existed at the time of the invention a known problem for which there was an obvious solution encompassed by the patent's claims." *Id.* at 420.

In the decade-plus since *KSR*, however, the Federal Circuit has often swung the pendulum too far in the other direction—as it did in the decision below. As here, the Federal Circuit has taken *KSR*'s instruction to apply an "expansive and flexible" approach as a license to find obviousness without articulating clear and predictable standards. Indeed, in the decision below, the Federal Circuit eschewed *KSR*'s guiderails by finding obviousness when the problem identified and solved by the claimed invention was *not* known in the prior art. App. 7a–9a. Instead, the court below

stretched *KSR* and looked to a malleable set of factors, including a hindsight-driven analysis of the patents' own specification, to find obviousness. App. 9a–11a.

This Court's review is warranted to restore the balance. As this Court recognized in *Graham* v. *John Deere Co. of Kan. City*, patent law depends on "uniformity and definiteness" in the obviousness determination. 383 U.S. 1, 18 (1966); *see also* App. 27a (Newman, J., dissenting) ("The statutory standards of novelty and nonobviousness require objectivity, consistency, and predictability."). The Federal Circuit's unguided approach in this case detracts from those goals. The need for clarity is even greater in the context of the biochemical arts—the so-called unpredictable arts—where *KSR*'s invitation to consider the "predictable results" of modifications to prior art can lead courts astray. 550 U.S. at 416. More than a half-century has passed since the Court last addressed obviousness in the chemical sciences. *See United States* v. *Adams*, 383 U.S. 39 (1966) (decided the same day as *Graham*). This Court's guidance is warranted now.

A. The Court Has Recognized The Need For Both "Flexibility" And "Definiteness" In The Obviousness Analysis

In *KSR*, the Court reined in the Federal Circuit's test for obviousness, finding its application had strayed too far from the statute and the Court's precedents in imposing too rigid a standard. Specifically, the Court considered the Federal Circuit's application of its "teaching, suggestion or motivation" ("TSM") test for obviousness, in which the Court explained a patent claim is "only proved obvious if 'some motivation or suggestion to combine the prior art teachings' can be found in the prior art, the nature of the problem, or the knowledge of a person having ordinary skill in the art."

KSR, 550 U.S. at 407 (citation omitted). The Court found that the Federal Circuit's TSM test had "transform[ed] the general principle into a rigid rule that limits the obviousness inquiry," and applied an approach that was inconsistent with the court's obviousness cases. *Id*. at 419. The Court thus suggested that the obviousness inquiry must be "expansive and flexible," and would consider a variety of factors that encompass "[t]he diversity of inventive pursuits and of modern technology." *Id.* at 415, 419.

But the Court made clear that the obviousness inquiry was not boundless. It recognized that courts must protect against the "distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning." *Id.* at 421. And the Court underscored the need for "uniformity and definiteness" in the analysis as core to the stability of the patent system. *Id*. at 415 (quoting *Graham*, 383 U.S. at 18).

Among the more important guiderails the Court recognized as critical to achieving objectivity and predictability in the obviousness analysis was the call 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. The Court 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." *Id*. at 418–19. Thus, to combat the force of hindsight bias in such cases, courts should focus on whether "there existed at the time of invention a known problem for which there was an obvious solution encompassed by the patent's claims." *Id*. at 420.

B. In The Decision Below, The Federal Circuit Strayed Too Far From *KSR* And The Statutory Principles

In the years since *KSR*, however, including in the decision below, the Federal Circuit has strayed too far away from the goal of uniformity and predictability in the obviousness analysis, and toward a more subjective standard susceptible to hindsight bias. In the case here, the Federal Circuit ignored *KSR*'s guiderails and protections against hindsight bias, and rooted its obviousness findings in sources and factors beyond those sanctioned by *KSR* or elsewhere in the patent law. The Court should grant review to restore reliability in the obviousness analysis.

First, the Federal Circuit ignored the need to find that there was a "known problem" that the claimed invention solved. Indeed, the court found obviousness in the *absence* of any evidence of a known problem of glargine aggregation—the problem addressed and solved by the patents' claims. *See* App. 25a (Newman, J., dissenting). Instead, the Federal Circuit held that it sufficed to identify a different problem—aggregation in insulins with markedly different characteristics and mechanisms of action than glargine—a problem not addressed or solved by the claimed invention. The Federal Circuit's failure to insist on precision and accuracy in conducting this critical analysis eviscerated one of the core protections against hindsight bias that *KSR* recognized.

Second, the Federal Circuit expanded the factors that *KSR* said were probative of obviousness to include the patents' own shared specification. Rather than consider whether there was evidence of design need, market pressure, creativity or even "common sense," the Federal Circuit turned to the inventors' own

description of the invention and the insights it disclosed. That, too, was a deviation from the guidelines *KSR* imposed and an invitation to allow hindsight bias to seep into the analysis. *See KSR*, 550 U.S. at 418–19. Indeed, the Federal Circuit has elsewhere acknowledged that a court cannot "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*, 475 U.S. 809 (1986).

Specifically here, however, the Federal Circuit held that it was proper for the PTAB to rely on the specification's statements regarding the proneness of *insulin* to aggregate under certain conditions as evidence of a prior art recognition of a *glargine* aggregation problem. App. 9a–11a. But the specification could not have been summarizing the prior art as it related to glargine because the cited prior art *nowhere discussed* glargine. Rather, drawing the link between glargine and an aggregation issue was the discovery and contribution of the inventors. As Judge Newman's dissent emphasized, any suggestion in the specification that *glargine* had a tendency to aggregate is "evidence not of obviousness, but of non-obviousness, for glargine had undergone clinical development without this problem being apparent." *Id*. at 25a.

Third, the improper analysis here is consistent with other cases in which the Federal Circuit has eschewed *KSR*'s guiderails to find obviousness by stretching the criteria *KSR* set forth. In *I/P Engine, Inc.* v. *AOL Inc.*, 576 F. App'x 982 (Fed. Cir. 2014), for example, the Federal Circuit found obvious patent claims for a method of combining two different types of information filtering systems in search engine results, even though there was no evidence of a reason why a person

skilled in the art would have done so. *See id.* at 998 (Chen, J., dissenting) ("What is needed—and what is missing from the cited testimony—is some explanation of why one would use the query as the asserted claims do."). Likewise, in *Chapman* v. *Casner*, 315 F. App'x 294 (Fed. Cir. 2009), the Federal Circuit found patent claims obvious, even though, contrary to *KSR*, there was no showing that the problem solved by the invention was previously known. *See id.* at 299–300 (Rader, J., dissenting) ("Because no other persons had discovered and solved this problem as Chapman did, his invention is the product of innovation and not of 'ordinary skill and common sense.'").

The Federal Circuit here, however, imposed "a fresh spin on the law, to the detriment of consistency and reliability." App. 28a (Newman, J., dissenting). As the dissent below emphasized, "[i]nnovation requires stable laws and consistent application of those stable laws, . . . lest the incentive for innovation be diminished." *Id*. at 27a. Although some case-by-case flexibility is required in administering any standard, the obviousness analysis must be bounded by some objective criteria. As this Court held in *Graham*, "strict observance of the requirements laid down here will result in that uniformity and definiteness which Congress called for in the 1952 Act." *Graham*, 383 U.S. at 18. This Court's review to reestablish those objective criteria is vital to maintaining the stability the law of innovation requires.

Finally, this Court's review is particularly warranted in the context of nonobviousness in the biochemical arts. The biochemical arts, in contrast to the mechanical arts considered in *KSR* and most of this Court's obviousness cases, are "unpredictable": Scientists often cannot predict how even a few modifications, substitu-

tions or additions will alter biological processes, especially as they relate to the effects of those changes on the human body. Experimentation is required. Thus, as the dissent below emphasized, "[t]he 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." App. 24a (Newman, J., dissenting).

To be sure, *KSR* did not purport to announce an obviousness standard that was limited to the mechanical arts or any other field. Still, there is a danger that, as happened here, factfinders may rely on passages of *KSR* that are not well-suited for considering the obviousness of advances in the unpredictable biochemical field. Here, for example, the PTAB found the patents obvious by relying on *KSR*'s observation that a patent may be obvious if "the improvement is [no] more than the predictable use of prior art elements according to their established functions." *Id*. at 64a (quoting *KSR*, 550 U.S. at 517). This line of analysis, however, fares poorly when applied to the biochemical arts. Whether the combination of known elements behaves "predictably"—to the extent predictions can even be made—often cannot be determined without experimentation. When such experimentation validates a suggested hypothesis, it can lead courts to conclude, in hindsight, that the invention was obvious. *See id*. at 25a (Newman, J., dissenting) ("[T]he behavior of a new composition inside the body requires experimentation and evidence, not speculation and hindsight."). This Court should grant review to clarify the obviousness analysis as it relates to innovation in the biochemical arts.

C. The Claims Are Not Obvious Under The Correct Obviousness Analysis

Under a proper obviousness analysis, the invention of reformulated glargine is not obvious. *KSR* insisted on an application of objective factors and a "functional approach" to the obviousness consideration. 550 U.S. at 415. Those factors point unidirectionally against finding obviousness here.

First, the real-world history and experience with glargine shows that, at the time of the invention, there was no known problem of aggregation with the original glargine formulation. That formulation had undergone extensive stability testing, including in the course of obtaining FDA approval, and had been offered on the market in Europe, all without any indication of any aggregation problem in the vials. C.A. App. 13082, 14275, 14284.

Second, once reports of sporadic aggregation began to emerge, the *cause* of that aggregation was not readily identified or understood. *See id.* at 15098–15102, 15104–15105, 15125–15132. Rather, it took extensive further study, investigation and discovery to uncover the reason for the glargine aggregation problems. In other words, at the time of the invention, not only was the problem of glargine aggregation unknown—even to the Sanofi inventors—so was the cause of that problem. Understanding those causes was an equally innovative contribution of the reformulation's inventors.

Third, a person of ordinary skill in the art would have had no reason to suspect any latent aggregation problem with glargine because the prior art overwhelmingly suggested that aggregation in the vial was *not* a problem in commercial formulations.

Specifically, the prior art showed that "aggregation of insulin does *not* appear to be a significant problem in the commercially available syringes." App. 24a (quoting C.A. App. 6953) (emphasis added); *see also* C.A. App. 14260–14261, 14307–14308. The prior art references the Federal Circuit (and the PTAB before it) cited did not address *glargine* nor did they address aggregation in ordinary commercial settings or patient use, but instead in either laboratory experiments designed to induce aggregation so it could be studied, or in continuous pump infusion systems that have vastly different properties than vials.[9] App. 12a, 14a. That is, the references relied on were related to *different* insulins being stored under *different* conditions, administered using a *different* delivery system, often with conditions chosen to purposefully cause aggregation for the purposes of academic research. Indeed, the prior art showed that vial formulations were "uniformly stable" and did not "require[] further steps to ensure stability." C.A. App. 6732. A person of ordinary skill in the art would not have relied on such references to suspect—without any real-world evidence—an aggregation problem with glargine stored in a vial.

Fourth, the solution claimed by the challenged patents was contra-indicated—a skilled artisan would not have "anticipated success" in modifying the formulation as the inventors did. *KSR*, 550 U.S. at 402, 421. Unlike insulins, glargine's unique mechanism of action requires beneficial aggregation to work. App. 3a–4a. Surfactants, like those added to the glargine

[9] Continuous infusion pumps are worn by the patient and deliver a fast-acting insulin directly into the body constantly throughout the day in order to mimic the basal levels of insulin in healthy patients. Insulins stored in pumps are subject to significantly more stress compared to insulins stored in a vial.

reformulation, were thought to work by *impeding* aggregation. C.A. App. 14376–14377. In other words, even if a person of ordinary skill in the art were concerned about aggregation in glargine, they would not have predicted that adding a surfactant that could destroy glargine's mechanism of action would work to solve it.

Taken together, this real-world evidence, under a reliable and predictable standard like that announced in *KSR*, should have resulted in a finding of nonobviousness.

CONCLUSION

This Court should grant the petition for a writ of certiorari.

Respectfully submitted,

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June 26, 2020

APPENDIX

APPENDIX A

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.

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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

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[1] David R. Owens, et al., *Pharmacokinetics of ^{125}I-Labeled Insulin Glargine (HOE 901) in Healthy Men: Comparison with*

one or more of three secondary references.[2] The parties do not dispute that, for each claim, the asserted combinations of 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,

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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).

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.

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 nonobviousness." *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

[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.

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 prep-

> arations, 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 con-

firmed 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

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[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 non-obviousness, 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

[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*

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.

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

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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.

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.

APPENDIX B

Trials@uspto.gov Paper No. 89
571-272-7822 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];
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

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[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).

[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).

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 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

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[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.

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. 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 infor-

mation 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

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[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

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 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

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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).

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 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 subcu-

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[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.

taneous 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]

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

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

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.

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,

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

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 expecta-

tion 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

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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.

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.

Patent Owner also contends that an ordinarily skilled artisan would have expected insulin glargine

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[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).

"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). 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

[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).

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]

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[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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APPENDIX C

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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];

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[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).

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];

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

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

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

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

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 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]

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 suc-

[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.

cess 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

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[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

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 (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

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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).

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 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 subcu-

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[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.

taneous 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

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

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, 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]

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

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; 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 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

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[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.

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 formula-

tion. *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 cites—Hoogwerf.[14] *Id.* Patent Owner bases this argument on what it contends is a

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[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.

[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).

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 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

[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"

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 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

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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).

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

[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.

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 1–20 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.

PETITIONER:

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APPENDIX D

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.

ORDER

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

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

January 28, 2020
Date

APPENDIX E

RELEVANT CONSTITUTIONAL AND STATUTORY PROVISIONS

The United States Constitution provides in relevant part as follows:

Article II, § 2, cl. 2

* * *

[The President] shall nominate, and by and with the Advice and Consent of the Senate, shall appoint Ambassadors, other public Ministers and Consuls, Judges of the supreme Court, and all other Officers of the United States, whose Appointments are not herein otherwise provided for, and which shall be established by Law: but the Congress may by Law vest the Appointment of such inferior Officers, as they think proper, in the President alone, in the Courts of Law, or in the Heads of Departments.

* * *

Title 35 of the United States Code provides in relevant part as follows:

§ 103. Conditions for patentability; non-obvious subject matter.

* * *

A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

* * *