Appeal Nos. 2019-1368, 2019-1369

IN THE UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

SANOFI-AVENTIS DEUTSCHLAND GMBH,

Appellant,

v.

MYLAN PHARMACEUTICALS INC.,

Appellee.

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

CORRECTED OPENING BRIEF FOR APPELLANT

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April 26, 2019

CERTIFICATE OF INTEREST

Counsel for Appellant, Sanofi-Aventis Deutschland GmbH, certifies the following (use "None" if applicable; use extra sheets if necessary):

1. Full name of Party represented by me:

Sanofi-Aventis Deutschland GmbH.

2. Name of Real Party in Interest (Please only include any Real Party in Interest NOT identified in Question 3) represented by me is:

Sanofi-Aventis Deutschland GmbH;

Sanofi-Aventis U.S. LLC; and

Sanofi Winthrop Industrie.

3. Parent corporations and publicly held companies that own 10% or more of stock in the party:

Sanofi.

4. The names of all law firms and the partners or associates that appeared for the Party or amicus now represented by me in the trial court or agency or are expected to appear in this court (and who have not or will not enter an appearance in this case) are:

None.

5. The title and number of any case known to counsel to be pending in this or any other court or agency that will directly affect or be directly affected by this court's

decision in the pending appeal. See Fed. Cir. R. 47.4(a)(5) and 14.5(b). (The parties should attach continuation pages as necessary).

Sanofi-Aventis Deutschland GmbH v. Mylan Pharmaceuticals Inc., No. 19-1369 (Fed. Cir.) (consolidated with the instant lead case); and

Sanofi-Aventis U.S. LLC, Sanofi-Aventis Deutschland GmbH, and Sanofi Winthrop Industrie v. Mylan GmbH, Biocon Ltd., Biocon Research LTD., Biocon SDN.BHD., and Biocon S.A., C.A. No. 17-cv-09105-SRC-CLW (D.N.J.)

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STATEMENT OF RELATED CASES

Appellant Sanofi-Aventis Deutschland GmbH ("Sanofi") and its undersigned counsel are unaware of any other appeal in or from this proceeding that was previously before this Court or any other appellate court. The two patents involved in this consolidated appeal, U.S. Patent Nos. 7,476,652 and 7,713,930, have also been asserted and are involved in a pending litigation before the U.S. District Court for the District of New Jersey styled *Sanofi-Aventis U.S. LLC, Sanofi-Aventis Deutschland GmbH, and Sanofi Winthrop Industrie v. Mylan GmbH, Biocon Ltd., Biocon Research LTD., Biocon SDN. BHD., and Biocon S.A.*, C.A. No. 17-cv-09105-SRC-CLW.

INTRODUCTION

Sanofi's insulin glargine formulation, commercialized under the tradename Lantus® and first launched in the United States in 2001, was a major breakthrough in diabetes therapy and has improved the lives of millions of patients. Unlike prior insulin therapies, which required patients to administer multiple daily injections to coincide with meals, glargine has a long-acting profile, enabling patients to control their blood glucose levels with a once-daily administration of the drug. Scientists designed glargine to achieve this result by altering the amino acid structure of naturally occurring human insulin. These molecular alterations resulted in a glargine therapeutic that has profoundly different properties and mechanisms of action than naturally occurring and synthetic insulins.

After the commercial launch of Lantus®, however, unexpected problems regarding turbidity (cloudiness) arose in a small, but still concerning, number of vials. This turbidity was surprising because there had been no prior disclosure of any turbidity problems with glargine and no recognition of why the turbidity occurred. After much analysis, Sanofi scientists both figured out the problem—unexpected aggregation of glargine molecules—and invented a solution, a glargine reformulation that is claimed in the two patents that are the subject of this appeal. This new formulation included certain nonionic surfactants, such as polysorbate and/or poloxamers, that had the unexpected benefit of stabilizing the glargine, reducing undesirable aggregation and solving the turbidity problems. The success of this reformulation was unexpected and

surprising. Unlike natural and synthetic insulins, glargine's mechanism of action depends on a certain amount of *desirable* aggregation to achieve its long-acting effects. The prior art, however, taught that adding nonionic surfactants could impede, or even prevent, the formation of the necessary aggregates for glargine to do its job. The two patents-in-suit claim this new formulation.

In the proceedings below, the Patent Trial and Appeal Board ("PTAB") held that Sanofi's claimed formulation would have been obvious and invalidated the patents. This conclusion rests on a number of legal errors, each of which independently warrants reversal. *First*, the PTAB abandoned the requirement that to demonstrate obviousness, there must be a showing that a person of ordinary skill in the art ("POSITA") would have both recognized the specific problem recognized by the inventors and been motivated to modify the prior art to solve it. The PTAB held instead that, "as a matter of law," the "prior art need *not* expressly articulate or suggest that insulin glargine had a tendency to aggregate"—the specific problem recognized and solved by the inventors here. Appx31, Appx83 (emphasis added). Rather, the PTAB held that Mylan could demonstrate obviousness by showing only that a POSITA "would have understood that aggregation *generally* was a concern in developing *insulin* formulations"—that is, aggregation problems with *different* prior art references, *different* active ingredients, and *different* formulations. *Id.* (emphasis added).

The PTAB's only support for adopting this erroneous standard was a misapplication of the Supreme Court's decision in *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S.

398 (2007). The PTAB understood *KSR* to hold that that obviousness may be established merely "if 'the improvement is [no] more than the predictable use of prior art elements [of the invention] according to their established functions.'" Appx31, Appx83 (quoting *KSR*, 550 U.S. at 417). But *KSR* held exactly to the contrary: an invention "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 (emphasis added). Instead, *KSR* emphasized that the test is "whether there was an *apparent reason* to combine the known elements in the fashion claimed by the patent at issue," including whether "there existed at the time of the invention a *known problem*" that the invention solves. *Id.* at 418, 420 (emphasis added).

Thus, obviousness cannot be found unless the prior art discloses the specific problem recognized by the inventors that would have motivated a POSITA to modify the prior art and solve the problem. Asking, as the PTAB did here, whether there would have been an aggregation problem with *insulins*—which is not the claimed invention—is not the law. Instead, under the correct legal standard, the claimed invention would not have been obvious because the *undisputed* record is clear that there is no prior art disclosure of a glargine aggregation problem. And the PTAB cannot make up for this absence of evidence by assuming that glargine shared the same aggregation properties as insulins or by relying on evidence that does not concern aggregation at all. There is no evidence in the record that a POSITA would have known about a *glargine* aggregation

problem based on prior art disclosures about *insulins*. Indeed, all record evidence is to the contrary.

Second, the PTAB further erred as a matter of law by impermissibly relying on the teachings of the specification of the challenged patents itself as a "roadmap" to find the invention obvious. That is impermissible hindsight. The undisputed record contains no prior art disclosure that glargine had a tendency to aggregate. The PTAB did not and could not identify any such prior art disclosure. So, the PTAB impermissibly relied on the teachings of the challenged patents themselves to conflate glargine with the entirely different body of prior art insulin molecules.

Third, the PTAB compounded the above legal errors by failing to identify prior art teachings showing that any such aggregation would have motivated a POSITA to modify the commercial, FDA-approved, stability-tested Lantus® formulation. Nor could the PTAB make that required showing because the prior art contains no such motivation. To the contrary, the undisputed record shows that none of the commercial insulin vial formulations on the market at the time of the invention contained a surfactant to address aggregation.

Fourth, the PTAB erred in disregarding the undisputed evidence showing that adding a surfactant to glargine would have been expected to disrupt glargine's unique mechanism of action that allows its long-acting profile. Unlike insulins, glargine depends on a certain amount of desirable aggregation to achieve its long-acting effect and the prior art taught that surfactants could prevent this aggregation from occurring.

Yet the PTAB erred in again conflating glargine with insulins, holding that a surfactant would have been successful in stabilizing glargine because it was successful in stabilizing insulins. That conclusion was irrational and backwards: the fact that surfactants could stabilize other insulins is precisely the reason why adding a surfactant to glargine would have been expected to disrupt its mechanism of action, which depends on desirable aggregation to work. The PTAB also erred in dismissing additional negative consequences of adding a surfactant to glargine, relying on evidence Mylan submitted at the very end of the PTAB proceedings while denying Sanofi a full and fair opportunity to respond with counter evidence.

Finally, the PTAB erred in discounting Sanofi's objective evidence of the invention's non-obviousness, including the commercial success of reformulated Lantus®. The PTAB found that Sanofi's so-called "blocking patents" on the glargine molecule itself diluted the import of the commercial success of reformulated Lantus®, a finding that rested on analyzing the performance of Lantus® in a market consisting only of glargine. But all parties agree that the economically relevant market is one that includes *all* long-acting insulins, including those that compete with glargine. Lantus® has been highly successful in that market, and Sanofi holds no blocking patents for non-glargine long-acting insulins. In addition, the PTAB ignored Sanofi's evidence showing that, but for its reformulation of Lantus® to address aggregation concerns, it would have lost significant sales and been subject to negative regulatory and consumer effects.

These legal errors require reversal, or, at the very least, that this Court vacate the Final Written Decisions and remand.

JURISDICTIONAL STATEMENT

Sanofi appeals from the PTAB's Final Written Decisions ("FWDs") in *Inter Partes* Review proceeding numbers IPR2017-01526 and IPR2017-01528, regarding all claims of U.S. Patent Nos. 7,476,652 and 7,713,930. Sanofi timely filed notices of appeal from the FWDs on January 4, 2019. This Court has jurisdiction under 35 U.S.C. §§ 141, 319, and 28 U.S.C. § 1295(a)(4)(A).

STATEMENT OF THE ISSUES

I. Whether the PTAB committed legal error in finding that a POSITA would have had a reason to modify the prior art because it:

(a) abandoned the legal requirement of a showing based on the prior art that a POSITA would have recognized the specific problem of glargine aggregation and been motivated to modify the prior art to solve it, and held instead that obviousness may be shown even when the prior art did not "expressly articulate" or even implicitly "suggest" that glargine had a tendency to aggregate, a misapplication of the Supreme Court's decision in *KSR*;

(b) relied on the teachings of the challenged patents-in-suit, rather than the prior art, to purport to show the existence of a known problem of glargine aggregation; and

(c) failed to identify any teaching in the prior art to meet the legal requirement of showing that a POSITA would have known of a problem with glargine aggregation and

been sufficiently motivated by any such concerns to solve it by modifying the FDA-approved, stability-tested Lantus® formulation.

II. Whether the PTAB erred in finding that a POSITA would have reasonably expected success in adding a surfactant to the prior Lantus® formulation because:

(a) the prior art disclosed that surfactants would have been expected to interfere with glargine's unique mechanism of action and thus would have prevented glargine's long-acting benefits; and

(b) the PTAB relied on contested evidence Mylan introduced at the very end of the proceedings while denying Sanofi a full and fair opportunity to respond to that evidence with counter evidence.

III. Whether the PTAB erred in discounting Sanofi's evidence of objective indicia of non-obviousness by:

(a) improperly limiting the relevant market to only glargine, rather than the broader market for all long-acting insulins in which Sanofi does not hold blocking patents for non-glargine long-acting insulins; and

(b) failing to consider the evidence that but for the glargine reformulation invention, Lantus® sales would have suffered.

STATEMENT OF THE CASE

I. Factual Background

A. Sanofi Develops Glargine, A Long-Acting Insulin Analog

Insulin is a naturally occurring molecule comprising a string of amino acids that acts in the body to reduce blood glucose levels. Appx6489, Appx14247-14248. Individuals with an impaired ability to produce insulin can have a condition known as diabetes. Appx15031-15033. The longstanding standard therapeutic treatment for diabetes has been injections of insulins derived from both natural and synthetic sources. Appx6490, Appx14260-14261.

Naturally occurring and prior synthetic insulins have a relatively short duration of action requiring patients to inject themselves multiple times a day to control blood glucose levels. Appx6508, Appx15034-15035, Appx14263-14264. Because each injection of regular insulin can cause a spike in a patient's blood insulin levels, patients must coordinate their injections with meals to prevent dangerously low blood glucose levels. Appx15184-15185, Appx6690. The timing and frequency of these injections were enormously disruptive to patients' lives. *Id.* Thus, among the consistent goals of insulin therapy was developing treatments that reduce the frequency of insulin administration and flattening the post-administration peak of blood insulin levels.

Sanofi's invention of glargine, an insulin *analog*, achieved that goal. In developing glargine, Sanofi scientists altered the human insulin molecule at the molecular, amino acid level, thereby fundamentally changing the characteristics of insulin to give patients

a steady release of glargine that allowed for a life-changing therapeutic with only a single daily administration. Among other things, glargine has a different primary structure than human insulin, with 53 amino acids (as compared to 51 amino acids in human insulin), and substituting one amino acid for another one at a key position. Appx6509, Appx14261-14262. Glargine interacts with the same receptors in the body as insulin, thereby producing similar glucose-lowering effects in the bloodstream. Appx14262, Appx14441-14442. But the modifications to glargine's primary structure give it vastly different properties than regular insulin. *Id.*

Specifically, glargine has an elevated isoelectric point—the pH at which it is least soluble and therefore precipitates (forms) as a solid—at a neutral pH of 7. Appx6509, Appx14263. In contrast, naturally occurring and prior synthetic insulins have a lower isoelectric point—for example, acidic pH of about 5.4 for human insulin. *Id.* This means that, unlike insulins, glargine is soluble—*i.e.*, remains clear and stays in solution—in acidic environments. Appx6540, Appx6742. As Mylan itself observed, "[i]nsulin glargine's mechanism of action centers on its altered isoelectric point, resulting in the therapeutic preparation being more soluble in acidic environment[s]; by contrast, native human insulin formulations are more soluble at neutral pH." Appx362, Appx6509. Glargine's elevated isoelectric point is critical to its mechanism of action. When glargine is injected into the neutral environment of a patient's tissue, it precipitates out of its solution and forms a solid storage reservoir in the patient's body, allowing a slower and

more stable release of the drug. Appx362-363, Appx6509, Appx105 at 2:58-61, Appx6690.

In addition, although the physiologically active form of insulins is a single-molecule unit known as a monomer (Appx6491-6492, Appx14249-14253), glargine, both in its solution and when it precipitates upon injection, forms six-unit aggregate structures known as hexamers. Appx6509, Appx14242, Appx14262-63. This "native"—or desirable—aggregation into hexamers is also key to glargine's unique long-acting mechanism of action. The glargine hexamers slowly dissociate over time into monomers, where they are absorbed into the bloodstream to provide therapeutic effect. Mylan's expert explained that this process, too, is critical to glargine's long-acting profile: "[w]hen insulin glargine is administered . . . it precipitates . . . to a hexameric structure" and this "slows the dissociation of [glargine] into monomers, which are the physiologically active form of insulin." Appx6509. Human insulin, by contrast, rapidly breaks apart into monomers upon injection. Appx6491-6492.

The table below summarizes the key differences between human insulin in a typical pharmaceutical formulation, and glargine in Lantus®, upon administration:

<table>
<tr><th>Human Insulin</th><th>Glargine</th></tr>
<tr><td>51 amino acids divided into an A chain with 21 and B chain with 30</td><td>53 amino acids divided into an A chain with 21 and a B chain with 32.
In addition, glycine substituted for asparagine at the end of the A chain</td></tr>
<tr><td>Stored at approximately pH 7</td><td>Stored at approximately pH 4</td></tr>
<tr><td>Mixture of dimers and hexamers in solution</td><td>Mostly hexameric in solution</td></tr>
<tr><td colspan="2">Injected subcutaneously using a syringe</td></tr>
<tr><td rowspan="2">Rapidly breaks apart into monomers</td><td>Immediately precipitates and forms a solid depot in the subcutaneous tissue</td></tr>
<tr><td>Subcutaneous depot slowly breaks apart into monomers over the course of 24 hours</td></tr>
<tr><td colspan="2">Monomers enter the bloodstream and provide therapeutic effect</td></tr>
</table>

B. Sanofi Identifies And Solves An Unexpected Aggregation Problem With Glargine

Sanofi's commercialized glargine product, marketed under the tradename Lantus®, successfully passed rigorous stability testing in connection with earning regulatory approval in the United States and Europe. Appx14275, Appx14284. Lantus® launched in Europe in 2000 and in the United States in 2001. Appx15125. Shortly after its U.S. launch, however, Sanofi began to receive confidential reports that a small, but unacceptable, number of Lantus® vials were turning turbid, or cloudy—approximately 1 in 10,000 vials. Appx14319, Appx14498, Appx15125-15126.

This was unexpected for a number of reasons. First, the prior Lantus® formulation was dispensed in vials and, as the prior art confirms, vial formulations of prior insulins were "uniformly stable" and required no further stabilization.

Appx14260-14261 (citing Appx6732, Appx6802 and Appx14640), Appx14307-14308. In fact, none of the commercial insulin formulations sold in vials at the time of the invention contained a surfactant. Appx14307-14308 (citing Appx14937 and Appx14406-14407). Moreover, because Lantus® had successfully passed regulatory approval in the United States and Europe that included rigorous demonstrations of stability, a POSITA would not have expected any significant instability in the formulation. Appx14284.

Second, as Mylan's expert admitted, Lantus® contained zinc and m-cresol (a phenolic molecule), both of which are stabilizing agents that were known to promote the formation of stable hexamers. Appx6493, Appx6510 ("structural analysis of insulin glargine showed that it interacted with zinc and phenolic molecules, which promoted the formation of stable hexamers in solution"); Appx14284-14286 (citing Appx14442-14443, Appx14628, Appx14940, and Appx6758).

Third, the prior art explained that the glargine molecule, because of its altered chemical structure, was known to bind to *more* m-cresol than other insulins, which would have been expected to *increase* the stabilizing effect of m-cresol in Lantus® as compared to prior insulin formulations. *See* Appx14284-14285 (citing Appx14628, Appx6742, Appx6753), Appx6755-6757.

Fourth, unlike some prior insulins that were thought to be more prone to instability in acidic solution, glargine's altered isoelectric point made it uniquely "soluble

and stable" in an acidic solution such as Lantus®, which Mylan's expert admitted. Appx6540, Appx6567, Appx6589-6590, Appx6608, Appx6624-6625, Appx6639.

To better understand this unexpected turbidity, Sanofi assembled a cross-functional team that conducted extensive root-cause analysis of the Lantus® product. This team examined shipping and storage, the types of needles, vials and stoppers used, the gas filled in the vials, the steps in the manufacturing process, and the components of the product formulation. Appx15098-15102, Appx15104-15105, Appx15125-15132, Appx15134.

Eventually, Sanofi discovered that nonionic surfactants such as polysorbate and poloxamers stabilized the Lantus® formulation while not disrupting glargine's unique mechanism of action. This, too, was unexpected because it was thought that surfactants would have been expected to interfere with glargine's mechanism of action, which depends on a certain amount of "native"—*i.e.*, desirable—aggregation to be effective. Specifically, as noted above, when glargine is injected into subcutaneous tissue, it precipitates into aggregated hexamer forms. Appx105 at 2:58-61, Appx6509, Appx6690, Appx14262-14263. Mylan's expert acknowledged that the slow dissociation of the hexamer form into physiologically-active monomers provides glargine's long-acting, 24-hour duration of therapy. Appx6509 (Glargine's "hexameric structure … slows the dissociation of the hexamer into monomers…. These properties of insulin glargine result in delayed absorption at neutral pH, making it suitable for use as a long-acting insulin and once-daily administration."); *see also* Appx14309 (citing Appx14442-

14443). But, as Mylan's own expert also admitted, nonionic surfactants were thought to disrupt the native formation of these hexamer forms, and thus would impede glargine's ability to achieve a long-acting effect. Appx14376-14377 (discussing Appx6971).

Sanofi was granted two U.S. patents capturing its discovery of certain aggregation tendencies in glargine and the unexpected stabilizing effects of polysorbate and other claimed molecules on acidic formulations of insulin glargine.[1] The specification describes stability testing performed on acidic glargine formulations with added surfactant, reporting an increase in formulation stability and a delay in the formation of visible cloudiness. Appx106-107 at 3:41-45, 5:46-57.

Following the invention, the Lantus® *vial* product was reformulated to embody the patented invention and later approved by the FDA. Appx15035-15036. Reformulated Lantus® has enjoyed tremendous commercial success, with U.S. sales growing from $1.1 billion at the product's introduction to approximately $2.6 billion in 2017. Appx15040-15041, Appx15074. Since June 2006, sales of reformulated Lantus® have accounted for approximately 33% of all sales of long-acting injectable insulin and/or insulin analog therapies. Appx15041-15042. The reformulation was critical to the success of the Lantus® product because it enabled Sanofi to avert potential regulatory action and negative reputational and sales impacts that might have occurred

[1] The two patents-in-suit share a common specification. For simplicity, this brief cites to the specification of the '652 patent.

had Sanofi not remedied the unexpected aggregation problem. Appx14319-14322, Appx15045-15047.

II. Proceedings Below

A. The Alleged Prior Art and Grounds of Invalidity

On June 5, 2017, Mylan petitioned for *inter partes* review of the '652 and '930 patents, asserting that they were invalid as obvious over a combination of (a) either one of two primary references—Lantus Label[2] and Owens[3]—with (b) any one of three secondary references—Lougheed,[4] Insuman Infusat[5] and Grau.[6] Appx361, Appx436. Lantus Label and Owens disclose the original commercially available, FDA-approved acidic glargine formulation without a surfactant. Neither primary reference discloses that glargine has a tendency to aggregate in its acidic solution. To the contrary, both references explain that glargine in Lantus® is soluble and clear in its acidic storage environment. Appx6690 (noting that glargine "[a]t pH 4 … is completely soluble"); Appx 6697 (noting that glargine is injected "as a clear acidic solution" at pH 4).

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[2] 2001 Physicians' Desk Reference Entry for LANTUS. Appx6684-6694.

[3] D.R. Owens et al., *Pharmacokinetics of 125 I-Labeled Insulin Glargine (HOE 901) in Healthy Men*, Diabetes Care 23:813-19 (June 2000). Appx6697-6703.

[4] W.D. Lougheed et al., "Physical Stability of Insulin Formulations," *Diabetes* 32:424-32 (May 1983). Appx6704-6712.

[5] 2000 FASS Entry for INSUMAN INFUSAT (January 2000). Appx6719-6726.

[6] U. Grau and C.D. Saudek, "Stable Insulin Preparation for Implanted Insulin Pumps," *Diabetes* 36:1453-59 (December 1987). Appx6727-6733.

Nor do any of Mylan's secondary references disclose a glargine aggregation tendency, or even discuss glargine at all. Indeed, to the extent these references discuss aggregation among *any* categories of insulins, they describe aggregation as an issue only in insulin pumps. And even then, these references describe insulin aggregation, not as it exists in any commercialized vial product, but that has been provoked under extreme laboratory conditions. These conditions were specifically designed to induce aggregation so that it can be studied—including continuous rapid shaking for weeks on end at an elevated temperature—not to replicate normal storage and use conditions.

Specifically, Mylan's secondary reference Lougheed describes testing conducted on solutions of recrystallized porcine insulin—not glargine—under a variety of non-standard conditions that were designed to cause aggregation. Appx6710. To the extent that Lougheed reported aggregation to be an issue of insulins, it did so solely in the context of "open-loop systems … for the continuous infusion of insulin," *i.e.*, in pumps. Appx6704, Appx14396-14398 (Dr. Yalkowsky confirms that Lougheed does not disclose that aggregation was a problem outside of pumps).

Secondary reference Insuman Infusat is a prior pump formulation of insulin available only in Europe that contained a poloxamer. This is the only known commercial formulation of prior insulin (*not* glargine) that contained a surfactant, and was for use *only* in pumps. Appx14281.

Secondary reference Grau discloses a "semi-synthetic human insulin" (*not* glargine) at neutral pH, that was "specifically formulated for implanted insulin pumps."

Appx6727. Grau notes that even for prior insulins, formulations for subcutaneous injection (*i.e.*, vial formulations) are "uniformly stable and highly purified," and in contrast only "insulin for implantable infusion pumps requires further steps to ensure stability." Appx6732.

Mylan's Petitions also rely heavily on references by Brange, which (like Grau) confirms that insulin formulations in vials were considered stable, and that "[d]uring the first 60 years of insulin therapy, fibrillation-related stability problems during normal handling, storage, or use of insulin preparations were *rarely* encountered." Appx6801 (emphasis added). It was only when pumps were introduced that it "became evident that commercial insulin formulations were not sufficiently stable for long-term use in infusion pumps." *Id.* (emphasis added). Brange also explains that even among prior insulins, different insulins (with different amino acid sequences) have different degrees of susceptibility to aggregation under extreme conditions. Appx6797.

B. Procedural History and the PTAB's Decision

After Mylan filed its Petitions, and Sanofi filed its Preliminary Patent Owner Responses, the PTAB initiated *inter partes* review of the patents on December 13, 2017. In its Patent Owner's Responses, Sanofi argued, *inter alia*, that Mylan's expert had no support for his opinion that surfactants such as polysorbates and poloxamers had "long been used to stabilize commercially available and regulatory agency-approved insulins." Appx1340-1341, Appx6475-6476.

In its Petitioner's Replies, for the first time, Mylan introduced a brand-new expert who filed an 88-page report and cited previously unidentified protein formulations that allegedly included a surfactant. *See* Appx12283-12290. Sanofi asked the PTAB to either strike this belatedly submitted expert report and evidence or, in the alternative, allow Sanofi to have the opportunity to respond with evidence to controvert Mylan's purported showing. Appx2414-2415, Appx2417-2418, Appx15270-15272, Appx15274, Appx15288-15289. The PTAB denied Sanofi's request to exclude Mylan's new evidence and denied Sanofi's alternative request to respond with additional rebuttal evidence of its own. Appx10, Appx59, Appx15304-15306. Instead, the PTAB permitted Sanofi to file a *three-page* lawyer response to address the new evidence. Appx15304-15306. Sanofi had no opportunity to introduce any counter evidence. *Id.*

On December 12, 2018, the PTAB issued its Final Written Decisions finding the patents invalid as obvious. Appx1-101. First, with respect to the reason to modify the prior art, the PTAB "disagree[d]" that "to meet its burden as a matter of law, Petitioner must provide prior art evidence that insulin glargine had a tendency to aggregate." Appx31, Appx83. Instead, the PTAB found it was sufficient "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." *Id.* To support that conclusion, the PTAB relied on an out-of-context snippet from the Supreme Court's decision in *KSR*, writing that "'a patent claiming the combination of elements of prior art' may be shown to be obvious if 'the improvement is [no] more than the

predicable use of prior art elements according to their established functions.'" Appx31, Appx83 (quoting *KSR*, 550 U.S. at 516).

The PTAB cited passages in the patents' specification discussing aggregation in non-glargine insulins, and noted that "[t]he '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." Appx32, Appx83.[7] The PTAB thus found that a "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." Appx32, Appx83-84. As an example, the PTAB cited bovine, porcine, and human insulin (which have different amino acids), and concluded that "they all were known to aggregate," but noted that they did so "albeit to different degrees." Appx32, Appx84.

The PTAB also noted that "[t]he '652 patent also does not suggest that aggregation due to hydrophobic surfaces occurred only in pumps." Appx32, Appx84. As evidence, however, the PTAB cited a variety of references that, as described below (*see infra* pp. 41–43), concerned aggregation only in pumps. Appx32-33, Appx84.

Additionally, the PTAB held that "Petitioner demonstrates, by a preponderance of the evidence, a reasonable probability of success." Appx37, Appx89. As part of this

[7] The PTAB made the identical findings regarding the '930 patent, which shares the same specification. *See* Appx83. References to the PTAB's findings about the '652 patent thus apply equally to the '930 patent.

analysis, the PTAB did not provide a reasoned analysis of Sanofi's evidence that "introducing a surfactant would interfere with insulin glargine's mechanism of action or efficacy." Appx31, Appx82. Instead, the PTAB summarily held that "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." Appx39, Appx90. In reaching that conclusion, the PTAB relied on new evidence Mylan submitted at the very end of the proceedings while denying Sanofi a full and fair opportunity to respond with counter evidence of its own. Appx38 and Appx89 (citing Appx12283-12290), Appx40 and Appx 91 (citing Appx12907, Appx12911). Finally, the PTAB rejected Patent Owner's evidence of commercial success, finding it "weak in light of Patent Owner's blocking patents covering the insulin glargine compound." Appx43, Appx95.

On January 4, 2019, Sanofi timely noticed its appeals from the FWDs. Appx3301-3306, Appx3374-3379.

SUMMARY OF ARGUMENT

I.A. The PTAB committed legal error in holding that a POSITA would have been motivated to modify the prior art. Central to the obviousness analysis is whether a POSITA "would have recognized the ... problem recognized by the inventor." *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377–78 (Fed. Cir. 2012). The PTAB abandoned this threshold requirement. It held, "as a matter of law," that "[t]he prior art need *not* expressly articulate or suggest that insulin glargine had a tendency to aggregate"—the

specific problem recognized and solved by the inventors here. Appx31, Appx 83 (emphasis added). Instead, the PTAB held that Mylan could sustain its burden simply by showing that a POSITA "would have understood that aggregation *generally* was a concern in developing *insulin* formulations." *Id.* (emphasis added). This was a clear departure from this Court's precedent and *KSR*. Rather than asking whether a POSITA would have had a reason to modify *glargine*, the PTAB asked whether there was motivation to modify *different insulin* formulations in the prior art that behave in *opposite* ways from glargine.

The PTAB supported its adoption of an erroneous legal standard by misapplying *KSR*. Citing *KSR*, the PTAB held that obviousness could be shown "if 'the improvement is [no] more than the predictable use of prior art elements [of the invention] according to their established function.'" Appx31, Appx83 (citing *KSR*, 550 U.S. at 417). But *KSR* held the opposite: an invention "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 (emphasis added). Indeed, *KSR* reinforced the legal requirement that obviousness requires a showing that "there was an apparent *reason* to combine the known elements [of the invention] in the fashion claimed by the patent at issue," including whether "there existed at the time of the invention a *known problem*" that the invention solves *Id.* at 418, 420 (emphasis added). The PTAB, however, jettisoned this requirement by asking whether there was motivation to modify *different* prior art elements than are claimed in the invention.

This error was critical because under the correct legal standard, the claimed inventions would not have been obvious. The *undisputed* record shows that nothing in the prior art disclosed aggregation concern with *glargine* and thus there was no motivation for a POSITA to modify the prior art Lantus® formulation. Nor could the PTAB make up for this lack of evidence by simply assuming that glargine shared the same aggregation tendencies as other insulins or relying on references that do not discuss aggregation at all. In fact, the record—including admissions by Mylan's own expert—showed the opposite: many of glargine's unique characteristics, including those tied to its essential mechanism of action, made glargine more stable and less prone to aggregation than other insulins. Accordingly, there was no legal or evidentiary basis for the PTAB to conclude that Mylan could satisfy its burden to demonstrate obviousness by pointing to aggregation concerns with *insulins* generally rather than the specific problem of *glargine* aggregation. The link between glargine and prior insulins, as it relates to aggregation, is simply missing in the prior art.

B. The PTAB doubled-down on its legal errors when it relied on the specification of the challenged patents itself to provide that missing link. This Court's cases could not be clearer that the PTAB commits a classic hindsight error when it "looked to knowledge taught by the inventor … and then uses 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). The PTAB observed that the specification recited that "insulins" had a "known tendency to aggregate," and reasoned that this

understanding must apply to glargine, too, because the specification "does not exclude insulin glargine when describing the tendency for insulins to aggregate." Appx32, Appx83. But any insight that glargine behaved like other insulins when it came to aggregation was the *inventors*' contribution—not a description of the prior art. It is undisputed—even Mylan's expert agreed—that the prior art did not link glargine specifically to any aggregation problems that existed in other insulins. The PTAB legally erred in treating the patents' teachings as prior art.

C. The PTAB committed legal error by deviating from this Court's precedent in another important respect: even assuming (*arguendo*) that the PTAB correctly found that a POSITA would have identified an aggregation "concern" with glargine, it never made a reasoned finding—and there was no substantial evidence to find—that a POSITA would have been motivated to modify glargine to address it. This was a legally deficient gap in its analysis. Although all proteins can aggregate, not all aggregation demands a solution. Indeed, at the time of Sanofi's invention, *none* of the commercialized insulins sold in vials (like the Lantus® formulation at issue here) had a surfactant added for stabilization. The PTAB failed to apply the law requiring a showing that glargine's supposedly known aggregation tendency was so concerning that it justified deviating from how other insulins had been handled for decades.

II. The PTAB also erred in holding that a POSITA reasonably would have expected success in adding a surfactant to glargine. The uncontested evidence shows that a POSITA reasonably would have thought that a surfactant would interfere with

glargine's unique mechanism of action because glargine depends on a certain amount of desirable aggregation to deliver its long-acting pharmaceutical effects. In the *one sentence* it wrote on this issue, the PTAB found Sanofi's argument "unpersuasive" because surfactants have had "success stabilizing other insulins and proteins." Appx39, Appx90. But the whole point is that *glargine's* unique method of action, which unlike other insulins depends on desirable aggregation, could be disrupted by the addition of a surfactant that prevents aggregation. In other words, the fact that a surfactant has worked to moderate aggregation in other insulins and proteins is *exactly* why it was thought to inhibit glargine's mechanism of action.

III. Finally, the PTAB erred in dismissing Sanofi's evidence of commercial success as objective indicia of non-obviousness. The PTAB relied on Sanofi's so-called blocking patents on the glargine molecule itself to find the evidence of commercial success "weak," a finding that rested on analyzing the performance of Lantus® in a market consisting only of *glargine*. Appx43, Appx95. But that analysis was misplaced. The economically relevant market to analyze is that for all long-acting insulins, in which reformulated Lantus® has been highly successful, and Sanofi holds no alleged blocking patents on non-glargine long-acting insulins. In addition, the PTAB ignored Sanofi's argument that a nexus has been established between the success of Lantus® and the reformulation, given that but for addressing aggregation issues, Lantus® could have earned far lower sales and faced certain negative regulatory and reputational effects.

STANDARD OF REVIEW

"Obviousness is a question of law based on underlying factual findings: (1) the scope and content of the prior art; (2) the differences between the claims and the prior art; (3) the level of ordinary skill in the art; and (4) objective indicia of nonobviousness" and must include a showing that "a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *InTouch Techs., Inc. v. VGO Commc'ns, Inc.*, 751 F.3d 1327, 1347 (Fed. Cir. 2014). This Court reviews the PTAB's determination of obviousness and its "compliance with the governing legal standards" *de novo*, while the PTAB's factual findings are reviewed for substantial evidence. *Id.*; 5 U.S.C. §706(2)(E). "On the factual components of the inquiry, we ask whether a reasonable fact finder could have arrived at the agency's decision, which requires examination of the record as a whole, taking into account evidence that both justifies and detracts from an agency's decision." *Pers. Web Techs., LLC v. Apple, Inc.*, 848 F.3d 987, 991 (Fed. Cir. 2017) (citations and alterations omitted).

ARGUMENT

I. The PTAB Committed Legal Error By Misapplying *KSR* And Ignoring The Legal Requirement That The Prior Art Disclose The Problem Recognized By The Inventors And A Motivation To Solve It

This Court has held that the obviousness analysis must focus not on "what a skilled artisan would have been *able* to do," but on "what a skilled artisan would have been *motivated* to do at the time of the invention." *Polaris Indus., Inc. v. Arctic Cat, Inc.*, 882

F.3d 1056, 1068 (Fed. Cir. 2018). The PTAB defied this key legal principle in three ways.

First, the PTAB circumvented *KSR* and the law that obviousness requires a showing in the prior art that a POSITA would have recognized and been motivated to solve the problem solved by the inventors—here, a problem of glargine aggregation. The PTAB held instead that it sufficed to show that a POSITA merely would have generally had a concern about *insulin* aggregation. This is demonstrably the wrong standard because it asks not whether a POSITA would have had a reason to modify the specific invention claimed, but whether a POSITA would have had a reason to modify different technology based on different prior art. Here, the PTAB could not have found the invention obvious because it is undisputed that the prior art does not disclose an aggregation concern about glargine. Nor can the PTAB make up for this lack of evidence by simply assuming that glargine shares the same aggregation properties as insulins or by relying on art that does not mention aggregation at all. In the end, nothing in the prior art links glargine aggregation to aggregation problems in other insulins. *See infra* Section I.A.

Second, in the absence of any prior art disclosure of a glargine aggregation problem, the PTAB committed a separate legal error by relying on the specification of the challenged patents to try to fill that gap. The teachings of the patent are not the teachings of the prior art, and the PTAB legally erred in treating the specification as such. *See infra* Section I.B.

Third, the PTAB did not find—and there was no evidence in the record to find—that any aggregation concern with glargine would have been sufficient to motivate a POSITA to modify the FDA-approved, stability tested Lantus® formulation. To the contrary, if anything, the record showed that a POSITA would not have expected a glargine aggregation problem, and would not have had a reason to modify the original Lantus® formulation to address it. *See infra* Section I.C.

Each of these errors independently warrants reversal.

A. The PTAB Committed Legal Error Because It Bypassed The Law And Held Instead That The Prior Art Did Not Need To "Articulate" Or Even Implicitly "Suggest" A Glargine Aggregation Problem

1. The PTAB Disavowed The Well-Established Legal Standard And Misapplied *KSR*

Central to this Court's obviousness analysis is whether a POSITA "would have been motivated to combine the prior art to achieve the claimed invention." *In re NuVasive, Inc.*, 842 F.3d 1376, 1381 (Fed. Cir. 2016) (citation omitted); *see also InTouch Techs.*, 751 F.3d at 1352 (warning against "succumb[ing] to hindsight bias" by focusing on whether "one of ordinary skill in the art *could* combine these references, not that they *would* have been motivated to do so."); *Polaris Indus.*, 882 F.3d at 1068 (same). As the Supreme Court has explained, the key task is "to determine whether there was an apparent reason to combine the known elements [of the invention] in the fashion claimed by the patent in issue." *KSR*, 550 U.S. at 418.

Because "an invention can often be the recognition of a problem itself," *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1353 (Fed. Cir. 2013), an essential component of the motivation-to-modify analysis is whether the problem solved by the invention was known in the prior art. A patent can be proved obvious "by noting that there existed at the time of the invention a *known problem* for which there was an obvious solution encompassed by the patent's claims." *KSR*, 550 U.S. at 420 (emphasis added). But "[w]ithout the knowledge of the problem, one of ordinary skill in the art would not have been motivated to modify" the prior art. *Novartis Pharm. Corp. v. Watson Labs., Inc.*, 611 F. App'x 988, 996 (Fed. Cir. 2015). That is, "[t]he ordinary artisan would first have needed to recognize the problem… . Only after recognizing the existence of the problem would an artisan then turn to the prior art and attempt to develop" the claimed invention. *Leo Pharm.,* 726 F.3d at 1354. Thus, to avoid a "prohibited reliance on hindsight," this Court has insisted that a petitioner must prove—and the PTAB must find—that a POSITA "would have recognized the . . . problem recognized by the inventors." *Mintz*, 679 F.3d at 1377–78.

Applying these core principles here, the essential threshold question is whether a POSITA "would have recognized" the problem of glargine aggregation and would have been motivated to modify the FDA-approved Lantus® glargine formulation to solve it. But the PTAB never asked that question. Instead, the PTAB held, "*as a matter of law*," that "the prior art need *not* expressly articulate or suggest that insulin glargine had a tendency to aggregate." Appx31, Appx83 (emphasis added); *see also id.* (Mylan did

not need to "provide prior art evidence that insulin glargine had a tendency to aggregate."). Instead, the PTAB held that the claimed invention here would be obvious if Mylan showed only that "aggregation *generally* was a concern in developing *insulin* formulations"—that is, aggregation problems with *different* prior art references, *different* active ingredients, and *different* formulations. *Id.* (emphasis added). By holding that the prior art need not even implicitly "*suggest*" the existence of this problem, the PTAB erroneously eviscerated this core standard and its protection against hindsight bias in the obviousness analysis. *See In re Sang Su Lee*, 227 F.3d 1338, 1344 (Fed. Cir. 2002) (rejecting the Board's conclusion that there is no "need for 'any specific hint or suggestion in a particular reference' to support the combination of" prior art elements).

The PTAB's only explanation for adopting a different and incorrect legal standard was a quotation from a single sentence from *KSR*. *See* Appx31, Appx83. The PTAB held, quoting *KSR*, that an invention is "obvious if 'the improvement is [no] more than the predictable use of prior art elements according to their established functions.'" *Id.* (quoting *KSR*, 550 U.S. at 417) (alteration in original). But *KSR* in fact held exactly the opposite: an invention "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 (emphasis added). Instead, KSR reinforced the core principle requiring knowledge of the problem in the prior art. *KSR* reiterated that the pertinent test is "whether there was an apparent *reason* to combine the known elements in the fashion claimed by the patent at issue." *Id.* at 418 (emphasis added). Under this analysis, an invention may be

obvious if "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 (emphasis added). Analyzing, as the PTAB did, whether the prior art disclosed a problem involving *different* elements from those claimed by the patent does not pass muster.

Indeed, this Court has consistently understood *KSR* in exactly this way—to reinforce the requirement of identifying a *reason* to modify the specific prior art. *See, e.g.*, *InTouch Techs.*, 751 F.3d at 1351 (citing *KSR* for the proposition that a "reason for combining disparate prior art references is a critical component of an obviousness analysis"); *NuVasive*, 842 F.3d at 1381 ("'It can be important to identify a reason that would have prompted a [PHOSITA] to combine the elements in the way the claimed new invention does.'") (quoting *KSR*, 550 U.S. at 418) (alterations omitted); *Pers. Web Techs.*, 848 F.3d at 991–92 (same). In fact, this Court has previously explained that "[t]he Supreme Court's passage [in *KSR*] does *not* establish that it suffices for obviousness that a variation of the prior art would predictably work." *Belden, Inc. v. Berk-Tek, LLC*, 805 F.3d 1064, 1075 (Fed. Cir. 2015). Rather, the core consideration arising from *KSR* is whether a POSITA would have had a reason "to pursue the variation." *Id.*

It is unsurprising, then, that Mylan recognized as much when framing its burden in the Petitions. There, Mylan explained that it had to show that a "PHOSITA would especially have had [a] *reason* because *insulin glargine* was likely prone to aggregation." Appx384, Appx457 (emphasis added). Asking, as the PTAB erroneously did, whether a POSITA would have identified a problem with, and thus had a motivation to modify,

a different product (or even all insulins generally) does not answer that question. Instead, it conflates demonstrable differences between the molecules.

In sum, the PTAB's decision to bypass the core requirement of showing a known problem with glargine and a motivation to solve it was a legal error requiring reversal. *See Sang Su Lee*, 277 F.3d at 1344 ("Omission of a relevant factor required by precedent is both legal error and arbitrary agency action.").

2. The Undisputed Record Shows That The Prior Art Did Not Disclose A Glargine Aggregation Problem As The Correct Legal Standard Requires

Under the correct legal standard, the claimed invention would not have been obvious. The record contains *no* prior art evidence that *glargine* had a tendency to aggregate. Specifically, Mylan's primary references—Lantus Label and Owens—both disclosed the *opposite*, teaching that glargine is "completely soluble" in its solution (Appx6690) and that glargine is injected "as a clear acidic solution." Appx6697.[8] To the extent that other prior art cited by the PTAB discussed aggregation at all, as admitted by Mylan's expert, it was limited to the physical instability of human, animal and other

[8] Mylan argued below that the Lantus Label disclosed an aggregation problem with glargine because it warned patients that Lantus "must only be used if the solution is clear and colorless with no particles visible." Appx374-375. But not even the PTAB relied on this statement as prior art evidence disclosing the aggregation problem that reformulated glargine solved. This Court may consider only the evidence that the PTAB itself relied on. *See DSS Tech. Mgm't, Inc. v. Apple Inc.*, 885 F.3d 1367, 1376 n.4 (Fed. Cir. 2018) ("Under the *Chenery* doctrine, we decline Apple's invitation to consider evidence that the Board did not cite in its decision.") (citing *S.E.C. v. Chenery Corp.*, 332 U.S. 194, 196 (1947)).

insulins—different molecules, with different structures and different properties from glargine.[9]

The PTAB erroneously attempted to make up for this lack of prior art evidence by (1) conflating glargine with other insulins without any evidentiary foundation to show that they shared similar properties; and (2) citing references that do not discuss aggregation at all. Both of these efforts fail. To begin, the "factual inquiry whether to combine references must be *thorough and searching* and the need for *specificity* pervades [this Court's] authority on the PTAB's motivation to combine." *NuVasive*, 842 F.3d at 1381–82 (emphasis added); *see also Arendi S.A.R.L. v. Apple, Inc.*, 832 F.3d 1355, 1361, 1362 (Fed. Cir. 2016) (PTAB's assumptions about the prior art "cannot be used as wholesale substitute for reasoned analysis and evidentiary support.").

With respect to (1), the PTAB assumed that because glargine is an "insulin" it behaves like other "insulins," notwithstanding the differences between glargine and insulins. But the PTAB cannot merely assume that because the prior art purportedly disclosed that other forms of insulin can aggregate (albeit under extreme conditions), glargine must aggregate, too. Rather, Mylan had the burden of *proving*—with evidence—

[9] For example, Lougheed described properties of "recrystallized porcine insulin," Appx6704-6712, Brange's studies concerned human and animal insulins, Appx6760-6795, and Thurow addressed effects relating to "bovine, porcine and human insulin." Appx6908. And Mylan's own expert admitted that nothing in the prior art disclosed aggregation concerns specifically with glargine: he could not "say definitively that insulin glargine is covered" by prior art concerning insulin aggregation. Appx14387-14388.

that glargine shares the aggregation tendencies of other insulins despite their differences. *See, e.g.*, *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1378 (Fed. Cir. 2016) ("Neither the Board nor the petitioner explained why borrowing the rationale for combining one set of references equally applies to the second set of references, which was particularly necessary here where the two primary references plainly operate in different manners. This constituted an improper shifting of the burden to Magnum, the patentee, to prove that the claimed invention would not have been obvious."). And, just like nothing in the record before the PTAB showed aggregation concerns specifically with glargine, nothing in the record shows that glargine shared the same pertinent characteristics as other insulins.

If anything, the prior art showed that the Lantus® glargine formulation had specific properties that would have led a POSITA to believe that glargine was *less likely* to aggregate than other insulins. Above all, because Lantus® was FDA-approved, and thus had undergone rigorous stability testing, a POSITA would not have expected any instability in the formulation, absent some express indication of a problem in the prior art. Appx14284. There was none. Moreover, as Mylan's own expert agreed, modifications to glargine's structure "allow insulin glargine to be soluble and stable in an acidic solution." Appx6540; *see also* Appx14284-14286; *supra* pp. 12–13. And, the Lantus® formulation contained additional elements known in the prior art to improve its stability, including zinc and m-cresol. Appx14284-14286, Appx14442-14443, Appx14628, Appx14940, Appx6758. The record before the PTAB was completely

devoid of evidence linking glargine to aggregation problems in insulins generally; in fact, all indications in the record were to the contrary.

Indeed, even the PTAB's own analysis of the evidence on this point is at odds with itself. The PTAB found 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." Appx32, Appx83-84. But the only examples the PTAB gave as evidence on this point show exactly the opposite: a protein's molecular structure, including the number and type of amino acids, directly affects the protein's tendency to aggregate. *See id.*

Specifically, the PTAB recognized that bovine, porcine and human insulins are structurally different and were therefore known to aggregate "to different degrees." *Id.* Likewise the PTAB acknowledged that, in light of their structural differences, "bovine insulin has a *greater tendency* to aggregate than human and porcine insulin." *Id.* (emphasis added). Thus, the PTAB's own findings show that the molecular structure of an insulin protein matters for its tendency to aggregate. That is a reason to distinguish glargine from other insulins, not to equate them as the PTAB erroneously did.

With respect to (2), the PTAB also relied on references that say nothing about glargine aggregation at all to manufacture evidence of a glargine aggregation problem. This is likewise improper. *See NuVasive*, 842 F.3d at 1382 ("[T]he PTAB must make the necessary findings and have an adequate 'evidentiary basis for its findings.'") (internal

citation omitted). Specifically, the PTAB "consider[ed]" a reference in Jones[10] for the proposition that "insulin glargine is more monomeric than other insulin preparations" and thus, presumably, more prone to aggregation. Appx35, Appx87. But Jones does not discuss aggregation at all. It simply says that "insulin analogs, such as insulin glargine, are also monomeric compared to pharmaceutical preparations in which insulin is usually present as a hexamer." Appx6989. Jones does not go on to say that this finding has any impact on glargine's aggregation properties. And, in any event, as even Mylan's expert agreed, the single statement in Jones was based only on a prior reference (Hoogwerf[11]), which discussed only *fast-acting* insulins—not glargine. Appx14412-14416; Appx14659.[12]

This case mirrors *Novartis Pharm. Corp. v. Watson Labs., Inc.*, 611 F. App'x 988, 996 (Fed. Cir. 2015), where this Court affirmed a finding of non-obviousness of patent claims directed to a pharmaceutical formulation of rivastigmine in combination with an antioxidant to combat oxidative degradation. This Court found that even though the

[10] Richard Jones, *Insulin glargine Aventis Phama* 3 IDrugs 1081 (2000). Appx6989-6995.

[11] Hoogwerf, et al., *Advances in the Treatment of Diabetes Mellitus in the Elderly – Development of Insulin Analogues*, 6 Drugs & Aging 438-48 (1996). Appx14659-14669.

[12] The PTAB disputed that Jones meant to cite Hoogwerf, *see* Appx35, Appx86-87, but the text of Jones is unambiguous that Hoogwerf is the only reference cited in the pertinent discussion in Jones. *See* Appx6989-6995. Indeed, if Jones did not rely on Hoogwerf, then his conclusions would be *wholly unsupported* and thus not deserving of any evidentiary weight.

prior art disclosed oxidative instability issues with a physostigmine—a compound closely related to rivastigmine—the prior art did not disclose any oxidative instability issues relating *specifically* to rivastigmine. *Id.* at 996. As this Court emphasized, "[w]ithout the knowledge of a problem, one of skill in the art would not have been motivated to modify" rivastigmine formulations; knowledge of concerns regarding the related compound were insufficient. *Id.*

Just as in *Novartis*, not one piece of prior art in the record or cited by the PTAB disclosed an aggregation problem specifically with the glargine formulation at issue here. That should have resulted in a finding of non-obviousness.

B. The PTAB Committed Legal Error Because It Used The Specification Of The Challenged Patents Itself To Show That A POSITA Would Have Recognized A Glargine Aggregation Problem

Because nothing in the prior art disclosed an aggregation problem specifically with glargine, the PTAB relied on the patents' own teachings to link glargine aggregation with aggregation concerns observed in other insulin formulations. This was another classic hindsight error: using "the invention to define the problem that the invention solves." *Mintz*, 679 F.3d at 1377.

The Supreme Court and this Court's precedents consistently warn against "slipping into the use of hindsight" by avoiding the "temptation to read into the prior art the teachings of the invention at issue." *Graham v. John Deere Co.*, 383 U.S. 1, 36 (1966). And for that reason, it is a longstanding tenet of this Court's jurisprudence that an inventor's own disclosure cannot be used to guide the obviousness analysis or as a

substitute for evidence in the prior art. "To draw on hindsight knowledge of the patented invention, when the prior art does not contain or suggest that knowledge, is to use the invention as a template for its own reconstruction." *Sensonics, Inc. v. Aerosonic Corp.*, 81 F.3d 1566, 1570 (Fed. Cir. 1996); *see also In Touch Techs.*, 751 F.3d at 1351-52 (rejecting attempt to rely on the "patent itself as [a] roadmap for putting what [the expert] referred to as pieces of a 'jigsaw puzzle' together."). Thus, the PTAB cannot merely "look[] to the knowledge taught by the inventor" in its patents "and then use[] that knowledge against its teacher." *Panduit Corp.*, 774 F.2d at 1092.

Here, however, the PTAB did exactly what the Supreme Court and this Court instruct it not to do: it used the teachings of the patents' specification itself as a "roadmap" to link the inventors' innovations with the prior art. Before discussing *any* prior art, the PTAB found that "[t]he '652 patent explains that insulins had a known tendency to aggregate in the presence of hydrophobic surfaces that come into contact with insulin formulations." Appx32, Appx83. The PTAB then concluded that the specification's description must apply to glargine, too, because "[t]he '652 patent *does not exclude* insulin glargine when describing the tendency for insulins to aggregate due to interactions with hydrophobic surfaces." *Id.* (emphasis added). And, the PTAB found that "[t]he '652 patent also does not suggest that aggregation due to hydrophobic surfaces occurred only in pumps." Appx32, Appx84. Based on these findings, the PTAB concluded that the patents' disclosures were "*consistent*" with the prior art. *Id.* (emphasis added). This analysis suffers from two flaws.

First, the PTAB's analysis is backwards, walking directly into the hindsight problem created by relying on the patents' specification itself as prior art. The PTAB started its analysis with the patents' specification, and then concluded that the prior art was "consistent" with it. But the correct analysis proceeds in the opposite direction. It asks whether a POSITA, familiar with the prior art, would have recognized the problem recognized by the inventors and been motivated to modify the existing prior art to solve that problem. Finding that the patent disclosures are consistent with prior art does not answer that question. At a basic level, any successful invention is likely to be consistent with the prior art. That does not make the invention obvious.

Second, to the extent that the patents could be read, as the PTAB did, to disclose that glargine aggregates just like insulin, that analysis conflates the inventors' own contributions with knowledge in the prior art. It is clear that none of the pertinent references cited in the patents' specification concern glargine specifically; they all instead unambiguously concern other insulin formulations. Brange concerned prior human and animal insulins, not glargine. Appx106, Appx6797-6799. And Sluzky reports the results of certain testing on *bovine* solutions and does not discuss glargine. Appx106, Appx14270-14271, Appx14533-14534.

So, the fact that "[t]he '652 patent does not exclude insulin glargine when describing the tendency for insulins to aggregate" (Appx32, Appx83) is for good reason—it reflects the contributions of the inventors. Because the prior art was silent about glargine aggregation, any understanding from the specification that glargine has

a problematic tendency to aggregate was new knowledge contributed by the inventors. It could not have been a description of the prior art. Likewise, it is not surprising that, as the PTAB found, "[t]he '652 patent does not suggest that aggregation due to hydrophobic surfaces occurred only in pumps." Appx32, Appx84. The problem the inventors identified and solved was unexpected aggregation concerns with the Lantus® *vial* formulation. Because glargine is not delivered in pumps, the inventors had no reason to limit their discussion to aggregation problems in pumps when describing the problem they solved.

C. The PTAB Committed Legal Error In Failing To Identify A Prior Art Teaching Of Any Glargine Aggregation Problem That Would Have Motivated A POSITA To Modify The FDA-Approved Lantus® Formulation

Even assuming (*arguendo*) that the PTAB correctly found that the prior art disclosed an aggregation concern with glargine, the PTAB never asked or answered the next pertinent question: whether a POSITA would have thought that any glargine aggregation tendency was a sufficiently serious problem that required modifying FDA-approved Lantus®. Instead, the PTAB skipped that essential step, evidently supposing that any known amount of aggregation, under any circumstances, concerning any insulin product, would have been sufficient motivation for a POSITA to modify Lantus®. That flawed and conclusory analysis does not comport with this Court's cases and the requirement that the PTAB conduct a "thorough and searching" analysis of motivation. *NuVasive*, 842 F.3d at 1381-82.

Most significantly, the PTAB's premise finds no support in—and is indeed at odds with—the record. As Mylan's expert conceded, *all* proteins—including any insulin formulation—are "prone to aggregation" because they can be made to aggregate under certain conditions. Appx14399-14400. But not every protein-based pharmaceutical has been modified to deal with potential aggregation that might occur. Indeed, of the approximately 180 different insulin formulations commercially available at the time of Sanofi's invention, *not a single vial formulation* contained a surfactant to address an aggregation concern. Appx14307-14308. This makes perfect sense because, as Mylan's expert agreed, there was no evidence that insulin aggregation was ever reported to be a problem outside of pumps. Appx14405-14406, Appx14408-14409.

Moreover, the same references that the PTAB and Mylan cited as evidence for an alleged aggregation tendency in prior insulins actually confirm that aggregation was *not* considered a problem outside of pumps and that insulin *vial* formulations—like glargine—required no further stabilization. *See Polaris Indus.*, 882 F.3d at 1067–69 ("[A] reference must be considered for all that it taught, [including] disclosures that diverged and taught away from the invention.").

For example, Brange disclosed that "[d]uring the first 60 years of insulin therapy, fibrillation-related stability problems during normal handling, storage, or use of insulin preparations *were rarely encountered*." Appx6801 (emphasis added). It was only upon the advent of insulin infusion *pumps* that it "became evident that commercial insulin formulations were not sufficiently stable for long-term use in *infusion pumps*." *Id.*

(emphasis added). Likewise, Grau disclosed that "[w]hereas clinical preparations for subcutaneous injection are now *uniformly stable* and highly purified, insulin for implantable *infusion pumps* requires further steps to ensure stability." Appx6732 (emphasis added); *see also* Appx6767 ("More recently, insulin aggregation has complicated the use of insulin delivery systems, especially in implantable pumps.").

The PTAB did not discuss these portions of these references at all.[13] Rather, the PTAB discussed other references that, according to the PTAB, established that aggregation occurred in vials. But even a cursory examination of those references shows the contrary: the references squarely address *infusion devices (pumps)*—not vials. For example, the PTAB relied on Lougheed (referred to as "Ex. 1006" in the decision) (*see* Appx32-33, Appx84), but Lougheed discusses only "continuous infusion" devices, and uses vials agitated in the lab solely to simulate the conditions found typically in pumps. Appx6704; *see also* Appx6705 (study designed "to simulate the most severe [conditions] encountered in an *implantable* delivery system"). Likewise, the PTAB cited Thurow (referred to as "Ex. 1021"),[14] a reference concerned with aggregation problems observed in "programmable delivery devices for continuous infusion." Appx6906; *see*

[13] The PTAB did cite Brange (referred to as "Ex. 1014" and "Ex. 1015" in the decision) (*see* Appx33, Appx84), but as discussed those references clearly stated that aggregation was known to be a problem in "devices for continuous insulin infusion (insulin pumps)" not vials. *See, e.g.*, Appx6801.

[14] H. Thurow & K. Geisen, *Stabilization of Dissolved Proteins Against Denaturation at Hydrophobic Interfaces*, 27 Diabetologia 212-218 (1984). Appx6906-6912.

also id. (discussing problems associated with "the surfaces of materials now used in pumps"). Another of the PTAB's references, Chawla (referred to as "Ex. 1026"),[15] finds that, *even as to pumps*, "[u]nder normal use by the patient, aggregation of insulin *does not* appear to be a significant problem in commercially available [automatic] syringes and infusion sets tested." Appx6953.[16]

The PTAB used its flawed review of these references to "credit Dr. Langer's testimony that aggregation 'was known in the art not to be unique to pumps,' [citation] over Dr. Trout's testimony that 'insulin fibrillation was also known to be an issue confined to insulin pumps.'" Appx33, Appx84-85. But once again, the PTAB erred. In the cited portion of Dr. Langer's testimony, Dr. Langer simply quoted from the patents' specification. *See* Appx12246. Relying on the specification as prior art is wrong for the reasons discussed above. And, in any event, the study cited by the patent specification—the 1991 Sluzky study—concerned bovine insulin (which has an elevated propensity to aggregate, *see* Appx14533), not glargine. Appx14269-14271.

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[15] Chawla et al., *Aggregation of Insulin, Containing Surfactants, in Contact with Different Materials*, 34 Diabetes 420-424 (1985). Appx6949-6953.

[16] The PTAB also cited Sluzky et al., Proc. Natl. Acad. Sci. 88:9377-9381 (1991) ("Sluzky"). Appx33, Appx84. The PTAB quotes Sluzky (referred to as "Ex. 2012") for the proposition that "It has been suggested that insulin is destabilized by adsorption at hydrophobic interfaces (air-water or water-pump materials)," but then ignores the very next sentence of the reference: "These elements alone, however, fail to describe insulin aggregation behavior." Appx14535.

II. The PTAB Erred In Holding That A POSITA Would Have Had A Reasonable Expectation Of Success In Adding A Surfactant To Glargine

In addition to showing that a POSITA would have had a motivation to modify the prior Lantus® formulation by adding a surfactant, Mylan was also required to prove that a POSITA would have reasonably expected success in adding a surfactant to claimed Lantus® formulation. *In re Stepan Co.*, 868 F.3d 1342, 1345–46 (Fed. Cir. 2017). The undisputed evidence showed the contrary for two reasons: First, a POSITA would have reasonably expected that a surfactant would have interfered with or even destroyed glargine's unique mechanism of action that drives its therapeutic effect. Second, the evidence showed that adding a surfactant would have resulted in a number of additional negative consequences.

In finding that Mylan nonetheless met its burden here, the PTAB erred. It devoted a *single sentence* to Sanofi's first argument, reaching a facially irrational and unreasoned result. And it dismissed Sanofi's second argument based on its selective consideration of evidence Mylan introduced at the eleventh hour, which Sanofi did not have a full and fair opportunity to address with counter evidence.

A. The PTAB Irrationally Dismissed Sanofi's Evidence Showing That Adding A Surfactant To Glargine Would Have Been Expected To Interfere With Glargine's Mechanism Of Action

To "enable[] the court to exercise its duty to review the PTAB's decisions," *NuVasive*, 842 F.3d at 1382, the PTAB must "examine the relevant data and articulate a satisfactory explanation for its action including a *rational connection* between the facts

found and the choice made." *Id.* (quoting *Sang Su Lee*, 277 F.3d at 1343–44) (emphasis added). The PTAB utterly failed to do this here. Instead, the PTAB summarily dismissed Sanofi's evidence without explanation. "[I]t is not adequate" for the Board merely "to summarize and reject arguments without explaining why the PTAB accepts the prevailing argument." *NuVasive*, 842 F.3d at 1383.

Sanofi argued—and presented uncontested evidence showing—that the prior art taught that a surfactant would have been expected to interfere with glargine's unique mechanism of action. Glargine provides long-acting effectiveness in part because, unlike other forms of insulin, it exhibits a high degree of native (or desirable) aggregation both in its storage solution and upon injection. Once injected in its hexameric form, glargine slowly dissociates into the physiologically active monomer, slowing its absorption in the body, and providing long-acting effect. Significantly, there is no dispute about this process: Mylan's own expert agreed that glargine has an ability to "form hexamers in pharmaceutical formulations to delay the onset of insulin action" and that glargine "precipitates readily at the neutral tissue pH . . . to a hexametric structure." Appx6492; Appx6509; *see also* Appx14309, Appx6690; *supra* pp. 12–13.

It is also undisputed that surfactants were known in the art to disrupt hexamer formation and speed up insulin absorption. In fact, Mylan's own expert has described surfactants in insulin formulations as "absorption enhancers" that prevent "the aggregation of insulin from monomer to dimer or hexamer." Appx6971, Appx14376-14377. This is precisely what a POSITA would have wished to avoid for glargine,

because its therapeutic effect depends on the formation of hexamers and resulting slowed absorption in the body. Surfactants would interfere with, or even prevent, that vital process from occurring.

Notwithstanding this agreement about the unrefuted teachings of the prior art, the PTAB did not expressly address the issue. Although the PTAB acknowledged that Sanofi made the argument, Appx31, Appx82, the PTAB did not resolve Sanofi's contention with any meaningful discussion. The sum total of what the PTAB said about this issue was:

> For the same reason,[17] 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 of their success stabilizing other insulins and proteins. Resp. 46–51.

Appx39, Appx90.

The PTAB's one-sentence discussion reaches an irrational result. Once again, the PTAB justified its conclusions by comparing glargine to other forms of insulin when the undisputed record pointed to marked contrasts between them. The essential point

[17] The "same reason" the PTAB refers to appears to be its conclusion that "[t]he 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." Appx38, Appx90. As explained in the text, any success in adding a surfactant to stabilize *non-glargine* proteins is beside the point and does not contend with the undisputed evidence that a surfactant was thought to interfere with *glargine*'s mechanism of action precisely because of meaningful differences between glargine and other insulins.

is that glargine has a *unique* mechanism of action—*distinct* from "other insulins and proteins"—that a surfactant would likely disrupt. And on this point, as noted above, there was agreement among both sides' experts.

Indeed, this one sentence "analysis" does not even take into account Sanofi's argument on the expected disruption of glargine's mechanism of action. This is improper. As this Court has said, the PTAB may adopt or reject a party's arguments, but it must provide its reasoned analysis for doing so. *See NuVasive*, 842 F.3d at 1383 ("conclusory statements alone are insufficient and, instead, the finding must be supported by a reasoned explanation").

B. The PTAB Erred in Discrediting Evidence Of Additional Potential Negative Consequences Of Adding A Surfactant To Lantus®, By Relying On Late-Produced and Contested Evidence That Sanofi Was Denied A Full And Fair Opportunity To Controvert With Counter Evidence

Sanofi's arguments against reasonable expectation of success also included evidence regarding numerous potential negative consequences that a POSITA would have expected to occur if a surfactant were added to Lantus®. Not only did the PTAB generically reject Sanofi's arguments as "unpersuasive" without any analysis, it did so on a prejudicially incomplete record. Specifically, the PTAB rested its holding on evidence Mylan introduced late in the proceedings, to which the PTAB denied Sanofi a full and fair opportunity to respond with expert testimony and evidence.

Although Mylan's Petitions and expert declaration initially argued that surfactants such as polysorbates and poloxamers had "long been used to stabilize

commercially available and regulatory agency-approved insulins," Mylan's expert Dr. Yalkowsky later testified that he had *no support* for that opinion. Appx14407. Accordingly, in the Patent Owner Responses, Sanofi presented argument and evidence of the potential negative consequences that would have been expected if a surfactant were added to the Lantus® formulation, including hydrolysis of the surfactant, potential discoloration of the formulation, interference between surfactants and other components of the Lantus® formulation, and the potential for surfactants to form harmful peroxides in the formulation upon storage. Appx1346-1350.

In response to Sanofi's arguments, Mylan took a mulligan and retained a new expert who provided an 88-page declaration citing previously unidentified references allegedly disclosing formulations of insulins and other proteins that allegedly included a surfactant. *See* Appx12283-12290. Sanofi requested that this late-breaking new evidence be struck or, in the alternative that Sanofi be given an opportunity to present expert testimony and evidence for why a POSITA would not have expected success based on this new evidence. Appx2414-2415, Appx2417-2418, Appx15270-15272, Appx15274, Appx15288-15289.

The PTAB denied Sanofi's motion to strike as well as Sanofi's request to submit responsive expert evidence and testimony. Appx10, Appx59, Appx15304-15306. All Sanofi was permitted to submit was a three-page lawyer response to address the new evidence. Yet the PTAB boldly and impermissibly relied on this same belated new evidence to find the claims obvious, Appx38 and Appx89 (citing Appx12283-12290),

Appx40 and Appx 91 (citing Appx12907, Appx12911), and in so doing, deprived Sanofi of its due process right to respond to Mylan's argument with evidence of its own. *See EmeraChem Holdings, LLC v. Volkswagen Grp. of Am., Inc.*, 859 F.3d 1341, 1348 (Fed. Cir. 2017) ("The agency must timely inform the patent owner of 'the matters of fact and law asserted,' give all interested parties the opportunity to submit and consider facts and arguments, and allow a party '*to submit rebuttal evidence* . . . as may be required for a full and true disclosure of the facts.'") (citing 5 U.S.C. §§ 554(b)–(c), 556(d)) (emphasis added).

III. The PTAB Erred In Discounting Objective Indicia Of Non-Obviousness

When present, Courts must consider evidence of an invention's commercial success as objective evidence of a claim's non-obviousness. *Transocean Offshore Deepwater Drilling Inc. v. Maersk Drilling USA, Inc.*, 699 F.3d 1340, 1349-50 (Fed. Cir. 2012). As the PTAB found here, there is no dispute that the commercialized insulin glargine vial product—Lantus®—has been commercially successful. Appx42, Appx93. Nonetheless, the PTAB discounted this evidence by placing dispositive weight on so-called "blocking patents" held by Sanofi covering the insulin glargine molecule itself. This was error in two respects: (1) the PTAB placed undue weight on the blocking patents because it impermissibly narrowed the scope of the relevant market to only glargine products—rather than all long-acting insulin products; and (2) the PTAB acknowledged but then failed to address Sanofi's "but for" argument—the evidence that the commercial success of Lantus® would have been jeopardized if Sanofi had not

reformulated the vial product to address the aggregation problems it discovered. The PTAB's misapplication of the law on "blocking patents" and its failure to address Sanofi's "but for" arguments necessitates at the very least a remand.

A. The PTAB Placed Undue Reliance On Sanofi's "Blocking Patents"

The PTAB found Sanofi's commercial success evidence "weak" because of alleged "blocking patents" covering the glargine molecule itself that prevented others from entering the glargine market and therefore competing with Sanofi's Lantus® product. Appx43, Appx95. As an initial matter, the law does not mandate across-the-board discounting of commercial success simply because other patents cover the same drug. Rather, this Court has directed that the PTAB weigh evidence on a case-by-case basis, in light of the specific commercial success argument being made. *Acorda Therapeutics, Inc. v. Roxane Labs., Inc.*, 903 F.3d 1310, 1339 (Fed. Cir. 2018), *pet. for cert filed*, No. 18-1280 (U.S. Apr. 8, 2019) (noting that while a blocking patent "can be evidence that can discount the significance of evidence that nobody but the blocking patent's owners or licensees arrived at, developed, and marketed the invention covered by the later patent," the "magnitude of the diminution … is a fact-specific inquiry").

Analyzing the specific facts here, the PTAB erred by focusing on the commercial success of reformulated Lantus® relative to a market for only *glargine*, which was the only product that Mylan identified as implicated by the supposed blocking patents. Appx42, n.14 and Appx94, n.15 (citing Appx9787, Appx12249, Appx13843-13854) (noting that the alleged "blocking patents" were directed specifically to the insulin

glargine molecule and other insulin analog molecules). That analysis was impermissibly myopic because the correct market to analyze was the market for *all* long-acting insulin products that directly compete against Lantus® vials. Indeed, not even Mylan argued for a market consisting of only glargine formulations. *See* Appx13773-13774. And in the correct market, Sanofi's evidence showed that the Lantus® vial reformulation containing a polysorbate enjoyed substantial commercial success relative to other long-acting insulin products in the marketplace that did not have a surfactant added to them. Appx15040-15042; Appx14307-14309.

Moreover, it is undisputed that Sanofi's alleged "blocking patents" would neither have prevented competitors from entering the market for other non-glargine long-acting insulin formulations that competed with Lantus®, nor have prevented a competitor from adding a surfactant to those other non-glargine long-acting insulin products. *See* Appx42, n.14, Appx94, n. 15 (citing Appx12249, Appx13843-13854, Appx 9737). The relative success of Lantus®, which was reformulated to contain a surfactant to address a previously unknown aggregation problem, as compared to these other long-acting insulins that failed to address alleged aggregation, therefore shares a strong nexus with the claimed invention that the PTAB failed to consider.

B. The PTAB Acknowledged, But Rejected Without Analysis, Sanofi's "But For" Evidence

Sanofi's also argued that in the absence of its reformulation of Lantus® to address the turbidity concerns caused by glargine aggregation, Sanofi would have

suffered negative consequences, including lost sales, reputational damage and potential regulatory action. The PTAB recited this argument in its decision: "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.'" Appx41, Appx93 (emphasis added). But the PTAB did not address this argument. Indeed, rather than evaluating Sanofi's argument, the PTAB addressed a different one: "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." Appx43, Appx94-95 (emphasis added). As noted above, the PTAB has an obligation to explain, with reasoned analysis, why it chooses to accept and reject the arguments of the parties. *Cutsforth, Inc. v. MotivePower, Inc.*, 636 F. App'x 575, 578 (Fed. Cir. 2016); *Google, Inc. v. Intellectual Ventures II, LLC*, 701 F. App'x 946, 956 (Fed. Cir. 2017). The PTAB failed to do so yet again here.

The evidence demonstrates that had Sanofi failed to reformulate Lantus® to address the turbidity problem, there would have been significant negative sales, regulatory and reputational effects that would have substantially diminished the commercial success of the product. Without the benefits of the reformulation, the continued commercial success of Lantus® in vial would have been jeopardized. Appx15045-15047. Not only could these aggregation problems have resulted in lost sales, but if Sanofi had not timely addressed them, it could have faced the complete

removal of Lantus® vials from the market, like other pharmaceutical companies whose products failed to address safety concerns. *See* Appx15045-15047. For example, it is well known that the presence of unwanted protein aggregates in therapeutic formulations could lead to a host of safety and efficacy issues, including provoking unwanted immune responses. Appx14319-14322; *see also* Appx313-315 (Sanofi's counsel explaining the but-for argument to the PTAB panel). The PTAB erred by failing to substantively consider Sanofi's argument.

CONCLUSION

For the foregoing reasons, the Court should reverse the PTAB's Final Written Decisions or at the very least vacate the Final Written Decisions and remand.

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Respectfully submitted,

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