NOTE: This disposition is nonprecedential.

United States Court of Appeals for the Federal Circuit

SANOFI-AVENTIS DEUTSCHLAND GMBH,
Appellant

v.

MYLAN PHARMACEUTICALS INC.,
Appellee

2019-1368, 2019-1369

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

Decided: November 19, 2019

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

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

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

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

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

Dissenting opinion filed by *Circuit Judge* NEWMAN.

TARANTO, *Circuit Judge.*

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

I

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

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

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

'652 patent, col. 11, lines 21–28.

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

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

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

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

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[1] David R. Owens, et al., *Pharmacokinetics of ^{125}I-Labeled Insulin Glargine (HOE 901) in Healthy Men: Comparison with NPH Insulin and the Influence of Different Subcutaneous Injection Sites*, 23 DIABETES CARE 813 (2000) (Owens).

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

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

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

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

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

II

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

A

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

1

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

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

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

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

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

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

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

2

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

> The specific preparation of insulin glargine, which leads to the prolonged duration of action, is characterized, in contrast to previously described preparations, by a clear solution having an acidic pH. Especially at acidic pH, insulins, however, show a decreased stability and an increased proneness to aggregation on thermal and physicomechanical stress, which can make itself felt in the form of turbidity and precipitation (particle formation (Brange et al., J. Ph. Sci 86:517-525 (1997)).

> The proneness to aggregation can additionally be promoted by hydrophobic surfaces which are in contact with the solution (Sluzky et al., Proc. Natl. Acad. Sci. 88:9377-9381 (1991). Surfaces which can be considered as hydrophobic are the glass vessels of the preparations, the stopper material of the sealing caps or the boundary surface of the solution with the air supernatant. In addition, very fine silicone oil droplets can function as additional hydrophobic aggregation nuclei in the taking of the daily insulin dose by means of customary, siliconized insulin syringes and accelerate the process.

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

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

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

3

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

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

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

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

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

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

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

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

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

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

B

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

1

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

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

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

2

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

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

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

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

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

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

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

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

C

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

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

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

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

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

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

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

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

III

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

AFFIRMED

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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 nonobviousness, for glargine had undergone clinical development without this problem being apparent. Sanofi explained the uncertainties in insulin reactivity, citing the known potential for discoloration and peroxide formation, and that such reactions cannot be predicted. The PTAB brushed off these uncertainties as "unpersuasive" without any analysis, as do my colleagues. Maj. Op. at 16–17, 20. However, the behavior of a new composition inside the body requires experimentation and evidence, not speculation and hindsight.

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

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

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

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

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

The patent specification is not prior art

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

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

The law of innovation and obviousness

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

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

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

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

The recent ruling on the Appointments Clause of the Constitution

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

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

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

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

The majority errs in denying Sanofi's motion.