United States Court of Appeals for the Federal Circuit

MYLAN PHARMACEUTICALS INC.,
Appellant

v.

MERCK SHARP & DOHME CORP.,
Appellee

2021-2121

Appeal from the United States Patent and Trademark Office, Patent Trial and Appeal Board in No. IPR2020-00040.

Decided: September 29, 2022

ERIC THOMAS WERLINGER, Katten Muchin Rosenman LLP, Washington, DC, argued for appellant. Also represented by JITENDRA MALIK, Charlotte, NC; DEEPRO MUKERJEE, LANCE SODERSTROM, New York, NY.

JEFFREY A. LAMKEN, MoloLamken LLP, Washington, DC, argued for appellee. Also represented by CALEB HAYES-DEATS, MICHAEL GREGORY PATTILLO, JR.; LAUREN F. DAYTON, MARK W. KELLEY, New York, NY; STANLEY E. FISHER, BRUCE GENDERSON, DAVID M. KRINSKY, SHAUN PATRICK MAHAFFY, CHARLES MCCLOUD, Williams & Connolly LLP, Washington, DC.

Before LOURIE, REYNA, and STOLL, *Circuit Judges*.

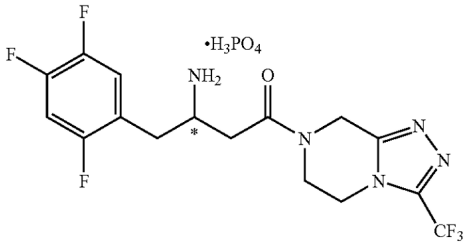
LOURIE, *Circuit Judge*.

Mylan Pharmaceuticals Inc. ("Mylan") appeals from the final written decision of the U.S. Patent and Trademark Office Patent Trial and Appeal Board (the "Board") holding that it failed to show that claims 1–4, 17, 19, and 21–23 of U.S. Patent 7,326,708 (the "'708 patent") were anticipated or would have been obvious over the cited prior art at the time the alleged invention was made. *See Mylan Pharms. Inc. v. Merck Sharp & Dohme Corp.*, No. IPR2020-00040, 2021 WL 1833325 (P.T.A.B. May 7, 2021) ("*Decision*"). For the reasons provided below, we affirm.

BACKGROUND

Merck Sharp & Dohme Corp. ("Merck") owns the '708 patent, which describes sitagliptin dihydrogenphosphate ("sitagliptin DHP"). Sitagliptin DHP is a dihydrogenphosphate salt of 4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro [1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine. Sitagliptin DHP belongs to the class of dipeptidyl peptidase-IV ("DP-IV") inhibitors, which can be used for treating non-insulin-dependent (i.e., Type 2) diabetes. Independent claim 1 recites a sitagliptin DHP salt with a 1:1 stoichiometry, and reads as follows:

> 1. A dihydrogenphosphate salt of a 4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro [1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine of Formula I:



or a hydrate thereof.

'708 patent col. 15 l. 64–col. 16 l. 15.

Sitagliptin contains a single asymmetric carbon, indicated by the asterisk in the above chemical structure. The (R)-configuration and (S)-configuration of sitagliptin DHP are recited in dependent claims 2 and 3, respectively. A crystalline monohydrate form of the (R)-configuration is recited in dependent claim 4.

Mylan petitioned for *inter partes* review ("IPR") of claims 1–4, 17, 19, and 21–23 of the '708 patent. J.A. 177. Mylan argued that claims 1–3, 17, 19, and 21–23 were anticipated by International Patent Publication WO 2003/004498 (the "'498 publication"), a Merck-owned publication, and the equivalent U.S. Patent 6,699,871 (the "'871 patent") (collectively, "Edmondson").[1]

Edmondson "is directed to compounds which are inhibitors of the dipeptidyl peptidase-IV enzyme ('DP-IV inhibitors') and which are useful in the treatment or prevention of diseases in which the dipeptidyl peptidase-IV enzyme is involved, such as diabetes and particularly type 2 diabetes." *Decision*, 2021 WL 1833325, at *6. Specifically, Edmondson discloses a genus of DP-IV inhibitors and 33 species, one of which is sitagliptin. '498 publication col. 54 l. 16–col. 60 l. 5. Edmondson further discloses that pharmaceutically acceptable salts can be formed using one of eight "[p]articularly preferred" acids. *Id.* at col. 10 ll. 14–15. Phosphoric acid is in the list of "particularly preferred" acids. Edmondson also discloses that the salts may

[1] The parties agree that the '498 publication and the '871 patent are identical in relevant part. Appellant's Br. 1; Appellee's Br. 5, n.1. The Board also treated them as identical in relevant part. *Decision*, 2021 WL 1833325, at *1, n.4.

exist in crystalline forms, including as hydrates. *Id.* at col. 9 ll. 32–34.

Mylan also argued that claims 1–4, 17, 19, and 21–23 would have been obvious over Edmondson and two additional publications titled "Structural Aspects of Hydrates and Solvates" ("Brittain")[2] and "Salt Selection and Optimisation Procedures for Pharmaceutical New Chemical Entities" ("Bastin").[3]

Brittain describes the pharmaceutical importance and prevalence of crystalline hydrates of pharmaceutical compounds. J.A. 438–94. Specifically, Brittain teaches that approximately one third of studied pharmaceutical active ingredients could form crystalline hydrates, and half of those one-third were monohydrates. J.A. 441. In other words, Brittain illustrates that approximately one sixth of the analyzed pharmaceutical compounds formed crystalline monohydrates. Brittain also cites various challenges that arise during the manufacturing and development of hydrates, including lower solubility, chemical instability, and discoloration. J.A. 440.

Bastin teaches salt selection and optimization procedures during the development of pharmaceutical compounds. J.A. 495–97. Specifically, Bastin teaches that a range of possible salts should be prepared for each new substance to compare adequately the properties of each salt during the development process. J.A. 495. Bastin also

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[2] Kenneth R. Morris, *Structural Aspects of Hydrates and Solvates*, *in Polymorphism in Pharmaceutical Solids* 125–181 (Harry G. Brittain ed., 1999).

[3] Richard J. Bastin, Michael J. Bowker, & Brian J. Slater, *Salt Selection and Optimisation Procedures for Pharmaceutical New Chemical Entities*, 4 *Organic Process Rsch. & Dev.* 427 (2000).

discloses disadvantages of certain salts used in drug formulations, including hydrochloric acid ("HCl"). J.A. 496.

First, the Board determined that there was no express disclosure of all of the limitations of the 1:1 sitagliptin DHP salt in Edmondson, and that Mylan could not fill in the gaps by arguing that a skilled artisan would "at once envisage" what is missing. *Decision*, 2021 WL 1833325, at *10, *12. The Board also concluded that Mylan had not proven an inherent disclosure of the 1:1 sitagliptin DHP salt in Edmondson, and that evidence, both experimental and from the technical literature, undeniably showed that 1:1 sitagliptin DHP does not form every time sitagliptin and DHP were reacted. *Id.* at *15–16. The Board concluded that claims 1–3, 17, 19, and 21–23 were neither expressly nor inherently anticipated by Edmondson. *Id.* at *16.

Next, the Board determined that claims 1–4, 17, 19, and 21–23 would not have been obvious in view of Edmondson, Bastin, or Brittain. First, the Board considered the threshold issue whether Merck could antedate Edmondson with evidence that it had reduced to practice the subject matter of claims 1, 2, 17, 19, and 21–23 before Edmondson had been published on January 16, 2003. *Id.* at *16–20. The Board concluded that Merck had reduced to practice at least as much, and in fact more, of the claimed subject matter than was shown in Edmondson. *Id.* at *20. Thus, Merck could successfully antedate the subject matter of claims 1, 2, 17, 19, and 21–23, and thus Edmondson was not a 35 U.S.C. § 102(a) reference, but merely a 35 U.S.C. § 102(e) (pre-AIA) reference. *Id.* Because it was undisputed that the inventions claimed in the '708 patent and the subject matter of Edmondson were commonly owned by Merck, or under obligation of assignment to Merck, at the time of the invention, the Board determined that the 35 U.S.C. § 103(c)(1) (pre-AIA) exception applied to claims 1, 2, 17, 19, and 21–23. *Id.* Merck did not assert a prior-reduction-to-practice argument for claims 3 and 4. *Id.*

The Board considered whether claim 3, which recites the (S)-configuration of sitagliptin DHP, and claim 4, which recites the crystalline monohydrate form of (R)-sitagliptin, would have been obvious in view of Edmondson, Bastin, and Brittain. The Board found that neither Edmondson nor Bastin disclosed anything related to (S)-sitagliptin or even a racemic mixture of any sitagliptin salt. *Id.* at *21. The Board thus concluded that Mylan did not show that claim 3 would have been obvious to a skilled artisan at the time the invention was made. *Id.* at *22. The Board also found that Mylan provided no rationale to explain why a person of ordinary skill would have been motivated to make the claimed crystalline monohydrate form of 1:1 sitagliptin DHP of claim 4 and failed to show that a skilled artisan would have had a reasonable expectation of success in making the crystalline monohydrate form of the 1:1 sitagliptin DHP salt. *Id.* at *24, *26. The Board thus concluded that Mylan failed to show that claim 4 would have been obvious to a person of ordinary skill at the time the invention was made. *Id.* at *26.

In summary, the Board concluded that Mylan had not demonstrated that claims 1–4, 17, 19, and 21–23 were anticipated or would have been obvious at the time the invention was made. Mylan appealed. We have jurisdiction under 28 U.S.C. § 1295(a)(4).

DISCUSSION

Mylan raises three challenges on appeal. First, Mylan contends that the Board erred in determining that a 1:1 stoichiometry of sitagliptin DHP was not anticipated, either expressly or inherently, by Edmondson. Second, Mylan contends that the Board erred in determining that the '708 patent antedates Edmondson.[4] Third, Mylan

[4] The '498 publication was published on January 16, 2003, and the '871 patent was published on May 29, 2003.

contends that the Board erred in determining that it failed to prove that claims 3 and 4 of the '708 patent would have been obvious over Edmondson, Brittain, and Bastin. We address each argument in turn.

We review the Board's legal determinations *de novo*, *In re Elsner*, 381 F.3d 1125, 1127 (Fed. Cir. 2004), but we review the Board's factual findings underlying those determinations for substantial evidence. *In re Gartside*, 203 F.3d 1305, 1316 (Fed. Cir. 2000). A finding is supported by substantial evidence if a reasonable mind might accept the evidence as adequate to support the finding. *Consol. Edison Co. v. NLRB*, 305 U.S. 197, 229 (1938). And "[i]f two 'inconsistent conclusions may reasonably be drawn from the evidence in the record, [the PTAB]'s decision to favor one conclusion over the other is the epitome of a decision that must be sustained upon review for substantial evidence.'" *Elbit Sys. of Am., LLC v. Thales Visionix, Inc.*, 881 F.3d 1354, 1356 (Fed. Cir. 2018) (alteration in original) (quoting *In re Cree, Inc.*, 818 F.3d 694, 701 (Fed. Cir. 2016)).

Anticipation is a question of fact. *Genentech, Inc. v. Hospira, Inc.*, 946 F.3d 1333, 1337 (Fed. Cir. 2020). The prior art may be deemed to disclose each member of a genus when, reading the reference, a person of ordinary skill can "at once envisage each member of this limited class." *In re Petering*, 301 F.2d 676, 681 (C.C.P.A. 1962).

Obviousness is a "mixed question of law and fact," and we review "the Board's ultimate obviousness determination *de novo* and underlying fact-findings for substantial evidence." *Hologic, Inc. v. Smith & Nephew, Inc.*, 884 F.3d 1357, 1361 (Fed. Cir. 2018).

Since the '498 publication was published earlier, we consider Edmondson, for purposes of antedation, to have been published on January 16, 2003.

I

We first consider Mylan's challenge to the Board's determination that it failed to prove that Edmondson anticipates claims 1–3, 17, 19, and 21–23. Mylan argues that Edmondson anticipates the claims because it discloses sitagliptin in a list of 33 compounds. Mylan further asserts that Edmondson discloses acids forming "pharmaceutically acceptable salts," including phosphoric acid in a list of eight "particularly preferred" acids. Mylan, therefore, asserts that sitagliptin DHP is effectively disclosed in Edmondson, and Edmondson thus anticipates the challenged claims.

Mylan further asserts that a skilled artisan would "at once envisage" a 1:1 stoichiometry of the sitagliptin DHP salt for two reasons. First, Example 7 of Edmondson discloses a sitagliptin hydrochloride salt ("sitagliptin HCl") having a 1:1 stoichiometry. Second, experimental data presented by Mylan's expert Dr. Chorghade illustrate that only a 1:1 sitagliptin DHP stoichiometry forms under conditions allegedly similar to those disclosed in Edmondson. Mylan contends that the Board thus erred in holding that a 1:1 stoichiometry was not anticipated by Edmondson.

Merck responds that the Board's holding that the claims are not anticipated by Edmondson was supported by substantial evidence. Merck asserts that a skilled artisan would not "at once envisage" all members of the entire genus of DP-IV-inhibitor salts disclosed in Edmondson. Merck further contends that the combined list of 33 compounds and eight preferred salts, taking into account various stoichiometric possibilities, would result in 957 salts, some of which may not even form under experimental conditions. That, Merck asserts, does not meet the standard set by the "at once envisage" theory. Merck argues that Mylan seeks to expand the theory inappropriately, improperly focusing on whether skilled artisans could have envisaged 1:1 sitagliptin DHP among the members of the class instead of envisaging each member of the disclosed class.

In essence, Merck asserts that Mylan uses hindsight to single out one compound from the large class. Merck further argues that Mylan's own expert conceded that Edmondson does not direct a skilled artisan to sitagliptin from among the 33 DP-IVs, nor does it disclose a phosphate salt of any DP-IV inhibitor.

We agree with Merck that the Board's decision was supported by substantial evidence. The Board did not err in determining that Edmondson does not expressly disclose a 1:1 sitagliptin DHP salt. The Board grounded its finding in the testimony from Mylan's own expert, Dr. Chorghade, stating that nothing in Edmondson directs a skilled artisan to sitagliptin from among the 33 listed DP-IV inhibitors. J.A. 2342, 2373–74; Chorghade Dep. 61:7–62:9, 188:6–189:8. Further, nothing in Edmondson singles out phosphoric acid or any phosphate salt of any DP-IV inhibitor, and the list of "pharmaceutically preferred" salts comes 44 pages earlier in the specification. The Board reasonably concluded that Edmondson does not expressly disclose the 1:1 sitagliptin DHP salt.

We also agree with Merck that the Board did not err in determining that Edmondson does not inherently disclose a 1:1 sitagliptin DHP salt. *In re Petering* stands for the proposition that a skilled artisan may "at once envisage each member of [a] *limited* class, even though the skilled person might not at once define in his mind the formal boundaries of the class." 301 F.2d at 681 (emphasis added). The key term here is "limited." As Merck asserted, and as the Board considered, the list of 33 compounds, with no direction to select sitagliptin from among them, plus the eight "pharmaceutically preferred" acids and various stoichiometric possibilities, results in 957 salts, some of which may not exist. That is a far cry from the 20 compounds "envisaged" by the narrow genus in *Petering*. *Id.* Mylan's own expert, Dr. Chorghade, even stated that salt formation is an unpredictable art that requires a "trial and error

process." *Decision*, 2021 WL 1833325, at *8; J.A. 2355–56; Chorghade Dep. 116:22–117:3.

We cannot provide a specific number defining a "limited class." *In re Petering*, 301 F.2d at 681. It depends on the "class." But we agree with Merck and hold that the Board did not err in finding that a class of 957 predicted salts that may result from the 33 disclosed compounds and eight preferred acids, some of which may not even form under experimental conditions, is insufficient to meet the "at once envisage" standard set forth in *Petering*.

II

We next consider Mylan's challenge to the Board's determination that Mylan failed to prove that claims 1–4, 17, 19, and 21–23 would have been obvious to a person of ordinary skill in the art at the time the invention was made.

A

We must first consider the threshold issue of Mylan's antedation challenge and application of the 35 U.S.C. § 103(c)(1) exception. Under 35 U.S.C. § 102(a) (pre-AIA), "[a] person shall be entitled to a patent unless the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent." But a party can overcome the § 102(a) barrier if it can antedate a reference "by showing that the invention was conceived before the effective date of the reference, with diligence to actual or constructive reduction to practice." *In re Steed*, 802 F.3d 1311, 1320 (Fed. Cir. 2015). To prove antedation, the patent owner must show that it reduced to practice at least as much as "the reference shows of the claimed invention" before the reference's publication date. *In re Clarke*, 356 F.2d 987, 991 (C.C.P.A. 1966).

Mylan does not dispute that Merck reduced 1:1 (R)-sitagliptin DHP salt to practice before Edmondson was

published, nor does it dispute that Merck commonly owned Edmondson and the '708 patent. Mylan, instead, argues that the Board erred in finding that Merck's reduction to practice of the 1:1 (R)-sitagliptin DHP salt antedates Edmondson, because Edmondson discloses sitagliptin hydrates, and Merck had not made hydrates of 1:1 sitagliptin DHP until March 2003, about two months after the January 16, 2003 Edmondson publication date. Mylan also argues that the Board erred in finding that Edmondson does not disclose hydrates of sitagliptin phosphate.

Merck responds that the Board did not err in finding that Merck's work on the subject matter in claims 1, 2, 17, 19, and 21–23 of the '708 patent antedated Edmondson. Merck argues that it had reduced to practice the subject matter of these claims before Edmondson had been published on January 16, 2003. As a result, Merck asserts, Edmondson could not serve as 35 U.S.C. § 102(a) prior art and would merely be a 35 U.S.C. § 102(e) reference. Because it is undisputed that the invention claimed in the '708 patent and the subject matter of Edmondson were commonly owned by Merck at the time of the invention, the exception in § 103(c)(1) applies. Section 103(c)(1) (pre-AIA) provides that "[s]ubject matter developed by another person, which qualifies as prior art only under one or more subsections (e), (f), and (g) of section 102, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the claimed invention was made, owned by the same person or subject to an obligation of assignment to the same person." Merck therefore argues that Edmondson cannot serve as an obviousness reference for claims 1, 2, 17, 19, and 21–23. Without Edmondson, the obviousness challenge to these claims fails. *Decision*, 2021 WL 1833325, at *20.

We agree with Merck that the Board's antedation determination was supported by substantial evidence. As Merck asserts, and as the Board considered, Merck showed that it developed a 1:1 sitagliptin DHP salt in December

2001 with experimental confirmation in early 2002. As Merck highlights, Mylan did not argue that claim 4, directed to a crystalline monohydrate, was anticipated by Edmondson, which it could have done had it believed that Edmondson disclosed a crystalline monohydrate. The Board's finding that Edmondson does not disclose 1:1 sitagliptin DHP was supported by substantial evidence; thus, the Board's finding that it does not disclose a hydrate of that salt was likewise supported by substantial evidence. We therefore agree with the Board that Merck reduced to practice "more . . . than what is shown in [Edmondson] for the claimed subject matter." *Decision*, 2021 WL 1833325, at *18.

B

We next turn to whether the Board erred in holding that Mylan failed to prove that claims 3 and 4 of the '708 patent would have been obvious to a skilled artisan at the time the invention was made.

Mylan argues that the Board erred in holding that it failed to prove that claim 3, which recites the (S)-configuration of 1:1 sitagliptin DHP, would have been obvious. Mylan argues that Edmondson, in combination with Bastin, would have allowed a skilled artisan to envisage and create 1:1 (S)-sitagliptin DHP. According to Mylan, Bastin, which cites disadvantages of hydrochloric acid in pharmaceutical formulations, would encourage a skilled artisan to replace the hydrochloric acid in Example 7 of Edmondson. Furthermore, Mylan states that sitagliptin has one asymmetric carbon, and a skilled artisan would thus have a reasonable expectation of success in creating both (R)-sitagliptin and (S)-sitagliptin.

Mylan further argues that the Board erred in holding that it failed to prove that claim 4, which recites the crystalline monohydrate form of (R)-sitagliptin, would have been obvious. Mylan asserts that a skilled artisan would have had a reasonable expectation of success in creating a

crystalline monohydrate in view of Edmondson in combination with Brittain. First, Mylan argues that Edmondson states that the described salts exist in more than one crystal structure and in the form of a hydrate. Second, Mylan argues that Brittain's discussion of hydrates would have provided motivation for a skilled artisan to explore hydrates in the development process.

Merck argues that the Board did not err in holding that claim 3 would not have been obvious, and that the Board's underlying factual findings were supported by substantial evidence. As the Board considered, Bastin does not provide a specific motivation, including any screening or optimization protocol that, combined with Edmondson, would lead to 1:1 sitagliptin DHP, the (S)-configuration, or even a racemic mixture.

Merck also argues that the Board did not err in holding that claim 4 would not have been obvious, and that the Board's underlying factual findings were supported by substantial evidence. Merck argues that the Board was correct in finding that Mylan did not provide a persuasive motivation for making the crystalline monohydrate form of sitagliptin. Merck asserts evidence that skilled artisans would avoid making hydrates due to solubility and stability challenges during the drug-production process. Merck also contends that the monohydrate has unexpectedly favorable properties, and that these properties are objective indicia of nonobviousness.

We agree with Merck that the Board's decision that Mylan failed to show that claims 3 and 4 of the '708 patent would have been obvious to a skilled artisan at the time the invention was made was supported by substantial evidence.

With respect to claim 3, the Board found that there was no motivation to combine Edmondson and Bastin to make sitagliptin DHP, that the two cited references did not provide motivation to make (S)-sitagliptin, and that there was

no reasonable expectation of success in combining the references. The Board adequately credited Dr. Chorghade's testimony, which stated that the (S)-enantiomer was not disclosed in Edmondson. *Decision*, 2021 WL 1833325, at *21. The Board further highlighted that Mylan advanced no expected or theoretical benefit to making the (S)-enantiomer of 1:1 sitagliptin DHP, and that the general disclosure on diastereomers in Edmondson encompasses millions of potential compounds and salts with no motivation to make the (S)-enantiomer with a reasonable expectation of success, particularly in an unpredictable activity like salt formation. *Id.* at *22. We thus agree with Merck that the Board's decision was supported by substantial evidence.

With respect to claim 4, the Board found that there was no motivation to combine Edmondson, Bastin, and Brittain, and that a person of ordinary skill would have had no reasonable expectation of success in doing so. The Board credited Dr. Chorghade's testimony, which stated that a skilled artisan "couldn't predict with any degree of certainty" hydrate formation. *Id.* at *21; Chorghade Dep. 238:8–18. The Board also addressed the numerous downsides of hydrates reported in the literature, including those stating that a skilled artisan would have several reasons for avoiding hydrates. *Decision*, 2021 WL 1833325, at *23. The Board also credited Merck's expert, Dr. Myerson, who stated that a skilled artisan would have sought to avoid hydrates, *Decision*, 2021 WL 1833325, at *22; Myerson Decl., ¶¶ 127–38, and that forming crystalline salts, including hydrates, is highly unpredictable. *Decision*, 2021 WL 1833325, at *24; Myerson Decl., ¶¶ 146–49. We thus agree with Merck that the Board's decision was supported by substantial evidence.

Finally, the Board did not err in its evaluation of purported objective indicia of nonobviousness. Although the Board did not consider in detail the alleged unexpected properties of the claimed crystalline monohydrate of claim 4, the Board stated that such unexpected results

served as further evidence undermining Mylan's challenge to claim 4. *See Hamilton Beach Brands, Inc. v. f'real Foods, LLC*, 908 F.3d 1328, 1343 (Fed. Cir. 2018) (holding that there is no need to reach objective indicia of nonobviousness where the petitioner has not made a showing necessary to prevail on threshold obviousness issues).

CONCLUSION

We have considered Mylan's remaining arguments, but we find them unpersuasive. The Board's decision was supported by substantial evidence and not erroneous as a matter of law. For the foregoing reasons, the decision of the Board is affirmed.

AFFIRMED