NOTE: This disposition is nonprecedential.

United States Court of Appeals for the Federal Circuit

MSN LABORATORIES PRIVATE LTD., MSN PHARMACEUTICALS, INC.,
Appellants

v.

BAUSCH HEALTH IRELAND LTD.,
Appellee

2024-1053

Appeal from the United States Patent and Trademark Office, Patent Trial and Appeal Board in Nos. IPR2022-00722, IPR2023-00016.

Decided: June 20, 2025

TUNG-ON KONG, Wilson, Sonsini, Goodrich & Rosati, PC, San Francisco, CA, argued for appellants. Also represented by RICHARD J. BERMAN, JANINE A. CARLAN, BRADFORD C. FRESE ArentFox Schiff LLP, Washington, DC.

JUSTIN JAMES HASFORD, Finnegan, Henderson, Farabow, Garrett & Dunner, LLP, Washington, DC,

argued for appellee. Also represented by BRYAN DINER, JOSHUA GOLDBERG.

Before LOURIE, DYK, and CHEN, *Circuit Judges*.

LOURIE, *Circuit Judge*.

MSN Laboratories Private Ltd. and MSN Pharmaceuticals, Inc. ("MSN") appeal from a final written decision of the United States Patent and Trademark Office Patent Trial and Appeal Board ("the Board") holding that it had not shown claims 1–6 of U.S. Patent 7,041,786 ("the '786 patent") to be unpatentable as obvious. *Mylan Pharms., Inc., v. Bausch Health Ireland Ltd.*, No. IPR2022-00722, 2023 WL 6161595 (P.T.A.B. Sept. 8, 2023) ("*Decision*"). For the reasons provided below, we *vacate* and *remand*.

BACKGROUND

Bausch Health Ireland Ltd. ("Bausch") owns the '786 patent, which claims a compound that is part of a group of structurally related peptides known as "guanylate cyclase receptor agonists." '786 patent col. 1 ll. 14–15. Guanylate cyclase receptor agonists play an important role in the operation of the GI tract. By binding to receptors, they stimulate the production of cyclic guanosine monophosphate ("cGMP"), which in turn activates a complex signaling pathway that regulates sodium and water secretion in the intestinal lumen. '786 patent col. 1 ll. 34–35. Guanylate cyclase receptor agonists can be administered in various formulations, such as "solutions, powders, suspensions, emulsions, tablets, capsules, transdermal patches, [or] ointments." '786 patent col. 13 ll. 24–27. Some guanylate cyclase receptor agonists exhibit what is known as "topoisomerism," meaning that an individual peptide can exist in different three-dimensional structures with different levels of biological activity. *Decision* at *8–9; J.A. 04279.

One such agonist in the prior art is uroguanylin, which is known to have two topoisomers: an active "A form" which can bind to receptors and stimulate production of cGMP, and an inactive "B form," which cannot. *Decision* at *8– 9; J.A. 03404. Obviousness of what is claimed in the '786 patent over uroguanylin is at issue in this appeal.

Claim 1 of the '786 patent, which is exemplary, reads as follows:

> 1. A peptide consisting of the amino acid of SEQ ID NO:20.

'786 patent, col. 37 ll. 2–3. SEQ ID NO:20 is the amino acid sequence for plecanatide, a synthetic analog of uroguanylin. *Id.* at col. 35; *Decision* at *3. The sole difference between uroguanylin and plecanatide, as shown below, is a single substitution at the third position: in plecanatide, aspartic acid (Asp) is replaced with glutamic acid (Glu).

> Uroguanylin: Asn^{1}-Asp^{2}-**Asp^{3}**-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}
>
> Plecanatide: Asn^{1}-Asp^{2}-**Glu^{3}**-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}

See Decision at *2. Glutamic acid and aspartic acid are chemically similar—the only difference is that glutamic acid has a second methylene moiety in its side chain. They are also the only two natural amino acids negatively charged at a neutral pH. Bausch markets and sells plecanatide under the brand name Trulance® for use as an oral laxative to treat constipation.

In March 2021, MSN and Mylan Pharmaceuticals Inc., ("Mylan") separately petitioned for *inter partes* review, asserting that all claims of the '786 patent would have been obvious over U.S. Patent 5,489,670 ("Currie"), an article entitled "Purification, cDNA Sequence, and Tissue

Distribution of Rat Uroguanylin" ("Li"), and other secondary references. Regarding claim 1, MSN and Mylan contended that a person of ordinary skill in the art would have been motivated to substitute aspartic acid with glutamic acid at uroguanylin's third position to arrive at plecanatide based on: (1) Currie's disclosure that uroguanylin "may . . . act as a laxative and be useful in patients suffering from constipation," J.A. 00237 (citing J.A. 01897), (2) Li's disclosure that the substitution would create a compound with affinity to guanylate cyclase receptors "comparable" to that of uroguanylin, J.A. 00237 (citing J.A. 01910), and (3) evidence that the substitution was "conservative." J.A. 00236–37 (citing J.A. 01347–48).

In its preliminary response, Bausch made two main arguments why MSN and Mylan had not established a reasonable likelihood that claim 1 would be shown to have been obvious. *Mylan Pharms., Inc., v. Bausch Health Ireland Ltd.*, No. IPR2022-00722, Paper No. 6, at 39–62 (P.T.A.B. Jun. 29, 2022). First, Bausch contended that a person of ordinary skill in the art would not have been motivated to select uroguanylin as a lead compound for modification. Second, Bausch argued that a person of ordinary skill in the art would not have been motivated to substitute aspartic acid with glutamic acid at uroguanylin's third position with a reasonable expectation of success.

The Board disagreed, and after joining the two petitions, granted institution. During the trial phase of the proceedings, Bausch reiterated its two prior arguments and also made a new contention. Specifically, Bausch argued that, even if there had been a motivation to select uroguanylin as a lead compound and substitute aspartic acid with glutamic acid at its third position, any case of obviousness was outweighed by plecanatide's unexpected results. J.A. 01114–23. In support of that additional argument, Bausch pointed to several experiments comparing properties of plecanatide and uroguanylin. *Id.* at 01115–23.

In its final written decision, the Board maintained that a person of ordinary skill in the art would have been motivated to select uroguanylin as a lead compound and substitute aspartic acid with glutamic acid at its third position. *Decision* at *7–14. Nevertheless, the Board held that MSN and Mylan had not established that the challenged claims would have been obvious, agreeing with Bausch that the experiments it proffered demonstrated plecanatide's unexpected results which were sufficient to outweigh the *prima facie* case of obviousness. *Id.* at *15–24. In so concluding, the Board found that Bausch's experiments "reflect the use of human uroguanylin as it naturally exists, i.e., a mixture with some interconversion between topoisomers, which is the closest prior art to the peptide of claim 1." *Id.* at *16. MSN and Mylan separately appealed and we consolidated the cases for briefing and oral argument. Mylan has since voluntarily dismissed its appeal, leaving only MSN's pending. We have jurisdiction under 28 U.S.C. § 1295(a)(4)(A).

DISCUSSION

We review the Board's decisions under the Administrative Procedure Act ("APA"). Taking "due account . . . of the rule of prejudicial error," we must hold unlawful and set aside agency action, findings, and conclusions found to be . . . arbitrary, capricious, an abuse or otherwise not in accordance with the law" or "unsupported by substantial evidence." 5 U.S.C. § 706(2)(A), (E). "Substantial evidence . . . means such relevant evidence as a reasonable mind might accept as adequate to support a conclusion." *Consol. Edison Co. of N.Y. v. NLRB*, 305 U.S. 197, 217 (1938). In applying those standards, "we will uphold a decision of less than ideal clarity if the agency's path may reasonably be discerned," but "we may not supply a reasoned basis for the agency's action that the agency itself has not given." *Rovalma, S.A. v. Bohler-Edelstahl GmbH & Co. KG*, 856 F.3d 1019, 1024 (Fed. Cir. 2017) (citations omitted). Accordingly, "the Board must, as to issues made material by the governing law, set forth a sufficiently detailed

explanation of its determinations both to enable meaningful judicial review and to prevent judicial intrusion on agency authority." *Id.*

On appeal, MSN argues that the Board erred in concluding that the experiments proffered by Bausch supported its argument of unexpected results. For its part, Bausch argues that the Board's conclusion as to unexpected results was supported by substantial evidence. Alternatively, Bausch argues that the Board's decision should be affirmed because its threshold finding that a person of ordinary skill in the art would have been motivated to select uroguanylin as a lead compound for modification was not supported by substantial evidence. We begin with Bausch's alternative affirmance argument.

I

Whether a new chemical compound would have been *prima facie* obvious depends in part on a comparison with its closest prior art. *See e.g.*, *In re Payne*, 606 F.2d 303, 315– 16 (CCPA 1979) (collecting cases). In doing so, a court may utilize what has become known as a "lead compound" analysis, which ordinarily follows a two-part inquiry. *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1291 (Fed. Cir. 2012). In such a case, the first inquiry is whether a person of ordinary skill in the art "would have selected the asserted prior art compound[] as [a] lead compound[], [*i.e.*,] . . . a compound in the prior art that would be most promising to modify in order to improve upon its activity and obtain a compound with better activity." *Id.* (citation omitted). The second inquiry "is whether the prior art would have supplied one of ordinary skill in the art with a reason or motivation to modify a lead compound to make the claimed compound with a reasonable expectation of success." *Id.* at 1292 (citations omitted).

The Board concluded that MSN had established a *prima facie* case of obviousness, first determining that a person of ordinary skill in the art would have recognized

uroguanylin as a good candidate for treating constipation and therefore selected it as a lead compound for further modification. *See Decision* at *7–9. That finding was supported by substantial evidence. As noted, Currie discloses that uroguanylin "may . . . act as a laxative and be useful in patients suffering from constipation." J.A. 01897. And although uroguanylin was known to interconvert between its active A form and inactive B form, particularly at low pH levels, thereby decreasing its affinity for guanylate cyclase receptors, MSN's expert testified that that instability could be mitigated using simple techniques known to a person of ordinary skill in the art. *Decision* at *9 (citing J.A. 03200 ¶ 29 (MSN expert declaration stating that a person of ordinary skill in the art could easily formulate a tablet of uroguanylin with a protective coating to target release in the higher pH environment of the small intestine as opposed to the lower pH environment of the stomach)). It was therefore reasonable for the Board to conclude that uroguanylin was a promising compound to modify to improve upon its already-known laxative effects.

Bausch contends that the Board's conclusion lacks substantial evidence support because another guanylate cyclase receptor agonist, bacterial ST peptide, was "a far more promising option" than uroguanylin for treating constipation. Resp. Br. 68. Specifically, Bausch argues that because bacterial ST peptide was "not afflicted with topoisomerism" and produced "remarkabl[y]" more cGMP than uroguanylin, a person of ordinary skill in the art would have been motivated to select bacterial ST peptide as a lead compound instead of uroguanylin. *Id.* at 68–69. But the Board already considered and reasonably rejected that argument. It explained that, although uroguanylin was in those respects "disadvantag[ous] relative to [bacterial ST peptide]," a person of ordinary skill in the art would still select uroguanylin over bacterial ST peptide as a lead compound because bacterial ST peptide was derived from pathogenic bacteria, and thus "dangerous" for administration in

humans. *Decision* at *8–9. That finding is consistent with Currie and Li. J.A. 01897 (Currie: bacterial ST peptide is known to be a "major cause" of diarrhea, causing dehydration); J.A. 01901 (Li: exposure to high levels of bacterial ST peptide "produces a watery diarrhea that can lead to dehydration and death"). Accordingly, the Board's conclusion that a person of ordinary skill in the art would have selected uroguanylin as the most promising compound to improve upon its effects as a laxative was supported by substantial evidence.

In view of the foregoing, and because Bausch does not challenge the Board's determination that a person of ordinary skill would have been further motivated to modify the third position of uroguanylin to make plecanatide with a reasonable expectation of success, we do not disturb the Board's determination that MSN established a *prima facie* case of obviousness. We accordingly move to the issue of unexpected results.

II

One way to rebut a *prima facie* case of obviousness is to demonstrate "unexpected results." *E.g.*, *In re Harris*, 409 F.3d 1339, 1343 (Fed. Cir. 2005). In the context of chemical compounds, such a showing is often made through comparative testing, *i.e.*, by demonstrating through experimentation that the "claimed compound[] possess[es] unexpectedly advantageous or superior properties" relative to a lead compound. *In re Payne*, 606 F.2d 303, 315–16 (CCPA 1979).

As noted, Bausch proffered several experiments comparing the chemical properties of plecanatide, uroguanylin, and other guanylate cyclase receptor agonists in support of its argument that substituting aspartic acid for glutamic acid at uroguanylin's third position produced unexpected results. Specifically, the experiments compared: (1) the amount of cGMP produced by each peptide at a neutral pH, (2) the amount of cGMP produced by each peptide across

different pHs found in the GI tract, (3) the binding affinity of each peptide for guanylate cyclase receptors, and (4) the ratio of active to inactive topoisomers after each peptide was incubated in an acidic solution.[1] Based on the results of those experiments, the Board found that plecanatide exhibited unexpectedly increased potency, pH sensitivity, binding affinity, and topoisomeric stability relative to uroguanylin, and that those unexpected results were sufficient to outweigh the *prima facie* case of obviousness. *Decision* at *15–24.

MSN argues that the Board legally erred by relying on those experiments. First, MSN argues that the experiments did not compare the claimed plecanatide with the "closest prior art." Open. Br. 26–31. Second, MSN asserts that the experiments did not comport with the requirement that unexpected results must be "commensurate in scope" with the challenged claims. *Id.* at 31–36. Third, MSN contends that the experiments were insufficient to support a finding of non-obviousness because they merely demonstrate "differences in degree," not the required "differences in kind." *Id.* at 36–44. And fourth, MSN argues that the experiments did not undermine the *prima facie* case of obviousness. *Id.* at 44–53. We need only address the first argument to resolve this appeal.

To demonstrate that unexpected results are attributable to a claimed compound as opposed to some other non-claimed factor, a patent owner "relying upon a comparative showing to rebut a prima face case must compare [the] claimed [compound] with the closest prior art"—*i.e.*, the most similar compound found in the prior art. *In re*

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[1] Bausch also proffered an experiment that it contended demonstrated that plecanatide was unexpectedly more heat stable than uroguanylin. The Board disagreed and Bausch does not appeal that finding. *Decision* at *21–22.

Merchant, 575 F.2d 865, 869 (CCPA 1978) (collecting cases). Thus, where one or both of the claimed or lead compounds can exist in different three-dimensional structures, it follows that for comparative testing to satisfy the closest-prior-art requirement, it must compare the "structurally closest" forms of those compounds. *See Astrazeneca Pharms. LP v. Teva Pharms. USA, Inc.*, 583 F.3d 766, 775 (Fed. Cir. 2009) (citing *Merchant*, 575 F.3d at 868)).

At the Board, MSN's argument that the experiments did not compare the claimed plecanatide with the closest prior art was built upon multiple premises. First, MSN asserted that plecanatide, like uroguanylin, exhibits topoisomerism and could exist in both an active A form and inactive B form. *See* J.A. 00928–29. And because the challenged claims did not recite any structural limitations, MSN asserted that they encompassed both the active A and inactive B forms of plecanatide. *Id.* In support of its position, MSN proffered submissions made by Bausch to the European Patent Office ("EPO") stating that plecanatide "can exist in two different iso[mers], only one of which is biologically active." *Id.* (citing J.A. 03352). Furthermore, MSN contended that the experiments only used the active A form of plecanatide. J.A. 00928 (citing J.A. 01371–72 ¶ 168)).

Next, MSN contended that highly pure active A-form uroguanylin could have been used for comparative testing. In support of this contention, MSN presented additional research showing that the highly pure active A form of uroguanylin had been shown to be easily purified and maintained in acidic and slightly alkaline solutions and as a lyophilized powder. *Id.* (citing J.A. 04286 Fig 6C: 1% interconversion of A- to B-form uroguanylin after one hour at pH 4.5 and 5% interconversion after 70 hours at pH 7.7, J.A. 04292 lyophilized powder of A-form uroguanylin remained 99% topoisomerically pure after one year in storage).

MSN therefore asserted that because Bausch's experiments compared the active A form of plecanatide with a *mixture* of active A- and inactive B-form uroguanylin, when similarly pure active A-form uroguanylin could have been used, the requirement that comparative testing must be between the claimed compound and the structurally closest lead compound was not satisfied. J.A. 00929.

The Board disagreed. It explained, relying on additional research presented by Bausch showing that "topological isomers of human uroguanylin are not stable in solution and are readily interconvertible," that "[s]ome amount of interconversion to the inactive conformation was inevitable in [] testing." *Decision* at *16 (citing J.A. 04291). Accordingly, the Board found that the closest prior art to the claimed plecanatide was not highly pure active A-form uroguanylin, but rather a "mixture" of A- and B-form uroguanylin. *Id.* It then found that such a mixture was used in the experiments. *Decision* at *16 ("Patent Owner's tests reflect the use of human uroguanylin as it naturally exists, i.e., a mixture with some interconversion between topoisomers.") (citing no evidence in support). The Board did not come to a conclusion as to whether plecanatide exhibits topoisomerism. *Id.* ("[T]he extent to which [plecanatide] interconverts between an active and inactive topoisomer, if at all, is not clear on this record."). Nor did it address the statements put forward by MSN that Bausch made at the EPO suggesting that plecanatide can exist in both active and inactive topoisomers. *Id.* Those would seem to be essential inquiries.

We therefore conclude that the Board's determination that the experiments compared the claimed invention with the closest prior art lacks adequate explanation, for three reasons. First, the Board sidestepped the critical threshold issue of whether the claims encompass plecanatide compounds in both the active and inactive forms. As noted, to satisfy the closest-prior-art requirement in this context, the patent owner must compare the "structurally closest"

forms of the claimed compound and lead compound. *See Astrazeneca*, 583 F.3d at 775 (citations omitted). Normally, that requires determining the structural characteristics of what is said to be the claimed compound. *See id.* But the Board did not do so here, explicitly leaving open the question whether the challenged claims encompass both active and inactive topoisomers of plecanatide. *Decision* at *16. We therefore will vacate and remand the Board's decision that testing the claimed compound showed unexpected properties over the prior art. On remand, the Board should determine, based on the evidence put forward by the parties, whether plecanatide exhibits topoisomerism and whether the testing of the challenged claims should encompass both the active and inactive forms.

Second, the Board did not address MSN's contention that highly pure A-form uroguanylin could be maintained as a lyophilized powder. Guanylate cyclase receptor agonists can be administered in both solution and powder formulations. '786 patent col. 13 ll. 24–27. If it is true, as MSN contends, that uroguanylin can be maintained and therefore tested in its active A form as a lyophilized powder, that would support MSN's argument that the experiments did not use the closest prior art. But in finding that the closest prior art is a "mixture" of A- and B-form uroguanylin, the Board only cited evidence stating that uroguanylin *solutions* could not be maintained for extended periods of time. *Decision* at *16 (citing J.A. 004291). Its broad conclusion that a mixture of A- and B-form uroguanylin—regardless of its formulation—is the closest prior art therefore does not reasonably follow from the solution-specific evidence it cited in support.

Finally, the Board did not address whether the experiments submitted by Bausch actually used what it determined to be the closest prior art—a solution consisting of a mixture of A- and B-form uroguanylin. Of the four experiments, only two (analyzing cGMP production and pH

sensitivity) provide any information regarding the precise composition of the peptide solutions used, stating that the peptides were "purified (>95% purity) using a published procedure (38)." '786 patent, col. 15 l. 55. But purity in this context can refer to either of two different things: purifying uroguanylin topoisomers from one another or purifying uroguanylin from other compounds. Published procedure 38 ("Klodt"), does not appear to specify what level of purity the procedure it used is referring to. *See* J.A. 04696–04704. As for the other two experiments, neither indicates whether the peptides used were purified at the topoisomer or compound level. J.A. 05372 (binding affinity experiment: broadly stating without explanation that the peptides analyzed "were purified by RP-HPLC" prior to testing); J.A. 05070–87 (interconversion experiment: providing no information as to how the analyzed peptides were initially purified). On remand, the Board will need to reevaluate the experimental evidence consistent with its determination regarding what is the closest prior art compound as discussed above.

To complicate this last issue further, *MSN* takes contradictory positions as to what level of purity Klodt refers. In the context of its closest-prior-art argument, MSN asserts that Klodt refers to purity with respect to other compounds, not topoisomerism. *See* Oral Arg. at 3:56–4:50, *available at* https://oralarguments.cafc.uscourts.gov/default.aspx?fl=24-1011_04072025.mp3 (Klodt "doesn't say topoisomeric purity, it just says purity, [which refers to] excluding other peptides, [not] isolating a particular topoisomer of a single peptide"); *see also* Reply Br. 5–6 ("The Board never accepted [that] ≥95%" purity meant the uroguanylin was "≥95% *topoisomerically-pure* A-form.") (emphasis in original). But for its commensurate-in-scope argument, MSN asserts that the same procedure in Klodt was used to purify peptides at the topoisomer level. *See* Open. Br. 31 (stating that because plecanatide was purified using the procedure outlined by Klodt, only "purified A-

form" plecanatide was used in the cGMP production and pH sensitivity experiments).

In sum, without more explanation from the Board as to its determination that the experiments compared the challenged claims to the closest prior art, we cannot reach a judgment on MSN's challenges to the Board's holding of non-obviousness. Should the Board determine that the experiments cannot be shown to have compared the closest prior art compound, their value with respect to its unexpected results determination is considerably diminished.

CONCLUSION

We have considered the parties remaining arguments and find them unpersuasive. For the foregoing reasons, we *vacate* the Board's decision and *remand* for further proceedings consistent with this opinion.

VACATED AND REMANDED

COSTS

The parties shall bear their own costs.