United States Court of Appeals for the Federal Circuit

NOVARTIS AG, MITSUBISHI PHARMA CORP.,
Appellants

v.

TORRENT PHARMACEUTICALS LIMITED, APOTEX INC., MYLAN PHARMACEUTICALS INC.,
Appellees

2016-1352

Appeal from the United States Patent and Trademark Office, Patent Trial and Appeal Board in Nos. IPR2014-00784, IPR2015-00518.

Decided: April 12, 2017

ROBERT TRENCHARD, Gibson, Dunn & Crutcher LLP, New York, NY, argued for appellants. Appellant Novartis AG also represented by JANE M. LOVE; MICHAEL A. VALEK, Dallas, TX; ALEXANDER N. HARRIS, San Francisco, CA.

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TERESA STANEK REA, Crowell & Moring, LLP, Washington, DC, argued for appellees. Appellee Apotex Inc. also represented by VINCENT JOHN GALLUZZO; JONATHAN M. LINDSAY, Irvine, CA.

MICHAEL K. LEVY, Andrews Kurth Kenyon LLP, New York, NY, for appellee Torrent Pharmaceuticals Limited.

SHANNON BLOODWORTH, Perkins Coie, LLP, Washington, DC, for appellee Mylan Pharmaceuticals Inc. Also represented by BRANDON MICHAEL WHITE; DAN L. BAGATELL, Hanover, NH.

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

CHEN, *Circuit Judge*.

This is an appeal from the Final Written Decision of the United States Patent and Trademark Office, Patent Trial and Appeal Board (Board) in two consolidated *inter partes* review (IPR) proceedings of U.S. Patent No. 8,324,283 (the '283 patent), owned by Novartis AG and Mistubishi Tanabe Pharma Corp. (collectively, Novartis). The Board instituted IPRs on all claims of the '283 patent based on petitions filed by Torrent Pharmaceuticals Limited, Apotex, Inc. and Mylan Pharmaceuticals Inc. (collectively, Petitioners). After reviewing the claims, receiving extensive briefing, and hearing oral argument, the Board found all original claims of the '283 patent and Novartis' proposed substitute claims unpatentable as obvious. *See Torrent Pharm. Ltd. v. Novartis AG*, Nos. IPR2014-00784, IPR2015-00518, 2015 WL 5719630 (PTAB Sept. 24, 2015) (*Final Written Decision*). Novartis raises a series of challenges to the Board's analysis of the evidence and ultimate determination of unpatentability. For the reasons stated below, we *affirm*.

BACKGROUND

I.

The '283 patent relates to a solid pharmaceutical composition suitable for oral administration, comprising a sphingosine-1 phosphate (S1P) receptor agonist and a sugar alcohol, which the patent explains is useful for the treatment of certain autoimmune diseases such as multiple sclerosis. '283 patent, col. 1, lines 11–14, 33–35; col. 12, lines 19–49. According to the specification, S1P receptor agonists generally exhibit properties that make formulations suitable for oral administration of a solid composition difficult to create. However, "solid compositions comprising a sugar alcohol provide formulations which are particularly well suited to the oral administration of S1P receptor agonists." *See id.* at col. 1, lines 36–39. They also "provide a convenient means of systemic administration of S1P receptor agonists, do not suffer from the disadvantages of liquid formulations for injection or oral use, and have good physiocochemical and storage properties." *Id.* at col. 1, lines 39–43. In such a composition, the S1P receptor agonist is the active ingredient and the sugar alcohol acts as an excipient—the substance formulated alongside the active ingredient as a diluent, carrier, filler and/or bulking agent for the composition. *See id.* at col. 9, lines 53–54.

The '283 patent states that there are multiple known S1P receptor agonists appropriate for use in the claimed invention, set forth in the specification as formulas I–XIII. *Id.* at col. 1, line 51 to col. 8, line 4. The '283 patent also states that a "particularly preferred S1P receptor agonist of formula I is FTY720, i.e., 2-amino-2-[2-(4-octylphenyl) ethyl]propane-1,3-diol in free form or in a pharmaceutically acceptable salt form . . . ." *Id.* at col. 8, lines 23–26. FTY720 is also known as fingolimod. The '283 patent further discloses that the specific sugar alcohol used in the claimed composition "may suitably be mannitol,"

because of its non-hygroscopic properties (i.e., it is not likely to absorb moisture, which is beneficial in manufacturing solid oral pills). *Id.* at col. 9, lines 53–54.

Claims 1 and 19 of the '283 patent are the only independent claims and are illustrative of the claimed subject matter:

> 1. A solid pharmaceutical composition suitable for oral administration, comprising:
>
> > (a) a S1P receptor agonist which is selected from 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol, 2-amino-2-[4-(3-benzyloxyphenoxy)-2-chlorophenyl]propyl-1,3-propane-diol, 2-amino-2-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]propyl-1,3-propane-diol, or 2-amino-2-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-ethyl-1,3-propane-diol, and its phosphates or a pharmaceutically acceptable salt thereof; and
> >
> > (b) a sugar alcohol.
>
> 19. A solid pharmaceutical composition suitable for oral administration, comprising mannitol and 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol or a pharmaceutically acceptable salt thereof.

Id. at col. 17, lines 2–11; col. 18, lines 7–10. Thus, claim 1 is directed towards a solid oral composition comprised of the combination of one of a handful of S1P receptor agonists and any sugar alcohol, whereas claim 19 is directed towards the specific combination of fingolimod and mannitol in a solid oral composition.

The dependent claims are directed towards various refinements of the composition, including for example, the addition of a lubricant:

> 20. A composition according to claim 19, further comprising a lubricant.

Id. at col. 18, lines 11–12. Other claims are directed towards adjusting the respective amount of ingredients:

> 22. A composition according to claim 19, wherein the compound 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol, or a pharmaceutically acceptable salt thereof, is present in an amount of 0.5 to 5% by weight, based on the total weight of the composition.
>
> 23. A composition according to claim 19, wherein mannitol is present in an amount of 90 to 99.5% by weight, based on the total weight of the composition.

Id. at col. 18, lines 15–22.

While the application leading to the '283 patent was pending at the Patent Office, Novartis applied to the U.S. Food and Drug Administration (FDA) for approval to sell a fingolimod-mannitol pill to treat multiple sclerosis under the "Gilenya" brand name. The FDA approved Gilenya for the treatment of multiple sclerosis in 2010.

II.

On May 27, 2014, Torrent filed a petition to institute an *inter partes* review of claims 1–32 of the '283 patent. Torrent's petition presented three separate patentability challenges:

> 1. claims 1–32 are unpatentable as obvious over the combination of U.S. Patent No. 6,004,565 (Chiba) and *Pharmaceutics: The Science of Dosage Form Design* (Aulton); and
>
> 2. claims 1–4, 7, 8, 19, 22 and 32 are unpatentable as anticipated by U.S. Patent No. 6,277,888 (Sakai); and

3. claims 1–32 are unpatentable as obvious over Chiba and Sakai.

Chiba teaches the use of immunosuppressive compounds with fingolimod as the preferred species. J.A. 18442.[1] Chiba also teaches that these immunosuppressive compounds are useful for treating "autoimmune diseases such as . . . multiple sclerosis," among other diseases and conditions. J.A. 18443. Chiba goes on to disclose oral administration of fingolimod, including "admix[ing] with [a] carrier, excipient, diluent, and so on and formulat[ion] into . . . capsules [or] tablets . . . for administering to patients." J.A. 18444. In discussing the preparation of these capsules and tablets for oral administration of fingolimod, Chiba teaches that "pharmaceutically or physiologically acceptable carriers or excipients for use with the . . . compounds noted herein are known in the art or can be readily found by methods and tests known in the art." J.A. 18446. In other words, Chiba teaches a solid oral composition of fingolimod combined with a generic excipient.

Aulton teaches the use of tablets and capsules to administer drugs orally. J.A. 19041. It specifically teaches that "[t]he successful formulation of a stable and effective solid dosage form depends on the careful selection of the excipients which are added to facilitate administration, promote the consistent release and bioavailability of the drug and protect it from degradation." J.A. 19066–167. Aulton recommends mannitol as a common diluent used in "[t]ableting by the wet granulation process," which Aulton describes as "the most widely used method for pharmaceutical materials." J.A. 19074–77. Aulton describes mannitol as "expensive," but "commonly used" as an excipient in solid oral compositions. J.A. 19077.

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[1] Citations to "J.A. ____" refer to the Joint Appendix filed by the parties.

Sakai describes a pharmaceutical composition containing fingolimod as an active ingredient. J.A. 18421. More particularly, Sakai discloses that the composition can be formulated into a liquid preparation, or can be a solid lyophilized (freeze-dried) product. J.A. 18421–22. Sakai further discloses that the addition of a saccharide, such as sugar alcohol, to the composition can result in a less irritating resulting liquid solution. J.A. 18421. Sakai discloses a list of eight exemplary saccharides, including mannitol. J.A. 18422. The saccharide, such as mannitol, can be dissolved in the liquid for dissolution, or alternatively may be contained in the lyophilized product along with the active ingredient. J.A. 18422. Sakai teaches that this liquid pharmaceutical composition can be used for immunosuppression in connection with organ or bone marrow transplantation, autoimmune diseases, or allergic diseases. *Id.* In short, Sakai teaches the specific combination of fingolimod and mannitol for a liquid formulation.

III.

On December 1, 2014, the Board granted in part Torrent's petition and instituted trial to review patentability of the challenged claims in IPR2014-00784. Specifically, the Board instituted on the first ground, the combination of Chiba and Aulton, but declined to institute on grounds two or three. The Board found that Chiba discloses the use of fingolimod in a solid formulation for oral administration when combined with conventional excipients. It then found that Aulton teaches the use of mannitol as a conventional excipient that a person of skill in the art would have looked to when formulating a solid composition with fingolimod.

The Board found Sakai to be an improper anticipatory reference because the reference does not describe a solid composition suitable for oral administration. It then rejected the grounds predicated on the combination of

Chiba and Sakai for similar reasons, noting that, unlike Aulton, "Sakai does not identify mannitol as a 'conventional excipient' in solid pharmaceutical compositions, and Sakai's stated reasons for using mannitol in liquid pharmaceutical compositions are inapplicable to its potential use in connection with solid pharmaceutical compositions." J.A. 72.

Apotex and Mylan thereafter filed a separate petition seeking to institute an IPR of claims 1–32 of the '283 patent based on the already-instituted Chiba/Aulton grounds and requested joinder with the Torrent proceedings. On February 17, 2015, the Board instituted trial in this follow-on proceeding in IPR2015-00518 and joined it with the Torrent proceeding.

After briefing and oral argument, the Board issued its Final Written Decision in the consolidated proceeding. The Board concluded that Chiba and Aulton collectively teach each limitation of claims 1–32 of the '283 patent. It first addressed claim 19, directed towards the specific combination of fingolimod and mannitol. The Board found that Chiba and Aulton together strongly suggested the claimed two-ingredient combination:

> First, Chiba teaches that a person of ordinary skill in the art would have been able to identify or easily determine excipients that would have been compatible with fingolimod . . . ("pharmaceutically or physiologically acceptable carriers or excipients for use with the . . . compounds noted herein are known in the art or can be readily found by methods and tests known in the art"). Second, Aulton teaches that mannitol is not only a known diluent for direct compression manufacturing, but also commonly used in wet granulation, which Aulton teaches is "the most widely used method for pharmaceutical materials." . . . This combination of teachings already strongly suggests that man-

> nitol likely would have been a target of investigation for a person of ordinary skill in the art interested in finding an excipient compatible with fingolimod . . . .

Final Written Decision, 2015 WL 5719630, at *8. After finding that the two references themselves strongly suggested the claimed invention, the Board expressly found "additional evidence of the reason to combine fingolimod and mannitol." *Id.* First, the Board noted that Sakai "directly instructs that the two ingredients should be combined." *Id.* Although Novartis argued in its briefs below that Sakai's teaching is narrowly limited to liquid-phase pharmaceutical compositions, as opposed to the claimed solid oral dosage forms, the Board observed that Novartis' own expert, Dr. Stephen Byrn, had written an article describing how "solution studies can be very helpful" in understanding drug degradations in the solid state. *Id.* Despite Novartis' attempt to minimize the article's meaning, the Board concluded that "a suggestion to combine ingredients in the liquid phase would have been relevant to the determination of a person of ordinary skill in the art to combine the same ingredients in the solid phase." *Id.*

Acknowledging that it had denied instituting the IPR based on Sakai alone (per § 102) or in combination with Chiba (per § 103), the Board distinguished its final decision's usage of Sakai, explaining that its final decision simply relied on Sakai as a background reference that offered additional motivation evidence to combine Chiba with Aulton. The Board explained that even though Sakai did not "teach that mannitol is a conventional excipient for use in solid pharmaceutical compositions," *id.*, the record evidence relating to Dr. Byrn's article, which was debated by the parties, supported a finding that "Sakai's teaching would have been relevant to the decision on which excipient to use in formulating a solid oral dosage form of fingolimod." *Id.*

The Board went on to find that several additional background references in the proceeding demonstrate that mannitol provides advantages when used as a diluent in tableting, further supporting a reason to combine. The Board concluded its motivation to combine analysis:

> Given (1) the knowledge in the art that mannitol provided advantages in formulating tablets generally, (2) Chiba's teaching that a person of ordinary skill in the art would have been able to identify or easily determine excipients that would have been compatible with fingolimod, (3) Aulton's teaching that mannitol was a diluent commonly used in the most common form of pharmaceutical manufacture, (4) Sakai's teaching that mannitol and fingolimod should be combined in the liquid phase, and (5) Dr. Byrn's statement that liquid-phase compatibility was relevant to the prediction of solid-phase compatibility, we conclude that Petitioners have shown a reason to combine the teachings of Chiba and Aulton.

Id. at *9.

The Board next turned to the objective indicia of nonobviousness. First, it found that independent claims 1 and 19 were "not commensurate in scope" with the purported unexpected result of fingolimod's low concentration stability when combined with mannitol, because the independent claims are "not limited to any particular dose or dose range of fingolimod." *Id.* at *10. Therefore, the Board concluded, "even if the stability of the mannitol-fingolimod combination at low doses was unexpected, it is insufficient to support a legally significant finding of unexpected results." *Id.* at *11. The Board also rejected Novartis' long-felt but unsolved need, industry praise, and commercial success arguments because all of Novartis' proffered evidence was directed solely toward the fact that

Gilenya was a solid oral multiple sclerosis treatment, which was already known in the prior art.

The Board then analyzed the dependent claims in turn. Relevant to this appeal, the Board turned to dependent claims 8, 10, 22, and 23, and proposed amended claims 40, 42, 54, and 55, directed towards concentrations with low percentages of fingolimod by weight. The Board found that "Petitioners provide evidence that the selection of the relative amounts of the constituents of the claimed formulation is the result of routine optimization." *Id.* at *16. It further noted, "[w]e have not been directed to any evidence of record contradicting this evidence, so we find that a person of ordinary skill in the art familiar with Chiba and Aulton would have been able and motivated to optimize the amount of fingolimod . . ." *Id.*

In conclusion, the Board held every claim unpatentable as obvious and denied Novartis' motion to amend for essentially the same reasons it rejected the original claims. Appellants timely appealed. We have jurisdiction under 28 U.S.C. § 1295(a)(4)(A).

DISCUSSION

We review Board decisions using the standard set forth in the Administrative Procedure Act (APA), 5 U.S.C. § 706. *In re Sullivan*, 362 F.3d 1324, 1326 (Fed. Cir. 2004) (citing *Dickinson v. Zurko*, 527 U.S. 150, 154 (1999)); *see also Belden Inc. v. Berk–Tek LLC*, 805 F.3d 1064, 1080 (Fed. Cir. 2015). Under the APA, we must "hold unlawful and set aside agency action . . . not in accordance with law [or] . . . without observance of procedure required by law." 5 U.S.C. § 706.

We review the Board's legal conclusions de novo but review for substantial evidence any underlying factual determinations. *See Nike, Inc. v. Adidas AG*, 812 F.3d 1326, 1332 (Fed. Cir. 2016); *In re Giannelli*, 739 F.3d 1375, 1378–79 (Fed. Cir. 2014). Substantial evidence is

"such relevant evidence as a reasonable mind might accept as adequate to support a conclusion." *Consol. Edison Co. v. NLRB*, 305 U.S. 197, 229 (1938); *see In re Applied Materials, Inc.*, 692 F.3d 1289, 1294 (Fed. Cir. 2012).

On appeal, Novartis first contends that the Board violated the APA when it relied on Sakai in the Final Written Decision without affording Novartis proper notice and a chance to be heard. Novartis goes on to argue that the Board also erred on the merits, specifically in its analysis of the motivation to combine evidence and in its treatment of the alleged objective indicia of nonobviousness.

I. APA Due Process

We first turn to Novartis' argument that the Board violated the requirements of notice and an opportunity to respond found in the APA when it used the Sakai reference as part of its motivation to combine analysis in the Final Written Decision. According to Novartis, the Board ruled Sakai entirely out of the case in the Institution Decision, and on that basis, denied institution of the two proposed grounds based on Sakai. Novartis contends that it relied on that ruling and consequently submitted a "vastly different" record than it would have if it had known Sakai was still a live issue.

In a formal adjudication, such as an IPR, the APA imposes certain procedural requirements on the agency. The Patent and Trademark Office, including the Board, must provide the patent owner with timely notice of "the matters of fact and law asserted," and an opportunity to submit facts and argument. 5 U.S.C. §§ 554(b)–(c), 557(c); *Dell Inc. v. Acceleron, LLC*, 818 F.3d 1293, 1301 (Fed. Cir. 2016). The notice and opportunity to be heard provisions of the APA have been applied "to mean that 'an agency may not change theories in midstream without giving respondents reasonable notice of the change' and 'the opportunity to present argument under the new theory.'"

Belden, 805 F.3d at 1080 (quoting *Rodale Press, Inc. v. FTC*, 407 F.2d 1252, 1256–57 (D.C. Cir. 1968)). In this case we conclude that the relevant APA provisions were satisfied.

A.

We first disagree with Novartis that the Board ruled Sakai out of the case entirely in the Institution Decision. In the Institution Decision, the Board declined to read Sakai as an anticipatory reference or primary obviousness reference because Sakai does not disclose "mannitol as a 'conventional excipient' in solid pharmaceutical compositions, and Sakai's stated reasons for using mannitol in liquid pharmaceutical compositions are inapplicable to its potential use in connection with solid pharmaceutical compositions." J.A. 72. In other words, although Sakai discloses the combination of fingolimod and mannitol, it does not expressly disclose the combination in a solid pharmaceutical composition nor does its teaching of a liquid composition necessarily translate to a solid oral composition.

This conclusion, however, is not contrary to the Board's discussion of Sakai in the Final Written Decision that Sakai's teachings would have nevertheless been relevant to one of skill in the art in deciding which excipients to use in formulating a solid oral dosage form of fingolimod. Having already found that Chiba and Aulton strongly suggest the combination of fingolimod and mannitol in a solid oral composition, the Board found that Sakai merely reinforced its finding that the person of ordinary skill in the art would have expected mannitol to be compatible with fingolimod because Sakai discloses a stable combination of these two ingredients suitable for long-term preservation. The Board's discussion of Sakai in the Final Written Decision was not inconsistent with its review of Sakai in the Institution Decision.

B.

We also reject as unfounded Novartis' complaints of "surprise" and contention that, following the Institution Decision, the parties "paid Sakai scant attention in subsequent proceedings." The parties debated Sakai at length throughout the proceeding and in the same context that it was discussed by the Board in the Final Written Decision.

As an initial matter, we note that in addition to asserting Sakai as a primary reference, Torrent's petition also argued that several references, including Sakai, further support the motivation to combine the teachings of Chiba and Aulton. Specifically, Torrent argued in connection with the combination of Chiba and Aulton that "Sakai (Ex. 1005) reinforced the expectation to the ordinarily-skilled artisan that mannitol would have been compatible with FTY720 [fingolimod] because Sakai discloses pharmaceutical injectable compositions containing FTY720 [fingolimod] and mannitol in solution, as well as lyophilized product meant for long-term preservation in vials containing FTY720 [fingolimod] and mannitol." J.A. 6832. And in support of their petition, Apotex and Mylan also explained that Sakai would direct the person of ordinary skill in the art to the combined teachings of Chiba with Aulton. It reiterated the argument raised in the Torrent petition that the ordinarily skilled artisan would have naturally considered mannitol because of its known compatibility with fingolimod, again citing Sakai's disclosure of a stable composition comprised of these two ingredients.

Following institution of the Apotex/Mylan proceeding and joinder with the Torrent proceeding, the relevance of Sakai's compatibility-disclosure to support a motivation to combine Chiba and Aulton was an ongoing, debated issue that Novartis addressed directly, on multiple occasions. In its Patent Owner's Response, Novartis specifically

argued that Petitioners' reliance on Sakai's stability-disclosure in connection with the motivation to combine inquiry lacked merit because Sakai is relevant only to liquid compositions. Petitioners continued to press the issue in their Reply, contending that Sakai "would have provided a [person of skill in the art] with a reasonable expectation that mannitol is compatible with fingolimod." J.A. 7782.

Furthermore, both Petitioners' expert and Novartis' expert went into significant detail in their post-institution declarations discussing Sakai and its applicability to the motivation to combine inquiry. Novartis' counsel then questioned Petitioners' expert at length about Sakai. And Novartis' submitted Observations on Cross Examination repeatedly explained why Sakai did not support Petitioners' motivation to combine argument. At the hearing, both parties submitted demonstrative slides dedicated to Sakai and spent considerable attention discussing Sakai's relevance as a background reference supporting the motivation to utilize mannitol with fingolimod in an oral formulation. Based on this record, it is quite clear that Novartis had more than sufficient notice and opportunity to be heard on Sakai's potential relevance, and in fact actively and repeatedly attempted to distinguish Sakai to defeat the very argument relied on by the Board in the Final Written Decision.

In sum, we reject Novartis' contention to this court that it believed Sakai was not at issue in the proceeding.[2] For this reason we reject Novartis' APA challenge.

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[2] Indeed, had Novartis believed the Board eliminated Sakai from the proceeding, it had various procedural mechanisms at its disposal to respond to any perceived impropriety with Petitioners' continued reliance on the reference. In particular, Novartis could have moved to

C.

Finding no APA violation for the reasons discussed above, we nevertheless also reject Novartis' characterization of Sakai as the "missing link" in the Board's obviousness analysis. Contrary to Novartis' contention, Sakai was discussed by the Board as one of several independent grounds supporting the motivation to combine fingolimod and mannitol in a solid oral composition. In finding a motivation to combine, the Board explained that the teachings of Chiba and Aulton alone "already strongly

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exclude the Sakai reference. *See Genzyme Therapeutic Prods. v. Biomarin Pharm. Inc.*, 825 F.3d 1360, 1368 (Fed. Cir. 2016). We find meritless Novartis' argument that it did in fact move to exclude Sakai from the proceeding. *See* Oral Arg. at 53:30–53:51: *available at* http://oralarguments.cafc.uscourts.gov/default.aspx?fl=2016-1352.mp3. Although not provided in the Joint Appendix, Novartis' counsel invited the court to review its motion to exclude. That invitation, unfortunately, led the court on a road to nowhere. In its motion, Novartis moved to exclude over fifty exhibits, including Sakai, all identified by exhibit number only and listed in one long string cite, based on one conclusory sentence: "Petitioners rely on numerous exhibits that are incomplete and/or irrelevant to the sole issue for review identified by the Board – *i.e.*, (non)obviousness of the '283 Patent in light of Chiba over Aulton)." Patent Owner's Motion to Exclude at 20, Paper No. 73. This superficial treatment amounts to little more than a request that the Board peruse the cited evidence and piece together a coherent argument on Novartis' behalf. It is far from sufficient to raise a meaningful challenge to any of the several dozen exhibits, let alone to sensitize the Board to the complained-of use of Sakai in particular.

suggests that mannitol likely would have been a target of investigation for a person of ordinary skill in the art interested in finding an excipient compatible with fingolimod." *Final Written Decision*, 2015 WL 5719630, at *8.

Nevertheless, the Board continued to bolster its analysis with "additional evidence of the reason to combine fingolimod and mannitol." *Id.* And Sakai's teaching to combine fingolimod and mannitol was just one of those additional reasons. The Board further explained that "[i]n addition to the direct teaching in Sakai that mannitol and fingolimod should be combined, several documents that would have been known to a person of ordinary skill in the art teach that mannitol provides advantages when used as a diluent in tableting." *Id.* at *9. The Board went on to explain that these references—all unchallenged on appeal—describe known advantages of using mannitol as an excipient in solid oral compositions that "provide a strong reason to combine Chiba's teaching of a solid oral dosage form of fingolimod and Aulton's teaching of mannitol as an excipient for making solid oral dosage forms." *Id.* These additional references are also substantial evidence supporting the Board's motivation to combine conclusion, independent of Sakai. This is not a case where Sakai provided the linchpin of the Board's analysis, as Novartis contends.

For all these reasons, we find no violation of the APA with respect to the Board's discussion of Sakai in the Final Written Decision.

II. OBVIOUSNESS

We turn to Novartis' remaining challenges to the Board's obviousness analysis.

Obviousness is a mixed question of fact and law. The Board's ultimate conclusion that the claims are not obvious is a legal determination subject to de novo review,

however, the subsidiary factual findings are reviewed for substantial evidence. *In re Gartside*, 203 F.3d 1305, 1316 (Fed. Cir. 2000). Motivation to combine is one of those underlying factual issues. *Id.* ("The presence or absence of a motivation to combine references in an obviousness determination is a pure question of fact."). Whether objective indicia support a finding of nonobviousness is also a factual question. *Merck & Cie v. Gnosis S.P.A.*, 808 F.3d 829, 833 (Fed. Cir. 2015).

A. Motivation to Combine

Novartis argues that the Board further erred in its motivation to combine analysis because it failed to read the prior art as a whole and overlooked critical evidence of mannitol's known disadvantages as an excipient for solid compositions. In particular, Novartis argues that it pointed out mannitol's negative properties, including difficulty to manufacture, the existence of impurities, and expense. Because the Board did not expressly state that it was weighing all of these negatives against mannitol's positives, Novartis contends that the Board's motivation to combine analysis was legally flawed. In support of its contention, Novartis directs the court to *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157 (Fed. Cir. 2006). In *Medichem*, this court explained that "[w]here the prior art contains 'apparently conflicting' teachings (i.e., where some references teach the combination and others teach away from it) each reference must be considered 'for its power to suggest solutions to an artisan of ordinary skill . . . consider[ing] the degree to which one reference might accurately discredit another.'" *Id.* at 1165 (quoting *In re Young*, 927 F.2d 588, 591 (Fed. Cir. 1991)).

Contrary to Novartis' contention, the record reflects that the Board considered Novartis' arguments regarding motivation to combine, weighed them against the competing evidence and argument, and concluded that despite Novartis' contentions, one of skill in the art would have

been motivated to combine fingolimod with mannitol in a solid composition. Indeed, the Board expressly discussed one of mannitol's negative properties in the Final Written Decision—its expense—but noted that, despite this potentially discouraging characteristic, it was still "commonly used." *Final Written Decision*, 2015 WL 5719630, at *5. And it went on to cite the portion of the Patent Owner's Response discussing the arguments Novartis highlights on appeal when rejecting Novartis' teaching-away argument.

Moreover, the Board's consideration of mannitol's negative properties in the Final Written Decision was at least commensurate with Novartis' presentation of those issues to the Board in its Patent Owner Response. In a lengthy brief, Novartis' discussion was relegated to one passing, unsupported sentence, stating that "[w]hile mannitol has some positive properties, it also has negative ones, including expense, poor machinability and possible impurities." J.A. 7354. Novartis did not direct the Board to the expert declarations it now highlights on appeal, nor did it direct the Board to any record evidence at all. And there is no indication in the record that Novartis elsewhere meaningfully advanced these suggested negatives or developed them in such a fashion as to necessarily overcome the numerous advantages of mannitol identified by Petitioners and discussed in the Final Written Decision. Thus, we are not persuaded that Novartis presented its arguments against the use of mannitol in such a way that it would be appropriate to find fault in the Board's arguably limited treatment of those arguments in the Final Written Decision.

This court's discussion in *Medichem* does not change our conclusion. Although the court there stated that prior art must be considered as a whole and the disadvantages of a reference must be considered in addition to the benefits, 437 F.3d at 1165, there is no requirement that the Board expressly discuss each and every negative and

positive piece of evidence lurking in the record to evaluate a cursory argument. In addition, this court has said on multiple occasions that failure to explicitly discuss every issue or every piece of evidence does not alone establish that the tribunal did not consider it. *See, e.g.*, *Carolina Tobacco Co. v. Bureau of Customs & Border Prot.*, 402 F.3d 1345, 1350 (Fed. Cir. 2005) ("[T]he failure of Customs to explicitly discuss the six factors when it initially increased Carolina's bond does not establish that it did not consider them."); *Lab. Corp. of Am. Holdings v. Chiron Corp.*, 384 F.3d 1326, 1332 (Fed. Cir. 2004) (stating that a district court's failure to discuss an issue does not necessarily establish that the court did not consider it); *Charles G. Williams Const., Inc. v. White*, 326 F.3d, 1376, 1380 (Fed. Cir. 2003) ("The Board's failure to discuss the evidence upon which Williams relies does not mean that it did not consider it"). The Board is "not require[d] . . . to address every argument raised by a party or explain every possible reason supporting its conclusion." *Synopsys, Inc. v. Mentor Graphics Corp.*, 814 F.3d 1309, 1322 (Fed. Cir. 2016). Here, given that the Board cited to the relevant pages of Novartis' Patent Owner Response, we find no reason to assume the Board failed to consider mannitol's cited negatives simply because they were not recited at length in the Board's Final Written Decision.

Having dispatched Novartis' numerous procedural arguments, we ask finally whether substantial evidence supports the Board's finding on the motivation to combine Chiba and Aulton. Here, we conclude that substantial evidence supports the Board's finding that, despite mannitol's potentially negative characteristics, it was nevertheless a valid consideration as an excipient for solid oral pharmaceuticals and a person of skill in the art would have been motivated to combine fingolimod and mannitol in the manner claimed by the '283 patent. Indeed, the Board cites to multiple pieces of evidence establishing mannitol as one of a handful of excipients used in solid

oral compositions and its primacy as a non-hygroscopic and compressible diluent which makes it particularly valuable in tableting.

We, therefore, find no legal error in the Board's treatment of the motivation to combine evidence nor do we find a lack of substantial evidence supporting its conclusion.

B. Objective Indicia of Nonboviousness

Novartis next argues that the Board erred in its assessment of the various objective indicia of nonobviousness. We address each argument in turn.

i. Unexpected Results

According to Novartis, the Board erred when it grouped several dependent claims with their independent claims when considering Novartis' unexpected results evidence. Novartis argues that it presented persuasive evidence to the Board that the combination of fingolimod and mannitol solved the problem of fingolimod's unexpected low dose instability. The Board rejected that argument with respect to independent claims 1 and 19 because those claims contain no dosage limitation, and therefore, the unexpected results evidence was not commensurate in scope with the claims. Novartis does not appeal that Board finding as it relates to claims 1 and 19. Instead, Novartis argues that the Board should have reassessed the unexpected results argument when it found unpatentable dependent claims 8, 10, 22, and 23, and proposed amended claims 40, 42, 54, and 55.[3] In Novartis' view, these claims recite the "low dosage" limitation lacking in claims 1 and 19.

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[3] Proposed amended claims 40, 42, 54, and 55 are identical to, and would have replaced, original claims 8, 10, 22, and 23, respectively.

At the outset, we note that the argument raised to the Board below was quite different than Novartis' characterization of that argument on appeal. In appeals from the Board, "we have before us a comprehensive record that contains the arguments and evidence presented by the parties and our review of the Board's decision is confined to the four corners of that record." *In re Watts*, 354 F.3d 1362, 1367 (Fed. Cir. 2004) (internal quotation marks and citation omitted). Thus, we must first determine whether Novartis preserved this argument for appeal. While the court "retains case-by-case discretion over whether to apply waiver," *Harris Corp. v. Ericsson Inc.*, 417 F.3d 1241, 1251 (Fed. Cir. 2005) (citations omitted), we have held that a party waives an argument that it "failed to present to the Board" because it deprives the court of "the benefit of the Board's informed judgment," *Watts*, 354 F.3d at 1367–68. We turn our attention to the unexpected results argument Novartis actually presented to the Board.

The undeniable focus of Novartis' arguments throughout the proceeding, including its Patent Owner's Response, was the patentability of the combination of fingolimod and mannitol, as broadly recited in claim 19. The Argument section of the Patent Owner's Response alerts the Board in the very first paragraph that Novartis' arguments are directed to claim 19. What follows in the Patent Owners' Response is Novartis' explanation for why there was no ex ante reason to combine fingolimod with mannitol or to reasonably expect success in the combination—untethered from any specific dosage or concentration limitation and with no discussion of any dependent claims.

Novartis' objective indicia argument under the heading "Objective Indicia Prove the Fingolimod-Mannitol Invention" is similarly generic. Novartis there contends that the objective indicia "overwhelmingly prove the patentability of the fingolimod-mannitol formula." J.A.

7362. Given the reference to the fingolimod-mannitol formula only and the failure to identify any specific claim, this section is simply a continuation of Novartis' defense of claim 19. And turning to the unexpected results section in particular, we see the entirety of Novartis' argument in a few short sentences:

> First, mannitol unexpectedly is stable with fingolimod *throughout the full dosage range*. Excipient stability normally does not vary with dose proportions. Drs. Kent and Kibbe each confirmed that fact in their depositions. [Citing deposition transcripts]. So do Dr. Byrn, Dr. Pudipeddi, and Mr. Oomura. [Citing declarations]. Petitioners do not address this unexpected result at all.

J.A. 7363 (emphasis added). Novartis did not identify the dependent claims at issue now or discuss specific dosages or concentrations at all. Nor do any of the supporting citations. The only fair characterization of Novartis' argument is that the combination of fingolimod and mannitol was unexpectedly stable irrespective of concentration, i.e., "throughout the dosage range." *Id.* Novartis' Motion to Amend likewise fails to present any separate argument for proposed amended claims 40, 42, 54, and 55.

We thus find no fault in the Board's observation that Novartis offered no separate argument with respect to dependent claims 8, 10, 22, and 23, or proposed amended claims 40, 42, 54, and 55. The sole focus of the proceeding, including Novartis' unexpected results argument, was on claim 19. Novartis even conceded at oral argument that the focus of its unexpected results argument was that fingolimod was unexpectedly stable *across the entire dosage range*. Oral Arg. at 48:40–48:49 and 53:00–53:08, *available at* http://oralarguments.cafc.uscourts.gov/default.aspx?fl=2016-1352.mp3. We find no evidence that Novartis distinctly argued an unexpected result specific to the dependent

claims Novartis now raises on appeal. That argument is therefore waived.

ii. Nexus

Novartis next argues that the Board erred as a matter of law in its analysis of the "nexus" requirement with respect to the objective evidence of nonobviousness. Before the Board, Novartis contended that its drug, Gilenya, enjoyed commercial success, industry praise, and met a long-felt but previously unsolved need, due to Gilenya being the first commercially available solid oral treatment for multiple sclerosis. On appeal, Novartis complains that the Board wrongly discounted this evidence in light of the disclosure of solid oral multiple sclerosis drug formulas in prior art references, which, in the Board's view, precluded Novartis' argued for basis for a nexus between the '283 patent's invention and the objective indicia—even though none of those drugs were available to the market until after the '283 patent was filed. Distilled down, Novartis argues that, as a matter of law, a feature that is known in the art but not actually available to the market—i.e., in commerce—cannot be used to disprove Novartis' attempts to establish a nexus based on that claimed feature.

We disagree. None of the cases cited by Novartis, or any that we are aware of, stand for such a sweeping proposition. For objective indicia evidence to be accorded substantial weight, we require that a nexus must exist "between the evidence and the merits of the claimed invention." *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010).[4] "Where the offered secondary

[4] This is not a case where Novartis argues that the required nexus may be presumed and the presumption was disregarded by the Board. Moreover, any presumption of nexus is nevertheless rebuttable by evidence that

consideration actually results from something other than what is both claimed and *novel* in the claim, there is no nexus to the merits of the claimed invention." *In re Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011); *see also Tokai Corp. v. Easton Enters., Inc.*, 632 F.3d 1358, 1369 (Fed. Cir. 2011) ("If commercial success is due to an element in the prior art, no nexus exists."); *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1312 (2006) ("[I]f the feature that creates the commercial success was known in the prior art, the success is not pertinent.").

In evaluating whether the requisite nexus exists, the identified objective indicia must be directed to what was not known in the prior art—including patents and publications—which may well be the novel combination or arrangement of known individual elements. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418–19 (2007); *Veritas Techs. LLC v. Veeam Software Corp.*, 835 F.3d 1406, 1414-15 (Fed. Cir. 2016). Our opinion in *Asyst Technologies, Inc. v. Emtrak, Inc.*, 544 F.3d 1310 (Fed. Cir. 2008), is instructive. In *Asyst,* the trial court concluded that patent owner Asyst failed to link the objective indicia to the claimed invention because the proffered evidence lacked a nexus to any feature of the invention's commercial embodiments that was not already disclosed in a prior art patent—the Hesser patent. 544 F.3d at 1316. The court found "even though commercial embodiments of [Asyst's] '421 invention may have enjoyed commercial success, Asyst's failure to link that commercial success to the features of its invention that were not disclosed in [the] Hesser [patent] undermines the probative force of the evidence pertaining to the success of Asyst's [] prod-

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the proffered objective evidence was due to extraneous factors other than the merits of the claimed invention. *See, e.g.*, *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1329 (Fed. Cir. 2016).

ucts." *Id.* We explained, "[w]hile the evidence shows that the overall system drew praise as a solution to a felt need, there was no evidence that the success of the commercial embodiment of the '421 patent was attributable to the substitution of a multiplexer for a bus, which was the only material difference between [the] Hesser [patent] and the patented invention." *Id.*

Here, Novartis' nexus argument for its objective indicia evidence is based solely on a single premise—Gilenya being the first commercially-available solid oral multiple sclerosis treatment. The treatment of multiple sclerosis with a solid oral composition, however, was indisputably known in the prior art. The Board found evidence that Chiba itself suggested treating multiple sclerosis using a solid oral form of fingolimod. And at least two other solid oral multiple sclerosis treatments were disclosed in the prior art literature before the '283 patent's priority date. The fact that Gilenya was the first to receive FDA approval for commercial marketing does not overcome the fact that solid multiple sclerosis compositions were already known. Thus, we agree with the Board that Novartis' proffered evidence is not probative of the nonobviousness inquiry.[5]

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[5] Novartis raises an additional challenge to the Board's analysis of Novartis' commercial success evidence in particular. Having concluded that Novartis failed to establish a sufficient nexus between its proffered commercial success and the claims, the Board continued, "setting aside the issue of whether commercial success of Gilenya should be probative of nonobviousness, we are not convinced that Patent Owners have carried their threshold burden to show 'significant sales in a relevant market.'" *Final Written Decision*, 2015 WL 5719630, at *14. The Board then proceeded to dismiss Novartis' commercial success argument due to its concerns with Novartis'

CONCLUSION

For the foregoing reasons, we *affirm* the Board's decision. We have considered all of Novartis' remaining arguments but conclude that they are without merit.

AFFIRMED

COSTS

No costs.

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assessment of the relevant market and the completeness of its market share data. Because we agree with the Board that Novartis failed to establish a nexus between the claims and all purported evidence of nonobviousness—including commercial success—we need not and do not reach the Board's additional grounds for rejecting this evidence.