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Paper 112
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

TORRENT PHARMACEUTICALS LIMITED
and
APOTEX, INC. AND MYLAN PHARMACEUTICALS INC.,
Petitioners,

v.

NOVARTIS AG AND MITSUBISHI PHARMA CORP.,
Patent Owners.

Case IPR2014-00784
Case IPR2015-00518
Patent 8,324,283 B2

Before LORA M. GREEN, CHRISTOPHER M. KAISER, and ROBERT A. POLLOCK, *Administrative Patent Judges*.

KAISER, *Administrative Patent Judge*.

FINAL WRITTEN DECISION

35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

INTRODUCTION

Torrent Pharmaceuticals Limited ("Torrent") filed a Petition to institute an *inter partes* review of claims 1–32 of U.S. Patent No. 8,324,283 B2 ("the '283 patent," Ex. 1001). Paper 2 ("Pet.").[1] On December 1, 2014, the Board instituted trial to review patentability of the challenged claims. Paper 11 ("Dec. on Inst."). Apotex, Inc. and Mylan Pharmaceuticals Inc. ("Apotex," or, together with Torrent, "Petitioners") filed a separate Petition also seeking to institute an *inter partes* review of claims 1–32 of the '283 patent. IPR2015-00518, Paper 1 ("IPR-518 Pet."). This second Petition was accompanied by a motion seeking joinder with the trial that had been instituted in IPR2014-00784. IPR2015-00518, Paper 2 ("IPR-518 Joinder Mot."). On February 17, 2015, the Board instituted trial in IPR2015-00518 and joined the proceedings in IPR2014-00784 and IPR2015-00518. IPR2015-00518, Paper 8 ("IPR-518 Dec.").

Thereafter, Novartis AG and Mitsubishi Pharma Corp. ("Patent Owners") filed a Response (Paper 28 ("PO Resp.")), and Petitioners filed a Reply (Paper 55).[2] Patent Owners also filed a motion to amend the challenged claims by replacing them with proposed amended claims 33–64 (Paper 26 ("Mot. to Amend")), Petitioners filed an opposition to this motion (Paper 52 ("Mot. to Amend Opp.")), and Patent Owners filed a reply (Paper

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[1] This decision refers to papers and exhibits filed in both the joined proceedings (IPR2014-00784 and IPR2015-00518). Except where noted otherwise, citations are to the papers and exhibits filed in IPR2014-00784.

[2] Redacted versions of the Response and Reply were filed as Paper 30 and Paper 54, respectively.

62 ("Mot. to Amend Reply")).[3] Both Petitioners and Patent Owners requested oral argument, and an oral hearing was held July 31, 2015. A transcript of the oral argument is included in the record.[4] Paper 111 ("Tr.").[5] Each side filed a motion to exclude certain evidence submitted by the other side. Paper 73; Paper 78. The parties filed oppositions to these motions to exclude, Paper 80; Paper 83, as well as replies to the oppositions, Paper 91, Paper 94. In addition, there are multiple pending motions to seal various pleadings and exhibits.

We have jurisdiction under 35 U.S.C. § 6(c), and we issue this Final Written Decision pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73. We conclude Petitioners have established by a preponderance of the evidence that claims 1–32 of the '283 patent are unpatentable. We also conclude that Patent Owners have failed to establish by a preponderance of the evidence that proposed amended claims 33–64 are patentable. In addition, we deny in

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[3] Redacted versions of the Motion to Amend, the Opposition to the Motion to Amend, and the Reply to the Opposition to the Motion to Amend were filed as Paper 27, Paper 53, and Paper 63, respectively.

[4] The parties are directed to file a redacted version of the transcript that will be publicly available. The redacted version of the transcript shall be filed no later than one week after the entry of the present decision.

[5] Patent Owner filed objections to the demonstrative exhibits used by Petitioners at the hearing. Paper 105. In reaching our decision on the merits, we have considered arguments and evidence that are presented in the demonstrative exhibits only where those arguments and evidence were presented previously and are supported by the record. We expunge all the demonstrative exhibits themselves from the record, because they constitute neither evidence nor, to the extent that they differ from the written briefing, argument allowable under our rules.

part and dismiss in part each side's motion to exclude evidence, we seal certain pleadings and exhibits, and we unseal several exhibits that we substantively rely on in reaching our decision.

The '283 Patent

The '283 patent relates to a solid pharmaceutical composition suitable for oral administration, wherein the composition comprises a sphingosine-1 phosphate (S1P) receptor agonist and a sugar alcohol. Ex. 1001, 1:11–14, 1:33–35. "The sugar alcohol may act as a diluent, carrier, filler or bulking agent, and may suitably be mannitol." *Id.* at 9:53–54. The '283 patent indicates that solid compositions comprising a sugar alcohol are "particularly well suited to the oral administration of S1P receptor agonists," "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 physicochemical and storage properties." *Id.* at 1:36–42. According to the '283 patent, a "particularly preferred S1P receptor agonist . . . is FTY720, i.e. 2-amino-[2-(4-octylphenyl)ethyl]propane-1,3-diol." *Id.* at 8:23–25. FTY720 is also known as fingolimod. Ex. 2007 ¶ 13; Tr. 31:13–15. The '283 patent further describes that solid compositions comprising a sugar alcohol "may show a high level of uniformity in the distribution of the S1P receptor agonist through the composition, as well as high stability" and "may be manufactured on high speed automated equipment." Ex. 1001, 1:42–48. S1P receptor agonists are immunomodulating compounds, and solid pharmaceutical compositions comprising S1P receptors may be useful for

treating and preventing organ/tissue transplant rejection, autoimmune disease/inflammatory conditions, or viral myocarditis and viral diseases caused by viral mycocarditis. *Id.* at 1:18–22, 12:19–37.

Claims 1 and 19 of the '283 patent are independent claims and are illustrative of the claimed subject matter. They are reproduced below.

> 1. A solid pharmaceutical composition suitable for oral administration, comprising:
>
> (a) a SIP receptor agonist which is selected from 2-amino-2-[4-(3-benzyloxyphenoxy)-2-chlorophenyl]propyl-1,3-propane-diol or 2-amino-2-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]propyl-1,3-propane-diol, 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 17:2–11, 18:7–10.

Reviewed Ground of Unpatentability

The Board instituted trial to review the patentability of the challenged claims on the following ground:

Claim(s) Challenged	Basis	References
1–32	§ 103	Chiba[6] and Aulton[7]

[6] Chiba et al., US 6,004,565, issued Dec. 21, 1999 ("Chiba," Ex. 1006).

ANALYSIS

Claim Construction

In an *inter partes* review, the Board interprets a claim term in an unexpired patent according to its broadest reasonable construction in light of the specification of the patent in which it appears. 37 C.F.R. § 42.100(b); *see In re Cuozzo Speed Techs., LLC*, 793 F.3d 1268, 1276–79 (Fed. Cir. 2015). Under that standard, absent any special definitions, we assign claim terms their ordinary and customary meaning, as understood by a person of ordinary skill in the art, in the context of the entire patent disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Only terms which are in controversy need to be construed, and then only to the extent necessary to resolve the controversy. *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999). For this reason, we do not construe several terms for which constructions were proposed in the Petition but about which the parties do not disagree.

Solid Pharmaceutical Composition Suitable for Oral Administration

In our decision instituting trial, we construed "solid pharmaceutical composition suitable for oral administration" as "solid composition capable of delivering a pharmaceutical effect when administered orally." Dec. on Inst. 5. In the post-institution briefing, neither party challenged this construction, and we have not identified any reason to change it.

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[7] PHARMACEUTICS: THE SCIENCE OF DOSAGE FORM DESIGN, 223–321 (Michael E. Aulton ed., 1988) ("Aulton," Ex. 1021).

Accordingly, we maintain our previous construction of "solid pharmaceutical composition suitable for oral administration" as "solid composition capable of delivering a pharmaceutical effect when administered orally."

Is Stable

Patent Owners propose constructions for three terms used in the proposed amended claims. First, they argue that "is stable," with respect to a pharmaceutical composition, means "meets stability requirements of a test required by FDA for approval." Mot. to Amend Reply 26–27. Petitioners disagree with this proposed construction but do not offer an alternative construction, arguing instead merely that the '283 patent itself would not lead a person of ordinary skill in the art to any understanding of the meaning of "is stable" at all. Mot. to Amend Opp. 19–21. We are not persuaded by this argument. Claim terms are to be construed in the context of the entire patent disclosure, but they are also to be construed from the perspective of the understanding of a person of ordinary skill in the art. Here, there is evidence that a person of ordinary skill in the art would understand the requirement for stability "in the context of requirements for FDA approval." Ex. 2042 ¶¶ 73–75.[8] We have not been directed to any contrary evidence. Accordingly, we construe "is stable" to mean "meets stability requirements of a test required by FDA for approval."

[8] A public version is available at Ex. 2263 ¶¶ 73–75.

Has Substantially Uniform Distribution . . . Throughout the Composition

Patent Owners propose that a pharmaceutical composition that "has substantially uniform distribution . . . throughout the composition" is one that "meets content uniformity requirements for active ingredients in solid oral unit dosage forms as defined by the [United States Pharmacopeia]." Mot. to Amend 27–28. Petitioners argue that this is incorrect, pointing out first that the content uniformity requirements in the United States Pharmacopeia are designed to ensure a consistent dose of an active ingredient from one oral dosage unit (e.g., a tablet or capsule) to the next, and noting next that "uniform distribution . . . throughout the composition" would instead be interpreted by a person of ordinary skill in the art to refer to a uniform distribution of the active ingredient throughout a single oral dose unit. Mot. to Amend Opp. 17–19. Petitioners are correct that the United States Pharmacopeia is directed at ensuring a minimum of variation from one oral dosage unit to the next. Ex. 2072, 3–5.[9] But there is evidence of record that "[a] person skilled in formulation in 2003 would have also used [the United States Pharmacopeia] analysis to infer that the drug was homogeneously distributed within each tablet," Ex. 2280 ¶ 49,[10] and this evidence is unrebutted. Accordingly, we construe a pharmaceutical composition that "has substantially uniform distribution . . . throughout the composition" as one that "meets content uniformity requirements for active

[9] Unless stated otherwise, our citations are the page numbers of the exhibit itself rather than to the page numbers of the original document from which the exhibit is extracted.

[10] A public version is available at Ex. 2285 ¶ 49.

ingredients in solid oral unit dosage forms as defined by the [United States Pharmacopeia]."

Rough Particle Surface

Patent Owners argue that "rough particle surface" means "with higher surface area than a sphere." Mot. to Amend 28. Petitioners dispute this construction but do not provide an alternative, arguing instead only that a person of ordinary skill in the art would be unable to determine the meaning of this term at all. Mot. to Amend Opp. 21–22. Patent Owners' evidence shows that "rough particle surface," with respect to sugar alcohol particles, includes sugar alcohol particles "having a higher surface area than a routine sugar alcohol particle obtained from a spray-dry method." Mot. to Amend 28 (citing Ex. 1001, 9:60–10:1; Ex. 2042 ¶¶ 76–81). But "rough particle surface" should not be limited to this narrow embodiment. *See Phillips v. AWH Corp.*, 415 F.3d 1303, 1323 (Fed. Cir. 2005) (en banc) ("[A]lthough the specification often describes very specific embodiments of the invention, we have repeatedly warned against confining the claims to those embodiments."). That said, to construe "rough particle surface" to mean merely "with higher surface area than a sphere," as Patent Owners suggest, would be to interpret the term as essentially unbounded. Any particle, even a perfect sphere, could be said to have a surface area higher than that of an unspecified sphere, which could be arbitrarily small. In order to avoid this problem, we construe a particle with a "rough particle surface" to be a particle "with higher surface area than a sphere of a diameter equal to the average diameter of the particle in question."

Prior Art Disclosures

Chiba

Chiba teaches immunosuppressive compounds with fingolimod as the preferred species. Ex. 1006, 4:64–5:5. Chiba also teaches that the immunosuppressive compounds it teaches are useful for treating "transplantation rejection of organs or tissues" and "autoimmune diseases such as . . . multiple sclerosis," among other diseases and conditions. *Id.* at 6:26–49. Chiba teaches 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." *Id.* at 8:19–26. In discussing the preparation of these capsules and tablets for oral administration of fingolimod, Chiba teaches that

> [o]ne skilled in the art is familiar with numerous methods and tests for determining the effectiveness of a selected route of administration. Furthermore, 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.

Id. at 11:22–28.

Aulton

Aulton teaches the use of tablets and capsules to administer drugs orally. Ex. 1021, 5. It also teaches that "[t]he successful formulation of a stable and effective solid dosage form depends on the careful selection of excipients which are added to facilitate administration, promote the consistent release and bioavailability of the drug and protect it from

degradation." *Id.* at 30–31. Aulton recommends a short list of "[p]rimary excipients . . . for initial screening for table[t] and capsule formulations," *id.* at 31, Table 13.16, although no sugar alcohol appears on the list. Despite this, Aulton lists 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." *Id.* at 39–41, Table 18.1; *see also id.* at 38 (identifying mannitol among the "[m]aterials currently available as direct compression diluents"). Aulton teaches that mannitol is "expensive," but still "commonly used." *Id.* at 41. In addition to these teachings regarding mannitol, Aulton teaches that magnesium stearate "is the most popular lubricant used" in tableting. *Id.* at 42.

Obviousness of Challenged Claims over Chiba and Aulton

Petitioners argue that claims 1–32 would have been obvious over Chiba and Aulton. Pet. 20–43. Petitioners rely on the Declaration of John S. Kent, Ph.D., to support the Petition. Ex. 1004. Patent Owners dispute the unpatentability of claims 1–32, supported by the Declarations of Supriya Rane, M.S. (Ex. 2007); Madhusudhan Pudipeddi, Ph.D. (Ex. 2041); Stephen Byrn, Ph.D. (Ex. 2042); Tomoyuki Oomura, M.S. (Ex. 2043); Fred D. Lublin, M.D. (Ex. 2044); and David Blackburn, Ph.D. (Ex. 2045). In addition, Petitioners' Reply relies on the Reply Declaration of John S. Kent, Ph.D. (Ex. 1031) and the Declaration of Joel W. Hay, Ph.D. (Ex. 1041).

After reviewing the complete record, we conclude Petitioners have shown that Chiba and Aulton teach or suggest each limitation of claims 1–32

of the '283 patent, that a person of ordinary skill in the art[11] would have had a reason to combine the teachings of Chiba and Aulton, and that a person of ordinary skill in the art would have had a reasonable expectation of success in combining the teachings of Chiba and Aulton. Even when considering the record evidence of objective indicia of nonobviousness, we conclude that Petitioners have shown, by a preponderance of the evidence, that each of the challenged claims would have been obvious over the combination of Chiba and Aulton.

Claim 19

Independent claim 19 recites "[a] solid pharmaceutical composition suitable for oral administration, comprising mannitol and [fingolimod] or a pharmaceutically acceptable salt thereof." Ex. 1001, 18:7–10.

There is no dispute that Chiba and Aulton together teach all the limitations of claim 19. Chiba teaches the claimed "solid pharmaceutical composition suitable for oral administration, comprising" fingolimod, and Aulton teaches the claimed mannitol excipient. Ex. 1006, 3:25–43, 4:64–5:5, 8:19–28, 11:20–34; Ex. 1021, 40–41; Ex. 1004 ¶¶ 93–94, 170. The remaining questions regarding whether claim 19 would have been obvious over the combination of Chiba and Aulton are whether a person of ordinary

[11] The parties do not dispute the level of skill in the art. We also note that "[a] specific finding on the level of skill in the art is not . . . required where the prior art itself reflects an appropriate level and a need for testimony is not shown." *Litton Indus. Prods., Inc. v. Solid State Sys. Corp.*, 755 F.2d 158, 163–64 (Fed. Cir. 1985).

skill in the art would have had a reason to combine the teachings of the references and whether that person would have had a reasonable expectation of success in doing so. In addition, Patent Owners argue that several objective indicia show that claim 19 would not have been obvious.

1. Reason to Combine Chiba's Fingolimod Teaching and Aulton's Mannitol Teaching

In arguing against the unpatentability of claim 19, Patent Owners argue first that the inventors of the '283 patent discovered the reason to combine mannitol and fingolimod and that Petitioners have failed to prove adequately that a person of ordinary skill in the art at the time of the invention would have had any reason to combine them. PO Resp. 34–48.

As an initial matter, we agree with Patent Owners that Petitioners bear the burden of persuasion with respect to a reason for the person of ordinary skill in the art to combine the teachings of Chiba and Aulton. Petitioners "bear the burden of proving a proposition of unpatentability by a preponderance of the evidence," 35 U.S.C. § 316(e), and, to the extent that Petitioners seek to prove the unpatentability of claim 19 by establishing that it would have been obvious over the combined teachings of Chiba and Aulton, they must establish as part of their "proposition of unpatentability" that a person of ordinary skill in the art would have had a reason to combine those teachings.

We disagree, however, with Patent Owners' argument that the inventors' mere discovery of a new reason to combine fingolimod and mannitol renders nonobvious an invention that was known in the prior art.

Where the prior art teaches the claimed invention, a claim is not rendered patentable by virtue of being motivated in the inventors' minds by a newly-discovered advantage of the prior-art combination; allowing such a claim to stand "would remove from the public that which is in the public domain." *In re Wiseman*, 596 F.2d 1019, 1022 (CCPA 1979); *see also Cross Med. Prods., Inc. v. Medtronic Sofamor Danek, Inc.*, 424 F.3d 1293, 1323 (Fed. Cir. 2005) ("One of ordinary skill in the art need not see the identical problem addressed in a prior art reference to be motivated to apply its teachings."). Here, Patent Owners argue that the newly discovered low-dose instability of fingolimod when mixed with common excipients motivated the inventors' choice of the allegedly less common mannitol as an excipient. PO Resp. 12–15 (citing Ex. 2043 ¶¶ 14–19, 22, 24–36). As explained above, though, it does not matter that the prior art failed to recognize this advantage of a fingolimod-mannitol combination. "[T]he motivation in the prior art to combine the references does not have to be identical to that of the [patentee] to establish obviousness." *In re Kemps*, 97 F.3d 1427, 1430 (Fed. Cir. 1996).

We are not persuaded otherwise by *Leo Pharmaceutical Products, Ltd. v. Rea*, discussed by Patent Owners at pages 35–36 of the Response. In that case, although the inventors argued that they discovered a stability problem with a combination of ingredients known in the prior art, in fact there was evidence that the prior art taught away from combining those ingredients. *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1353–54 (Fed. Cir. 2013). Patent Owners have not alleged, and the record does not support, that the prior art here taught away from combining mannitol and fingolimod.

Thus, the fact that the inventors of the '283 patent may have discovered a new advantage of a combination of prior-art ingredients is not sufficient to render the claims of the '283 patent patentable, as long as there was some reason to combine the prior-art teachings that those ingredients should be used. Patent Owners argue that Petitioners have failed to prove such a reason to combine, PO Resp. 41–49, but the record establishes otherwise. 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. Ex. 1006, 11:24–28 ("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."[12] Ex. 1021, 39–41, Table 18.1. This combination of teachings already strongly 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, but there is additional evidence of the reason to combine fingolimod and mannitol.

[12] There is additional evidence that wet granulation is "[o]ne of the most common steps in the manufacture of capsules and tablets." Ex. 1031 ¶ 43.

One prior-art reference, Sakai,[13] directly instructs that the two ingredients should be combined. Ex. 1005, 10:31–48. Patent Owners argue that Sakai's teaching of the combination of fingolimod and mannitol is irrelevant because Sakai is limited to liquid-phase pharmaceutical compositions, as opposed to the claimed solid oral dosage forms. PO Resp. 41 (citing Ex. 2042 ¶ 30[14] ("The excipients used in liquid formulations are not relevant for solid formulations.")). But Patent Owners' own declarant (as the author of Ex. 2042), Dr. Stephen Byrn, wrote an article stating otherwise: "Most, but not all, drug degradations in the solid state take place via chemical mechanisms that are identical to those that occur in solution. Hence, a mechanistic understanding gained from solution studies can be very helpful." Ex. 1030, 5. Although Patent Owners note that Exhibit 1030 goes on to discuss specific exceptions to this rule, Tr. 42:13–16, we have not been directed to any evidence of record that suggests that any of those exceptions applies here. The fact is that, according to Patent Owners' own declarant, 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.[15]

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[13] Sakai et al., US 6,277,888 B1, issued Aug. 21, 2001 ("Sakai," Ex. 1005).

[14] A public version is available at Ex. 2263 ¶ 30.

[15] Our conclusion in our institution decision that Sakai's teaching of a combination of mannitol and fingolimod in the liquid phase was not sufficient on its own to "teach that mannitol is a conventional excipient for use in solid pharmaceutical compositions," Dec. on Inst. 12, does not require us to ignore the record evidence that Sakai's teaching would have been relevant to the decision of which excipient to use in formulating a solid oral

In 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. Remington's Pharmaceutical Sciences, described as "[a] textbook and reference work for pharmacists, physicians and other practitioners of the pharmaceutical and medical sciences," lists mannitol as one of nine diluents used "to make tableting possible." Ex. 2050, 5, 86. It also states that mannitol is one of nine "common diluents" that are useful as "[d]irect-compression vehicles or carriers" because they "have good flow and compressible characteristics." *Id.* at 96. The Theory and Practice of Industrial Pharmacy, described as "a comprehensive reference source on modern industrial pharmacy" that is "useful to practitioners in the pharmaceutical and allied health sciences . . . and others seeking information concerning the design, manufacture, and control of pharmaceutical dosage forms," lists mannitol as one of fourteen diluents in a table of "[c]ommon [t]ablet [e]xcipients." Ex. 2049, 3, 39. The Handbook of Pharmaceutical Excipients describes mannitol as "widely used . . . as a diluent . . . in tablet formulations, where it is of particular value since it is not hygroscopic." Ex. 1014, 5. In addition, "[g]ranulations containing mannitol have the advantage of being dried easily," and "[m]annitol does not undergo Maillard reactions." *Id.* at 5, 8. These known

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dosage form of fingolimod. Furthermore, "the knowledge of [a person of ordinary skill in the art] is part of the store of public knowledge that must be consulted when considering whether a claimed invention would have been obvious." *Randall Mfg. v. Rea*, 733 F.3d 1355, 1362 (Fed. Cir. 2013).

advantages of mannitol as a tableting excipient[16] 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. *Dystar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick, Co.*, 464 F.3d 1356, 1368 (Fed. Cir. 2006) ("[A]n implicit motivation to combine exists . . . when . . . the combination of references results in a product or process that is more desirable. . . . [T]here exists in these situations a motivation to combine prior art references even absent any hint of suggestion in the references themselves.").

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

[16] Mannitol has other advantages, such as a sweet taste and a negative heat of solution, that are more relevant to chewable tablets than to other solid oral dosage forms. Ex. 1021, 41. Although the claims of the '283 patent are not limited to non-chewable tablets, there is evidence of record that suggests that fingolimod would be unlikely to be administered in a chewable tablet, making these advantages less relevant to the reason-to-combine analysis. Ex. 2263 ¶ 53; Ex. 2043 ¶ 38. Still, the evidence of record does not support Patent Owners' contention that mannitol was used only in chewable tablets. *See* Ex. 1031 ¶ 27 (citing Ex. 1032; Ex. 1033; Ex. 1034; Ex. 1042; Ex. 1043; Ex. 1044; Ex. 1045; Ex. 1046; Ex. 1047) (listing non-chewable tablets and capsules containing mannitol that were marketed before 2003).

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.[17] It is irrelevant that Petitioners have failed to establish that the inventors' actual subjective reason for combining mannitol and fingolimod was known in the prior art.

2. Reasonable Expectation of Success in Combining Fingolimod and Mannitol

Patent Owners argue next that Petitioners have failed to establish that Chiba and Aulton provided a reasonable expectation of success in combining mannitol and fingolimod. PO Resp. 49–51. According to Patent Owners, because Chiba does not discuss mannitol specifically, and because Aulton does not discuss fingolimod specifically, the combination of Chiba and Aulton would not "have provided a reasonable expectation that fingolimod and mannitol would be stable." *Id.* at 50. Thus, argue Patent Owners, a person of ordinary skill in the art only would have been motivated to "vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful," which is not sufficient to

[17] Because the reason to combine mannitol and fingolimod is provided by a teaching or suggestion in the prior art, we need not reach Petitioners' alternate reasons to combine, such as the theory that Patent Owners describe as an "obvious to try" argument. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (requirement of "teaching, suggestion, or motivation to combine known elements . . . captured a helpful insight").

establish a reasonable likelihood of success. *Id.* (quoting *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) (quoting *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988)) (internal quotation marks omitted). We are not persuaded by this argument.

First, Sakai's direct teaching that mannitol and fingolimod should be combined would have provided a reasonable expectation that the combination would be suitable for the purpose that Sakai teaches, pharmaceutical administration, including any stability necessary to that purpose. Second, the general stability of drug combinations with mannitol was known in the art. A 1969 article by Ward[18] studied the compatibility of mannitol with various active drug compounds and concluded that mannitol was "inert[] . . . in various mechanisms associated with drug-excipient compatibility." Ex. 1020, 7. Given the direct teaching by Sakai that mannitol and fingolimod should be combined, and given the knowledge in the art that mannitol was unlikely to react with active drug compounds when used as an excipient, Petitioners have established that a person of ordinary skill in the art would have had a reasonable expectation of success in combining fingolimod and mannitol.

[18] Donald R. Ward, Lyle B. Lathrop, & Matthew J. Lynch, *Dissolution and Compatibility Considerations for the Use of Mannitol in Solid Dosage Forms*, 58 J. PHARMACEUTICAL SCI. 1464, 1464–67 (Dec. 1969) ("Ward," Ex. 1020).

3. Objective Indicia of Nonobviousness

Finally, Patent Owners argue that objective indicia of nonobviousness show that the claimed combination of mannitol and fingolimod would not have been obvious to a person of ordinary skill in the art. PO Resp. 52–58. These objective indicia include two separate forms of unexpected results, a long-felt but unmet need, industry praise, and commercial success. *Id.*

(a) Unexpected Results

Patent Owners first argue that the claimed combination of fingolimod and mannitol shows unexpected results. "It is the established rule that 'objective evidence of non-obviousness must be commensurate in scope with the claims which the evidence is offered to support.'" *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 965 (Fed. Cir. 2014) (quoting *In re Tiffin*, 448 F.2d 791, 792 (CCPA 1971)). This is as true for evidence of unexpected results as it is for any other type of objective evidence of non-obviousness. *See In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003) ("the applicant's showing of unexpected results must be commensurate in scope with the claimed range"); *In re Clemens*, 622 F.2d 1029, 1035 (CCPA 1980) ("In order to establish unexpected results for a claimed invention, objective evidence of non-obviousness must be commensurate in scope with the claims which the evidence is offered to support."). The evidence of unexpected results made of record is not commensurate in scope with claim 19.

First, according to Patent Owners, the claimed combination was stable at low doses of fingolimod, even though combinations of fingolimod and

other excipients were unstable at those same low doses. PO Resp. 54; *see also id.* at 11–15 (citing Ex. 2042 ¶¶ 39–40; Ex. 2043 ¶¶ 14–19, 22, 24–36) (describing difference in results between low-dose fingolimod-mannitol mixtures and mixtures of low doses of fingolimod with other excipients). But, as Petitioners note, Reply 3–4 (citing Ex. 1031 ¶ 85; Ex. 2271, 50:21–51:9[19]), claim 19 is not limited to any particular dose or dose range of fingolimod. Instead, claim 19 recites only a solid oral dosage form containing mannitol and either fingolimod or a pharmaceutically acceptable salt of fingolimod. Ex. 1001, 18:7–10. Thus, 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.

Second, Patent Owners argue that the stability achieved with mannitol "is superior to other choices [of excipient] to a surprising extent," given that "mannitol preserves 4.5 to 11 times as much fingolimod as lactose, microcrystalline cellulose, and starch." PO Resp. 54 (citing Ex. 2007 ¶¶ 12–13). This evidence of unexpected results suffers from the same flaw discussed above. *See* Reply 17 (citing Ex. 1031 ¶ 85). Not only is this evidence limited to low doses of fingolimod, it is limited to a single, specified dose, 0.25 mg. Ex. 2007, 5 (stating that testing was performed using 25 µL of a 10 mg/mL drug substance solution). As such, it is evidence of unexpected results only across a tiny portion of the unlimited dose range

[19] A public version is available at Ex. 2276, 50:21–51:9.

of claim 19, which is insufficient to support a finding of unexpected results.[20]

(b) Long-Felt but Unmet Need

Next, Patent Owners argue that the invention claimed in claim 19 satisfied the long-felt but previously unmet need "for a solid oral [multiple sclerosis] treatment." PO Resp. 55 (citing Ex. 2044 ¶¶ 25–27). The supporting evidence is a declaration stating that "some patients are resistant, afraid, or even unwilling to use needles," which caused some patients to "drop[] the [multiple sclerosis] treatment"; that "parenteral medications were universally inconvenient," making patients less likely to take their medication; and that "there were a number of side effects commonly associated with parenteral [multiple sclerosis] treatments" that "discouraged patients from continuing with their prescribed course[s] of treatment." Ex. 2044 ¶¶ 25–27. Although no other evidence is cited in Patent Owners'

[20] Moreover, Ex. 2007, the only evidence cited to support Patent Owners' argument that mannitol "is superior to other choices [of excipient] to a surprising extent," PO Resp. 54, is a declaration filed by a witness who was not made available for cross-examination. For this additional reason, we accord it little weight. Ex. 1029, 20:23–21:22. To the extent that Ex. 2007 shows a difference between the stability of mannitol and the stability of other excipients that is contradicted by Ex. 1025, which does not suffer from the evidentiary flaws of Ex. 2007, we give greater weight to Ex. 1025 and its evidence that mannitol and the other excipients tested have similar stability. *See* Ex. 1025, 13:37–53.

briefing,[21] additional record evidence shows that patients asked about the availability of an oral medication as early as 1993, *id.* ¶ 34, and that the introduction of the first oral medication in 2010 caused a "'major shift in the treatment landscape,'" with "'many patients . . . switching to oral therapy,'" *id.* ¶ 37 (quoting Ex. 2012, 1).

Petitioners argue, Reply 18–19, that there is no evidence that the long-felt need was for claim 19's combination of fingolimod and mannitol; instead, as Patent Owners acknowledge, PO Resp. 55, the need was merely "for a solid oral [multiple sclerosis] treatment." According to Petitioners, any need for a solid oral dosage form of a multiple sclerosis treatment was satisfied by treatments that were known in the prior art but did not receive FDA approval until after Patent Owners' Gilenya product did. Reply 18–19. Therefore, argue Petitioners, there was no longer any long-felt need by the time of the invention claimed in the '283 patent. *Id.*

We find Petitioners' argument persuasive. If objective indicia of nonobviousness are "due to an element in the prior art, no nexus exists." *Tokai Corp. v. Easton Enters., Inc.*, 632 F.3d 1358, 1369 (Fed. Cir. 2011) (discussing commercial success). Here, the evidence of long-felt need shows that there was a need merely for a solid oral multiple sclerosis medication, not specifically for a medication of the form recited in claim 19. But the general need for a solid oral multiple sclerosis medication was

[21] Patent Owners are reminded that 37 C.F.R. § 42.23(a) requires a Response to "comply with the content requirements for motions," and 37 C.F.R. § 42.22(a)(2) requires motions to include "a detailed explanation of the significance of the evidence."

satisfied in the prior art. In 1999, Chiba itself suggested treating multiple sclerosis using a solid oral form of fingolimod. Ex. 1006, 6:26–49, 8:19–26. In addition, teriflunomide, marketed in solid tablet form as Aubagio®, was known in the prior art at least by April 1, 2002, when it was disclosed to be useful for treating multiple sclerosis when administered in tablets or capsules. Ex. 1037, at [22], 1:19–30, 2:60–3:2, 5:1–21; Ex. 2045 ¶ 63.[22] Similarly, a capsule form of dimethyl fumarate for the treatment of multiple sclerosis, marketed as Tecfidera™, Ex. 1070, 2, was disclosed in U.S. Patent No. 6,509,376 B1, issued January 21, 2003. Ex. 1097, at [45], 2:64–67, 4:25–27, 4:31–33.

Because the prior art contained solid oral multiple sclerosis treatments using active ingredients other than fingolimod, the fingolimod claimed in claim 19 was not necessary to satisfy any long-felt need for a solid oral multiple sclerosis treatment. Nor was the mannitol recited in claim 19: the evidence of record shows that sugar alcohols were not necessary to make even fingolimod suitable for oral administration. Ex. 2271, 250:10–251:15.[23] Accordingly, claim 19 did not solve any need for a solid oral multiple sclerosis treatment that was not already solved in the prior art.

(c) Industry Praise

Patent Owners next argue that Gilenya, which is alleged to be a commercial embodiment of claim 19, "has received copious acclaim,"

[22] A public version of Ex. 2045 ¶ 63 is available at Ex. 2265 ¶ 63.

[23] A public version is available at Ex. 2276, 250:10–251:15.

reflecting "the market's view that the creation of a solid oral [multiple sclerosis] treatment was a substantial achievement." PO Resp. 58 (citing Ex. 2044 ¶¶ 40–44). The cited supporting evidence shows that the authors of the Phase III clinical trial study of Gilenya described an "oral treatment option for relapsing-remitting multiple sclerosis [as] highly desirable," that the National MS Society spoke to the FDA "in favor of Gilenya's approval," that the FDA granted Gilenya priority-level review and approved Gilenya as the first oral MS treatment, that the European Medicines Agency approved Gilenya noting its "benefit of being taken by mouth," that the Research and Development Council of New Jersey awarded the Thomas Alva Edison Patent Award in the Pharmaceutical Formulation category to Novartis for the '283 patent, and that multiple patients using Gilenya have praised it "with particular emphasis on its oral formulation." Ex. 2044 ¶¶ 40–44.

Industry praise must be linked to the patented invention. *Power-One, Inc. v. Artesyn Techs.*, Inc., 599 F.3d 1343, 1352 (Fed. Cir. 2010). Again, if objective indicia of nonobviousness are "due to an element in the prior art, no nexus exists." *Tokai Corp.*, 632 F.3d at 1369. Here, the evidence shows that what was praised about Gilenya was not the specific formulation recited in claim 19, but rather the general fact that Gilenya was a solid oral multiple sclerosis medication. As discussed above, however, a solid oral multiple sclerosis formulation was known in the prior art, so there is no nexus between the claimed invention and the industry praise.

(d) Commercial Success

Lastly, Patent Owners argue that the commercial success of Gilenya shows that claim 19 would not have been obvious. Here, Petitioners bear the burden of proving the unpatentability of claim 19 by a preponderance of the evidence. 35 U.S.C. § 316(e). Part of the evidence weighed in determining the unpatentability of claim 19 is any relevant evidence of commercial success. "Commercial success is relevant because the law presumes an idea would successfully have been brought to market sooner, in response to market forces, had the idea been obvious to persons skilled in the art." *Merck & Co., Inc. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1376 (Fed. Cir. 2005). But commercial success is relevant only when it is "due to [something] disclosed in the patent . . . which was not readily available in the prior art." *Richdel, Inc. v. Sunspool Corp.*, 714 F.2d 1573, 1580 (Fed. Cir. 1983). That is, as discussed above with respect to other objective indicia of nonobviousness, "[i]f commercial success is due to an element in the prior art, no nexus exists" between the commercial success and the claimed invention. *Tokai Corp.*, 632 F.3d at 1369. Patent Owners bear a burden of production with respect to evidence of commercial success; they must show "significant sales in a relevant market, and that the successful product is the invention disclosed and claimed in the patent." *Ecolochem, Inc. v. S. Cal. Edison Co.*, 227 F.3d 1361, 1377 (Fed. Cir. 2000). If Patent Owners make such a showing, Petitioners may rebut the evidence of commercial success by showing that "the commercial success was instead due to other factors extraneous to the patented invention," *id.*, such as "the

FDA approval process, Patent Owners' promotion and marketing, and the FDA's new warnings to the labels of . . . other MS drugs," Reply 25.

Thus, our first question is whether the success of Gilenya was due to something in the prior art or to some feature claimed in claim 19. As discussed above, at the time that Gilenya was introduced, it was the first oral multiple sclerosis medication to be approved by the FDA, and there was significant pent-up demand for such a drug. Patients and other interested parties praised Gilenya because it was the first treatment for multiple sclerosis not to suffer from the drawbacks of injectable medications. Accordingly, it is not surprising that Gilenya would have seen large sales figures; much of the demand for Gilenya was simply the demand for an oral multiple sclerosis medication generally. Patent Owners do not identify any evidence to the contrary. In fact, Patent Owners themselves argue that "Gilenya's sales, prescriptions and profits have been extraordinary in comparison . . . especially [to] injectable treatments," that "third-party observers such as securities analysts attribute that success to Gilenya's solid oral form," that "Novartis's marketing materials emphasize the oral dose form," and that Novartis's "surveys show that doctors rate Gilenya's oral form as a major reason for prescribing it." PO Resp. 57 (citing Ex. 2045 ¶¶ 30–39). Patent Owners' evidence, the declaration of Dr. Blackburn, discusses the solid oral formulation feature of Gilenya as the only feature recited in the '283 patent that is responsible for Gilenya's commercial success. Ex. 2045 ¶¶ 29–43. As discussed above, however, solid oral dosage forms of multiple sclerosis medications were known in the prior art, so any commercial success attributable merely to Gilenya's solid oral

formulation is not relevant to the issue of commercial success showing the nonobviousness of claim 19. Because all the record evidence of commercial success shows that Gilenya's sales were driven by the known solid oral dosage form feature, we find insufficient evidence of commercial success that is relevant to proving claim 19's nonobviousness.

Moreover, 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." *Ecolochem*, 227 F.3d at 1377. We have not been directed to any evidence as to what the relevant market in which Gilenya competes is. Patent Owners' briefing does not mention the relevant market at all, while Dr. Blackburn sometimes suggests that the market might be all oral and injectable multiple sclerosis treatments, Ex. 2045 ¶¶ 20, 23–24, and sometimes suggests that the market might be limited to second-line (or later) multiple sclerosis therapies, *id.* ¶ 21. In either case, Dr. Blackburn excluded from his analysis any data regarding sales of Tysabri, *id.* ¶ 20 n.24,[24] a multiple sclerosis drug that generates more than $1 billion in annual sales, Ex. 1041 ¶ 38; Ex. 1057, 5–6; Ex. 1058, 37. Dr. Blackburn's evidence of Gilenya's market share is biased towards more significant sales of Gilenya by this exclusion and, thus, is unreliable as evidence that Gilenya's sales are significant in relation to the relevant market as a whole. As for Dr. Blackburn's testimony regarding Gilenya's absolute sales (such as net sales, gross profits, contribution profits, and number of prescriptions), this type of

[24] A public version is available at Ex. 2265 ¶ 20 n.24.

information does not show commercial success in the absence of additional evidence "as to what sales would normally be expected in the market." *Ex parte Jellá*, 90 USPQ2d 1009, 1012 (BPAI 2008) (precedential) (citing *Ex parte Standish*, 10 USPQ2d 1454, 1458 (BPAI 1988)). Because we have not been directed to any record evidence of what level of sales should have been expected to which the actual sales of Gilenya can be compared, and because the evidence of Gilenya's market share is flawed, Patent Owners have not borne the burden of production necessary to trigger Petitioners' burden to explain Gilenya's commercial success as due to factors extraneous to the claimed invention. Accordingly, we find insufficient evidence of commercial success that is relevant to the determination of the obviousness of claim 19 over the combination of Chiba and Aulton.

4. Conclusion with Respect to Claim 19

Chiba and Aulton together teach every limitation of claim 19, and the evidence of record shows that a person of ordinary skill in the art would have had a reason to combine the teachings of the references and a reasonable expectation of success in doing so. In addition, there is insufficient evidence of objective indicia of nonobviousness that is relevant to the determination of whether claim 19 would have been obvious over the combination of Chiba and Aulton. Accordingly, we conclude that claim 19 would have been obvious over the combination of Chiba and Aulton.

Other Claims

In addition to claim 19, Petitioners challenge the remainder of claims 1–32 as obvious over the combination of Chiba and Aulton.

1. Claims 1, 3, 4, and 32

Petitioners challenge claims 1, 3, 4, and 32, and Patent Owners offer no separate argument as to these claims. Claim 1 differs from claim 19 in that it broadens the choice of excipient to include "a sugar alcohol" rather than claim 19's "mannitol." Ex. 1001, 17:2–11, 18:7–10. The mannitol recited in claim 19 is a species of the genus "sugar alcohol" recited in claim 1. *Id.* at 9:53–59. Claim 1 also broadens the choice of S1P receptor agonists beyond the "[fingolimod] or a pharmaceutically acceptable salt thereof" recited in claim 19. *Id.* at 17:2–11, 18:7–10. The list of S1P receptor agonists in claim 1 includes fingolimod, because fingolimod is recited as "the S1P receptor agonist" in claim 32, which depends from claim 1. *Id.* at 18:40–43. Thus, while the scope of claim 19 is limited to mannitol and fingolimod, claim 32's scope includes all sugar alcohols and fingolimod, and claim 1's scope includes all sugar alcohols and a genus of S1P receptor agonists that includes fingolimod. Accordingly, claim 1 and claim 32 are each broader than claim 19, and claim 1 and claim 32 each include within their scope the entire scope of claim 19. Under these circumstances, neither claim 1 nor claim 32 can be nonobvious if claim 19 is obvious. *See Callaway Golf Co. v. Acushnet Co.*, 576 F.3d 1331, 1344 (Fed. Cir. 2009) (holding that a broader claim cannot be nonobvious where a narrower claim

is obvious). Because we have already concluded that claim 19 is obvious, we conclude that claims 1 and 32 are obvious.

Similarly, claims 3 and 4 both are broader than claim 19 but contain within their scope all of claim 19's scope. Claim 3 depends from claim 1 but narrows the scope of "sugar alcohol" to those that are non-hygroscopic, while claim 4 depends from claim 1 but narrows the scope of "sugar alcohol" to mannitol. Ex. 1001, 17:14–18. The mannitol of claim 19 is a non-hygroscopic sugar alcohol, *id.* at 9:55–56; Ex. 1014, 5, so it falls within the scope of claim 3's recited "non-hygroscopic sugar alcohol." Of course, the mannitol recited in claim 19 is the same as the mannitol recited in claim 4. Because claims 3 and 4 are both broader than claim 19 but contain within their scope the entire scope of claim 19, and because claim 19 is obvious over the combination of Chiba and Aulton, we conclude that claims 3 and 4 are obvious over the combination of Chiba and Aulton.

2. Claim 2

Petitioners challenge claim 2, and Patent Owners offer no separate argument as to this claim. Claim 2 depends from claim 1, narrowing it by requiring the claimed S1P receptor agonist to be present as a hydrochloride salt. Ex. 1001, 17:12–13. Chiba teaches fingolimod hydrochloride as a preferred embodiment. Ex. 1006, 4:63–68. Accordingly, claim 2 is obvious over the combination of Chiba and Aulton.

3. Claims 5, 6, 20, and 21

Petitioners challenge claims 5, 6, 20, and 21, and Patent Owners offer no separate argument as to these claims. Claims 5 and 6 depend from claim 1 and narrow it by requiring the addition of a lubricant to the claimed solid oral dosage form (claim 5) or by requiring the addition of a lubricant that comprises magnesium stearate to the claimed solid oral dosage form (claim 6). Ex. 1001, 17:19–22. Claims 20 and 21 depend from and narrow claim 19 similarly. *Id.* at 18:11–14. Aulton teaches that lubricants are commonly added to solid oral dosage forms of pharmaceutical compositions and that magnesium stearate is a commonly used lubricant for this purpose. Ex. 1021, 42. Accordingly, claims 5, 6, 20, and 21 are obvious over the combination of Chiba and Aulton.

4. Claims 7–12 and 22–24

Petitioners challenge claims 7–12 and 22–24, and Patent Owners offer no separate argument as to these claims. Claims 7–12 depend either directly or indirectly from claim 1 and specify the percentage by weight of the claimed solid pharmaceutical composition that is S1P receptor agonist (claims 7 and 8), sugar alcohol (claims 9 and 10), or lubricant (claims 11 and 12). Ex. 1001, 17:23–34. Claims 22–24 depend from claim 19 and similarly specify the percentage by weight of the claimed solid pharmaceutical composition that is fingolimod (claim 22), mannitol (claim 23), or lubricant (claim 24). *Id.* at 18:15–25. Petitioners provide evidence that the selection of the relative amounts of the constituents of the claimed formulation is the result of routine optimization. Ex. 1004 ¶¶ 188 (“the amount of active

present in a formulation is well within the skill of the ordinary artisan to manipulate and optimize for the appropriate use"), 194 ("ordinarily skilled artisans in formulation development certainly had the desire to optimize excipient amounts appropriate for the formulation, approached the formulation exercise with that intention, and had the skill to do so"), 195 (same). We 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, the amount of mannitol, and the amount of lubricant to obtain an appropriately effective formulation. Accordingly, claims 7–12 and 22–24 would have been obvious to a person of ordinary skill in the art over the combined teachings of Chiba and Aulton.

5. Claims 13 and 14

Petitioners challenge claims 13 and 14, and Patent Owners offer no separate argument as to these claims. Claim 13 depends from claim 1 and requires that the S1P receptor agonist included in the claimed composition be "micronized." Ex. 1001, 17:35–36. Claim 14 depends from claim 13 and further requires that the S1P receptor agonist be "pre-screened with a 400 to 500 μm mesh screen." *Id.* at 17:37–39. Petitioners argue that these limitations are process steps in product-by-process claims and, therefore, that they "do[] not add . . . patentably distinguishing element[s] to the claim 1 composition from which [they] depend[]." Pet. 38; *see* Pet. 39. We agree. Claims 13 and 14 claim particular products, and these limitations focus on the method of making those products. "In determining [the patentability] of

a product-by-process claim, the focus is on the product and not on the process of making it," because "an old product is not patentable even if it is made by a new process." *Amgen Inc. v. F. Hoffman-La Roche Ltd.*, 580 F.3d 1340, 1369–70 (Fed. Cir. 2009). Accordingly, the limitations that claims 13 and 14 add to claim 1, from which they depend, add nothing to the patentability analysis, making claims 13 and 14 obvious over the combined teachings of Chiba and Aulton for the same reasons that claim 1 was obvious.

6. Claims 15, 16, 25, and 26

Petitioners challenge claims 15, 16, 25, and 26, and Patent Owners offer no separate argument as to these claims. Claims 15 and 16 depend from claim 1 and require that the claimed solid pharmaceutical composition be a tablet (claim 15) or a capsule (claim 16). Ex. 1001, 17:40–43. Similarly, claims 25 and 26 depend from claim 19 and require that the claimed solid pharmaceutical composition be a tablet (claim 25) or a capsule (claim 26). *Id.* at 18:26–29. Aulton teaches both tablets and capsules as dosage forms used for delivering pharmaceutical compositions. Ex. 1021, 5. Chiba also teaches that fingolimod can be administered as a tablet or capsule. Ex. 1006, 8:19–26. Accordingly, claims 15, 16, 25, and 26 are obvious over the combination of Chiba and Aulton.

7. Claims 17 and 18

Petitioners challenge claims 17 and 18, and Patent Owners offer no separate argument as to these claims. Claims 17 and 18 depend from claim

1 and require that the claimed solid pharmaceutical composition be administered to a subject to treat "organ or tissue transplant rejection, graft versus host disease, an autoimmune disease, an inflammatory condition, viral myocarditis or a viral disease caused by viral myocarditis" (claim 17) or to treat multiple sclerosis (claim 18). Ex. 1001, 17:44–18:6. Chiba teaches both treating autoimmune diseases generally and treating multiple sclerosis using fingolimod. Ex. 1006, 6:26–49. Accordingly, claims 17 and 18 are obvious over the combination of Chiba and Aulton.

8. Claims 27–31

Petitioners challenge claims 27–31. Patent Owners argue the patentability of these claims separately. PO Resp. 59. Claims 27–31 depend from claim 19 and specify various parameters of the mannitol particles used to make the claimed solid pharmaceutical composition. Ex. 1001, 18:30–39. Claims 27 and 28 require that the mannitol particles have "a mean particle size of" between 100 and 300 µm (claim 27) or between 150 and 250 µm (claim 28). *Id.* at 18:30–33. Claims 29 and 30 require that the mannitol have "a bulk density of" between 0.4 and 0.6 g/mL (claim 29) or between 0.45 and 0.55 g/mL (claim 30). *Id.* at 18:34–37. Claim 31 requires that the mannitol have "a single point surface area of $1m^2$/g to 7 m^2/g." *Id.* at 18:38–39. Petitioners argue that, according to the specification of the '283 patent, a form of mannitol was known in the prior art and commercially available at the time the application that issued as the '283 patent was written. Pet. 41–42 (citing Ex. 1001, 10:10–12). According to Petitioners, "[i]t would have been a matter of routine optimization for an ordinarily skilled artisan to

select this commercially available mannitol product," particularly given that these claimed ranges of mannitol particle properties are not critical. *Id.* at 41.

In response, Patent Owners argue that claims 27–31 "reflect the inventors' discovery that mannitol of certain sizes and shapes promotes fingolimod's content uniformity." PO Resp. 59. According to Patent Owners, "the inventors here discovered a reason unknown in the art to use mannitol of particular sizes and shapes," and, because "Petitioners point to no other motivation to combine these elements" than Patent Owners' own motivation, "Petitioners' arguments fail." *Id.*

With respect to content uniformity, Patent Owners identify evidence that shows that Novartis, in developing Gilenya, encountered problems with maintaining an even distribution of fingolimod particles through a mixture of mannitol particles. Ex. 2041 ¶ 31. The first attempt to solve this problem involved "micronizing the fingolimod substance prior to formulation" in order to "more uniformly distribute fingolimod in the mixture." *Id.* ¶ 30. When this proved insufficient, the inventors decided to try the commercially available mannitol particle described in the specification of the '283 patent, Parteck M200. *Id.* ¶ 32. This mannitol improved content uniformity, which the inventors found surprising, because the difference in size between the large mannitol particles and the small fingolimod particles should have reduced content uniformity. *Id.* ¶¶ 33–34. Later, the inventors theorized that the "rougher structure" of Parteck M200 (compared to other available mannitol particles) "might promote fingolimod adhesion to the Parteck mannitol surface." *Id.* ¶ 36.

This evidence shows that Patent Owners discovered a reason to use Parteck M200 mannitol in formulating a solid pharmaceutical composition containing mannitol, but it does not show that this reason was unknown in the prior art. There is some record evidence to suggest that "combining larger excipient particles with smaller active ingredient particles was contrary to the conventional thinking at the time that all particles within a formulation should be controlled within a similar range," Ex. 2042 ¶ 80, but the record also contains evidence that this approach was known in the prior art to improve content uniformity, particularly with low-dose drugs. Ex. 1031 ¶¶ 73–83; Ex. 1052, 2–3; Ex. 1053, 2, 5. Accordingly, the preponderance of the evidence contradicts Patent Owners' argument that claims 27–31 reflect a discovery that was unknown in the prior art.

Moreover, we have not been directed to any evidence of record that the ranges of mannitol particle properties that are claimed in claims 27–31 are critical in achieving the desired content uniformity. All the evidence shows is that, whatever particular (but unspecified) properties Parteck M200 has, mannitol with those properties is better than mannitol with the unspecified properties possessed by some other commercially available mannitol particles. Thus, we are persuaded by Petitioners' argument that it was within the skill of a person of ordinary skill in the art to optimize the properties of the mannitol particles used in formulating a solid oral dosage form of fingolimod. Accordingly, claims 27–31 are obvious over the combination of Chiba and Aulton.

Motion to Amend

Because we find each of claims 1–32 unpatentable, we next address Patent Owners' motion to amend, in which claims 33–64 are proposed. Motions to amend are permitted by 35 U.S.C. § 316(d) and 37 C.F.R. § 42.121. In moving to amend their claims, as the moving the party, Patent Owners have the burden to show entitlement to the relief requested. 37 C.F.R. § 42.20(c). "The burden is not on the petitioner to show [the] unpatentability [of the proposed claims], but on the patent owner to show patentable distinction over the prior art of record and also [the] prior art known to the patent owner." *Idle Free Sys., Inc. v. Bergstrom, Inc.*, Case IPR2012-00027, slip op. at 7 (PTAB June 11, 2013) (Paper 26) (representative). The "prior art of record" includes "any material in the prosecution history of the patent," "any material art of record in the current proceeding, including art asserted in grounds on which the Board did not institute review," and "any material art of record in any other proceeding before the Office involving the patent." *MasterImage 3D, Inc. v. RealD Inc.*, Case IPR2015-00040, slip op. at 2 (PTAB July 15, 2015) (Paper 42) (representative). If Patent Owners

> set forth a *prima facie* case of patentability of narrower substitute claims over the prior art of record, the burden of production shifts to Petitioner. In its opposition, Petitioner may explain why Patent Owner did not make out a *prima facie* case of patentability, or attempt to rebut that *prima facie* case, by addressing Patent Owner's evidence and arguments and/or by identifying and applying additional prior art against proposed substitute claims. Patent Owner has an opportunity to respond in its reply. The ultimate burden of persuasion remains with

> Patent Owner, the movant, to demonstrate the patentability of the amended claims.

Id. at 4 (citing *Microsoft Corp. v. Proxyconn, Inc.*, 789 F.3d 1292, 1306 (Fed. Cir. 2015)). As discussed below, we determine that Patent Owners have not carried the burden of demonstrating the patentability of any of the proposed claims.

Claim 51

As a replacement for claim 19, Patent Owners propose claim 51. Mot. to Amend 38–39. Claim 51 is identical to claim 19 but for the addition of three new limitations: "wherein the composition is stable, wherein the composition has substantially uniform distribution of the agonist throughout the composition, and wherein the composition is made on automated equipment." *Id.* Patent Owners argue that the stability and content uniformity limitations contribute to patentability because "Petitioners fail to offer any motivation to combine Chiba (or any other fingolimod-related art) with a sugar alcohol to achieve stability and content uniformity." *Id.* at 15–16. As discussed above, Patent Owners argue that the inventors of the '283 patent were the first to discover fingolimod's low-dose stability and content uniformity issues, so the prior art does not address these requirements of claim 51. With respect to the requirement that the composition be made on automated equipment, Patent Owners argue that the problems with content uniformity were "especially acute when employing automated equipment." *Id.* at 6.

Petitioners argue that each of the new limitations of claim 51 is taught by Aulton as "a standard goal in the development of a pharmaceutical dosage form." Mot. to Amend Opp. 10 (citing Ex. 2052). We agree. Aulton teaches that

> [t]he *principal objective of dosage form design* is to achieve a predictable therapeutic response to a drug included in a formulation which is *capable of large scale manufacture with reproducible product quality*. To ensure product quality, numerous features are required — *chemical and physical stability*, with suitable preservation against microbial contamination if appropriate, *uniformity of dose of drug*, acceptability to users including both prescriber and patient, as well as suitable packaging and labelling.

Ex. 2052, 15 (emphases added). Thus, according to Aulton, each of the new limitations of claim 51 was known to be a standard "principal objective of dosage form design." *Id.* In addition to these teachings regarding stability, uniformity, and large-scale manufacture, other evidence exists in the record that the manufacture of tablets and capsules on automated equipment was part of the ordinary skill in the art.[25] Ex. 2049, 21–29, 93–103. As discussed above, the original limitations of claim 19, from which claim 51 depends, are taught by Chiba and Aulton, a person of ordinary skill in the art would have had a reason to combine the teachings of Chiba and Aulton, and a person of ordinary skill in the art would have had a reasonable expectation of success in combining the teachings of Chiba and Aulton.

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[25] Moreover, at least with respect to Patent Owners' argument that the inventors of the '283 patent were the first to discover fingolimod's low-dose stability and content uniformity issues, claim 51 is not limited to low doses (or to any range of doses at all).

Patent Owners also argue that objective indicia of nonobviousness support the patentability of claim 51. Mot. to Amend 23–26. The particular objective indicia Patent Owners point to are precisely the same ones that Patent Owners argued supported the patentability of the existing claims of the '283 patent, discussed above. *Compare id. with* PO Resp. 52–58. For the reasons discussed above, the evidence of record does not support a finding that any of the referenced objective indicia of nonobviousness—unexpected results, long-felt but unmet need, industry praise, and commercial success—were present in any legally significant way. Accordingly, claim 51 would have been obvious over the combination of Chiba and Aulton, so Patent Owners have not demonstrated the patentability of claim 51.

Claims 33, 35, and 36

Claim 33 is identical to claim 51, except that claim 33 recites "a sugar alcohol" instead of claim 51's mannitol. *Compare* Mot. to Amend 30–31 *with id.* at 38–39. This makes claim 33 broader in scope than claim 51, with the entire scope of claim 51 included within claim 33's scope. Accordingly, because claim 51 is obvious over the combination of Chiba and Aulton, so is claim 33. *See Callaway*, 576 F.3d at 1344. Claims 35 and 36 are narrower than claim 33, limiting the recited sugar alcohol to one "selected from the group consisting of mannitol, maltitol, inositol, xylitol and lactitol" (claim 35) or to mannitol (claim 36). Claim 35 is broader than claim 51 and contains within its scope the entire scope of claim 51, while claims 36 and 51 have identical scope. Accordingly, claims 35 and 36 are both obvious

over the combination of Chiba and Aulton. Patent Owners have not demonstrated the patentability of claims 33, 35, and 36.

Claims 39, 40, and 54

Claim 39 depends from claim 33 and limits the amount of fingolimod in the claimed composition to between 0.1 and 10 weight percent. Mot. to Amend 33. Claim 40 depends from claim 39 and further limits the amount of fingolimod in the claimed composition to between 0.5 and 5 weight percent. *Id.* at 34. Similarly, claim 54 depends from claim 51 and limits the amount of fingolimod in the claimed composition to between 0.5 and 5 weight percent. *Id.* at 40. Patent Owners argue that these content limitations impart patentability over the prior art because the inventors of the '283 patent were the first to discover that fingolimod was difficult to formulate and had stability and content uniformity problems at low doses, and these limitations require low-dose fingolimod. *Id.* at 4–5. Petitioners argue that these limitations do not limit the fingolimod to any particular dose range and that the prior art teaches or suggests tablets with fingolimod concentrations falling within the claimed range. Mot. to Amend Opp. 12–13; *see e.g., id.* at 12 n.1 ("Neither the specification nor this limitation recite a dose as the total weight is not provided.").

As discussed above, there is evidence of record that the selection of the relative amounts of the constituents of the claimed formulation is the result of routine optimization. Ex. 1004 ¶ 188 ("the amount of active present in a formulation is well within the skill of the ordinary artisan to manipulate and optimize for the appropriate use"). Patent Owners do not

direct us 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 to obtain an appropriately effective formulation. Accordingly, claims 39, 40, and 54 would have been obvious over Chiba and Aulton, so Patent Owners have not demonstrated the patentability of these claims.

Claim 64

Claim 64 depends from claim 33 and requires that "the sugar alcohol ha[ve] a rough surface." Mot. to Amend 43–44. Patent Owners argue that this claim is patentable because the inventors were the first to discover that fingolimod had content uniformity problems during manufacture that could be solved using rough-surface mannitol particles. *Id.* at 6. Petitioners argue that using rough-surface mannitol would have been obvious because, under Patent Owners' proposed construction of "rough particle surface," "all of the commercially available spray-dried or granular forms of mannitol meet the limitation of a rough surface because their surface [area] is necessarily greater than [that of] a perfect sphere." Mot. to Amend Opp. 13–14. We agree. As discussed above, and as suggested by Patent Owners, we construe a particle with a "rough particle surface" to be a particle "with higher surface area than a sphere of a diameter equal to the average diameter of the particle in question." Under this construction, both Parteck M200 mannitol (the mannitol particle that Patent Owners argue solved the content uniformity problem) and SD200 mannitol (the mannitol particle with which the content uniformity problem occurred) have a rough surface. Ex. 2041 ¶¶ 35–36; *see*

Ex. 2271, 142:23–143:4[26] ("a rough particle is anything that has a higher surface area than a theoretically perfect sphere"). Because both types of mannitol are "rough," and because content uniformity was a problem with one type of mannitol but not with the other, the "rough surface" limitation of claim 64 is not relevant to solving the issue of content uniformity. Accordingly, given the above claim construction, there is insufficient evidence to support Patent Owners' argument that rough-surface mannitol adds anything to the patentability of claim 64. Thus, claim 64 is obvious over Chiba and Aulton for the same reasons that claim 33, from which it depends, is obvious. Patent Owners have not demonstrated the patentability of claim 64.

Claims 47 and 48

Claims 47 and 48 depend from claim 64 and require the claimed pharmaceutical composition to be made on automated equipment. Mot. to Amend 36–37. Claim 47 requires the composition to be in the form of a tablet, while claim 48 requires the composition to be in the form of a capsule. *Id.* As discussed above, Aulton teaches the manufacture of drugs on automated equipment. Ex. 2052, 15 ("The *principal objective of dosage form design* is to achieve a predictable therapeutic response to a drug included in a formulation which is *capable of large scale manufacture with reproducible product quality*." (emphases added)). In addition, other evidence exists in the record that manufacture of tablets and capsules on automated equipment was part of the ordinary skill in the art. Ex. 2049, 21–

[26] A public version is available at Ex. 2276, 142:23–143:4.

29, 93–103. Further, both Chiba and Aulton teach the use of tablets and capsules. Ex. 1006, 8:19–28; Ex. 1021, 5. Accordingly, claims 47 and 48 would have been obvious over the combination of Chiba and Aulton. Patent Owners have not demonstrated the patentability of these claims.

Claims 34, 37, 38, 41–46, 49, 50, 52, 53, and 55–63

The remaining claims proposed in Patent Owners' motion to amend (claims 34, 37, 38, 41–46, 49, 50, 52, 53, and 55–63) are not amended from their original forms (claims 2, 5, 6, 9–14, 17, 18, 20, 21, and 23–31), except to change their dependency from the existing claims to the proposed amended claims. These claims are obvious over the combination of Chiba and Aulton for the reasons discussed above with respect to claims 2, 5, 6, 9–14, 17, 18, 20, 21, 23–31, 33, 35, 36, 39, 40, 47, 48, 51, 54, and 64. Patent Owners have not demonstrated the patentability of these claims.

Petitioners' Motion to Exclude

Petitioners move to exclude (1) portions of Ex. 2041 and Ex. 2043 under Federal Rule of Evidence ("FRE") 602 and FRE 802; (2) all of Ex. 2047 under FRE 802; and (3) portions of Ex. 2042 and Ex. 2280 under FRE 602, FRE 702, and 37 C.F.R. § 42.65. Paper 78, 1. In addition, Petitioners seek exclusion of portions of Paper 62, Ex. 2280, Ex. 2281, and Ex. 2283 on the ground that they are beyond the scope of a proper reply in support of a motion to amend. *Id*. at 16–17. Finally, Petitioners move to exclude Ex. 2045, Ex. 2281, and portions of Ex. 2044, Ex. 2275, Paper 26, and Paper 31

because these documents try, but fail, to show the presence of objective indicia of nonobviousness. *Id.* at 17–20.

Ex. 2041

Petitioners argue that paragraphs 4–6, 8, 11–13, 21, and 22 of Ex. 2041 should be excluded under FRE 602 and FRE 802 because Dr. Pudipeddi, the declarant, lacks personal knowledge of the facts to which he testifies, rendering his statements hearsay. Paper 78, 10–11. We do not rely on any of the cited paragraphs of Ex. 2041, so we dismiss this portion of Petitioners' motion to exclude as moot.

Ex. 2043

Petitioners argue that paragraphs 6–21 of Ex. 2043 should be excluded because Mr. Oomura, the declarant, lacks personal knowledge of the facts to which he testifies, rendering his statements hearsay. *Id.* at 1, 4–8. We do not rely on paragraphs 6–13, 20, or 21, so we dismiss Petitioners' motion to exclude those paragraphs as moot. As to paragraphs 14–19, we note that Mr. Oomura's personal knowledge of the low-dose compatibility problems with fingolimod discovered by Yoshitomi comes from his review of Yoshitomi documents and his discussions with Yoshitomi personnel. Ex. 2273, 13:3–7, 16:25–17:7, 20:14–17. This is ample basis for him to testify with personal knowledge of the facts under FRE 602. As to the hearsay objection, FRE 803(3) makes admissible statements that describe the declarant's state of mind, and the testimony in paragraphs 14–19 goes to the subjective motivation of Mr. Oomura and his colleagues to solve what

they perceived as a low-dose compatibility problem with fingolimod. Accordingly, we deny Petitioners' motion to exclude paragraphs 14–19 of Ex. 2043.

Ex. 2047

Petitioners move to exclude the entirety of Ex. 2047 as hearsay. Paper 78, 9–10. We do not rely on Ex. 2047, so we dismiss this portion of Petitioners' motion to exclude as moot.

Ex. 2042

Petitioners move to exclude paragraphs 2–4, 13, and 39–50 of Ex. 2042 because those paragraphs merely retell the story told by Mr. Oomura, without any personal knowledge on the part of Dr. Byrn, the declarant. Paper 78, 8–9, 11. Petitioners also argue that this same testimony, as well as paragraphs 11–13 and 76 of Ex. 2042, should be excluded under FRE 702, both because it relies on tests performed by others for which Dr. Byrn had access to the results but not information about "how the data was generated," and because Dr. Byrn did not conduct any independent analysis into how the testing was accomplished. *Id.* at 11–16. We are not convinced that either problem warrants exclusion of this testimony. Expert witnesses are allowed to describe the facts that their opinions rest on, so Dr. Byrn's retelling of Mr. Oomura's story need not be excluded simply because Dr. Byrn lacks personal knowledge of that story. To the extent Petitioners argue that it was improper for Dr. Byrn to rely on testing performed by others and about which he did not know every detail, Dr. Byrn disagrees, providing evidence

that sufficient information about the testing was made available to render his reliance on that testing reasonable under FRE 702. *See* Ex. 2280 ¶ 32. Accordingly, we deny Petitioners' motion to exclude paragraphs 39, 40, and 76 of Ex. 2042. Because we do not rely on paragraphs 2–4, 11–13, or 41–50 of Ex. 2042, we dismiss Petitioners' motion to exclude those paragraphs as moot.

Ex. 2280

Petitioners move to exclude paragraphs 3, 4, 19, and 29–32 of Ex. 2280 because these paragraphs merely retell the story told by Mr. Oomura, without any personal knowledge on the part of Dr. Byrn, the declarant. Paper 78, 8–9. We do not rely on any of the cited paragraphs, so we dismiss Petitioners' motion to exclude this testimony as moot.

Argument and Evidence Beyond Proper Scope of Reply

Petitioners seek exclusion of pages 2–9 of Paper 62; paragraphs 2–37 of Ex. 2280; Ex. 2281; and paragraphs 3–20 of Ex. 2283 on the ground that they are beyond the scope of a proper reply in support of a motion to amend. *Id.* at 16–17. A motion to exclude is not the proper vehicle for challenging the scope of a reply. *Conopco, Inc. v. Proctor & Gamble Co.*, IPR2013-00505, slip op. at 29 (PTAB Feb. 10, 2015) (Paper 69). Accordingly, Petitioners' motion to exclude pages 2–9 of Paper 62; paragraphs 2–37 of Ex. 2280; Ex. 2281; and paragraphs 3–20 of Ex. 2283 is denied.

Argument and Evidence of Objective Indicia of Nonobviousness

Finally, Petitioners move to exclude Ex. 2045; Ex. 2281; paragraphs 16–44 of Ex. 2044; unspecified portions of Ex. 2275; pages 55–58 of Paper 26; and pages 24–26 of Paper 31 because this testimony makes only an unsuccessful case of the presence of objective indicia of nonobviousness. *Id.* at 17–20. This is an attack on the sufficiency of the evidence, not on its admissibility. Such an attack has no place in a motion to exclude. *Microsoft Corp. v. Surfcast, Inc.*, Case IPR2013-00292, slip op. at 52–53 (PTAB Oct. 14, 2014) (Paper 93). Accordingly, we deny Petitioners' motion to exclude Ex. 2045; Ex. 2281; paragraphs 16–44 of Ex. 2044; unspecified portions of Ex. 2275; pages 55–58 of Paper 26; and pages 24–26 of Paper 31.

Patent Owners' Motion to Exclude

Patent Owners move to exclude (1) portions of Ex. 1004 and Ex. 1031 under FRE 702; (2) portions of Ex. 1041 under FRE 702; and (3) 53 separate exhibits under FRE 402 and FRE 403. Paper 73, 4–20.

Ex. 1004 and Ex. 1031

Patent Owners seek to exclude paragraphs 75–96, 102–106, 146–152, 162–165, 168–196, and 198 of Ex. 1004 and paragraphs 10, 11, 13, 14, 34–48, 72, and 77 of Ex. 1031. *Id.* at 5 n.2. According to Patent Owners this testimony fails to satisfy the requirements of FRE 702 because the declarant, Dr. Kent, offers only an "obvious to try" theory of obviousness that cannot succeed as a matter of law. *Id.* at 5–8. This attack on the sufficiency of the evidence is improper in a motion to exclude. *Microsoft Corp. v. Surfcast,*

Inc., Case IPR2013-00292, slip op. at 52–53 (PTAB Oct. 14, 2014) (Paper 93). In any case, as discussed above, we do not agree that Dr. Kent relied on the theory of obviousness that Patent Owners describe as an "obvious to try" theory, in which a person of ordinary skill in the art would have been motivated, at most, to choose mannitol as just one of a large number of excipients to test for compatibility with fingolimod. Instead, the evidence of record shows that a person of ordinary skill in the art would have been directed by Sakai to combine mannitol and fingolimod and that mannitol had several well-known advantages that would have motivated a person of ordinary skill in the art to choose it as a pharmaceutical excipient. This is sufficient, as discussed above, to show the obviousness of the fingolimod-mannitol combination.

Patent Owners also argue that this testimony should be excluded because Dr. Kent failed to provide evidence sufficient to show how a formulator would "develop a list of excipients to test with fingolimod *ex ante*." Paper 73, 12. Again, this is an improper attack on the sufficiency of the evidence, so we deny the motion to exclude. In any case, the obviousness of the mannitol-fingolimod combination does not depend on the *ex ante* prediction of a perfect fit between the active ingredient and the excipient, but rather requires only a reasonable expectation of success. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007). As discussed above, the evidence of record here shows the requisite reasonable expectation of success.

Finally, Patent Owners argue that this testimony should be excluded because Dr. Kent's analysis is unreliable under FRE 702 due to its reliance

on Budde,[27] a phase I safety study, as teaching that a low dose of fingolimod should be used in the formulation of a dosage form. Paper 73, 13–14. But the evidence of record shows that Budde describes a clinical effect of a low dose of fingolimod and that a formulator would attempt to use the proper effective dose when studying compatibility with excipients. Ex. 2098, 1073 ("Single oral doses of FTY720 ranging from 0.25 to 3.5 mg . . . caused a reversible selective lymphopenia."); Ex. 1010, 5 ("drug-excipient ratios should be selected and studies based on what is likely to be a reasonable drug-excipient ratio in the final tablet or capsule"); Ex. 1012, 51 (drug-excipient ratio "should be consistent with the ratio most likely to be encountered in the final tablet"). Accordingly, Dr. Kent's reliance on Budde's teaching of a low effective dose is not a reason to exclude his testimony.

We do not rely on paragraphs 75–92, 95, 96, 102–106, 146–152, 162–165, 168, 169, 171–187, 189–193, 196, and 198 of Ex. 1004 or on paragraphs 10, 11, 13, 14, 34–48, and 72 of Ex. 1031, so we dismiss Patent Owners' motion to exclude these paragraphs as moot. Because none of Patent Owners' arguments for excluding paragraphs 75–96, 102–106, 146–152, 162–165, 168–196, and 198 of Ex. 1004 and paragraphs 10, 11, 13, 14, 34–48, 72, and 77 of Ex. 1031 is persuasive, we deny the motion to exclude

[27] Klemens Budde, Robert L. Schmouder, Reinhard Brunkhorst, Bjorn Nashan, Peter W. Lücker, Thomas Mayer, Somesh Choudhury, Andrej Skerjanec, Gerolf Kraus, & Hans H. Neumayer, *First Human Trial of FTY720, a Novel Immunomodulator, in Stable Renal Transplant Patients*, 13 J. AM. SOC'Y NEPHROLOGY 1073–83 (2002) ("Budde," Ex. 2098).

the paragraphs we do rely on, paragraphs 93, 94, 170, 188, 194, and 195 of Ex. 1004 and paragraph 77 of Ex. 1031.

Patent Owners also seek to exclude paragraphs 182 and 183 of Ex. 1004 and paragraphs 94–98, 100, and 102 of Ex. 1031 because the Dr. Kent, the declarant in Ex. 1004 and Ex. 1031, is not qualified to opine on objective indicia of nonobviousness and presents only conclusory opinions. Paper 73, 14–17. We do not rely on any of the cited paragraphs in reaching our decision on the merits, so we dismiss Patent Owners' motion to exclude these paragraphs as moot.

Ex. 1041

Patent Owners move to exclude paragraphs 28–31, 34–36, 40–42, 57–64, 76–83, 88–89, 91–94, and 96–112 of Ex. 1041. We do not rely on any of the cited paragraphs, so we dismiss Patent Owners' motion to exclude these paragraphs as moot.

Other Exhibits

Patent Owners seek to exclude Exhibits 1005, 1008–1021, 1023–1025, 1030, 1032–1034, 1036, 1038, 1042–1047, 1050, 1056–1065, 1067–1069, 1072, 1074–1079, 1091, and 1103 under FRE 402 and FRE 403 as "incomplete and/or irrelevant." Paper 73, 20. Alternatively, Patent Owners argue that, pursuant to FRE 106, additional portions that "Novartis identifies in its objections" should be considered along with the portions of the documents that make up these 53 exhibits. *Id.* With respect to Patent Owners' argument that these documents should be excluded pursuant to

FRE 402 and FRE 403, Patent Owners do not explain why each of these exhibits (or, indeed, any individual one of these exhibits) is irrelevant and therefore inadmissible under FRE 402 or why any of the exhibits has "probative value [that] is substantially outweighed by" any of the concerns expressed in FRE 403. To the extent that Patent Owners explained their arguments in their objections rather than in their motion to exclude, we note that our rules prohibit incorporation of arguments by reference from Patent Owners' objections into their motion to exclude. 37 C.F.R. § 42.6(a)(3) ("Arguments must not be incorporated by reference from one document into another document."). Accordingly, we deny the motion to exclude Exhibits 1005, 1008–1021, 1023–1025, 1030, 1032–1034, 1036, 1038, 1042–1047, 1050, 1056–1065, 1067–1069, 1072, 1074–1079, 1091, and 1103 under FRE 402 and FRE 403. Patent Owners' request to have additional portions of these exhibits considered under FRE 106 is not properly the subject of a motion to exclude evidence and is not developed fully in its motion briefing. In any case, we have considered all the evidence of record, including that submitted by Patent Owners, in reaching our decision on the merits.

Pending Motions to Seal

The parties have filed multiple unopposed motions to seal. Paper 42; Paper 48; Paper 51; Paper 64; Paper 71; Paper 76; Paper 82; Paper 84; Paper 87; Paper 93; Paper 95; Paper 101; Paper 103; Paper 109. Collectively, these motions seek to seal Exhibits 1031, 1041, 1107, 1110–1112, 2041, 2271–2274, 2280, 2281, and 2299, as well as Patent Owners' Response, Petitioners' Reply, Petitioners' Opposition to the Motion to Amend, Patent

Owners' Reply to Petitioners' Opposition to the Motion to Amend, Petitioners' Motion to Exclude, Patent Owners' Motion to Exclude, Patent Owners' Opposition to Petitioners' Motion to Exclude, Patent Owners' Reply to Petitioners' Opposition to Patent Owners' Motion to Exclude, Petitioners' Motion for Observations, Patent Owners' Motion for Observations, Petitioners' Response to Patent Owners' Motion for Observations, Petitioners' Demonstrative Exhibits, Patent Owners' Demonstrative Exhibits, and Patent Owners' Objections to Petitioners' Demonstrative Exhibits.[28]

The Board's standards for granting motions to seal are discussed in *Garmin International, Inc. v. Cuozzo Speed Technologies, LLC*, Case IPR2012-00001 (PTAB Mar. 14, 2013) (Paper 34). In summary, there is a strong public policy for making all information filed in *inter partes* review proceedings open to the public. *Id.* at 1–2. The standard for granting a motion to seal is "good cause." 37 C.F.R. § 42.54. The moving party bears the burden of showing that the relief requested should be granted. 37 C.F.R. § 42.20(c). Meeting the burden includes showing that the information is truly confidential, and that such confidentiality outweighs the strong public interest in having an open record. In addition, a motion to seal must include a certification that the moving party has in good faith conferred, or attempted to confer, with the opposing party in an effort to come to an agreement on the scope of the protection sought. *Garmin*, slip op. at 3.

[28] In addition, we previously sealed Exhibits 2042, 2043, 2045, 2047, 2055, 2187, and 2266–2268, as well as Patent Owners' Motion to Amend. Paper 41.

Having reviewed the motions to seal these documents, the documents sought to be sealed, and the redactions in those cases where a redacted, public version of a document has been filed, we find that the parties have demonstrated good cause to grant the motions. Accordingly, except as discussed below, we will seal the documents listed above.

We have previously informed the parties that, "if our Final Written Decision substantively relies on any information in a sealed exhibit, that exhibit will be unsealed by an Order of the Board." Paper 41, 8. The present decision substantively relies on non-public material from the following exhibits that are the subject of pending motions to seal or previously have been sealed: Ex. 1031, Ex. 1041, Ex. 2041, Ex. 2042, Ex. 2043, and Ex. 2045. Accordingly, these exhibits will be unsealed 45 days after entry of the present decision. Before that time, the parties may move instead to expunge these exhibits and replace them with public versions that redact any confidential material not referred to in this decision.

CONCLUSION

Petitioner has shown, by a preponderance of the evidence, that claims 1–32 of the '283 patent would have been obvious over the combination of Chiba and Aulton. Patent Owner has failed to show, by a preponderance of the evidence that proposed amended claims 33–64 are patentable. The parties' motions to exclude are dismissed in part as moot (to the extent that they seek exclusion of evidence we do not rely on) and denied in part (to the extent that they seek exclusion of evidence we rely on).

ORDER

Accordingly, it is

ORDERED that claims 1–32 of the '283 patent are unpatentable;

FURTHER ORDERED that Patent Owners' motion to amend is denied;

FURTHER ORDERED that Petitioners' motion to exclude paragraphs 4–6, 8, 11–13, 21, and 22 of Ex. 2041; paragraphs 2–4, 11–13, and 41–50 of Ex. 2042; paragraphs 6–13, 20, and 21 of Ex. 2043; Ex. 2047; and paragraphs 3, 4, 19, and 29–32 of Ex. 2280 is dismissed as moot;

FURTHER ORDERED that Petitioners' motion to exclude paragraphs 14–19 of Ex. 2043; paragraphs 39, 40, and 76 of Ex. 2042; pages 2–9 of Paper 62; paragraphs 2–37 of Ex. 2280; Ex. 2281; and paragraphs 3–20 of Ex. 2283; Ex. 2045; Ex. 2281; paragraphs 16–44 of Ex. 2044; unspecified portions of Ex. 2275; pages 55–58 of Paper 26; and pages 24–26 of Paper 31 is denied;

FURTHER ORDERED that Patent Owners' motion to exclude paragraphs 75–92, 95, 96, 102–106, 146–152, 162–165, 168, 169, 171–187, 189–193, 196, and 198 of Ex. 1004; paragraphs 10, 11, 13, 14, 34–48, 72, 94–98, 100, and 102 of Ex. 1031; and paragraphs 28–31, 34–36, 40–42, 57–64, 76–83, 88–89, 91–94, and 96–112 of Ex. 1041 is dismissed as moot;

FURTHER ORDERED that Patent Owners' motion to exclude paragraphs 93, 94, 170, 188, 194, and 195 of Ex. 1004; paragraph 77 of Ex. 1031; and Exhibits 1005, 1008–1021, 1023–1025, 1030, 1032–1034, 1036, 1038, 1042–1047, 1050, 1056–1065, 1067–1069, 1072, 1074–1079, 1091, and 1103 is denied;

FURTHER ORDERED that the pending motions to seal are granted to the extent that Exhibits 1107, 1110–1112, 2271–2274, 2280, 2281, and 2299, as well as Patent Owners' Response, Petitioners' Reply, Petitioners' Opposition to the Motion to Amend, Patent Owners' Reply to Petitioners' Opposition to the Motion to Amend, Petitioners' Motion to Exclude, Patent Owners' Motion to Exclude, Patent Owners' Opposition to Petitioners' Motion to Exclude, Patent Owners' Reply to Petitioners' Opposition to Patent Owners' Motion to Exclude, Petitioners' Motion for Observations, Patent Owners' Motion for Observations, Petitioners' Response to Patent Owners' Motion for Observations, Petitioners' Demonstrative Exhibits, Patent Owners' Demonstrative Exhibits, and Patent Owners' Objections to Petitioners' Demonstrative Exhibits are sealed;

FURTHER ORDERED that Exhibits 1031, 1041, 2041, 2042, 2043, and 2045 shall be unsealed and shall become publicly available 45 days after entry of this decision, provided that the parties may move within 45 days of entry of this decision to expunge these exhibits and replace them with public versions that redact any confidential information not referred to herein;

FURTHER ORDERED that the parties shall file no later than one week after the entry of this decision a redacted version of Paper 111, to be made publicly available as a record of the oral hearing;

FURTHER ORDERED that Papers 99, 100, 107, and 108 shall be expunged from the record; and

FURTHER ORDERED that, because this is a final written decision, parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

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