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Paper 8
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC.,
Petitioner,

v.

ALLERGAN, INC.,
Patent Owner.

Case IPR2016-01131
Patent 8,648,048 B2

Before SHERIDAN K. SNEDDEN, TINA E. HULSE, and CHRISTOPHER G. PAULRAJ, *Administrative Patent Judges*.

SNEDDEN, *Administrative Patent Judge*.

DECISION
Institution of *Inter Partes* Review
37 C.F.R. § 42.108

I. INTRODUCTION

Mylan Pharmaceuticals Inc. ("Petitioner") filed a Petition to institute an *inter partes* review of claims 1–23 (Paper 3; "Pet.") of US 8,648,048 B2 (Ex. 1001; "the '048 patent"). Allergan, Inc. ("Patent Owner") filed a Patent Owner Preliminary response. Paper 7 ("Prelim. Resp.").

We have jurisdiction under 35 U.S.C. § 314, which provides that an *inter partes* review may not be instituted "unless . . . there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a). Upon consideration of the above-mentioned Petition and Preliminary Responses, we conclude that Petitioner has established that there is a reasonable likelihood that it will prevail with respect to at least one of the challenged claims. We institute an *inter partes* review as to claims 1–23 of the '048 patent.

A. Related Proceedings

The parties indicate that the following judicial matter may affect or be affected by a decision in this proceeding: *Allergan, Inc. v. Teva Pharmaceuticals USA, Inc., et al.,* No. 2:15-cv-01455 (E.D. Texas), *Allergan, Inc., v. Innopharma, Inc. and Pfizer, Inc., N*o. 2:15cv1504 (E.D. Texas), and *Allergan, Inc. v. Famy Care, Ltd*., No. 2:16-cv-0401 (D. Texas). Pet. 12; Paper 6, 2.

Moreover, Petitioner has sought inter partes review for related patents in the following proceedings: Case IPR2016-01127 (U.S. Patent No. 8,685,930 B2), Case IPR2016-01128 (U.S. Patent No. 8,629,111 B2), Case IPR2016-01129 (U.S. Patent No. 8,642,556 B2), Case IPR2016-01130 (U.S. Patent No. 8,633,162 B2), and Case IPR2016-01132 (U.S. Patent No. 9,248,191 B2).

B. The '048 patent (Ex. 1001)

The '048 patent generally relates to methods of providing therapeutic effects using cyclosporin components, and more specifically to a formulation containing, *inter alia*, cyclosporin-A ("CsA") and castor oil emulsions for treating dry eye syndrome (i.e., keratoconjunctivitis sicca). Ex. 1001, 2:55–3:11. According to the specification, the prior art recognized the use of emulsions containing CsA and CsA derivatives to treat ophthalmic conditions. *Id.* at 1:26–65. The specification notes, however, that "[o]ver time, it has been apparent that cyclosporin A emulsions for ophthalmic use preferably have less than 0.2% by weight of cyclosporin A." *Id.* at 1:66–2:1. Moreover, if reduced amounts of CsA are used, reduced amounts of castor oil are needed because one of the functions of castor oil is to solubilize cyclosporin A. *Id.* at 2:1–2:6.

Accordingly, the specification states that "[i]t has been found that the relatively increased amounts of hydrophobic component together with relatively reduced, yet therapeutically effective, amounts of cyclosporin component provide substantial and advantageous benefits." *Id.* at 2:35–38. The relatively high concentration of hydrophobic component provides for a more rapid breaking down of the emulsion in the eye, which reduces vision distortion and/or facilitates the therapeutic effectiveness of the composition. *Id.* at 2:42–48. Furthermore, using reduced amounts of cyclosporin component mitigates against undesirable side effects or potential drug interactions. *Id.* at 2:48–51.

The patent identifies two particular compositions that were selected for further testing, as shown below:

	Composition I wt %	Composition II wt %
Cyclosporin A	0.1	0.05
Castor Oil	1.25	1.25
Polysorbate 80	1.00	1.00
Premulen ®	0.05	0.05
Glycerine	2.20	2.20
Sodium hydroxide	qs	qs
Purified Water	qs	qs
pH	7.2-7.6	7.2-7.6
Weight Ratio of Cyclosporin A to Castor Oil	0.08	0.04

Id. at 14:15–30. Based on the results of a Phase III clinical study, the specification concludes that "Composition II . . . provides overall efficacy in treating dry eye disease substantially equal to that of Composition I." *Id.* at 14:35–40. The patent indicates that "[t]his is surprising for a number of reasons." *Id.* at 14:41. According to the specification, a reduced concentration of CsA in Composition II would have been expected to result in reduced overall efficacy in treating dry eye disease. *Id.* at 14:41–44. Moreover, although the large amount of castor oil relative to the amount of CsA in Composition II might have been expected to cause increased eye irritation, it was found to be substantially non-irritating in use. *Id.* at 14:44–49. Accordingly, the specification states that physicians can prescribe Composition II "to more patients and/or with fewer restrictions and/or with reduced risk of the occurrence of adverse events, e.g., side effects, drug interactions and the like, relative to providing Composition I." *Id.* at 15:4–8.

C. Illustrative Claims

Petitioner challenges claims 1–23 of the '048 patent. Independent claims 1, 18, and 22 are illustrative of the challenged claims, and are reproduced below:

> 1. A method of increasing tear production in the eye of a human, the method comprising topically administering to the eye of the

human in need thereof an emulsion at a frequency of twice a day, wherein the emulsion comprises cyclosporin A in an amount of about 0.05% by weight, polysorbate 80, acrylate/C10–30 alkyl acrylate cross-polymer, water, and castor oil in an amount of about 1.25% by weight; and

wherein the topical ophthalmic emulsion is effective in increasing tear production.

18. A method of treating keratoconjunctivitis sicca, the method comprising the step of topically administering to an eye of a human in need thereof an emulsion at a frequency of twice a day, the emulsion comprising:

cyclosporin A in an amount of about 0.05% by weight;

castor oil in an amount of about 1.25% by weight;

polysorbate 80 in an amount of about 1.0% by weight;

acrylate/C10–30 alkyl acrylate cross-polymer in an amount of about 0.05% by weight;

a tonicity component or a demulcent component in an amount of about 2.2% by weight;

a buffer; and

water;

wherein the emulsion is effective in treating keratoconjunctivitis sicca and wherein the topical ophthalmic emulsion has a pH in the range of about 7.2 to about 7.6.

22. A method comprising:

administering an emulsion topically to the eye of a human having keratoconjunctivitis sicca at a frequency of twice a day, wherein the emulsion comprises:

cyclosporin A in an amount of about 0.05% by weight;

castor oil in an amount of about 1.25% by weight;

polysorbate 80 in an amount of about 1.0% by weight;

acrylate/C10–30 alkyl acrylate cross-polymer in an amount of about 0.05% by weight;

glycerine in an amount of about 2.2% by weight;

sodium hydroxide; and

water; and

wherein the emulsion is effective in increasing tear production in the human having keratoconjunctivitis sicca.

Claims 2–17 depend from claim 1, either directly or indirectly. Claims 19–21 depend from claim 18, either directly or indirectly. Claim 23 depend from claim 22, either directly or indirectly.

D. The Asserted Grounds

Petitioner challenges claims 1–23 of the '048 patent on the following grounds. Pet. 17–18.

Ground	Reference[s]	Basis	Claims challenged
1	Ding '979, [1] and Sall[2]	§ 103	1–10, 12–14, 16–20, 22, and 23
2	Ding '979, Sall, and Acheampong[3]	§ 103	11 and 21
3	Ding '979, Sall, and Acheampong, and Glonek[4]	§ 103	15

Petitioner further relies on the Declarations of Dr. Mansoor Amiji, Ph.D. (Ex. 1002).

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[1] Ding et al., U.S. Patent No. 5,474,979, issued December 12, 1995 (Ex. 1006, "Ding '979").

[2] Kenneth Sall et al., *Two Multicenter, Randomized Studies of the Efficacy and Safety of Cyclosporine Ophthalmic Emulsion in Moderate to Severe Dry Eye Disease*, 107 OPHTHALMOLOGY 631–639 (2000) (Ex. 1007, "Sall").

[3] Andrew Acheampong et al., *Cyclosporine Distribution Into The Conjunctiva, Cornea, Lacrimal Gland, And Systemic Blood Following Topical Dosing Of Cyclosporine To Rabbit, Dog, And Human Eyes*, *in* LACRIMAL GLAND, TEAR FILM, AND DRY EYE SYNDROMES 2, BASIC SCIENCE AND CLINICAL RELEVANCE, 1001–1004 (1998) (Ex. 1008, "Acheampong").

[4] Glonek et al., U.S. Patent No. 5,578,586, issued Nov. 26, 1996. Ex. 1009 ("Glonek").

II. ANALYSIS

A. Claim Interpretation

We interpret claims using the "broadest reasonable construction in light of the specification of the patent in which [they] appear[]." 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs. LLC v. Lee,* 136 S. Ct. 2131, 2144–46 (2016). Under the broadest reasonable construction standard, claim terms are generally given their "ordinary and customary meaning," as would be understood by one of ordinary skill in the art at the time of the invention. *In re Translogic Tech., Inc*., 504 F.3d 1249, 1257 (Fed. Cir. 2007) (quoting *Phillips v. AWH Corp*, 415 F.3d 1303, 1312 (Fed. Cir. 2006)). "Absent claim language carrying a narrow meaning, the PTO should only limit the claim based on the specification . . . when [it] expressly disclaim[s] the broader definition." *In re Bigio*, 381 F.3d 1320, 1325 (Fed. Cir. 2004) (citation omitted). "Although an inventor is indeed free to define the specific terms used to describe his or her invention, this must be done with reasonable clarity, deliberateness, and precision." *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

1. "effective in treating"

Claims 1–17 and 22–23 recite that the emulsion is "effective in increasing tear production," whereas claims 18–21 recite an emulsion that is "effective in treating keratoconjunctivitis sicca." The dependent claims recite other variations such as an emulsion that is "substantially therapeutically effective as a second emulsion" or achieves "at least as much therapeutic effectiveness as a second emulsion."

Petitioner asserts that because the plain meaning of the word "therapeutic" includes palliative as well as curative treatments, the broadest

reasonable interpretation of the terms includes "an emulsion that is effective in increasing tear production is an example of an emulsion therapeutically effective in treating dry eye disease/KCS" palliative and curative treatments. Pet. 14–15 (citing Ex. 1002 ¶¶ 41–44; Ex. 1022, 3, 7)

Patent Owner argues that an emulsion that is "effective in treating keratoconjunctivitis sicca" must treat the disease itself, and not just its symptoms. Prelim. Resp. 21–23. Patent Owner also argues that the inability to produce tears is a hallmark of dry eye disease and that an emulsion that is "effective in increasing tear production" must address the inability to produce natural tears, as opposed to supplementing with artificial tears. *Id.* at 21–22. According to Patent Owner, its construction is supported by a dictionary definition of "therapeutic," defined as "[r]elating to therapeutics or to the treatment, remediating, or curing of a disease or disorder." *Id.* at 22 (citing Ex. 2005). Patent Owner contrasts this definition of "therapeutic" with the definition of "palliative," defined as "[r]educing the severity of; denoting the alleviation of symptoms without curing the underlying disease," thereby suggesting that the phrase "therapeutically effective" would not include palliative effects. *Id.* at 22 n.3 (citing Ex. 2007).

We disagree. The definition of "therapeutic" provided by the Patent Owner does not require a cure of a disease or disorder, but also includes either treatment or remediating of a disease or disorder; a cure is not necessarily required. We thus conclude, on the current record, that the ordinary meaning of the phrase "therapeutically effective" is not so specific so as to exclude palliative effects.

Patent Owner further argues that the specification supports its construction because the '048 patent uses the word "therapeutic" in

connection with the action of cyclosporin. *Id.* at 22. Patent Owner further argues that "the '048 patent specification does not use the word 'therapeutic' to refer to the activity of the other components of the emulsion, including castor oil." *Id.* at 22. We disagree. Contrary to Patent Owner's assertion, the specification does refer to the "therapeutic effects" of castor oil: "it is believed that castor oil includes a relatively high concentration of ricinoleic acid which itself may be useful in benefitting ocular tissue and/or in providing one or more therapeutic effects when administered to an eye." Ex. 1001, 9:50–55 (emphasis added). Thus, notwithstanding Patent Owner's extrinsic evidence it offers in support of its more-limited construction (Prelim. Resp. 21–23), we decline to construe the claims in a manner inconsistent with the specification.

That being said, at this stage of the proceeding, we find that "effective in increasing tear production" does not require further construction as its meaning is clear on its face. We also find that "effective in treating keratoconjunctivitis sicca" encompasses both the treatment of the symptoms of dry eye disease as well as the disease itself.

2. Remaining Claim Terms

We determine that no explicit construction of any claim term is necessary to determine whether to institute a trial in this case. *See, e.g.*, *Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011) ("[C]laim terms need only be construed 'to the extent necessary to resolve the controversy.'") (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)).

At this stage of the proceeding, we have not made a final determination as to the construction of any claim term.

B. Principles of Law

An *inter partes* review may be instituted only if "the information presented in the [Petition and Preliminary Response] shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a). To prevail in its challenges to the patentability of the claims, a petitioner must establish facts supporting its challenges by a preponderance of the evidence. 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d).

We analyze the proposed grounds of unpatentability in accordance with the following stated principles.

A patent may not be obtained if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains. 35 U.S.C. § 103(a). The legal question of obviousness is resolved on the basis of underlying factual determinations, including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of skill in the art; and (4) objective evidence of nonobviousness, i.e., secondary considerations. *See Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

In *KSR International Co. v. Teleflex Inc.*, the Supreme Court stated that an invention may be found obvious if trying a course of conduct would have been obvious to a person having ordinary skill:

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads

> to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

550 U.S. 398, 421 (2007). "*KSR* affirmed the logical inverse of this statement by stating that § 103 bars patentability unless 'the improvement is more than the predictable use of prior art elements according to their established functions.'" *In re Kubin*, 561 F.3d 1351, 1359–60 (Fed. Cir. 2009) (citing *KSR*, 550 U.S. at 417).

The factual inquiries for an obviousness determination also include secondary considerations based on evaluation and crediting of objective evidence of nonobviousness. *Graham*, 383 U.S. at 17–18. Notwithstanding what the teachings of the prior art would have suggested to one with ordinary skill in the art at the time of the invention, the totality of the evidence submitted, including objective evidence of nonobviousness, may lead to a conclusion that the claimed invention would not have been obvious to one with ordinary skill in the art. *In re Piasecki*, 745 F.2d 1468, 1471–72 (Fed. Cir. 1984).

Such a conclusion, however, requires the finding of a nexus to establish that the evidence relied upon traces its basis to something novel in the claim and not to something in the prior art. *Institut Pasteur & Universite Pierre et Marie Curie v. Focarino*, 738 F.3d 1337, 1347 (Fed. Cir. 2013). Generally, objective evidence of nonobviousness must be shown to have a nexus. *In re GPAC Inc.*, 57 F.3d 1573, 1580 (Fed. Cir. 1995) (nexus generally); *In re Kao*, 639 F.3d 1057, 1069 (Fed. Cir. 2011) (unexpected results); *In re Huang*, 100 F.3d 135, 140 (Fed. Cir. 1996) (commercial

success); *Rambus Inc. v. Rea*, 731 F.3d 1248, 1256 (Fed. Cir. 2013) (long-felt need).

Objective evidence of nonobviousness also must be reasonably commensurate in scope with the claim. *Kao*, 639 F.3d at 1068. This does not mean that the proffered evidence must reach every embodiment within the scope of the claim, so long as there is an "adequate basis to support the conclusion that other embodiments falling within the claim will behave in the same manner." *Id.*

C. Content of the Prior Art

Petitioner relies upon the following prior art in its challenges.

1. Ding '979 (Ex. 1006)

Ding '979, assigned to Patent Owner, relates to ophthalmic emulsions including cyclosporin, castor oil, and polysorbate 80 that have a high comfort level and low irritation potential. Ex. 1006, cover, 1:4–9. Ding '979 explains that cyclosporins have "known immunosuppressant activity" and have been found "effective in treating immune medicated keratoconjunctivitis sicca (KCS or dry eye disease) in a patient suffering therefrom." *Id.* at 1:10–16. Although the solubility of cyclosporins in water is extremely low, cyclosporins have some solubility in oily preparations containing higher fatty acid glycerides such as castor oil. *Id.* at 1:40–41, 2:39–42. Ding '979 notes, however, that formulations with a high concentration of oils have several drawbacks, including exacerbation of the symptoms of dry eyes and low thermodynamic activity of cyclosporin, which leads to poorer drug bioavailability. *Id.* at 2:42–57. Accordingly, Ding '979 "is directed to an emulsion system which utilizes higher fatty acid glycerides but in combination with polysorbate 80 which results in an

emulsion with a high comfort level and low irritation potential suitable for delivery of medications to sensitive areas such as ocular tissues." *Id.* at 2:65–3:3.

Ding '979 discloses that the preferable weight ratio of CsA to castor oil is below 0.16, and more preferably between 0.12 and 0.02. *Id.* at 3:15–20. Specifically, Ding '979 discloses several compositions as Example 1, shown below:

Example 1

	A	B	C	D	E
Cyclosporin A	0.40%	0.20%	0.20%	0.10%	0.05%
Castor oil	5.00%	5.00%	2.50%	1.25%	0.625%
Polysorbate 80	1.00%	1.00%	1.00%	1.00%	1.00%
Pemulen ®	0.05%	0.05%	0.05%	0.05%	0.05%
Glycerine	2.20%	2.20%	2.20%	2.20%	2.20%
NaOH	qs	qs	qs	qs	qs
Purified water	qs	qs	qs	qs	qs
pH	7.2–7.6	7.2–7.6	7.2–7.6	7.2–7.6	7.2–7.6

Id. at 4:32–43. Example 1 identifies compositions A through E, which contain varying amounts of CsA, castor oil, polysorbate 80, Pemulen®(an acrylate/C10-30 alkyl acrylate cross-polymer) (*id.* at 4:1–5), glycerine, sodium hydroxide, and purified water at a pH range of 7.2–7.6. *Id.* at 4:32–43. According to Ding '979, the formulations of Example 1 was "made for treatment of keratoconjunctivitis sicca (dry eye) syndrome." *Id.* at 5:10–12.

2. Sall (Ex. 1007)

Sall describes the results of two identical clinical trials—supported by a grant from Patent Owner—in which patients were treated twice daily with either CsA 0.05% or 0.1% ophthalmic emulsions or vehicle for six months. Ex. 1007, Abstract, 631. The study sought to compare the efficacy and

safety of CsA 0.05% and 0.1% to vehicle in patients with moderate to severe dry eye disease. *Id.* Sall found that "topical treatment with either CsA 0.05% or 0.1% resulted in significantly greater improvements than vehicle treatment in two objective signs of dry eye disease." *Id.* at 637. Sall also found that treatment with CsA 0.05% resulted in significantly greater improvements in several subjective parameters. *Id.* Sall also found that trough blood concentrations of CsA were undetectable in all samples of CsA 0.05%, whereas CsA was quantifiable in only six samples for six different patients in the CsA 0.1% group. *Id.*

Sall notes that the only treatments available for dry eye disease are palliative in nature. *Id.* at 638. In light of the results of the study, Sall states that it "represents the first therapeutic treatment specifically for dry eye disease and a significant breakthrough in the management of this common and frustrating condition." *Id.*

3. Acheampong (Ex. 1008)

Acheampong describes a study by Patent Owner as part of its evaluation of the clinical efficacy of 0.05%–0.4% cyclosporin emulsion for the treatment of immuno-inflammatory eye diseases such as dry eye syndrome. Ex. 1008, 1001. Acheampong describes the results of its research to determine the ocular tissue distribution of cyclosporin in rabbits and dogs, and to compare tissue concentrations in rabbits, dogs, and humans after topical administration. *Id.*

In the study of humans, the subjects with dry eye disease received an eyedrop of vehicle or 0.05%, 0.1%, 0.2%, or 0.4% cyclosporin emulsions twice daily for 12 weeks. *Id.* at 1002. Blood samples were collected from all subjects at morning troughs after 1, 4, and 12 weeks of dosing, and from

certain subjects at 1, 2, and 4 hours after the last dose at week 12. *Id.* Acheampong found that the human blood cyclosporin A concentrations were less than 0.2 ng/ml for each emulsion, which is lower than the 20–100 ng/ml blood trough concentration used for monitoring the safety of patients receiving systemic cyclosporin therapy. *Id.*

4. Glonek (Ex. 1009)

Glonek relates to a composition for augmenting and maintaining a stable tear film over the ocular surface and delivering a medicine to the eye without causing substantial blurring of vision. Ex. 1009, 1:21–29. Glonek explains that an emulsion over the surface of the eye is expected to cause blurring, which is likely to occur until the emulsion differentiates. *Id.* at 6:37–42. If the emulsion is too stable, excess emulsion will be discharged from the eye. *Id.* at 6:42–44. Thus, Glonek states that it is preferred that an emulsion be stable for long term storage, but rapidly differentiate in the eye. *Id.* at 6:48–50.

D. Asserted Grounds of Unpatentability

1. Obviousness of Claims 1–10, 12–14, 16–20, 22, and 23 Based on Ding '979 and Sall

Petitioner contends that claims 1–10, 12–14, 16–20, 22, and 23 are rendered obvious by the combined teachings of Ding '979 and Sall. Pet. 22–40. Petitioner sets forth the foregoing teachings of Ding '979 and Sall and provides a detailed discussion and claim charts explaining how each claim limitation of the challenged claims is disclosed in Ding '979 and/or Sall. *Id.* The issue before us is whether it would have been obvious to use the

particular concentrations of 0.05% CsA and 1.25% castor oil recited in the challenged claims. *Id.*

Ding '979 specifically identifies examples that include 0.05% CsA and 1.25% castor oil, albeit not as part of the same composition. Ex. 1006, 4:32–43. Petitioner contends, however, Sall "provides a strong rationale to deliver 0.05% CsA using the 1.25% castor oil vehicle taught by Ding '979 (Example 2C)." Pet. 31. Petitioner contends that Sall teaches that either the 0.05% or 0.10% CsA emulsion is therapeutically effective in increasing tear production and treating dry eye disease/KCS. *Id.* (citing Ex. 1007, 632, 638; EX1002 ¶¶ 83, 106). Petitioner contends that Sall discloses that the vehicle used in the study reported in Sall (castor oil) "contributed to the overall improvements observed in all treatment groups in this study." *Id.* Petitioner further contends that:

> The 1.25% castor oil vehicle is the only vehicle from Ding '979 Example 2 for which both 0.05% and 0.10% CsA have a ratio of CsA-to-castor oil inside Ding '979's more preferred range of between 0.12 and 0.02 (*id.* at 3:17-20) and also within the ratio range found with each of the Example 1 emulsions (0.04-0.08).

Id. at 31 (citing Ex. 1006, 3:17–20). Finally, Petitioner provides the following rationale for combining Ding '979 and Sall:

> In light of Ding '979 and Sall, a person of ordinary skill in the art would have had a reasonable expectation that this emulsion would be effective in treating KCS and in increasing tear production (including in a human with KCS). EX1002, ¶109. As explained by Dr. Amiji, it would have been a routine matter for a skilled artisan to make and then confirm the efficacy of the emulsion comprising 1.25% castor oil and 0.05% CsA.

> EX1002, ¶109; EX1001, 14:14–16 ("These compositions are produced in accordance with well known techniques[.]").

Id. at 32.

Patent Owner argues in its Preliminary Response that this case is closely analogous to *Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293 (Fed. Cir. 2015), in which the court addressed the obviousness of claims requiring specific amounts of about 0.01% bimatoprost and about 200 ppm benzalkonium chloride (BAK) over prior art that generally taught a formulation comprising 0.001%–1% bimatoprost and 0–1000 ppm BAK. Prelim. Resp. 24–37. We agree that the issues are similar. In *Allergan*, the court reiterated the framework for evaluating obviousness in the context of a claimed invention falling within a broader range disclosed in the prior art:

> [W]here there is a range disclosed in the prior art, and the claimed invention falls within that range, a relevant inquiry is whether there would have been a motivation to select the claimed composition from the prior art ranges . . . . In those circumstances, "the burden of production falls upon the patentee to come forward with evidence that (1) the prior art taught away from the claimed invention; (2) there were new and unexpected results relative to the prior art; or (3) there are other pertinent secondary considerations."

796 F.3d at 1304–5 (citation omitted) (quoting *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 737–38 (Fed. Cir. 2013)).

Upon consideration of the arguments set forth in the Petition and Preliminary Responses, we conclude that Petitioner has shown a reasonable likelihood that a skilled artisan would have found it obvious to optimize the castor oil concentration in the emulsion to reach the claimed amount of 1.25% by balancing the need to minimize any undesirable effects associated with castor oil used at an excessive concentration with the desire to take

advantage of the "substantial palliative benefits" of castor oil for the treatment of dry eye. Prelim. Resp. 29 (citing Ex. 1007, 8). *See In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003) ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); *In re Boesch*, 617 F.2d 272, 276 (CCPA 1980) ("[D]iscovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art.").

Petitioner's evidence of obviousness, in accordance with *Allergan*, shifts the burden of production to Patent Owner to come forward with evidence of teaching away, unexpected results, or other secondary considerations. As evidence of unexpected results, Patent Owner points to data presented as part of the Declarations of Dr. Rhett Schiffman and Dr. Mayssa Attar, which were submitted during prosecution. Prelim Resp. 15–17, 20–21. Patent Owner asserts that these data "show[ed] that the claimed emulsions . . . performed better than the Ding '979 emulsions containing 0.05% cyclosporin/0.625% castor oil, and at least as well as the Ding '979 emulsions containing 0.10% cyclosporin/1.25% castor oil, despite PK data that predicted the opposite should have been true." *Id.* at 31–32. We have considered the declarations submitted during prosecution, but note that neither Dr. Schiffman nor Dr. Attar has yet been subject to cross-examination in this proceeding.[5] At this preliminary stage, we determine

[5] Routine discovery in an *inter partes* review includes "the deposition of witnesses submitting affidavits or declarations." *See* 35 U.S.C. § 316(a)(5)(A).

that it is more appropriate to allow further evidence regarding any alleged unexpected results or other secondary considerations to be developed during trial.

Patent Owner further argues that there was no reasonable expectation that increasing castor oil concentration would increase therapeutic efficacy. *Id.* at 29–31. In particular, Patent Owner contends that Sall distinguishes between therapeutic and palliative treatments, and that the vehicle is not responsible for the "clinically significant" effects observed. *Id.* at 30. Accordingly, Patent Owner asserts that a person of ordinary skill reading Sall would not have expected to achieve this level of efficacy by increasing the amount of castor oil relative to the amounts disclosed in Ding '979. *Id.* Patent Owner's argument, however, relies on its construction of "therapeutically effective" as excluding palliative treatments. As explained above, we decline to so limit the term. Accordingly, we are not persuaded by Patent Owner's argument.

Thus, based on the arguments presented and evidence of record, we determine that Petitioner has demonstrated a reasonable likelihood that claims 1–10, 12–14, 16–20, 22, and 23 are obvious over the teachings of Ding '979 and Sall.

2. Obviousness of Claims 11 and 21 Based on Ding '979, Sall, and Acheampong

Petitioner asserts that claims 11 and 21 are unpatentable as obvious over Ding '979, Sall, and Acheampong. Pet. 45–47. Patent Owner opposes for the same reasons stated with respect to claims 1 and 18 above. Prelim.

Resp. 34. We incorporate here our findings and discussion above regarding the teachings of Ding '979 and Sall.

Claims 11 and 21 depend directly from claims 1 and 18 and further recite as follows: "wherein, when the emulsion is administered to the eye of a human in an effective amount in treating keratoconjunctivitis sicca, the blood of the human has substantially no detectable concentration of the cyclosporin A." Petitioner asserts that Acheampong teaches that an emulsion with 0.05% CsA resulted in no detectable CsA in the blood, even at the maximum time point. Pet. 41–42 (citing Ex. 1008, 6 (Table 1); Ex. 1002 ¶ 120). Petitioner further asserts that "Acheampong and Sall together provide one of ordinary skill in the art with a reasonable expectation of success that when the 0.05% CsA emulsion is administered to the eye there is 'substantially no detectable concentration of cyclosporin A' in the blood." *Id.* at 41 (citing Ex. 1002 ¶ 121).

Based on the arguments presented and evidence of record, we determine that Petitioner has demonstrated a reasonable likelihood that claims 11 and 21 are obvious over the teachings of Ding '979, Sall, and Acheampong.

3. Obviousness over Ding '979, Sall, Acheampong, and Glonek

Claim 15 depends from claim 1, and further recites that "the emulsion breaks down more quickly in the eye of a human, . . . thereby reducing vision distortion in the eye of the human as compared to a second emulsion that contains only 50% as much castor oil."

Petitioner asserts that Glonek teaches minimizing blurring after instillation and that blurring occurs until the emulsion breaks into separate oil and aqueous layers on the sys surface. Pet. 42. Petitioner also asserts

that Glonek teaches that altering the ratio of surfactant to oil affects emulsion break time. *Id.* at 43. Accordingly, Petitioner argues that the ratio of surfactant to oil is a result effective variable for emulsion break time, which a person of ordinary skill in the art would have been able to optimizeusing routine skill. *Id.* at 48–49 (citing Ex. 1005 ¶ 224). Petitioner also argues that,

> [b]ased on Glonek, a skilled artisan would have reasonably expected a 1.25% castor oil emulsion to break down faster than a 0.625% castor oil emulsion because of the increased instability from the higher oil concentration, and that the faster differentiation would result in a reduction of blurring. *Id*., ¶¶125-27. Further, one would not expect the 0.05% CsA / 1.25% castor oil formulation to cause undue blurring because it is within the preferred ranges disclosed by Ding and because other prior art ophthalmic emulsions comprising castor oil in amounts up to 2% did not cause blurring. EX1002, ¶59; EX1017, p.2032.

Pet. 42–43.

In response, Patent Owner relies on the same reasoning given with respect to claim 1. Prelim. Resp. 34.

Based on the arguments presented and evidence of record, we are persuaded on the current record that Petitioner has demonstrated a reasonable likelihood that it would prevail in its assertion that claim 15 is unpatentable as obvious over the combination of Ding ’979, Sall, Acheampong, and Glonek.

III. CONCLUSION

We conclude that Petitioner has established a reasonable likelihood of prevailing on its assertions that claims 1–23 of the '048 patent are unpatentable as obvious.

At this stage of the proceeding, the Board has not made a final determination as to the patentability of any challenged claim or the construction of any claim term.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that pursuant to 35 U.S.C. § 314(a), an *inter partes* review is hereby instituted on the following grounds:

A. Claims 1–10, 12–14, 16–20, 22, and 23 as obvious over Ding '979 and Sall;

B. Claims 11 and 21 as obvious over Ding '979, Sall, and Acheampong; and

C. Claim 15 as obvious over Ding '979, Sall, Acheampong, and Glonek.

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trialcommencing on the entry date of this decision.

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