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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 IPR2016-01132
Patent 9,248,191 B2

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

HULSE, *Administrative Patent Judge*.

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

I. INTRODUCTION

Mylan Pharmaceuticals Inc. ("Petitioner") filed a Petition requesting an *inter partes* review of claims 1–27 of U.S. Patent No. 9,248,191 B2 (Ex. 1001, "the '191 patent"). Paper 3 ("Pet."). Allergan, Inc. ("Patent Owner") filed a Preliminary Response to the Petition. 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 considering the Petition and Preliminary Response, we determine that Petitioner has established a reasonable likelihood that it would prevail in showing the unpatentability of claims 1–27. Accordingly, we institute an *inter partes* review of those claims.

A. Related Proceedings

The parties identify several petitions for *inter partes* review previously filed by Apotex Corp. and Apotex Inc. and challenging claims of related patents. Pet. 11; Paper 6, 2 (referring to IPR2015-01278, IPR2015-01282, IPR2015-01283, IPR2015-01284, and IPR2015-01286). All of the petitions were terminated before institution decisions were entered. Pet. 11; Paper 6, 2. The parties also identify several district court cases that may affect or be affected by a decision in this proceeding: *Allergan, Inc. v. Teva Pharms. USA, Inc., et al.*, No. 2:15-cv-01455 (E.D. Tex.); *Allergan, Inc., v.*

Innopharma, Inc., No. 2:15-cv-1504 (E.D. Tex.); and *Allergan, Inc. v. Famy Care, Ltd.*, No. 2:16-cv-0401 (E.D. Tex.). Pet. 11; Paper 6. 2.

Petitioner has also sought *inter partes* review for related patents in the following proceedings: Case IPR2016-01127 (U.S. Patent No. 8,685,930 B2), Cases IPR2016-01128 and IPR2016-01232 (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 IPR2016-01131 (U.S. Patent No. 8,648,048 B2).

B. The '191 Patent

The '191 patent generally relates to methods of providing therapeutic effects using cyclosporin components, and more specifically to a formulation containing cyclosporin-A ("CsA") and castor oil emulsions for treating dry eye syndrome (i.e., keratoconjunctivitis sicca or "KCS"). Ex. 1001, 1:20–22, 1:60–67, 2:66–67. According to the specification, the prior art recognized the use of emulsions containing CsA and CsA-derivatives to treat ophthalmic conditions. *Id.* at 1:28–67. The specification notes, however, "[o]ver time, it has become apparent that cyclosporin A emulsions for ophthalmic use preferably have less than 0.2% by weight of cylcosporin A." *Id.* at 1:66–2:1. Moreover, if reduced amounts of cyclosporin are used, reduced amounts of castor oil are needed because one of the functions of castor oil is to solubilize CsA. *Id.* at 2:1–8.

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 2:38–41. 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 efficacy of the composition. *Id.* at 2:45–51. Furthermore, using reduced amounts of cyclosporin component mitigates against undesirable side effects or potential drug interactions. *Id.* at 2:51–54.

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 14:26–38. Based on the results of a Phase 3 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 14:42–46. The patent indicates "[t]his is surprising for a number of reasons." *Id.* at 14:47. 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 14:47–50. 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 14:50–55. 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 15:10–14.

C. Illustrative Claim

Petitioner challenges claims 1–27 of the '191 patent, of which claims 1, 13, 17, and 21 are independent claims. Claim 1 is illustrative, and is reproduced below:

> 1. A method of treating dry eye disease, the method comprising topically administering to a human eye in need thereof a first topical ophthalmic emulsion at a frequency of twice a day, wherein the first ophthalmic 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;
>
> wherein the method is therapeutically effective in treating dry eye disease;
>
> wherein the method provides overall efficacy substantially equal to administration of a second topical ophthalmic emulsion to a human eye in need thereof at a frequency of twice a day, the second emulsion comprising cyclosporin A in an amount of about 0.1% by weight and castor oil in an amount of about 1.25% by weight; and

> wherein the method results in substantially no detectable concentration of cyclosporin A in the blood of the human.

Independent claim 13 recites that the concentration of cyclosporin A in the blood of the human is less than about 0.1 ng/ml.

Independent claim 17 also recites that the first topical emulsion breaks down more quickly in the human eye compared to a second emulsion that contains only about 50% as much castor oil as the first emulsion.

Independent claim 21 recites a method of restoring tearing comprising administering a topical ophthalmic emulsion similar to claim 1.

D. The Asserted Grounds of Unpatentability

Petitioner challenges the patentability of claims 1–27 of the '191 patent on the following grounds:

References	**Basis**	**Claim(s) challenged**
Ding '979[1] and Sall[2]	§ 103(a)	1–16 and 21–27

[1] Ding et al., US 5,474,979, issued Dec. 12, 1995 (Ex. 1006).
[2] 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 631–39 (2000) (Ex. 1007).

References	Basis	Claim(s) challenged
Ding '979, Sall, and Acheampong[3]	§ 103(a)	1–16 and 21–27
Ding '979, Sall, and Glonek[4]	§ 103(a)	17–20
Ding '979, Sall, Acheampong, and Glonek	§ 103(a)	20

Petitioner also relies on the Declaration of Mansoor Amiji, Ph.D. Ex. 1002.

II. ANALYSIS

A. Person of Ordinary Skill in the Art

Petitioner asserts that as of September 15, 2003, a person of ordinary skill in the art would likely have had "some combination of: (a) experience formulating pharmaceutical products; (b) experience designing and preparing drug emulsions intended for topical ocular administration; and (c) the ability to understand results and findings presented or published by others in the field. Pet. 9 (citing Ex. 1002 ¶ 36). Petitioner further contends that this person typically would have an advanced degree, such as a medical degree, or a Ph.D. in organic chemistry, pharmaceutical chemistry, medicinal chemistry, pharmaceutics, physical pharmacy, or a related field, or

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[3] 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*, LACRIMAL GLAND, TEAR FILM, AND DRY EYE SYNDROMES 2: BASIC SCIENCE AND CLINICAL RELEVANCE 1001–04 (David A. Sullivan et al. eds., 1998) (Ex. 1008).
[4] Glonek et al., US 5,578,586, issued Nov. 26, 1996 (Ex. 1009).

less education but considerable professional experience in these fields. *Id.* (citing Ex. 1002 ¶ 35). Patent Owner does not explicitly address the level of ordinary skill in the art in its Preliminary Response.

On this record, we adopt Petitioner's definition of the level of ordinary skill in the art. We further note that the prior art itself demonstrates the level of skill in the art at the time of the invention. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (explaining that specific findings regarding ordinary skill level are not required "where the prior art itself reflects an appropriate level and a need for testimony is not shown") (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp.*, 755 F.2d 158, 163 (Fed. Cir. 1985)).

B. Claim Construction

In an *inter partes* review, the Board interprets claim terms in an unexpired patent according to the broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2142 (2016) (affirming applicability of broadest reasonable construction standard to *inter partes* review proceedings). Under that standard, and absent any special definitions, we generally give claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention. *See In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Any special definitions for claim terms must be set forth with reasonable clarity, deliberateness, and precision. *See In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

1. "therapeutically effective in treating dry eye disease" and "therapeutic efficacy

Claims 1–16 recite treatment methods utilizing a topical ophthalmic emulsion that is "therapeutically effective in treating dry eye disease" and claims 21–27 recite a method comprising administering a first emulsion that achieves at least as much "therapeutic efficacy" as a second emulsion. Petitioner asserts that the '191 patent teaches that cyclosporin A "acts to enhance or restore lacrimal gland tearing in providing the desired therapeutic effect." Pet. 15 (quoting Ex. 1001, 9:15–16). Petitioner then argues that in light of the specification, "an emulsion effective in increasing tear production is an example of an emulsion therapeutically effective in enhancing and restoring lacrimal gland tearing and in treating dry eye disease." *Id.* 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 palliative and curative treatments. *Id.* (citing Ex. 1002 ¶¶ 42–43; Ex. 1022, 7, 4, 5).

Patent Owner argues that Petitioner's proposed construction is too broad, and that the claims should be construed to require that "the emulsion treat the underlying disease," and not just its symptoms. Prelim. Resp. 21–22. Patent Owner argues that 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 Exs. 2005, 2006). 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.2 (citing Ex. 2007). We disagree. The definition of "therapeutic" provided by the Patent Owner is not limited to a cure of a disease or disorder, but also includes either treatment or remediating of a disease or disorder. We thus conclude, on the current record, that the ordinary meaning of the phrase "therapeutically effective" is not so limited as to exclude palliative effects.

Patent Owner further argues that the specification supports its construction because "throughout the specification, the '191 patent uses the word 'therapeutic' in connection with the action of cyclosporin. . . . In contrast, the '191 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, 9:58–62 (emphasis added). Thus, notwithstanding Patent Owner's extrinsic evidence it offers in support of its more-limited construction (Prelim. Resp. 23), we decline to construe the claims in a manner inconsistent with the specification.

Accordingly, at this stage of the proceeding, we find that "therapeutically effective in treating dry eye disease," "therapeutically

effective," and similar terms encompass both palliative and curative treatments of dry eye disease.

2. Remaining Claim Terms

Petitioner proposes constructions for a number of additional claim terms. At this stage of the proceeding, we determine it is unnecessary to expressly construe any other claim terms for purposes of this Decision. *See 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)).

C. Obviousness over Ding '979 and Sall

Petitioner argues that claims 1–16 and 21–27 are unpatentable as obvious over the combination of Ding '979 and Sall. Pet. 22–42. Petitioner relies on the testimony of Dr. Amiji in support. Ex. 1002 ¶¶ 91–115. Patent Owner opposes. Prelim. Resp. 24–33. Based on the current record, we determine that Petitioner has established a reasonable likelihood that it would prevail in showing claims 1–16 and 21–27 are unpatentable over the cited prior art.

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 cyclosporin 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 cyclosporin A, castor oil, polysorbate 80, Pemulen® (an acrylate/C10-30 alkyl acrylate cross-polymer), glycerine, sodium hydroxide, and purified water at a pH range of 7.2–7.6. *Id.* 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 cyclosporin A 0.05% or 0.1% ophthalmic emulsions or vehicle for six months. Ex. 1007, Abstract. The study sought to compare the efficacy and safety of cyclosporin A 0.05% and 0.1% to vehicle in patients with moderate to severe dry eye disease. *Id.* Sall found that topical treatment with either cyclosporin A 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 cyclosporin A 0.05% resulted in

significantly greater improvements in several subjective parameters. *Id.* Sall also found that trough blood concentrations of cyclosporin A were undetectable (i.e., below 0.1 ng/ml) in all samples of cyclosporin A 0.05%, whereas cyclosporin A was quantifiable in only six samples for six different patients in the cyclosporin 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. Analysis

Petitioner argues that the combination of Ding '979 and Sall teaches each limitation of claims 1–16 and 21–27 of the '191 patent. For example, Petitioner asserts that Ding '979 teaches emulsions for treatment of dry eye syndrome that are "suitable for topical application to ocular tissue." Pet. 25 (citing Ex. 1006, 5:9–11, 6:3–7). Petitioner also notes that Ding '979 teaches that cyclosporin A is "'an immunosuppressant' that works 'in the enhancement or restoring of lacrimal gland tearing" and has been found effective in treating KCS. *Id.* at 25–26 (citing Ex. 1006, 1:10–16, 37–39). Thus, Petitioner asserts that Ding '979 teaches the emulsion is "therapeutically effective in treating dry eye disease," as recited by claims 1 and 13, and "effective in restoring lacrimal gland tearing," as recited in claims 16 and 26.

Example 1D of Ding '979 teaches every ingredient of the emulsion in claims 1–27, except 0.05% cyclosporin A. Ex. 1006, 4:32–43. That is, Example 1D teaches an emulsion with 1.25% castor oil, 1.0% polysorbate 80, 0.05% Pemulen (i.e., acrylate/C10-30 alkyl acrylate cross-polymer), 2.2% glycerine, sodium hydroxide, and water. *Id.* Example 1E of Ding '979 teaches an emulsion with 0.05% cyclosporin A. *Id.* According to Dr. Amiji, a person of ordinary skill in the art would recognize Ding '979's emulsions to include an emulsion containing the cyclosporin A/castor oil amounts in the claimed combination, i.e., 0.05% cyclosporin A and 1.25% castor oil, because such an emulsion would fall within the preferred ratio of cyclosporin A to castor oil. Ex. 1002 ¶ 98 (citing Ex. 1006, 4:32–43).

Petitioner also asserts that Sall teaches treating patients twice daily with an emulsion containing 0.05% cyclosporin A. Pet. 29; Ex. 1007, 631. Sall concluded that both the 0.05% and the 0.10% cyclosporin A emulsions "were safe and effective in the treatment of moderate to severe dry eye disease . . . yielding improvements in both objective and subjective measures." Pet. 30 (quoting Ex. 1007, 631). As such, Petitioner asserts that one of ordinary skill in the art would have expected the castor oil emulsion vehicle containing 0.05% by weight cyclosporin A to be at least as safe and effective at enhancing and restoring lacrimal tear production and treating dry eye disease/KCS as the castor oil emulsion containing 0.10% cyclosporin A. *Id.* at 31. Moreover, Petitioner asserts that Sall provides a strong rationale to deliver 0.05% cyclosporin A using the 1.25% castor oil vehicle taught by

Ding '979 (i.e., Example 2C) in light of the preferred ratio of cyclosporin A to castor oil taught in Ding '979. Pet. 32–33; Ex. 1002 ¶ 110.

In its Preliminary Response, Patent Owner does not argue that the combination of references fails to teach any particular limitation of the claims. Accordingly, we are persuaded that Petitioner has shown sufficiently that the combination of Ding '979 and Sall teaches each limitation of claims 1–16 and 21–27. That is, 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. Thus, the only issue before us is whether it would have been obvious to use the particular concentrations of 0.05% CsA and 1.25% castor oil in the emulsion together, as recited in the challenged claims.

Patent Owner argues that this case is closely analogous to *Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1302 (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. 24–27. 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 1304–05 (quoting *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 738 (Fed. Cir. 2013)).

As discussed above, 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. Patent Owner argues that increasing the amount of castor oil to 1.25% and cutting the amount of cyclosporin in half without loss of efficacy was not only unexpected, but counterintuitive to a person of ordinary skill in the art. Prelim. Resp. 26–27, 31–32. As support, Patent Owner points to results from pharmacokinetic ("PK") experiments presented during prosecution as part of the Declarations of Dr. Rhett Schiffman and Dr. Mayssa Attar. Prelim Resp. 3 (citing Ex. 1023, 184–242); *see also id.* at 31–32. Patent Owner asserts that these results predicted that the claimed emulsion would have been less effective than the two emulsions disclosed in Ding '979. According to Patent Owner, it was surprising that the claimed emulsion was "***more effective*** than the 0.05%/0.625%/1.00% emulsion and ***at least as effective*** as the 0.1%/1.25%/1.00% emulsion." *Id.* at 3.

We have considered the declarations submitted during prosecution, but note that neither Dr. Schiffman nor Dr. Attar has been subject to cross-

examination in this proceeding. Moreover, Petitioner offers the declaration of Dr. Amiji, calling into question the alleged unexpected results based on the Schiffman and Attar Declarations. Ex. 1002 ¶¶ 131–155. At this preliminary stage, we determine that Petitioner has offered sufficient evidence to institute trial. That being said, we will be able to evaluate both parties' arguments regarding secondary considerations more thoroughly once the record is developed further during trial.

Patent Owner also argues that Sall would not have motivated a person of ordinary skill in the art to combine 0.05% cyclosporin with 1.25% castor oil. Prelim. Resp. 27–29. Contrary to Petitioner's argument, Patent Owner asserts that a person of ordinary skill in the art would not have assumed that both the 0.05% and 0.10% cyclosporin emulsions in Sall would have contained the same amount of castor oil (i.e., 1.25%). *Id.* at 28. Rather, Patent Owner contends that a skilled artisan would have expected the emulsions to have the same ratio of cyclosporin to castor oil (i.e., 0.05% cyclosporin with 0.625% castor oil, and 0.10% cyclosporin with 1.25% castor oil). *Id.* On the current record, however, we determine that Petitioner has shown sufficiently that a skilled artisan reading Ding '979 and Sall would have had a reason to formulate an emulsion with 0.05% cyclosporin A and 1.25% castor oil in light of the preferred cyclosporin to castor oil ratio taught by Ding '979. Ex. 1006, 3:17–20.

Patent Owner further argues that there was no reasonable expectation that increasing castor oil concentration would increase therapeutic efficacy. Prelim. Resp. 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 29–30. 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.* at 30. 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.

Upon considering the arguments set forth in the Petition and Preliminary Responses, we determine that Petitioner has shown a reasonable likelihood that it would prevail in showing claim 1 is unpatentable as obvious over the combination of Ding '979 and Sall. We have considered the parties' arguments and evidence with respect to claims 2–16 and 21–27, and we determine that Petitioner has made a sufficient showing as to those claims, as well.

D. Obviousness over Ding '979, Sall, and Acheampong

Petitioner also asserts that claims 1–16 and 21–27 are unpatentable as obvious over Ding '979, Sall, and Acheampong. Pet. 43–44. Patent Owner opposes for the same reasons stated above. Prelim. Resp. 34. We incorporate here our findings and discussion above regarding the disclosure of Ding '979 and Sall.

1. 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, 3–4. 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 4. 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.* at 6.

2. Analysis

Independent claims 1 and 13 and dependent claims 12, 22, and 27 recite that the method results in a CsA blood concentration that is substantially undetectable or below 0.1 ng/ml. Petitioner asserts that Acheampong teaches that CsA blood levels were substantially undetectable and below 0.1 ng/ml at both peak and trough levels after administration of an emulsion with 0.05% CsA. Pet. 43 (citing Ex. 1008, 1002; Ex. 1002 ¶

119). Petitioner further asserts that a person of ordinary skill in the art reading Acheampong and Sall would have had a reasonable expectation of success that when the 0.05% cyclosporin A emulsion is administered to the eye, there is "substantially no detectable concentration of cyclosporin A" in the blood. *Id.* at 44 (citing Ex. 1002 ¶ 120).

In response, Patent Owner relies on the same reasoning given with respect to claims 1, 13, and 21. Prelim. Resp. 34. For the same reasons stated above, we are persuaded on the current record that Petitioner has demonstrated a reasonable likelihood that it would prevail in its assertion that claims 1–16 and 21–27 are unpatentable as obvious over the combination of Ding '979, Sall, and Acheampong.

E. Obviousness over Ding '979, Sall, and Glonek

Petitioner asserts that claims 17–20 are unpatentable as obvious over Ding '979, Sall, and Glonek. Pet. 44–47. Patent Owner opposes for the same reasons stated with respect to claim 1 above. Prelim. Resp. 34. We incorporate here our findings and discussion above regarding the disclosure of Ding '979 and Sall.

1. 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.

2. Analysis

Independent claim 17 recites the same emulsion as claims 1, 13, and 21, but further recites that "the emulsion breaks down more quickly in the eye of a human, . . . thereby reducing vision distortion in the human eye as compared to a second topical ophthalmic emulsion that contains only 50% as much castor oil as the first topical ophthalmic emulsion." Petitioner asserts that Glonek teaches that "an emulsion over the surface of the eye is expected to cause blurring. The duration of the blurring is dependent upon the time required for the emulsion to differentiate and form separate layers." Pet. 46 (quoting Ex. 1009, 6:37–40). Moreover, Glonek teaches that "it is preferred that the emulsion be stable for long term storage, but ***rapidly differentiate in the eye***." *Id.* (quoting Ex. 1009, 6:48–50). Accordingly, Petitioner asserts that "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.* (citing Ex. 1002 ¶¶ 125–127).

In response, Patent Owner relies on the same reasoning given with respect to claims 1, 13, and 21. Prelim. Resp. 34. For the same reasons stated above, we are persuaded on the current record that Petitioner has demonstrated a reasonable likelihood that it would prevail in its assertion

that claims 17–20 are unpatentable as obvious over the combination of Ding '979, Sall, and Glonek.

F. Obviousness over Ding, Sall, Glonek, and Acheampong

Petitioner asserts that claim 20 is unpatentable as obvious over Ding, Sall, Glonek, and Acheampong. Pet. 47–48. Patent Owner opposes. Prelim. Resp. 35. We incorporate here our findings and discussion above regarding the disclosure of Ding '979, Sall, Glonek, and Acheampong.

Claim 20 depends from claim 17 and further recites "the method results in a concentration of cyclosporin A in the blood of the human of less than about 0.1 ng/ml." Petitioner asserts that claims 17–20 are obvious over Ding '979, Sall, and Glonek. Petitioner further relies on Acheampong as providing "additional teachings on the safety of topically administering CsA/castor oil emulsions to the eye, and particularly that the blood has less than 0.1 ng/ml CsA after topical ophthalmic treatment with 0.05% CsA in castor oil." Pet. 48. Thus, Petitioner asserts, claim 20 would have been obvious to person of ordinary skill in the art over the cited references.

Patent Owner argues that claim 20 is patentable for the same reasons as independent claim 17. Prelim. Resp. 35. For the same reasons stated above, we are persuaded on the current record that Petitioner has demonstrated a reasonable likelihood that it would prevail in its assertion that claim 20 is unpatentable as obvious over the combination of Ding '979, Sall, Glonek, and Acheampong.

III. CONCLUSION

We conclude that Petitioner has established a reasonable likelihood of prevailing on its assertions that claims 1–27 of the '191 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 1–16 and 21–27 as obvious over Ding '979 and Sall;

B. Claims 1–16 and 21–27 as obvious over Ding '979, Sall, and Acheampong;

C. Claims 17–20 as obvious over Ding '979, Sall, and Glonek; and

D. Claim 20 as obvious over Ding '979, Sall, Glonek, and Acheampong.

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 trial commencing on the entry date of this decision.

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