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Paper No. 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 IPR2016-01129
Patent 8,642,556 B2

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

PAULRAJ, *Administrative Patent Judge.*

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

I. INTRODUCTION

Mylan Pharmaceuticals, Inc. ("Petitioner") filed a Petition (Paper 3, "Pet."), requesting institution of an *inter partes* review of claims 1–20 of U.S. Patent No. 8,642,556 B2 (Ex. 1001, "the '556 patent"). Allergan, Inc. ("Patent Owner") timely filed a 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."

Upon consideration of the Petition and the Preliminary Response, and for the reasons explained below, we determine that Petitioner has shown that there is a reasonable likelihood that it would prevail with respect to at least one of the challenged claims. We thus institute an *inter partes* review of claims 1–20 of the '556 patent.

A. Related Proceedings

An IPR petition for the '556 patent was previously filed by Apotex Corp. and Apotex Inc. as IPR2015-01286, as were petitions for related U.S. Patent Nos. 8,629,111 (IPR215-01282), 8,648,048 (IPR2015-01284), 8,633,162 (IPR2015-01278), and 8,685,930 (IPR2015-01283), but all were terminated prior to institution decisions. Pet. 11. Additionally, concurrent IPR petitions for related patents were filed by Petitioner in IPR2016-1127, IPR2016-01128, IPR2016-01130, IPR2016-01131, and IPR2016-01132. *Id.* Furthermore, Petition and Patent Owner identify the following related litigation matters: *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., No. 2:15-cv-1504 (E.D. Texas); and *Allergan, Inc. v. Famy Care, Ltd.*, No. 2:16-cv-0401 (E.D. Texas). Pet. 11–12; Paper 6. 2.

B. The '556 Patent (Ex. 1001)

The '556 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, 1:18–20, 1:58–65, 2:63–64. 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 cylcosporin 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 1:66–2:6.

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 efficacy 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 15:1–13. 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 15:18–22. The patent indicates that "[t]his is surprising for a number of reasons." *Id.* at 15:23. 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 15:24–26. 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 15:26–32. 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 15:54–58.

C. Illustrative Claims

Petitioner challenges claims 1–20 of the '556 patent. Independent claim 1 is illustrative, and is reproduced below:

> 1. A first topical ophthalmic emulsion for treating an eye of a human, wherein the first topical 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; and
>
> wherein the first topical ophthalmic emulsion is therapeutically effective in treating dry eye disease; and
>
> wherein the first topical ophthalmic emulsion provides overall efficacy substantially equal to a second topical ophthalmic 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.

Independent claims 13, 14, and 15 also recite a topical ophthalmic emulsion comprising CsA in an amount of about 0.05% by weight and castor oil in an amount of 1.25% by weight, and further specify particular amounts for other components.

D. The Asserted Grounds of Unpatentability

Petitioner challenges the patentability of the claims of the '556 patent on the following grounds:

References	Basis	Claims challenged
Ding '979[1]	§ 102(b)	1–20
Ding '979 and Sall[2]	§ 103(a)	1–20
Ding '979, Sall, and Glonek[3]	§ 103(a)	14 and 19

[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).
[3] Glonek et al., US 5,578,586, issued Nov. 26, 1996 (Ex. 1009).

References	Basis	Claims challenged
Ding '979, Sall, and Acheampong[4]	§ 103(a)	11, 18, and 20
Ding '979, Sall, Glonek, and Acheampong	§ 103(a)	19

Petitioner further relies upon the declaration of Dr. Mansoor Amiji (Ex. 1002).

II. ANALYSIS

A. Claim Construction

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); *see also 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). "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). "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,

[4] 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).

deliberateness, and precision." *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

1. "therapeutically effective"

Independent claims 1 and 13 state that the emulsion is "therapeutically effective in treating dry eye disease." Petitioner asserts that because the plain meaning of the word "therapeutic" includes palliative as well as curative treatments, the broadest reasonable interpretation of the term includes palliative as well as curative treatments. Pet. 15–16 (citing Ex. 1002 ¶¶ 41–42; Ex. 1022, 4, 5, 7)

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. 21–23. 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 "reducing 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 "the '556 patent specification does not use the word 'therapeutic' to refer to the activity of the other components of the emulsion, including castor oil." Prelim. Resp. 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, 10:38–42 (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.

Accordingly, at this stage of the proceeding, we find that "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 that no explicit construction of any other claim term is necessary to determine whether to institute a trial in this case. *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)). 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

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

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).

1. Law of Anticipation

The Court of Appeals for the Federal Circuit summarized the analytical framework for determining whether prior art anticipates a claim as follows:

> If the claimed invention was "described in a printed publication" either before the date of invention, 35 U.S.C. § 102(a), or more than one year before the U.S. patent application was filed, 35 U.S.C. § 102(b), then that prior art anticipates the patent. Although § 102 refers to "the invention" generally, the anticipation inquiry proceeds on a claim-by-claim basis. *See Hakim v. Cannon Avent Group, PLC*, 479 F.3d 1313, 1319 (Fed. Cir. 2007). To anticipate a claim, a single prior art reference must expressly or inherently disclose each claim limitation. *Celeritas Techs., Ltd. v. Rockwell Int'l Corp.*, 150 F.3d 1354, 1361 (Fed. Cir. 1998). But disclosure of each element is not quite enough—this court has long held that "[a]nticipation requires the presence in a single prior art disclosure of all elements of a claimed invention *arranged as in the claim*." *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir.

> 1983) (citing *Soundscriber Corp. v. United States*, 175 Ct. Cl. 644, 360 F.2d 954, 960 (1966) (emphasis added)).

Finisar Corp. v. DirecTV Grp., Inc., 523 F.3d 1323, 1334–35 (Fed. Cir. 2008). We must analyze prior art references as a skilled artisan would. *See Scripps Clinic & Res. Found. v. Genentech, Inc.*, 927 F.2d 1565, 1576 (Fed. Cir. 1991) (to anticipate, "[t]here must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention").

When a patent claims a range, that range is anticipated by a prior art reference if the reference discloses a point within the broader range. *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 782 (Fed.Cir.1985). If the prior art discloses its own range, rather than a specific point, then the prior art is anticipatory insofar as it describes the claimed range with sufficient specificity. *ClearValue, Inc. v. Pearl River Polymers*, Inc., 668 F.3d 1340, 1345 (Fed. Cir. 2012); *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006).

2. Law of Obviousness

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 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, 1360 (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 (1966). 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 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); *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. *In re 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), 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 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 cCsA 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.* at 1004.

4. Glonek (Ex. 1009)

Glonek relates to a dry eye treatment process and a composition "capable of augmenting and maintaining a stable tear film over the ocular surface and/or delivering a medicant to said surface without causing substantial blurring of vision." Ex. 1009, 1:25–29. Glonek teaches that "an emulsion over the surface of the eye is expected to cause blurring" and "[t]he duration of blur is dependent upon the time required for the emulsion to differentiate and form separate layers replicating a tear film. . . . [I]t is preferred that the emulsion be stable for long term storage, but rapidly differentiate in the eye." *Id.* at 6:37–50. Glonek studied the effect of surfactant concentration in different emulsion formulations, and concluded that "[t]he lower concentrations resulted in poor to fair tear film formation up to about 0.05% surfactant content," whereas the "[b]est results were obtained within a range of from 0.05 to 0.15% surfactant. Additional

surfactant provided little improvement and blur ring occurred at the higher concentrations." *Id.* at 20:25–31.

D. Anticipation of Claims 1–20 by Ding '979

Petitioner contends that claims 1–20 of the '556 patent are anticipated by Ding '979. Pet. 22–33. In support of its assertion that Ding '979 teaches each element of the challenged claims, Petitioner sets forth the teachings of Ding '979 discussed above. Petitioner also provides a detailed claim chart including citations to Ding'979 and the Amiji Declaration. *Id.* at 31–33.

Patent Owner argues that Ding '979 does not disclose the specific composition of the challenged claims having 0.05% by weight CsA, 1.25% by weight castor oil, polysorbate 80, and an acrylate/C10-30 alkyl acrylate polymer. Prelim. Resp. 24. Patent Owner acknowledges that Ding '979 discloses that the weight ratio of cyclosporin to castor oil is below 0.16 and preferably between 0.12 and 0.02, but contends this range is "very broad." Prelim. Resp. 24–25; Pet. 27; Ex. 1006, 3:16–20. Patent Owner further acknowledges that Ding '979 discloses five specific compositions having the following CsA/castor oil ratios: 0.40%/5.00% (Sample A), 0.20%/5.00% (Sample B), 0.20%/2.50% (Sample C), 0.10%/1.25% (Sample D), and 0.05%/0.625% (Sample E). Prelim. Resp. 25 (citing Ex. 1003, 4:30–45). Patent Owner contends, however, that Ding '979 fails to disclose a specific composition containing 0.05% cyclosporin/1.25% castor oil. *Id.*

On the current record, there appears to be no dispute between the parties that a composition containing 0.05% cyclosporin/1.25% castor oil yields a weight ratio of cyclosporin to castor oil of 0.04 falling between within the range disclosed in Ding '979. Prelim. Resp. 24–29; Pet. 27.

Rather, the dispute between the parties appears to be whether Ding '979 describes the claimed amounts with sufficient specificity to anticipate this limitation of the challenged claims. As stated by the Federal Circuit:

> It is well established that the disclosure of a genus in the prior art is not necessarily a disclosure of every species that is a member of that genus. There may be many species encompassed within a genus that are not disclosed by a mere disclosure of the genus. On the other hand, a very small genus can be a disclosure of each species within the genus.

Atofina, 441 F.3d at 999 (internal citation omitted). In reaching our conclusion with regard to anticipation, we must determine whether Ding '979 discloses a broad genus such that different portions of the broad range would work differently. *ClearValue*, 668 F.3d at 1345; *see also, Ineos USA LLC v. Berry Plastics Corp*., 783 F.3d 865, 871 (Fed. Cir. 2015) ("Ineos is also correct that when the prior art discloses a range, rather than a point, the court must evaluate whether the patentee has established that the claimed range is critical to the operability of the claimed invention.").

In *Atofina*, the Federal Circuit reversed the district court's finding of anticipation where the claims recited temperature between 330–450 degrees Celsius and the prior art disclosed a "broader temperature range" of 100–500 degrees Celsius. *Atofina*, 441 F.3d at 1000. The key to the court's conclusion in *Atofina* "was the fact that the evidence showed that a person of ordinary skill in the art would have expected the [method] to operate differently, or not [at] all, outside of the temperature range claimed in the patent-in-suit." *Ineos*, 783 F.3d at 869 (citing *Atofina*, 441 F.3d at 999; *ClearValue*, 668 F.3d at 1345). Here, based on the current record, there is insufficient evidence demonstrating the criticality of the claimed amounts or

any difference across the range disclosed in the prior art.[5] *See ClearValue*, 668 F.3d at 1345 (explaining the importance of establishing the criticality of a claimed range to the claimed invention in order to avoid anticipation by a prior art reference disclosing a broader range); *see also Ineos*, 783 F.3d at 870 (Fed. Cir. 2015) (finding that patentee failed to establish that certain properties would differ if range from prior art patent was substituted for range of limitation); *OSRAM Sylvania, Inc. v. Am. Induction Techs., Inc.*, 701 F.3d 698, 705–06 (Fed. Cir. 2012) (emphasizing that "how one of ordinary skill in the art would understand the relative size of a genus or species in a particular technology is of critical importance").

Accordingly, on the current record, we determine that there is a reasonable likelihood that Petitioner would prevail in demonstrating the unpatentability of claims 1–20 as anticipated by Ding '979.

E. Obviousness of Claims 1–20 Based on Ding '979 and Sall

Petitioner contends that claims 1–20 are rendered obvious by the combined teachings of Ding '979 and Sall. Pet. 34–41. Petitioner has included claim charts for exemplary claims 1, 11, 15, 16, and 17 specific to this ground. *Id.* at 39–41. The issue before us is whether it would have been

[5] To the extent that Patent Owner relies upon the Examiner's conclusion that "the specific combination of 0.05% by weight cyclosporin A with 1.25% castor oil is surprisingly critical for the therapeutic effectiveness in the treatment of dry eye or keratoconjuctivitis sicca," which was based on the same declarations relied upon to assert unexpected results in response to Petitioner's obviousness challenges, we determine at this preliminary stage that it is more appropriate to allow further evidence to be developed during trial regarding any such alleged criticality. Prelim. Resp. 18–19 (citing Ex. 1004, 421).

obvious to use the particular concentrations of 0.05% CsA and 1.25% castor oil recited in the challenged claims.

As noted above, 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, that "Sall also provides a strong rationale to deliver 0.05% CsA using the 1.25% castor oil vehicle taught by Ding '979 (Example 2C)." Pet. 35. 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; EX1002 ¶¶ 82, 120–121). Petitioner contends that Sall discloses that the vehicle used is the study reported in Sall (castor oil) "contributed to the overall improvements observed in all treatment groups in this study." *Id.* (citing Ex. 1007, 632, 638). Petitioner further contends that "[t]he 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 . . . and also within the ratio range found with each of the Example 1 emulsions (0.04–0.08)." *Id.* (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 dry eye disease based on at least the success described by Sall: "Treatment with CsA, 0.05% or 0.1% gave significantly ($P \leq 0.05$) greater improvements than vehicle in two objective signs of dry eye disease." *Id.* at 631; EX1002, ¶116. 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, ¶¶ 99, 114; EX1001, 14:65-67 ("These compositions are produced in accordance with well known techniques[.]").

Id. at 36.

Patent Owner argues in its preliminary response 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. 29–33. 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)).

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 make 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. Pet. 36; Ex. 1007, 638. *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." (citations omitted)).

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. 14–17, 37–38. 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 0.1% cyclosporin/1.25% castor oil, despite PK data that predicted the opposite should have been true." *Id.* at 37. 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.[6] At this preliminary stage, we determine

[6] 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.

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

F. Obviousness of Claims 14 and 19 Based on Ding '979, Sall, and Glonek

Petitioner asserts that claims 14 and 19 are unpatentable as obvious over Ding '979, Sall, and Glonek. Pet. 41–43. Patent Owner opposes for the same reasons stated with respect to claims 1, 13, and 15 above. Prelim. Resp. 38. We incorporate here our findings and discussion above regarding the teachings of Ding '979 and Sall.

Claim 14 recites a topical ophthalmic emulsion with the same ingredients as claim 1, and further recites that the emulsion "breaks down more quickly in the eye of a human . . . thereby reducing vision distortion" as compared to a second emulsion with only half as much castor oil. Claim 19 depends from claim 14, and recites that "when the first topical ophthalmic emulsion is administered to an eye of a human . . . , the blood of the human has substantially no detectable concentration of cyclosporin A."

Petitioner asserts "Glonek discloses oil-in-water emulsions for the treatment of dry eye which are formulated so as 'blurred vision is reduced or eliminated and the residence time of tear film on the eye is prolonged." Pet. 42 (citing Ex. 1009, 3:3–7; Ex. 1002 ¶ 132). Petitioner also relies upon Glonek's teaching that "an emulsion over the surface of the eye is expected to cause blurring" wherein "[t]he duration of the blurring is dependent upon

the time required for the emulsion to differentiate and form separate layers," and that "it is preferred that the emulsion be stable for long term storage, but ***rapidly differentiate in the eye***." *Id.* (citing Ex. 1009, 6:37–40, 6:48–50) (emphasis by Petitioner).

Based on these teachings of Glonek, Petitioner contends 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 ¶¶ 132–135). Petitioner further contends that "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." *Id.* (citing Ex. 1002 ¶58; Ex. 1017, 2032). With respect to claim 19, Petitioner relies upon Sall's teachings as discussed above. *Id.* at 42–43.

Based on the arguments presented and evidence of record, we determine that Petitioner has demonstrated a reasonable likelihood that claims 14 and 19 are obvious over the teachings of Ding '979, Sall, and Glonek.

G. Obviousness of Claims 11, 18, and 20 Based on Ding '979, Sall, and Acheampong

Petitioner asserts that claims 11, 18, and 20 are unpatentable as obvious over Ding '979, Sall, and Acheampong. Pet. 43–44. Patent Owner opposes for the same reasons stated with respect to claims 1, 13, and 15

above. Prelim. Resp. 39. We incorporate here our findings and discussion above regarding the teachings of Ding '979, Sall, and Glonek.

Claims 11, 18, and 20 depend from independent claims 1, 13, and 15respectively and further recite that "when the first topical ophthalmic emulsion is administered to an eye of a human . . . , the blood of the human has substantially no detectable concentration of 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. 44 (citing Ex. 1008, 1002, 1004 (Table 1); Ex. 1002 ¶¶ 139–140). Petitioner asserts that Acheampong adds to Sall's teaching, and would provide a skilled artisan with a reasonable expectation of success that when the 0.05% CsA-in-castor oil emulsion is administered to the eye there is "substantially no detectable concentration of cyclosporin A" in the blood. *Id.*

Based on the arguments presented and evidence of record, we determine that Petitioner has demonstrated a reasonable likelihood that claims 11, 18, and 20 are obvious over the teachings of Ding '979, Sall, and Acheampong.

H. Obviousness of Claim 19 Based on Ding '979, Sall, Glonek, and Acheampong

Petitioner asserts that claim 19 is unpatentable as obvious over Ding '979, Sall, Glonek, and Acheampong. Pet. 45. Patent Owner opposes for the same reasons stated with respect to claims 1, 13, and 15 above. Prelim. Resp. 39. We incorporate here our findings and discussion above regarding the teachings of Ding '979, Sall, Glonek, and Acheampong.

Based on the arguments presented and evidence of record, we determine that Petitioner has demonstrated a reasonable likelihood that claim

19 is obvious over the teachings of Ding '979, Sall, Glonek, and Acheampong.

III. CONCLUSION

For the foregoing reasons, we determine that Petitioner has demonstrated that the information presented in the Petition and in the Preliminary Response shows that there is a reasonable likelihood that Petitioner would prevail in proving the unpatentability of claims 1–20 of the '556 patent for anticipation and obviousness.

At this stage of the proceeding, the Board has not made a final determination as to the patentability of any challenged claim or any underlying factual and legal issues. Thus, our view with regard to any conclusion reached in the foregoing could change upon consideration of Patent Owner's merits response and upon completion of the current record.

IV. ORDER

Accordingly, it is:

ORDERED that, pursuant to 35 U.S.C. § 314(a), an *inter partes* review is hereby instituted as to claims 1–20 of U.S. Patent No. 8,642,556 B2 based on the following grounds of unpatentability:

A. Claims 1–20 under 35 U.S.C. § 102(b) as anticipated by Ding '979,

B. Claims 1–20 under 35 U.S.C. § 103(a) as obvious over Ding '979 and Sall,

C. Claims 14 and 19 under 35 U.S.C. § 103(a) as obvious over Ding '979, Sall, and Glonek,

D. Claims 11, 18, and 20 under 35 U.S.C. § 103(a) as obvious over Ding '979, Sall, and Acheampong,

E. Claim 19 under 35 U.S.C. § 103(a) as obvious over Ding '979, Sall, Glonek, and Acheampong;

FURTHER ORDERED that *inter partes* review commences on the entry date of this Order, and 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; and

FURTHER ORDERED that the trial is limited to the grounds of unpatentability listed above, and no other grounds of unpatentability are authorized for *inter partes* review.

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