APPENDIX A

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

SENJU PHARMACEUTICAL CO., LTD,
MITSUBISHI CHEMICAL CORPORATION,
Appellants

v.

AKORN, INC.,
Appellee

2017-1511

Appeal from the United States Patent and Trademark Office, Patent Trial and Appeal Board in No. IPR2015-01205.

JUDGMENT

ANTON METLITSKY, O'Melveny & Myers LLP, New York, NY, argued for appellants. Also represented by LISA BARONS PENSABENE, FILKO PRUGO; JOHN C. KAPPOS, Newport Beach, CA.

CHANDRIKA VIRA, Sterne Kessler Goldstein & Fox, PLLC, Washington, DC, argued for appellee. Also represented by ELDORA ELLISON, RALPH WILSON POWERS, III, JON WRIGHT.

THIS CAUSE having been heard and considered, it is

ORDERED and ADJUDGED:

PER CURIAM (O'MALLEY, REYNA, and TARANTO, *Circuit Judges*).

AFFIRMED. See Fed. Cir. R. 36.

ENTERED BY ORDER OF THE COURT

August 8, 2018
Date

/s/ Peter R. Marksteiner
Peter R. Marksteiner
Clerk of Court

APPENDIX B

Trials@uspto.gov
571-272-7822

Paper No. 39
Entered: November 22, 2016

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AKORN, INC.,
Petitioner,

v.

SENJU PHARMACEUTICAL CO., LTD
MITSUBISHI CHEMICAL CORPORATION,
Patent Owners.

Case IPR2015-01205
Patent 6,114,319

Before DEBORAH KATZ, JACQUELINE WRIGHT BONILLA, and GRACE KARAFFA OBERMANN, *Administrative Patent Judges*.

Opinion for the Board filed by *Administrative Patent Judge* KATZ.

Additional views filed by *Administrative Patent Judge* KATZ.

KATZ, *Administrative Patent Judge*.

FINAL WRITTEN DECISION
35 U.S.C. § 318 and 37 C.F.R. § 42.73

We instituted a trial under 35 U.S.C. § 314 to review challenges brought by Akorn, Inc. ("Petitioner") against claims 1–4, 6–10, 12–14, and 18 of U.S. Patent No. 6,114,319 (Ex. 1001, "the '319 patent") in the Petition (Paper 1 ("Pet.")). *See* Paper 8 ("DI"). Senju Pharmaceutical Co., Ltd. and Mitsubishi Chemical Corporation. ("Patent Owners") filed a Response under 37 C.F.R. § 42.120 (Paper 13 ("PO Resp.")) and Petitioners filed a Reply (Paper 18 ("Pet. Reply")). Patent Owners do not seek to amend the challenged claims under 37 C.F.R. § 42.121.

Patent Owners filed observations on the cross-examination testimony of Dr. Xia given on June 24, 2016 (Exhibit 2095). Paper 28. Petitioner responded to these observations. Paper 33.

An oral argument was held on September 7, 2016. Transcript, Paper 36.

We conclude that Petitioner has shown by a preponderance of the evidence that the challenged claims are unpatentable.

A. Related proceedings

Petitioner identifies *Alcon Laboratories, Inc. et al. Inc. v. Akorn, Inc.,* C.A. No. 2:15-cv-00285-MCA-JBC (D.N.J.), as a related matter. Pet. 8. Patent

Owners report that this proceeding was stayed on January 8, 2016, pending a written decision in the instant review. PO Resp. 1–2.

B. The '319 patent (Ex. 1001)

The '319 patent issued September 5, 2000, from an application filed May 12, 1998. Ex. 1001, coversheet. On its face, the '319 patent indicates that it relies on a Japanese application filed May 14, 1997, for a priority date. *Id.* An *ex parte* reexamination certificate was issued May 18, 2004, determining that claim 1, as amended, was patentable, canceling claims 5, 11, and 15–17, and adding independent claim 18. Ex. 1001, 9.

The '319 patent is directed to compositions of difluprednate, a steroid drug that was known to have superior anti-inflammatory action for skin disorders. Ex. 1001, 1:5–25. The inventors of the '319 patent explain that difluprednate has extremely low solubility in water, making it difficult to prepare a stable eye, nose, or ear drop and resulting in aqueous suspensions that are uncomfortable and delivered unevenly. Ex. 1001, 1:26–52. The inventors solved this problem by preparing a composition of difluprednate as an emulsion with oil, water, and an emulsifier. Ex. 1001, 2:6–12.

Following reexamination, the '319 patent includes two independent claims: claims 1 and 18. Claim 1 recites[1]:

[1] Indentations added for clarity.

> A difluprednate emulsion in the form of an eye drop, a nasal drop or an ear drop comprising
>
> (a) difluprednate,
>
> (b) an oil selected from the group consisting of castor oil, peanut oil, cotton seed oil, soybean oil, olive oil and a medium chain fatty acid triglyceride,
>
> (c) water and
>
> (d) an emulsifier.

Ex. 1001, 9. Claim 18 recites[2]:

> A difluprednate emulsion in the form of an eye drop, a nasal drop or an ear drop comprising
>
> [a] difluprednate,
>
> [b] castor oil,
>
> [c] water and
>
> [d] polyoxyethylene (20) sorbitan monooleate.

Id.

C. Asserted Ground of Unpatentability

Petitioner challenges the patentability of claims 1–4, 6–10, 12–14, and 18 of the '319 patent under 35 U.S.C. § 103 as being obvious over the combination

[2] Bracketed letters and indentations added for clarity.

of the teachings of U.S. Patent 5,556,848[3] ("the '848 patent", Ex. 1006) and International patent application publication WO 95/31211[4] ("Ding", Ex. 1012). Pet. 27–60.

D. Analysis

1.

Claimed subject matter would have been obvious under 35 U.S.C. § 103 if the prior art shows that the improvement of a known substance would improve similar substances in the same way and if carrying out the improvement would have been within the ordinary skill of those in the art. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 417 (2007).

2.

Claim 18 of Patent Owner's '319 patent recites a difluprednate emulsion comprising difluprednate, castor oil, water and polyoxyethylene (20) sorbitan monooleate. Ex. 1001, 9. Petitioner's witness, Erning Xia, Ph.D.,[5] testifies that claim 18 is narrower

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[3] The '848 patent issued September 17, 1996.

[4] Ding was published November 23, 1995.

[5] Dr. Xia testifies that he has a Ph.D. in Pharmaceutics from the University of Iowa and that he is currently Distinguished Research Fellow and Chief Technology Officer at Fulcrum Technologies, Inc. Ex. 1018 ¶¶ 7, 9. He testifies further that he has nearly 30 years of experience in topical ophthalmic drug formulations, including in his doctoral research and employment at Bausch & Lomb as a senior formulation process scientist developing various ophthalmic eye drops and steroid preparations. *Id.* ¶¶ 10–12. We consider Dr. Xia to be qualified to present opinion testimony on the subject matter of this review.

than and is encompassed by claim 1 of the '319 patent because castor oil is one of the oils recited in claim 1 and polyoxyethylene (20) sorbitan monooleate is an emulsifier as recited in claim 1. Ex. 1018 ¶ 23; *see* Pet. 27; *see also* Prelim. Resp. 32. We focus our analysis on Petitioner's challenge to claim 18 because we agree that the subject matter of claim 18 is a subgenus of the subject matter recited in claim 1.[6]

3.

Petitioner cites the '848 patent to show that difluprednate was known in the art as an anti-inflammatory steroid useful for treating and preventing various disorders of the eye. Pet. 30 (citing Ex. 1006, abstract, 1:13–31). Specifically, the '848 patent teaches that difluprednate is a treatment for eye ailments including allergic conjunctivitis, vernal conjunctivitis, blepharitis marginalis, catarrhal conjunctivitis, and uveitis. Ex. 1006, abstract.

Petitioner cites Ding to show that it was known to formulate steroids in emulsions as recited in claim 18 of the '319 patent. Specifically, Ding teaches:

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[6] Patent Owners argue that even if Petitioner shows that claim 1 is unpatentable, it fails to show that claim 18 is unpatentable. PO Resp. 44. Although Patent Owners are correct that claim 18 is narrower than claim 1, our determination that claim 18 would have been obvious is also a determination that claim 1 would have been obvious because Patent Owners cite to the same arguments to counter Petitioner's challenges to both claims, and because claim 18 is directed to a subgenus of the subject matter of claim 1.

> While the preferable medications in accordance with the present invention include cyclosporin, other chemicals which are poorly soluble in water such as . . . steroids such as androgens, prednisolone, prednisolone acetate, fluorometholone, and dexamethasones, may be emulsified with castor oil and polysorbate 80 resulting in a composition with similar low irritation potential.

Ex. 1012, 9:24–30. Similarly, Ding teaches "novel pharmaceutical compositions incorporating chemicals which are poorly soluble in water . . . more particularly related to a novel ophthalmic emulsion including cyclosporine in admixture with castor oil and polysorbate 80 with high comfort level and low irritation potential." Ex. 1012, 1:8–14; *see* Pet. 29–30.

Petitioner explains that "polysorbate 80," the emulsifier taught in Ding, is also known as "polyoxyethylene (20) sorbitan monooleate," which is recited in claim 18. Pet. 25; *see* Ex. 1001, last page, Ex Parte Reexamination Certificate (equating polysorbate 80 and polyoxyethylene (20) sorbitan monooleate). Thus, Ding teaches an emulsion comprising a steroid, castor oil, and polyoxyethylene (20) sorbitan monooleate, and teaches that this emulsion has low irritation potential.

Petitioner challenges Patent Owners' claims by arguing that a person of ordinary skill in the art would have considered it obvious to formulate difluprednate with the emulsion taught in Ding be-

cause a drug with improved comfort, dose uniformity, and bioavailability would result. Pet. 30–34. According to Petitioner, an ordinary artisan would have known that the aqueous solution of difluprednate taught in the '848 patent contains particles that cause eye irritation. Pet. 31. Specifically, Petitioner argues that the '848 patent teaches difluprednate particles as large as 75 µm, which, according to Dr. Xia, were known to cause eye irritation. Pet. 31 (citing Ex. 1006, 6:22–25). Dr. Xia testifies that those of skill in the art would have known that ophthalmic solutions should contain particles sized less than 10 µm to minimize eye irritation. Pet. 31 (citing Ex. 1018 ¶ 44). Dr. Xia bases his testimony on the teachings of Remington's Pharmaceutical Sciences, Chapter 86: "Ophthalmic Preparation" (Ex. 1011, 1585[7] ("Particle size also plays an important part of irritation potential of the dosing system. . . . It has been recommended that particles be less than 10 µm in size to minimize irritation to the eye.")) and other publications (Ex. 1022, 189 ("To minimize any potential irritation to the eye, the particle size should be less than 10 µm.")). Ex. 1018 ¶ 44.

Petitioner also argues that those of skill in the art would have turned to Ding when formulating difluprednate because the emulsion taught therein would address the uniformity problems reported for the aqueous suspension in the '848 patent. Pet. 32–33. Specifically, the '848 patent reports that

[7] Page numbers reflect the numbering of the underlying document, unless otherwise specified.

difluprednate in aqueous suspension settles to the bottom of the container when stored and sometimes aggregates or cakes into larger clumps of particles. Ex. 1006, 1:53–57, 6:55–57. According to Petitioner, the emulsion of Ding solves this problem because cyclosporin was found to be physically stable upon long term storage. Pet 32–33 (citing Ex. 1012, 6:32–34 ("When cyclosporine is dissolved in the oil phase in accordance with the present invention, the emulsion is found to be physically stable upon long term storage.")).

Petitioner argues further that the emulsion of Ding would have addressed problems of drug delivery presented by difluprednate. Pet. 33–34. According to Petitioner, those of skill in the art would have relied on the teaching in Ding that the emulsion would reduce excessive tearing and drainage, thus providing better drug delivery. Pet. 33–34 (citing Ex. 1018 ¶ 86; Ex. 1012, 6:5–10, 18:9–11). Petitioner cites to data reported in Ding indicating that a castor oil emulsion was effective in delivering drug to eye tissues such as the lacrimal gland, cornea, and conjunctiva. *See* Ex. 1012, 6:5–10, 18:9–11.

Petitioner also argues that those of skill in the art would have had a reasonable expectation of success in formulating difluprednate with the emulsion of Ding because an ordinary artisan would have known that the emulsion was suitable for steroids that were poorly soluble in water, including prednisolone acetate. Pet. 35 (citing Ex. 1012, 9:24–30). Relying on Dr. Xia's testimony and the references he cites, Petitioner explains that difluprednate is a

derivative of prednisolone acetate and that both drugs are synthetic glucocorticoids. Pet. 35; Ex. 1018 ¶ 38 (citing Ex. 1004, 1:2–4, 1:56–72, 2–4). According to this testimony, those in the art would have expected difluprednate to be suitable for the emulsion of Ding and that the resulting combination would be suitable for its intended ophthalmic use. Pet. 35–36 (citing Ex. 1018 ¶¶ 38, 89).

4.

We are persuaded by the evidence Petitioner presents, specifically that the '848 patent shows that difluprednate was a known drug, useful for treating various eye ailments. We are also persuaded by the evidence discussed, specifically Ding, that emulsions as recited in the challenged claims were known for solving the formulation problems of similar steroids in ocular treatments.

In response to Petitioner's challenge, Patent Owners first argue Petitioner uses improper hindsight because there would have been no reason for those in the art to have looked to difluprednate or Ding. PO Resp. 6–16. Patent Owners argue that there were other options for anti-inflammatory treatments and that other steroids would have been more desirable than difluprednate. *Id*. at 6–9.

Patent Owners also argue that there were several ways of delivering drugs to the eye and that topical administration, such as with an emulsion, would have been very challenging and unpredictable. *Id*. at 9–12. According to Patent Owners, because difluprednate must reach the iris-ciliary bod-

ies interior to the eyeball to be effective against anterior uveitis, those of skill in the art would not have looked to topical applications. Patent Owners argue that other ophthalmic formulations known at the time were preferred over emulsions and that those of skill in the art would have looked to solutions, instead of emulsions. *Id.* at 10–16.

We are not persuaded by these arguments that Petitioner's challenge is based on hindsight. Patent Owners' claims are not directed to methods of treating the eye or methods of delivering drug to the eye. Thus, whether or not there were other drugs useful as anti-inflammatory eye treatments or other delivery methods that would have been thought to be better is not cogent in relation to the obviousness of the claimed formulation. Instead, because the '848 patent demonstrates that difluprednate was known to be useful in treating ophthalmic ailments and Ding teaches that emulsions were known as formulations for delivery to the eye, we are persuaded that those of ordinary skill in the art would have at least considered formulating difluprednate as an emulsion to have been obvious.

Patent Owners also argue that Petitioner fails to demonstrate there would have been a motivation to combine the teachings of the '848 patent and Ding. PO Resp. 17–25. Patent Owners argue that Ding targets a different tissue than the tissue where difluprednate is active. *Id.* at 17–22. According to Patent Owners, Ding targets only the lacrimal gland of the eye, which is external to the eyeball, not the interior of the eyeball, where the '319 patent indicates difluprednate is active. *Id.* We are not

persuaded by this argument because, for reasons that follow, we are not persuaded that difluprednate is useful only in the interior of the eyeball.

Patent Owners rely on the testimony of Dr. Majumdar[8] to support its argument that the target of difluprednate is interior to the eyeball. PO Resp. 18–19 (citing Ex. 2047 ¶ 41). Dr. Majumdar cites to the portion of the '848 patent[9] that reports anti-inflammatory action on the ailment acute uveitis and describes a test that measures proteins in the aqueous humor, a substance inside the eyeball. *See* Ex. 2047 ¶ 41 (citing Ex. 1006, 7:36–8:13). Dr. Majumdar also testifies that to treat uveitis, an active ingredient must reach the iris-ciliary bodies, which are interior to the eyeball. *See* Ex. 2047 ¶ 31.

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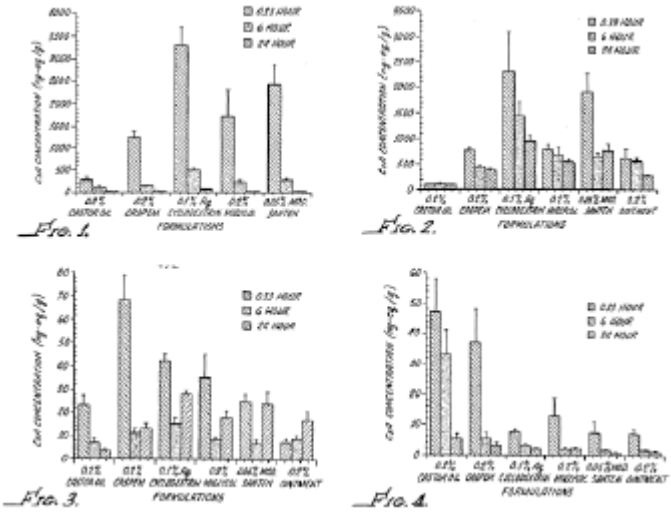
[8] Dr. Majumdar testifies that she has a Ph.D. in Pharmaceutical Sciences and Pharmacology from the University of Missouri-Kansas and has been an Associate Professor of Pharmaceutics and Drug Delivery at the University of Mississippi since 2011. Ex. 2047 ¶¶ 3, 4. She also testifies that she is the Associate Dean for Research and Graduate Programs in the School of Pharmacy, a Research Associate Professor in the Research Institute of Pharmaceutical Sciences, and an Associate Director of the Pii Center for Pharmaceutical Technology. Ex. 2047 ¶ 4. Dr. Majumdar testifies further that since 1993 she has held positions in the pharmaceutical industry, participating and leading teams in the development of pharmaceutical formulations, including ophthalmic formulations. Ex. 2047 ¶¶ 5, 6. We consider Dr. Majumdar qualified to present opinion testimony on the subject matter of this review.

[9] Patent Owners and Dr. Majumdar discuss the '319 patent, but cite to the '848 patent. *See* Resp. 18–19; Ex. 1006, 7:54–8:13; Ex. 2047 ¶ 41.

Uveitis is not the only ailment for which difluprednate is useful, though. Despite Dr. Majumdar's testimony and the cross-examination testimony of Dr. Xia to which Patent Owners cite (*see* PO Resp. 19 (citing Ex. 2017, 32:15–23, 32:25–33:8)), both the '848 patent and the '319 patent teach that difluprednate is also useful for treating a range of ailments, including allergic conjunctivitis, vernal conjunctivitis, blepharitis marginalis, catarrhal conjunctivitis, as well as uveitis. *See* Ex. 1006, abstract; Ex. 1001, 4:34–40; Pet. Reply 6–7. According to Dr. Majumdar, blepharitis is an ailment of the eyelids. Ex. 1025, 134:15–17. Thus, we are not persuaded that difluprednate was known to be useful only in the interior of the eyeball or that those of skill in the art would not have considered Ding because it teaches emulsions that target areas exterior to the eyeball.

Furthermore, Ding teaches that its emulsion is useful for delivery to the tissues where difluprednate is useful. Ding states broadly that its emulsion is suitable for "delivery of medication to sensitive areas, such as ocular tissues." Ex. 1012, 7:34–8:2, 8:14–17. The data presented in Ding supports this statement. Specifically, we consider Figures 1–4 of Ding, which are reproduced below.



Figures 1–4 of Ding show the concentration of drug in different ocular tissues after topical administration of different formulations, wherein Figure 1 depicts concentrations in the conjunctiva, Figure 2 depicts concentrations in the cornea, Figure 3 depicts concentrations in the ciliary body, and Figure 4 depicts concentrations in the lacrimal gland. Ex. 1012, 9:20–32. The results shown in Figures 1–4 demonstrate delivery by different formulations: castor oil only ("Castor Oil"), castor oil-in-water emulsion ("Caspem"), aqueous cyclodetrin ("cyclodextrin"), and miglyol oil-in-water emulsion ("miglyol"). Ex. 1012, 15, Table A; PO Resp. 19–20.

From this data, Ding concludes that the emulsions were effective in delivery of drug to the conjunctiva and cornea, as well as the lacrimal gland. Ex. 1012, 18:7–11; *see* Ex. 1016 ¶ 61; Pet. 21–22. Accordingly, we agree with Petitioner that the

emulsion of Ding is not limited to delivering drug to the lacrimal gland, but also provides benefits for delivery to other ocular tissues, such as the conjunctiva. Because the '848 patent indicates difluprednate is useful for ailments such as types of conjunctivitis and blepharitis marginalis, we find that those of skill in the art would have been motivated to combine the teachings of both references, and Patent Owners' arguments fail to persuade us otherwise.

Patent Owners argue further that there would not have been a reason to combine the '848 patent and Ding because the '848 patent had solved the problems of irritation with reduced particle size. PO Resp. 22–24. Similarly, Patent Owners argue that the suspension taught in the '848 patent did not demonstrate problems with redispersion. *Id.* at 24–25. These arguments are unpersuasive. Even if the '848 patent solved these problems, it would still have been obvious to formulate difluprednate as an emulsion because those of skill in the art knew that doing so also would solve the irritation problems, as discussed elsewhere in this Decision. "[W]hen a patent claims a structure already known in the prior art that is altered by the mere substitution of one element for another known in the field, the combination must do more than yield a predictable result." *KSR*, 550 U.S. at 416.

Patent Owners argue that there would not have been a reasonable expectation of success in combining the teachings of the '848 patent and Ding. PO Resp. 25–44. According to Patent Owners, those of skill in the art would have had to perform "countless

experiments" to make the selections of the claimed emulsion because without using the patented invention as a guide, there were many possible active ingredients and potential delivery approaches. PO Resp. 25–30. Patent Owners argue that those of skill in the art would not have selected difluprednate because it would have been expected to elevate intraocular pressure, an adverse event. *Id.* at 28–30.

These arguments are not persuasive because, as explained above, the challenged claims are not drawn to methods of treating an ailment with an emulsion of difluprednate. Whether or not skilled artisans would have chosen difluprednate is not the issue to be addressed in evaluating whether there would have been a reasonable expectation of success in formulating it as an emulsion. Patent Owners' claims do not include any limitations that read on choosing difluprednate for a recited purpose. Even if difluprednate is a not a drug of choice for treating a certain ailment, formulating it in an emulsion as taught in Ding still would have been obvious, as Petitioner has shown.

Patent Owners also argue that skilled artisans would not have reasonably expected a formulation of difluprednate in the emulsion of Ding to be successful because of the high concentration of surfactant. PO Resp. 30–35. Patent Owners cite to evidence that high concentrations of surfactants were known to cause irritation, to react with preservatives, and to change the physical properties of the membrane bilayer of eye tissues at the time. *See, e.g.,* Ex. 2024, 518; Ex. 1011, 1590; Ex. 2004, 140.

But Ding teaches that emulsions with higher fatty acid glycerides, such as castor oil, in combination with surfactant, such as polysorbate 80, provide a formulation with "high comfort level and low irritation potential suitable for delivery of medications to sensitive areas such as ocular tissues." Ex. 1012, 5:34–6:2; *see* Pet. Reply 12. Thus, the problems recited by Patent Owners do not seem to be of concern for the emulsion of Ding.

Patent Owners argue further that in contrast to Petitioner's argument and evidence, those in the art would not have had a reasonable expectation of success in formulating difluprednate as an emulsion because emulsions were not known to provide superior drug delivery before 1997. PO Resp. 35–39. This argument addresses Petitioner's arguments that the claimed emulsion does not demonstrate unexpected results by citing to the references Aviv, Ex. 1010, and Kassem, Ex. 1020. Given that Ding teaches its emulsion provides for delivery of drug to the eye tissues of interest, we are not persuaded that those of ordinary skill in the art would not have had a reasonable expectation of success in delivery of drugs to these tissues. We address whether the amount of delivery of difluprednate was unexpected when we address Patent Owner's evidence of secondary considerations below.

We note further that Patent Owners do not address Petitioner's argument that those of skill in the art would have reasonably expected difluprednate to be a successful emulsion because it is derived from prednisolone acetate, a steroid Ding expressly teaches can be formulated as the emulsion. *See* Pet.

35 (citing Ex. 1012, 9:24–30). Petitioner's argument, supported by Dr. Xia's testimony (Ex. 1018 ¶ 38) and the evidence he cites (Ex. 1004, 1:2–4) to show that difluprednate was derived from prednisolone acetate, is persuasive. Because Patent Owners do not direct us to evidence to the contrary, we determine there would have been a reasonable expectation of success making the claimed emulsion.

Patent Owners argue further that emulsions were known to be disseminated systemically, that is throughout the body instead of staying localized at the administration site, and that because of this, those of skill in the art would not have used emulsions with steroids. PO Resp. 39–41. Nevertheless, Ding teaches formulating steroids as emulsions. Patent Owners cite to other references that reportedly discuss systemic dissemination (*see* Exs. 1010, 1015, and 2052), but as Petitioner notes (Pet. Reply 16), Patent Owners do not direct us to statements in these references that caution against the use of emulsions or that indicate difluprednate would present any particular risks.

Patent Owners also argue that there would not have been a reason to choose polysorbate 80 (polyoxyethylene (20) sorbitan monooleate) in an emulsion. PO Resp. 41–42. Specifically, Patent Owners argue that van Pinxteren (Ex. 2004) reports that polysorbate 80 constricted uveal vessels and raised intraocular pressure. *Id.* (citing Ex. 2004, 136). We are not persuaded by this argument because, as Petitioner notes, van Pinxteren reports administering the emulsion intra-arterially, not topically, such as

in the form of an eye drop as claimed. *See* Pet. Reply 19 (citing Ex. 2004, abstract).

Patent Owners also argue that those of skill in the art would not have chosen castor oil from the other choices of oils because the prior art taught away from castor oil. PO Resp. 42–44. Citing references by Benitez del Castillo (Ex. 2015 and 2053), Patent Owners argue that castor oil, as well as olive oil, were shown to increase corneal epithelial permeability. As Petitioner notes, these references used formulations comprising at least 98% oil. *See* Ex. 2015, 51; Ex. 2053, 137; Pet. Reply 20. Because the amount of castor oil used in the emulsions of Ding is much lower (1.25%, *see* Ex. 1012, 15, Table A) and this adverse effect is not discussed, we are not persuaded that the references Patent Owners cite teach away from the use of castor or other oils in emulsion formulations as claimed.

5.

In *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17-18 (1966), the Supreme Court discussed "secondary considerations" such as commercial success, long felt but unsolved needs, and the failure of others that may be relevant to whether claimed subject matter is obvious. We consider evidence, such as comparative data in the specification, when determining whether the claimed invention is obvious. *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995).

Unexpected Results

Patent Owners argue that their claimed difluprednate emulsion produces unexpected results because it did not cause a large elevation in intraocular pressure or other adverse events. PO Resp. 44–52 (citing Ex. 2047 ¶¶ 75, 76; Ex. 2054, 609–10). According to Patent Owners, difluprednate would have been expected to significantly raise intraocular pressure because it was known to be a "strong steroid." PO Resp. 44–45 (citing Ex. 2047 ¶¶ 75, 76; Ex. 2054, 609–10). Patent Owners argue that, "[u]nexpectedly, difluprednate did not show this higher incidence of adverse events compared to other weaker steroids." PO Resp. 45. Each of the studies Patent Owners cites in support of these unexpected results uses either the drug Durezol, which Patent Owners argue is difluprednate in an emulsion within the scope of the claims (Ex. 2054, 609; Ex. 2055, 658), or a different preparation of difluprednate in a castor oil emulsion (Ex. 2056, 30). *See also* Ex. 2020 (remarking on the lower intraocular pressure elevations observed with difluprednate emulsion compared to other steroids).

The evidence of record does not persuade us that the claimed emulsion provides unexpected results because the lower intraocular pressure observed could have been due to difluprednate itself, a drug that was already known in the prior art, not its formulation as an emulsion. The evidence before us does not establish adequately that difluprednate raises intraocular pressure to a greater extent in other formulations. Patent Owner's argument and evidence in this regard compares difluprednate to

other drugs, but does not compare difluprednate in an emulsion to the same drug in non-emulsion formulations. Thus, even if the degree of elevation in intraocular pressure reported for difluprednate in an emulsion was surprising, it does not persuade us that Patent Owners' claimed subject matter, i.e., the emulsion formulation of the drug, was responsible.

Patent Owners argue further that difluprednate emulsions resulted in improved delivery of the drug when compared to difluprednate suspensions. *See* PO Resp. 48–49 (citing Ex. 2047 ¶ 73; *see* Ex. 1001, 10:1–12, Table 2). Patent Owners also rely on the testimony of Dr. Majumdar to argue that the enhanced bioavailability of the emulsion would have been unexpected. PO Resp. 48–52 (citing Ex. 2047 ¶ 73). When we consider all of the evidence before us, we are not persuaded that the results demonstrated by the claimed difluprednate emulsion would have been unexpected.

The '319 patent reports that 0.1 g of difluprednate prepared in a suspension and administered to the eyes of rabbits demonstrated intraocular transfer of 19.15 $\pm$ 2.8 ng/ml. Ex. 1001, 10:1–21, Table 2. In comparison, one half the amount of difluprednate (0.05 g) in an emulsion demonstrated intraocular transfer of 42.95$\pm$ 6.5 ng/ml. *Id.* Thus, the '319 patent reports that one half the dose of difluprednate in an emulsion resulted in over two times the intraocular transfer obtained with difluprednate in a suspension. *Id.* Dr. Majumdar testifies that this difference demonstrates "unexpectedly enhanced" biovailability, but he does not provide any further

discussion of the results. Ex. 2047 ¶ 73. Dr. Majumdar does not discuss whether or not emulsions were known to enhance bioavailability in general and, if so whether the enhanced bioavailability reported in the '319 patent was greater than expected with other emulsions. When we consider all the evidence of record together, we are not persuaded that the greater enhanced bioavailability of a drug formulated as an emulsion would have been unexpected.

Petitioner argues that those of skill in the art would have expected emulsions to lead to improved drug delivery, citing to Aviv (Ex. 1010), Kassem (Ex. 1020), and Ding (Ex. 1012) in support. Pet. 55–59. Aviv states that at the time "there [was] no doubt that a reduction in the irritating effect of a drug will enable increased ocular drug bioavailability . . . ." Ex. 1010, 1:26–28. Ding reports that the castor oil emulsion it teaches has low irritation potential. Ex. 1012, 9:23–30. According to this evidence, Petitioner argues that those of skill in the art would have expected greater bioavailability with an emulsion in the studies reported in Table 2 of the '319 patent because the emulsion was less irritating. Ex. 1010, 9:46–47.

Petitioner also points to Aviv for a comparison between delivery of a drug to the interior of the eyeball when formulated as an emulsion versus as a suspension. Pet. 55–56 (citing Ex. 1010, 11:22–65). In Example 15 of Aviv, three different formulations of the drug indomethacin were administered to the eyes of rabbits and the resulting concentration of the drug in the interior of the eyeball, the aqueous

humor, was measured at later time points. The three formulations of the drug included the commercially available form, called "INDOPTIC," which Petitioner indicates is a suspension, and two emulsions, one with 0.2% drug and the other with 0.4% drug, as prepared in Examples 11 and 10, respectively. Aviv reports in Table 4 that the 0.4% indomethacin emulsion yielded higher levels of the drug in the aqueous humor than did 1% INDOPTIC at 1 hour. Aviv reports further that the "area under the curve"[10] for 0.2% indomethacin emulsion was 2.2 times larger than that of the 1% INDOPTIC, even though there was more drug in the 1% INDOPTIC. Aviv concludes that the emulsion formulations provided for higher bioavailability. Ex. 1010, 11:63–66 ("Thus, a higher bioavailability of the drug is obtained for the compositions of the invention, while at the same time greatly reduced irritation is achieved.").

Patent Owners dispute the results reported in Aviv and the conclusions drawn by Petitioner. According to Patent Owners, INDOPTIC is not a suspension like the formulation used in the '848 patent because Aviv uses the term "solution" is some places. PO Resp. 35–36 (citing Ex. 101, 11:57–60). Aviv initially describes INDOPTIC as a "suspension" (*see* Ex. 1010, 11:27–28, 11:32), but when reporting and discussing the results in Example 15,

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[10] We understand the "area under the curve" to be a calculation from a plot of concentration of drug against time representing the total drug exposure over time. Both parties use of this term, which is not in dispute, is consistent with this understanding.

refers to it as a "solution." Thus, Aviv is somewhat ambiguous about the nature of the INDOPTIC formulation.

Nevertheless, Petitioner cites to other references that refer to INDOPTIC as a suspension. *See* Pet. Reply 14 (citing Ex. 1027, 166; Ex. 1031, 13:25). Patent Owners fail to direct us to other references showing that INDOPTIC is a solution, referring only to testimony by Dr. Majumdar and Dr. Xia about the language used in Aviv. *See* PO Resp. 36 (citing Ex. 2047 ¶ 58; Ex. 2071, 254:6–9). Considering all of the evidence on the record before us, we agree with Petitioner that Example 15 of Aviv provides the results of a comparison between a suspension of indomethacin (INDOPTIC) and an emulsion of indomethacin.

Patent Owners argue further that Aviv fails to present calculations of the area under curve for the results shown in Table 4 and that the results reported do not support the statement in Aviv that the area under the curve for the emulsion was 2.2 times higher than for INDOPTIC. PO Resp. 36 (citing Ex. 2047 ¶ 58). Although Patent Owners cite to Dr. Majumdar's declaration in support, on crossexamination he testified that after considering the difference in indomethacin concentration of INDOPTIC and the emulsions, the area under the curve for the 0.4% emulsion is greater than the same for the 1% INDOPTIC. *See* Ex. 1025, 124:24–125:2 ("Q. So the area under the curve for the 0.4 indomethacin emulsion was greater than the area under the curve for the 1 percent Indoptic; correct? A. That's correct."); Ex. 1024; Pet. Reply 14–15.

Patent Owners argue further that "it is not surprising that less indomethacin is being delivered as a solution across the corneal barrier because solutions were generally known to be less effective for delivery of lipophilic drugs such as indomethacin" and that contact time for solutions was known to be poor, contributing to poor drug absorption. PO Resp. 36. Patent Owners argue that because Aviv does not provide details about the specific formulation of INDOPTIC, those of skill in the art would not know whether emulsions provide superior drug delivery. PO Resp. 37. Patent Owners argue that a lack of viscosity enhancers, different buffering agents or pH in INDOPTIC could affect ocular bioavailability. *Id.* (citing Ex. 2047 ¶¶ 59, 60). None of these arguments persuade us that Aviv fails to show greater bioavailability of a drug formulated in an emulsion compared to in a suspension.

For example, in addition to Aviv, Petitioner relies on Kassem (Ex. 1020) to show that emulsions were generally known to provide increased bioavailability. Pet. 57–58. Kassem reports that biovailability of hydrocortisone administered to rabbit eyes as an emulsion was much higher than as a solution. Ex. 1020, 586. Patent Owners challenge the results reported in Kassem for lacking proper controls and details and for comparing emulsions to solutions, not suspensions. PO Resp. 37–38. Nevertheless, Kassem states: "The bioavailability from the emulsions is much higher than that from the solution; within the emulsion systems it is highest for the o/w/o system." Ex. 1020, 586.

To further support its argument for unexpected results, Patent Owners cite to Ellis (Ex. 2010). PO Resp. 38. According to Patent Owners, Ellis reports that the amount of a drug, pilocarpine, delivered from an emulsion was lower than or similar to the amount delivered from an aqueous solution. *Id.* (citing Ex. 2010, 123–26). Nevertheless, Ellis summarizes its findings, by stating that "pilocarpine concentrations were maintained within the aqueous humor of the eye for longer durations with both the gel and emulsion repository preparations than with comparable drop therapy." Ex. 2010, abstract; *see* Pet. Reply 15. The statements in Ellis, like Kassem, tend to support that those of skill in the art would have expected that emulsions allow for greater bioavailability.

Considering all the evidence presented by Patent Owners and Petitioner, we are not persuaded that those of skill in the art would have considered the increased bioavailability in Table 2 of the '319 patent to have been unexpected. The clearest evidence Patent Owners put forth is Dr. Majumdar's use of the term "unexpectedly enhanced." *See* Ex. 2047 ¶ 73. Although a witness's statement may suffice to establish unexpected results, evidence to the contrary must also be considered. *See In re Soni*, 54 F.3d at 751.

As discussed above, Aviv, Kassem, and Ellis indicate that those in the art would have expected some increase in bioavailability with an emulsion. In light of these statements, which were not made for purposes of this proceeding, Dr. Majumdar's single statement is less persuasive. Accordingly, we

are not persuaded that those of skill in the art would have considered the results reported in the '319 patent to have been unexpected.

Long-felt need

Patent Owners argue that the claimed inventions of the '319 patent solved a long-felt but unmet medical need. PO Resp. 52–55. According to Patent Owner, another steroid drug, prednisolone acetate, was available in aqueous suspension for ophthalmic use, but was hard to re-suspend, causing difficulties with administration and patient compliance. *Id.* Patent Owners argue that "[d]espite this need" and the knowledge of difluprednate since 1971, there were no "published uses" of it in an emulsion until the '319 patent issued. *Id.* at 54.

A long-felt need is "is analyzed as of the date of an articulated identified problem and evidence of efforts to solve that problem." *Texas Instruments Inc. v. U.S. Int'l Trade Comm'n*, 988 F.2d 1165, 1178 (Fed. Cir. 1993) (finding evidence to support a long-felt need where the semiconductor industry aggressively embraced the technique of packaging components in plastic by transfer molding between 1957 and 1963 and encountered specific problems in early attempts). Even if the problem of resuspension of a different steroid presented an articulated problem with ophthalmic use of difluprednate, evidence of record does not indicate any efforts to solve this problem occurred before the '319 patent was filed. *See* Pet. Reply 23 (citing PO Resp. 6 ("There were numerous options for a stable, effective, and safe anti-inflammatory eye drop formulation, including

both steroids and non-steroidal anti-inflammatory drugs ('NSAIDs').")). Accordingly, we are not persuaded that the claims of the '319 patent present a problem to a long-felt but unmet need. *See Iron Grip Barbell Co., Inc. v. USA Sports, Inc.,* 392 F.3d 1317, 1325 (Fed. Cir. 2004) ("Absent a showing of long-felt need or the failure of others, the mere passage of time without the claimed invention is not evidence of nonobviousness.").

Industry Acclaim

Patent Owners argue further that the industry acclaim accorded to the drug DUREZOL, which reportedly is encompassed by the claims of the '319 patent, is evidence of the non-obviousness of those claims. PO Resp. 55–57 (citing Exs. 2054, 2058, 2060–62). The praise to which Patent Owners cite is not sufficient to persuade us to find the challenged claims non-obvious. As Petitioner notes (*see* Pet. Reply 23–24), the record does not indicate sufficiently that the praise was based on the use of difluprednate formulated in an emulsion, as claimed, rather than the use of difluprednate itself, which was known in the prior art. For example, Patent Owner cites to Exhibit 2058, which concludes that "[d]ifluprednate ophthalmic emulsion is a potent new pharmaceutical agent that represents a major advance in topical steroid therapy." Ex. 2058, 624; *see* PO Resp. 56. Similarly, the other evidence to which Patent Owner cites praises difluprednate, not the formulation of difluprednate as an emulsion. *See* PO Resp. 56-57 (citing Exs. 2054, 2060–62). Ac-

cordingly, we are not persuaded that evidence of industry praise before us overcomes an otherwise strong showing of obviousness.

Copying

Finally, Patent Owners argue that alleged "deliberate" copying of DUREZOL to make a generic formulation is evidence of the non-obviousness of the claimed emulsions. PO Resp. 57–59. According to Patent Owner, because the inactive ingredients of DUREZOL were copied along with the active ingredient difluprednate, the claimed emulsion would not have been obvious. *Id.* We are not persuaded that the alleged copying here (of a branded product to make a generic version subject to an abbreviated new drug approval (ANDA) process at the FDA) overcomes the strong showing of obviousness in this case. Pet. Reply 25 (discussing the ANDA process); *see also Cable Elec. Prod., Inc. v. Genmark, Inc.*, 770 F.2d 1015, 1028 (Fed. Cir. 1985) (noting that "[i]t is simplistic to assert that copying per se should bolster the validity of a patent" because there may be many reasons for copying, such as a general lack of concern for patent property, contempt for the specific patent in question, or the ability or willingness of the patentee financially or otherwise to enforce the patent right), overruled on different grounds by *Midwest Indus., Inc. v. Karavan Trailers, Inc.*, 175 F.3d 1356 (Fed. Cir. 1999).

6.

Considering all the evidence of obviousness presented by the Petitioner and the evidence to contra-

dict it, including evidence of secondary considerations presented by Patent Owners, we conclude that the preponderance of evidence supports a determination that the emulsions of claims 1 and 18 of the '319 patent would have been obvious under 35 U.S.C. § 103. *See W. Union Co. v. MoneyGram Payment Sys., Inc.*, 626 F.3d 1361, 1373 (Fed. Cir. 2010) ("Moreover, weak secondary considerations generally do not overcome a strong prima facie case of obviousness. . . . Here, where the inventions represented no more than 'the predictable use of prior art elements according to their established functions,' *KSR,* 550 U.S. at 417, 127 S. Ct. 1727, the secondary considerations advanced by Western Union are inadequate to establish nonobviousness as a matter of law.")

7.

Claims 2–4 of the '319 patent recite ratios of the oil, water, and emulsifier components of the emulsion recited in claim 1 compared with the "per part by weight of difluprednate." Ex. 1001, 10:4–52. Petitioner asserts that in Examples 1A and 1E, Ding teaches ratios of oil, water, or emulsifier to drug that would provide similar ratios per part weight of difluprednate. Pet. 38–41, 43–44, 45–46 (citing Ex. 1012, 10:1–10; Ex. 1018 ¶¶ 100, 101). Petitioner also asserts that those of skill in the art would have obtained difluprednate emulsions with the claimed ratios through routine optimization because castor oil and difluprednate were known to affect the properties of an emulsion as results effective variables. Pet. 42–43 (citing Ex. 1018 ¶ 104). Dr. Xia testifies further that this optimization would have required

only laboratory tests known in the art and would have been routine. Ex. 1018 ¶ 105; *see* Pet. 42–43.

We are persuaded by Petitioner's arguments and cited evidence in this regard, and Patent Owners do not argue or direct us to evidence to contradict Petitioner's challenge of claims 2–4.

The preponderance of the evidence supports the conclusion that claim 2–4 of the '319 patent are unpatentable.

8.

Each of claims 6–9 of the '319 patent further defines the emulsifier recited in the difluprednate emulsion of claim 1. Ex. 1001, 10:57–11:3. As the narrowest of these claims,[11] claim 9 is limited to the polyoxyethylenesorbitan fatty acid ester selected from a group including polyoxyethylenesorbitan monooleate. Ex. 1001, 10:65–11:3. As Petitioner argued in regard to the obviousness of claim 1, Ding teaches emulsions with polyoxyethylene (20) sorbitan (polysorbate 80). Pet. 48–49 (citing Ex. 1012, 1:8–14, 8:7–10, 22–25; Ex. 1018 ¶ 117).

We are persuaded by Petitioner's arguments and cited evidence in this regard, and Patent Owners do

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[11] Claim 6 recites: "The emulsion of claim 1, wherein the emulsifier comprises a surfactant." Claim 7 recites: "The emulsion of claim 6, wherein the surfactant is a nonionic surfactant." Claim 8 recites: "The emulsion of claim 7, wherein the nonionic surfactant is a member selected from the groups consisting of polyoxyethylene hydrogenated castor oil and a polyoxyethylenesorbitan fatty acid ester." Ex. 1001, 10:57–64.

not argue or direct us to evidence to contradict Petitioner's challenge of claims 6–9.

The preponderance of the evidence supports the conclusion that claim 6–9 of the '319 patent are unpatentable.

9.

Claims 10 and 12–14 of the '319 patent depend on claims 1, 2, 3, and 4, respectively, and are limited to oil-in-water type emulsions. Ex. 1001, 11:4–12:2. Petitioner argues that Ding teaches such emulsions because it teaches preparing emulsions by "dispersing the oil phase in water." Pet. 49 (citing Ex. 1012, 5:25–28). Petitioner also argues that because water makes up the vast majority of the liquid in the emulsions taught in Ding, they are oil-in-water type emulsions. Pet. 49.

We are persuaded by Petitioner's arguments and cited evidence in this regard, and Patent Owners do not argue or direct us to evidence to contradict Petitioner's challenge of claims 10 and 12–14.

The preponderance of the evidence supports the conclusion that claims 10 and 12–14 of the '319 patent are unpatentable.

I. CONCLUSION

We determine that Petitioner has shown claims 1–4, 6–10, 12–14, and 18 are unpatentable under 35 U.S.C. § 103(a) over the '848 patent and Ding.

IV. ORDER

Petitioner has demonstrated, by a preponderance of the evidence, that claims 1–4, 6–10, 12–14,

and 18 of the '319 patent are unpatentable over the '848 patent and Ding under 35 U.S.C. § 103(a).

In consideration of the foregoing, it is hereby:

ORDERED that claims 1–4, 6–10, 12–14, and 18 of the '319 patent have been shown to be unpatentable;

This is a final decision. Parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

KATZ, *Administrative Patent Judge, additional views*

I write separately to express my view that Patent Owners have failed to meet their burden of showing that any unexpected results regarding intraocular pressure and other adverse events or any industry acclaim has a nexus to the features of claimed invention that make it patentable over the prior art. Specifically, Patent Owners failed to show that these unexpected results and industry acclaim were due to the formulation of difluprednate specifically as an emulsion and not due to difluprednate itself. Under the current case law, it is Patent Owners' burden to show that evidence of secondary considerations are attributable to something disclosed in the patent that was not available in the prior art. *Cf. J.T. Eaton & Co. v. Atl. Paste & Glue Co.*, 106 F.3d 1563, 1571-72 (Fed. Cir. 1997) ("If [Patent Owner] Eaton can demonstrate that the commercial

success of its product derives from the claimed invention and *is attributable to something disclosed in the patent that was not readily available in the prior art*, it is entitled, on the record in this case, to the presumption that the commercial success of its product is attributable to its patented invention.") (emphasis added); *see In re Baxter Travenol Labs.*, 952 F.2d 388, 391-92 (Fed. Cir. 1991) ("Baxter also argues that commercial success and unexpected results rebut a prima facie finding of obviousness. Since Baxter has not effectively argued that these particular claims differ from what is disclosed in [the prior art], this argument must fail."); *see also Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010) (rejecting patentee's contention that secondary considerations of obviousness are sufficient to nonobviousness because the "case law clearly establishes that the patentee must establish a nexus between the evidence of commercial success and the patented invention" but "Wyers relies solely on Master Lock's $20 million in sales of the accused product, and established no direct nexus to the sleeve feature." (citing *In re Huang,* 100 F.3d 135, 140 (Fed. Cir. 1996); *In re GPAC Inc.,* 57 F.3d 1573, 1580 (Fed. Cir. 1995))).

For PETITIONER:

Eldora L. Ellison
Chandrika Vira
Ralph W. Powers III
STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

eellison-PTAB@skgf.com
cvira-PTAB@skgf.com
tpowers-PTAB@skgf.com

For PATENT OWNER:

John Kappos
Filko Prugo
O'MELVENY & MYERS LLP
jkappos@omm.com
fprugo@omm.com

APPENDIX C

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

SENJU PHARMACEUTICAL CO., LTD,
MITSUBISHI CHEMICAL CORPORATION,
Appellants

v.

AKORN, INC.,
Appellee

2017-1511

Appeal from the United States Patent and Trademark Office, Patent Trial and Appeal Board in No. IPR2015-01205.

ON PETITION FOR PANEL REHEARING AND REHEARING EN BANC

Before PROST, *Chief Judge*, NEWMAN, LOURIE, DYK, MOORE, O'MALLEY, REYNA, WALLACH, TARANTO, CHEN, HUGHES, and STOLL, *Circuit Judges*.

PER CURIAM.

ORDER

Appellants Mitsubishi Chemical Corporation and Senju Pharmaceutical Co., Ltd. filed a combined peti-

tion for panel rehearing and rehearing en banc. A response to the petition was invited by the court and filed by Appellee Akorn, Inc. The petition was referred to the panel that heard the appeal, and thereafter the petition for rehearing en banc was referred to the circuit judges who are in regular active service.

Upon consideration thereof,

IT IS ORDERED THAT:

The petition for panel rehearing is denied.

The petition for rehearing en banc is denied.

The mandate of the court will issue on December 18, 2018.

FOR THE COURT

December 11, 2018
Date

/s/ Peter R. Marksteiner
Peter R. Marksteiner
Clerk of Court