PETITION FOR INTER PARTES REVIEW OF
U.S. PATENT NO. 8,642,556
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I. INRODUCTION

Pursuant to the provisions of 35 U.S.C. § 311 and § 6 of the Leahy-Smith America Invents Act (“AIA”), and to 37 C.F.R. Part 42, Teva Pharmaceuticals USA, Inc. (“Petitioner” or “Teva”) hereby requests review of U.S. Patent No. 8,642,556 to Acheampong et al. (“the ’556 patent,” EX1001) that issued on February 4, 2014. PTO records indicate the ’556 patent is assigned to Allergan, Inc. (“Patent Owner”). This Petition demonstrates that there is a reasonable likelihood that claims 1-20 of the ’556 patent are unpatentable for failure to distinguish over the asserted prior art. Additional petitions are being filed to address related patents that are assigned to Patent Owner. All challenged patents are continuations from the same family and are terminally disclaimed over one another. The patents claim an ophthalmic emulsion for the treatment of overlapping ocular disorders, or conventional methods of administering the emulsion.

The ’556 patent claims a topical ophthalmic emulsion as in related U.S. Patent No. 8,685,930, but further recites a comparative clause, where an effect of the emulsion is compared to a prior art emulsion. Yet each element of the claimed emulsion, including the claimed cyclosporin A (“CsA”) and castor oil percentages and other standard emulsion ingredients, was disclosed in a single prior art reference (Ding ’979) for the same therapeutic uses, i.e., treating dry eye disease.
During prosecution of a parent application, applicants even admitted that the claimed emulsion containing 0.05% CsA and 1.25% castor oil “is squarely within the teaching of the Ding [‘979] reference” and “would have been obvious” to a person of skill in the art at the time of the invention. EX1005, 0435; EX1025, ¶18.

Four years later, in prosecuting the ’556 patent as a continuation application, applicants changed course and attempted to withdraw these admissions. EX1004, 0007. They argued that data collected after their earlier admissions established patentability because of an alleged unexpected result that the emulsion was “equally or more therapeutically effective for the treatment of dry eye/keratoconjunctivitis sicca than the formulation containing 0.10% by weight cyclosporin A and 1.25% by weight castor oil.” EX1004, 0007, 0205; EX1025, ¶¶20-22. But the supposed “unexpected results” are weak, at best, and fail to rebut the strong evidence of obviousness. The data relied upon by applicants lack scientific parameters necessary to demonstrate statistical significance and materiality and, in many cases, appear to be copies of previously published graphs from a 102(b) prior art reference, Sall. Thus, Patent Owner’s cited evidence does not support non-obviousness of the claims, and merely confirms that the results were already disclosed in the prior art.
II. **Overview**

The Board has already issued its Decision Instituting *Inter Partes* Review ("Decision") on all challenged claims of the ’556 patent on the same grounds raised herein.

**Ground 1:** Claims 1–20 under 35 U.S.C. § 102(b) as anticipated by Ding ’979,

**Ground 2:** Claims 1–20 under 35 U.S.C. § 103(a) as obvious over Ding ’979 and Sall,

**Ground 3:** Claims 14 and 19 under 35 U.S.C. § 103(a) as obvious over Ding ’979, Sall, and Glonek,

**Ground 4:** Claims 11, 18, and 20 under 35 U.S.C. § 103(a) as obvious over Ding ’979, Sall, and Acheampong,

**Ground 5:** Claim 19 under 35 U.S.C. § 103(a) as obvious over Ding ’979, Sall, Glonek, and Acheampong.

*Mylan Pharmaceuticals Inc. v. Allergan Inc.*, IPR2016-01129 (Paper No. 8).

Petitioner Teva hereby files its own petition on the same grounds and concurrently seeks to join the instituted IPR proceedings on these challenged claims.

**A. Brief Overview of the ’556 Patent**

The ’556 patent has an earliest claimed priority date of September 15, 2003. Independent claim 1 recites an emulsion of 0.05% CsA, 1.25% castor oil,
polysorbate 80, acrylate/C10-30 alkyl acrylate cross-polymer (“cross-polymer”) and water that is therapeutically effective in treating dry eye disease and “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.” Claims 2-6 and 9-10 recite that the emulsion comprises a tonicity or demulcent agent, specifically glycerine, and/or a buffer, specifically sodium hydroxide. Claim 12 specifies a range of pH values for the emulsion of claim 6. Claims 7-8 are dependent claims that specify known weight percentages of polysorbate 80 and cross-polymer, respectively. Claim 11 recites that when the emulsion is administered to the eye there is substantially no detectable concentration of CsA in the blood.

Claims 13-15 are independent claims reciting the same emulsion ingredients as in claim 1. Claim 13 additionally recites that the emulsion is therapeutically effective in treating dry eye disease, and “achieves at least as much therapeutic effectiveness” as a second emulsion comprising 0.1% CsA and 1.25% castor oil. Claim 14 further recites that the emulsion “breaks down more quickly,” thereby reducing vision distortion, as compared to a second emulsion that contains only about 50% as much castor oil. Claims 15 further recites that the emulsion “demonstrates a reduction in adverse events” relative to a 0.1% CsA / 1.25% castor oil emulsion. Dependent claims 16 and 17 respectively specify that the adverse
events are side effects and that the side effects are visual distortion or eye irritation. Claims 18, 19, and 20 respectively depend from claims 12, 14, and 15, and further specify that when the emulsion is administered there is “substantially no detectable concentration of cyclosporin A” in the human’s blood.

B. Brief Overview of the Prosecution History

U.S. Patent Application No. 13/967,189 (“the ’189 application”) was filed on August 14, 2013, and issued six months later on February 4, 2014, as the ’556 patent. The ’189 application is a continuation, via U.S. applications 13/961,808 and 11/897,177, of U.S. application 10/927,857 (“the ’857 application,” EX1005), and claims the benefit of U.S. provisional application 60/503,137, filed September 15, 2003.

During prosecution of the related ’857 application, Patent Owner admitted that Composition II, which is identical to the emulsion claimed in the ’556 patent (EX1025, ¶¶18-19), was “squarely within the teachings of Ding [’979]”:

The applicants concede that it would have been obvious to modify examples 1A-1E of the Ding reference to arrive at Composition II of the present application. The differences are insignificant.... As the examiner correctly observes, one of ordinary skill in the art “would readily envisage” such a composition, especially in view of Example 1B: having selected 0.05% as the concentration of cyclosporin, Example 1B (wherein the ratio of cyclosporin to castor oil is 0.04) teaches that the concentration of castor oil should be 1.250% (0.05% / 1.250% = 0.04). The applicants concede that in making this selection (0.05% cyclosporin and 1.250% castor oil) there would have been a reasonable expectation of success; the differences between Examples 1A-1E and Composition II are too small to believe otherwise.
The formulation of Composition II is squarely within the teachings of the Ding reference, and the Office should disregard any statements by the applicants suggesting otherwise.

EX1005, 0435 (emphases added).

During prosecution of the ’189 application, the applicants acknowledged their prior admissions, but claimed that they had collected evidence to support the patentability of the claims “since these comments have been filed.” EX1004, 0007. The examiner then rejected the claims as obvious over Ding ’979. Id. at 0136-40. Patent Owner responded to the rejection, nakedly asserting that “the prima facie case of obviousness has not been properly established,” but arguing that the claims were patentable based on objective indicia. Id. at 0200. It also filed a terminal disclaimer for the applications or parent applications that resulted in the ’930, ’111, ’162, ’048, and ’191 patents. Id. at 0122-23.

In remarks accompanying a Notice of Allowance (id. at 0408; EX1025, ¶23) the examiner stated that applicants had failed to demonstrate commercial success or long-felt need. EX1004, 0417-19. However, relying on declarations submitted by Drs. Schiffman and Attar, the examiner concluded that, “the specific combination of 0.05% by weight cyclosporin A with 1.25% by weight castor oil is surprisingly critical for therapeutic effectiveness in the treatment of dry eye or keratoconjunctivitis sicca,” and therefore, “demonstrate[s] surprising and unexpected results.” Id. at 0421.
The alleged “unexpected results” are addressed in the declaration of Dr. Walter Chambliss that accompanies this Petition. EX1025, ¶¶145-69. As noted by Dr. Chambliss, the data presented by applicants lacked scientific parameters necessary to demonstrate statistical significance and materiality. In many cases, the data appear to be repackaged from graphs published in the prior art Sall reference that is presently asserted against the claims. Thus, the declarations do not support a finding of surprising or unexpected results. Id.

During prosecution, the Patent Owner did not identify, and the examiner did not address, deficiencies in the Schiffman and Attar Declarations discussed in this Petition that made them unreliable. As such, and because of the new information presented herein and supported by Dr. Chambliss’s testimony, the examiner’s conclusions based on one-sided information should not receive any deference by the Board.

In addition to demonstrating the flaws in Patent Owner’s alleged unexpected results, Dr. Chambliss’s declaration also provides insight not previously presented to the Patent Office about how a person of ordinary skill in the art would interpret the disclosure of Ding ’979. Among other things, Dr. Chambliss’s testimony establishes that the presently claimed emulsion would have been immediately apparent to one of ordinary skill in the art based on Ding ’979. EX1025, ¶¶97-98, 114. The Patent Owner’s alleged evidence of unexpected results cannot render

Further, this Petition presents new arguments based on expert testimony as to why the claims are obvious over Ding ’979 and other references that were not substantively analyzed during prosecution. Among other things, Dr. Chambliss explains that the 1.25% castor oil emulsion vehicle of Example 2C in Ding ’979 was the only vehicle that was most preferred for both the 0.05% and 0.10% CsA emulsions, and that Sall’s 0.05% and 0.10% CsA emulsions used the same castor oil vehicle. Petitioner provides an even stronger *prima facie* obviousness case than the examiner considered during prosecution. Accordingly, the Board should institute review without deference to the limited analysis during prosecution.

**C. Brief Overview of the Scope and Content of the Prior Art**

A prior art reference anticipates a claim if it discloses all of the elements of the claim in the claimed combination, or if the claimed combination would be “immediately apparent to one of ordinary skill in the art,” or “at once envisaged” from the prior art reference. *Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC*, 683 F.3d 1356, 1361 (Fed. Cir. 2012). In obviousness cases, *Graham v. John Deere Co. of Kansas City*, requires an evaluation of any differences between the claimed subject matter and the asserted prior art. 383 U.S. 1, 17-18 (1966). As noted in *KSR Int’l Co. v. Teleflex Inc.*, the obviousness inquiry may account for inferences
that would be employed by a person of ordinary skill in the art. 550 U.S. 398, 418 (2007).

i. U.S. Patent No. 5,474,979 to Ding et al. (“Ding ’979,” EX1006)

Ding ’979 issued on December 12, 1995, and is prior art under 35 U.S.C. § 102(b). EX1006. Ding ’979 teaches topical ophthalmic emulsions for the treatment of keratoconjunctivitis sicca (“KCS” or “dry eye disease/KCS”). Id. at 5:9-12; EX1025, ¶61. Claims 7-8 recite emulsions containing 0.05-0.40% CsA in 0.625-5.00% castor oil, 1.00% polysorbate 80, 0.05% Pemulen® (an acrylate/C10-30 alkyl acrylate cross-polymer), 2.20% glycerine, sodium hydroxide, and water, and having a pH range of 7.2-7.6. EX1006, 4:4-5; id. at 6:27-42; EX1025, ¶64. Ding ’979 teaches that CsA is effective in treating dry eye disease “as an immunosuppressant and in the enhancement or restoring of lacrimal gland tearing.” EX1006, 1:10-16, 37-39.

Ding ’979 discloses four examples of castor oil-based vehicles (Examples 2A-D) for delivery of CsA. EX1006, 4:44-54; EX1025, ¶65. Example 2C is the exact same castor oil vehicle used in the challenged claims. Ding ’979 also discloses CsA-containing emulsions in Example 1 using the vehicles from Example 2. EX1006, 4:32-54. The emulsions in Example 1 have CsA percentages and castor oil percentages covering the ranges disclosed in claims 7 and 8 (0.05% - 0.40% CsA and 0.625% - 5.00% castor oil) of Ding ’979. Id. at 4:32-43; EX1025,
¶66-67. One emulsion (Example 1D) specifically used the 1.25% castor oil vehicle (Example 2C) to deliver 0.10% CsA. EX1006, 4:32-43.

Ding ’979 explicitly sets forth a “more preferred” range for the ratio of CsA to castor oil of 0.02-0.12. *Id.* at 3:17-20; EX1025, ¶67. Each of the exemplified CsA-containing emulsions in Ding ’979 fall within an even narrower ratio range of 0.04-0.08, which, for the 1.25% castor oil vehicle (Example 2C) disclosed in Ding ’979, equates to a CsA range of 0.05% to 0.10% CsA. EX1006, 4:32-43; EX1005, 0435; EX1025, ¶¶67, 97.

ii. **Sall et al., Two Multicenter, Randomized Studies of the Efficacy and Safety of Cyclosporine Ophthalmic Emulsion in Moderate to Severe Dry Eye Disease, 107 OPHTH. 631 (2000) (EX1007)**

Sall is prior art under 35 U.S.C. § 102(b). Sall describes a multi-center, randomized, double-masked Phase 3 clinical trial that assesses the safety and efficacy of increasing tear production and treating dry eye disease/KCS by twice-daily ophthalmic administration of 0.05% or 0.10% CsA in a castor oil emulsion, compared to the emulsion vehicle without CsA in the same regimen. EX1007, 631-32 & n.1; *id.* at figs. 1-4; EX1025, ¶¶73-74. Sall teaches that the 0.05% CsA emulsion was safe and effective, was at least as effective as the 0.10% CsA emulsion, and resulted in fewer adverse side effects and in trough CsA blood concentrations below 0.1 ng/mL. EX1007, 631, 634-37; EX1025, ¶¶73-80. Sall does not expressly disclose the exact composition of the castor oil vehicle, but
compares the 0.05% and 0.10% CsA emulsions to the same vehicle. EX1007, 632; EX1025, ¶73, 120.

iii. A. 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, 2 LACRIMAL GLAND, TEAR FILM, AND DRY EYE SYNDROMES 1001 (1998) (“Acheampong,” EX1008)

Acheampong is prior art under 35 U.S.C. § 102(b). Acheampong describes a study in which CsA percentages ranging from 0.05%-0.4% were administered to human patients with dry eye disease. EX1008 at 1002; EX1025, ¶¶85-86. Acheampong measured CsA blood concentration at both peak and trough levels following topical ophthalmic administration. EX1008 at 1002. No detectable amount of CsA was measured in patients receiving the 0.05% CsA emulsion. EX1008 at 1002, 1004; EX1025, ¶¶85-86.


Glonek issued Nov. 6, 1996 and is prior art under 35 U.S.C. § 102(b). EX1009. Glonek teaches that “an emulsion over the surface of the eye is expected to cause blurring. The duration of the blurring is dependent upon the time required for the emulsion to differentiate and form separate layers.” EX1009, 6:37-40; EX1025, ¶88. Glonek discloses topical emulsions for the treatment of dry eye disease, “whereby blurred vision is reduced.” EX1009, 3:5-6; EX1025, ¶88. In comparing the relative amounts of surfactant and oil and their effects on visual
blurring, Glonek teaches that higher concentrations of oil lead to faster differentiation and decreased blurring. EX1009, 20:24-30; EX1025, ¶89.

D. Brief Overview of the Level of Skill in the Art

A person of ordinary skill in the relevant field as of September 15, 2003 would likely have some combination of: (a) experience formulating pharmaceutical products; (b) experience designing and preparing drug emulsions intended for topical ocular administration; and (c) the ability to understand results and findings presented or published by others in the field. EX1025, ¶36. Typically this person would have an advanced degree, such as a medical degree, or a Ph.D. in organic chemistry, pharmaceutical chemistry, medicinal chemistry, pharmaceutics, physical pharmacy, or a related field, or less education but considerable professional experience in these fields. Id. at ¶35.

Dr. Chambliss received a Ph.D. in Pharmaceutical Science/Biomaterials Science from Purdue University in 1992, and he has extensive experience with ophthalmic pharmaceutical emulsions, including castor oil emulsions. EX1025, ¶¶2-4; EX1026. Dr. Chambliss is well qualified as an expert, possessing the necessary scientific, technical, and other specialized knowledge and training to assist in an understanding of the evidence presented herein, as well as possessing the expertise necessary to determine and explain the level of ordinary skill in the art as of September 2003. EX1026.
III. **GROUNDS FOR STANDING**

Petitioner certifies that, under 37 C.F.R. § 42.104(a), the ’556 patent is available for *inter partes* review, and Petitioner is not barred or estopped from requesting *inter partes* review of the ’556 patent on the grounds identified.

IV. **Mandatory Notices under 37 C.F.R. § 42.8**

**Real Parties-in-Interest** (37 C.F.R. § 42.8(b) (1)): Teva Pharmaceuticals USA, Inc. is a real party-in-interest. Teva Pharmaceuticals USA, Inc. is a subsidiary of Teva Pharmaceuticals Industries, Inc.

**Related Matters** (37 C.F.R. § 42.8(b) (2)): Petitioner indicates that the following judicial matters may affect or be affected by a decision in this proceeding:

An IPR petition for the ’556 patent was previously filed by Apotex Corp. and Apotex Inc. as IPR2015-01286, as were petitions for the related patents U.S. Patent Nos. 8,648,048 (IPR2015-01284), 8,629,111 (IPR2015-01282), 8,633,162 (IPR2015-01278), and 8,685,930 (IPR2015-01283), but all were terminated prior to an institution decision.

An IPR petition for the ’556 patent was previously filed by Mylan as IPR2016-01129 and has been instituted.

IPR petitions for the related patents 8,685,930 (IPR2016-01127), 8,629,111 (IPR2016-01128), 8,633,162 (IPR2016-01130), 8,648,048 (IPR2016-01131), and
9,248,191 (IPR2016-01132) have been filed by Mylan and have been instituted. U.S. Application No. 15/011,159, filed January 29, 2016, claims the benefit of U.S. Application No. 14/222,478 (the ’191 patent), which is a continuation, via U.S. Application Nos. 13/961,828 and 11/897,177, of the ’857 application.

Teva filed IPR petitions for the related patents 8,685,930 (IPR2017-00), 8,642,556 (IPR2017-00579), 8,633,162 (IPR2017-00583), 8,648,048 (IPR2017-00585), and 9,248,191 (IPR2017-00586) on the same grounds and concurrently seeks to join these instituted IPR proceedings on the same challenged claims.

Petitioner and other entities are involved in litigation over the ’556 patent and related patents in the action styled Allergan, Inc. v. Teva Pharmaceuticals USA, Inc., et al., No. 2:15-cv-01455, filed by Allergan, Inc. in the Eastern District of Texas (EX1023). Petitioner also identifies the following pending actions involving the ’556 patent: Allergan, Inc., v. Innopharma, Inc. and Pfizer, Inc., No. 2:15cv1504, in the Eastern District of Texas.

Lead and Back-Up Counsel (37 C.F.R. § 42.8(b) (3)):

Lead Counsel: Gary J. Speier (Reg. No. 45,458)

Back-Up Counsel: Mark D. Schuman (Reg. No. 31,197)

Service Information (37 C.F.R. § 42.8(b) (4)):

Petitioner hereby consents to electronic service.
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V. STATEMENT OF THE PRECISE RELIEF REQUESTED

Petitioners request review of claims 1-20 of the ’556 patent under 35 U.S.C. § 311 and AIA § 6 and that each of the claims be canceled as unpatentable:

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<tr>
<th>Ground</th>
<th>Claims</th>
<th>Description</th>
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<tr>
<td>1</td>
<td>1-20</td>
<td>Anticipated under §102 by Ding ’979</td>
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<tr>
<td>2</td>
<td>1-20</td>
<td>Obvious under §103 over Ding ’979 and Sall</td>
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<td>3</td>
<td>14 and 19</td>
<td>Obvious under §103 over Ding ’979, Sall, and Glonek</td>
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<td>4</td>
<td>11, 18, and 20</td>
<td>Obvious under §103 over Ding ’979, Sall, and Acheampong</td>
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<tr>
<td>5</td>
<td>19</td>
<td>Obvious under §103 over Ding ’979, Sall, Glonek, and Acheampong</td>
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VI. STATEMENT OF NON-REUNDANCY

Each of the five Grounds raised in this Petition is meaningfully distinct. Ground 1 asserts anticipation of claims 1-20 by Ding ’979. Ground 2 asserts obviousness of claims 1-20 based on Ding ’979 and Sall. Sall expressly teaches certain properties intrinsic to the claimed emulsion, including efficacy, relative efficacy, relative adverse events, and substantially no detectable blood concentration at trough levels, and provides additional reasons to make and use the claimed emulsion to treat dry eye disease. Ground 3 challenges claims 14 and 19 based on Ding ’979, Sall, and Glonek. Glonek expressly teaches the reduction in blurring from more rapid emulsion break down, and the relationship between break down rate and oil concentration. Ground 4 asserts the obviousness of dependent claims 11, 18, and 20, based Ding ’979, Sall, and Acheampong. Acheampong expressly teaches the claimed emulsion results in substantially no detectable blood concentration at trough and peak levels. Ground 5 challenges dependent claim 19 based on Ding ’979, Sall, Glonek, and Acheampong based on the properties taught therein.

VII. CLAIM CONSTRUCTION

In an inter partes review, a claim in an unexpired patent is given its broadest reasonable construction in light of the specification. 37 C.F.R. § 42.100(b); In re Cuozzo Speed Techs., LLC, 793 F.3d 1268, 1275-1280 (Fed. Cir. 2015), cert.
granted sub nom. Cuozzo Speed Techs., LLC v. Lee, 2016 U.S. LEXIS 632 (U.S. Jan. 15, 2016) (No. 15-446). Claims terms are also “generally given their ordinary and customary meaning,” which is the meaning that the term would have to a person of ordinary skill in the art at the time of the invention in view of the specification. In re Translogic Tech., Inc., 504 F.3d 1249, 1257 (Fed. Cir. 2007). Under either standard, there is a reasonable likelihood that Petitioner will prevail with respect to the challenged claims. A few terms are discussed below.

A. “buffer”

The term “buffer” appears in claims 4-6, 9-10 of the ’556 patent. Claims 5 and 10 state “the buffer is sodium hydroxide.” The patent states, “[t]he pH of the emulsions can be adjusted in a conventional manner using sodium hydroxide ... to a physiological pH level.” EX1001, 13:4-6. In light of the specification, the broadest reasonable interpretation of the term “buffer” includes sodium hydroxide. EX1025, ¶38.

B. “substantially no detectable concentration”

The term “substantially no detectable concentration” appears in claims 11 and 18-20 of the ’556 patent with regard to measuring CsA in human blood. According to the specification, “[c]yclosporin component concentration in blood preferably is determined using a liquid chromatography-mass spectroscopy-mass spectroscopy (LC-MS/MS), which test has a cyclosporin component detection
limit of 0.1 ng/ml. Cyclosporin component concentrations below or less than 0.1 ng/ml are therefore considered substantially undetectable.” EX1001, 5:36 – 6:5. A skilled artisan could measure blood concentration at either peak or trough levels. EX1025, ¶39. In light of the specification, the broadest reasonable interpretation of the phrase “substantially no detectable concentration” includes a blood concentration below 0.1 ng/mL measured at either peak or trough levels.

C. “effective amount,” “therapeutically effective,” “overall efficacy,” and “therapeutic effectiveness”

Independent claims 1 and 13 state that the emulsion is “therapeutically effective in treating dry eye disease.” Claim 11 further recites administering “an effective amount in treating dry eye disease.” Keratoconjunctivitis sicca (“KCS”), an “inflammation of the conjunctiva and of the cornea” that is “associated with decreased tears,” is a species of, and is often used interchangeably with, or as a partial synonym of, dry eye disease. EX1022, 0003 (keratoconjunctivitis sicca); EX1025, ¶40, 47. The ’556 patent teaches that CsA “acts to enhance or restore lacrimal gland tearing in providing the desired therapeutic effect.” EX1001, 9:39-40. During prosecution, Patent Owner relied on an increase in tearing to assert unexpected therapeutic efficacy of the claimed emulsion for treating dry eye disease/KCS. EX1004, 0200-02; EX1025, ¶40. Thus, in the context of the ’556 patent, an emulsion effective in increasing tear production is an example of an emulsion therapeutically effective in treating dry eye disease.
Claims 1 and 13 respectively state that the emulsion “provides overall efficacy substantially equal to” and “achieves at least as much therapeutic effectiveness” as a second emulsion with 0.10% CsA and 1.25% castor oil. The plain meaning of the word “therapeutic” includes palliative (remediating) treatments as well as curative treatments. EX1025, ¶¶41-42; EX1022, 0007 (therapeutic), 0004 (palliative), 0005 (remedy). Accordingly, the broadest reasonable interpretation of these terms include palliative treatments as well as curative treatments.

D. **“adverse events” and “side effects”**

Claim 15 recites that the emulsion has fewer “adverse events” relative to a second emulsion, and claims 16-17 further recites that the “adverse events” are “side effects” and that the side effects may be “visual distortion” or “eye irritation.” The specification also defines adverse events to include “undesirable side effects.” EX1001, 15:51-58. The plain meaning of “side effects” is “A result of a drug or other therapy in addition to or in extension of the desired therapeutic effect; usually but not necessarily, denoting an undesired effect.” EX1022, 0006 (side effect). The broadest reasonable interpretation of the term “adverse events” thus includes undesirable side effects, including burning eye, stinging eye, and general eye pain. EX1025, ¶43.
E. “break down”

Claim 14 recites that the first emulsion “breaks down” more quickly in the eye of a human as compared to a second emulsion containing only 50% as much castor oil. The ’556 patent states that “a relatively high concentration of hydrophobic component is believed to provide for a more quick or rapid breaking down or resolving of the emulsion in the eye, which reduces vision distortion which may be caused by the presence of the emulsion in the eye and/or facilitates the therapeutic effectiveness of the composition.” EX1001, 2:42-48. As explained by Dr. Chambliss, a person of ordinary skill would understand the term “breaks down” as used in claim 14 to include that the emulsion differentiates into separate aqueous and oil layers on the eye. EX1025, ¶44.

VIII. Background Knowledge in the Art Prior to September 15, 2003

The background publications below reflect knowledge skilled artisans would bring to bear in reading the prior art at the time of the invention, i.e., September 15, 2003, and thereby assist in understanding why one would have been motivated to combine or modify the references as asserted in this Petition. Ariosa Diagnostics v. Verinata Health, Inc., No. 15-1215, slip op. 1, 11-12 (Fed. Cir. Nov. 16, 2015). As established in KSR, 550 U.S. at 406, the knowledge of a skilled artisan is part of the store of public knowledge that must be consulted when considering whether a
claimed invention would have been obvious. Randall Mfg. v. Rea, 733 F.3d 1355, 1362-63 (Fed. Cir. 2013).

Prior to September 15, 2003, it was known that inflammation contributed to dry eye diseases such as KCS. E.g., K. Kunert et al., Analysis of Topical Cyclosporine Treatment of Patients with Dry Eye Syndrome 118 ARCH. OPTHALMOL. 1489 (2000) (“Kunert,” EX1012); EX1025, ¶47. CsA, a known anti-inflammatory agent, had been shown to significantly reduce inflammation markers associated with dry eye upon topical ophthalmic administration. EX1012, 1489; EX1025, ¶48. Dry eye disease was defined in the art as, “a deficiency in either the aqueous or mucin components of the precorneal tear film. The most commonly encountered aqueous-deficient dry eye in the United States is keratoconjunctivitis sicca.” Medications for Dry Eye (1999) In PHISICIANS’ DESK REFERENCE FOR OPHTHALMOLOGY (27th ed.) Montvale, NJ: PDR Network (“Ophthalmic PDR,” EX1013) at 13. The Ophthalmic PDR also notes that a topical CsA therapy, Sandimmune®, was readily available, and was prescribed for ocular disorders including conjunctivitis and keratitis. Id. at 18; EX1025, ¶49.

Clinical trials establishing the efficacy and safety of CsA-in-castor oil emulsions for treatment of dry eye disease were known prior to September 2003. EX1025, ¶48. Several clinical studies were performed in the late 1990’s and early 2000’s. For example, Kunert established a decrease in lymphocyte activation
markers after topical ophthalmic administration of 0.05% CsA in a castor oil emulsion, teaching that treatment with 0.05% CsA in castor oil “may help to reduce the pathophysiological factors contributing to the development of KCS.”

EX1012, 1495. Turner established that the 0.05% CsA-in-castor oil emulsion was at least as effective in decreasing inflammation markers as the 0.10% CsA-incastor oil emulsion. K. Turner et al., Interleukin-6 Levels in the Conjunctival Epithelium of Patients with Dry Eye Disease Treated with Cyclosporine Ophthalmic Emulsion 19 CORNEA 492 (2000) (EX1014) at 492; EX1025, ¶¶48, 51. Stevenson conducted a Phase 2 clinical trial, and states that 0.05% and 0.10% CsA-in-castor oil emulsions were “the most appropriate formulations ... because no additional benefits were observed with the higher concentrations.” D. Stevenson et al. Efficacy and Safety of Cyclosporin A Ophthalmic Emulsion in the Treatment of Moderate-to-Severe Dry Eye Disease 107 OPHTHALMOL. 967 (2000) (“Stevenson,” EX1015) at 967.

It was further known that for effective topical ophthalmic treatment, “[t]issue concentrations [of CsA] in excess of minimal therapeutic levels (50 to 300 ng CsA/g tissue)” must be achieved. R. Kaswan, Intraocular Penetration of Topically Applied Cyclosporine 20 TRANSPL. PROC. 650 (1988) (“Kaswan,” EX1011) at 652. Tissue concentrations well in excess of this therapeutic range were achieved by Kaswan following topical ophthalmic administration of CsA in
an olive oil emulsion. However, it was known in the art that “CsA [in] castor oil drops resulted in higher concentrations of the drug in the aqueous humor and cornea than when CsA [in] olive oil drops were used.” A. Kanpolat et al., Penetration of Cyclosporin A into the Rabbit Cornea and Aqueous Humor after Topical Drop and Collagen Shield Administration 20 CLAO J. 119 (1994) (“Kanpolat,” EX1018) at 121; EX1025, ¶51. As conceded by Allergan’s experts during prosecution, “[i]t was known in the art at the time this application was filed that cyclosporin could be administered topically locally to the eye to target and treat dry eye by using cyclosporin A’s immunomodulatory properties[.]” EX1004, 0218, 0242; EX1025, ¶¶146-47.


Ding ’607 (EX1010) discloses topical ophthalmic emulsions containing castor oil for the “treatment of keratoconjunctivitis sicca (dry eye) syndrome.”
EX1010, 6:25-26. Ding ’607 teaches that these emulsions possess “a high comfort level and low irritation potential suitable for delivery of medications to sensitive areas such as ocular tissues,” (id. at 3:32-36), and that additional active agents can be added to increase the therapeutic efficacy of the emulsion. Id. at 3:48-52; EX1025, ¶¶53-54. Ding ’607 reports significant improvement in KCS severity as measured by various tests such as the Schirmer Tear Test, as well as corneal and conjunctival staining. Ding ’607 further establishes a correlation between the amount of castor oil in the emulsion and the mean ocular residence time of the emulsion, teaching, “long retention of the higher fatty acid glyceride [castor oil] when the emulsion is instilled into an eye. This in turn can retard water evaporation from the eye which alleviates dry eye symptoms.” EX1010, 3:66—4:3; EX1025, ¶54.

Clinical trials conducted prior to September 2003, also established that castor oil provided a “large therapeutic effect” to patients suffering from dry eye disease. EX1014, 492; EX1015, 973; EX1025, ¶55. This “therapeutic effect of the [castor] oil-in-water vehicle” was “expected, as topical application of certain lipid mixtures can accelerate epidermal barrier recovery after defined barrier insults in mice.” EX1014, 496. Further, the art also identified the anti-inflammatory properties of ricinoleic acid, the main component of castor oil, accounting for about 90% of castor oil, in providing direct relief of chronic dry eye syndromes. A.

The efficacy of the castor oil vehicle described in Turner (EX1014) was said to have led to denial of regulatory approval for Allergan’s dry eye treatment Restasis® in the late 1990’s. EX1025, ¶56; R. Murphy, *The Once and Future Treatment of Dry Eye*, REVIEW OF OPTOMETRY 1 (2000) (“Murphy,” EX1020) at 5. As Allergan was unable to demonstrate a statistically significant improvement using Restasis® compared to the vehicle, the committee recommended against FDA-approval. Murphy concluded: “In the meantime, someone should consider packaging castor oil as a treatment for dry eye. Apparently it’s the next best thing to cyclosporin.” EX1020, 5.

Thus, drug emulsions comprising both CsA and castor oil were well known in the art to provide effective therapeutic relief of dry eye disease by significantly reducing inflammation and increasing tear production. EX1025, ¶57, discussing EX1012; EX1014; EX1015; EX1010.

It was also well known in the art by September 15, 2003, that elevated concentrations of CsA in the bloodstream correlated with, and could result in,
serious adverse effects in a patient. EX1025, ¶52, discussing D. Small et al., Blood Concentrations of Cyclosporin A During Long-Term Treatment with Cyclosporin A Ophthalmic Emulsions in Patients with Moderate to Severe Dry Eye Disease 18 J. OC. PHARM. THERAP. 411 (2002) (“Small,” EX1021). Thus, it was routine in the art to measure blood concentrations of CsA using liquid chromatography-tandem mass spectrometry (LC-MS/MS) to determine if levels of CsA in the blood were elevated. Id. Small states that treatment of KCS with topical ophthalmic emulsions of CsA requires 2600-fold lower dosage than systemic treatment, and that the lower required dosages, such as 0.05% CsA in a castor oil emulsion, results in “practically undetectable” levels of CsA in the blood, based on a quantification limit of 0.1 ng/mL. Id. at 411-12.

IX. DETAILED EXPLANATION OF GROUNDS FOR UNPATENTABILITY

A. [Ground 1] Claims 1-20 are Anticipated under 35 U.S.C. § 102(b) by Ding ’979

Ground 1 establishes by a preponderance of the evidence that Ding ’979 (EX1006) anticipates the emulsion recited in claims 1-20 of the ’556 patent under 35 U.S.C. § 102(b).

i. Claims 1-10 and 12-13

Each of independent claims 1 and 13 recites a topical ophthalmic emulsion comprising 0.05% CsA and 1.25% castor oil, and other excipients. Claims 1 and 13 recite that the emulsion is therapeutically effective in treating dry eye disease. The
discussion that follows uses the elements and organization of claim 1 and its
dependent claims because the dependent claims cumulatively claim an emulsion
narrower than the emulsion claimed in claim 13. Thus, the teachings that render
claims 1-10 and 12 unpatentable also render claim 13 unpatentable. In re
Muchmore, 433 F.2d 824, 824-25 (C.C.P.A. 1970) (“Since we agree with the
board’s conclusion of obviousness as to these narrow claims, the broader claims
must likewise be obvious.”); accord Soverain Software LLC v. Victoria’s Secret
Direct Brand Mgmt., LLC, 778 F.3d 1311, 1315 (Fed. Cir. 2015) (a broader claim
cannot be valid if a narrower claim is invalid).

The elements of claims 1 and 7-8 that are comparable to the elements of
claim 13, are shown in the comparative table below (EX1025, ¶93), where
particular clauses and elements have been given item numbers for convenient
reference:
<table>
<thead>
<tr>
<th>Item</th>
<th>Claim 1</th>
<th>Claim 13</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>A first topical ophthalmic emulsion for treating an eye of a human, wherein the first topical ophthalmic emulsion comprises</td>
<td>A first topical ophthalmic emulsion for treating an eye of a human, wherein the first topical ophthalmic emulsion comprises</td>
</tr>
<tr>
<td>II</td>
<td>cyclosporin A in an amount of about 0.05% by weight</td>
<td>cyclosporin A in an amount of about 0.05% by weight</td>
</tr>
<tr>
<td>III</td>
<td>polysorbate 80,</td>
<td>polysorbate 80</td>
</tr>
<tr>
<td></td>
<td><strong>Claim 7</strong> (“polysorbate 80 in an amount of about 1.0% by weight”)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>acrylate/C10-30 alkyl acrylate cross-polymer,</td>
<td>acrylate/C10-30 alkyl acrylate cross-polymer,</td>
</tr>
<tr>
<td></td>
<td><strong>Claim 8</strong> (“acrylate/C10-30 alkyl acrylate cross-polymer in an amount of about 0.05% by weight”)</td>
<td><strong>Claim 8</strong> (“acrylate/C10-30 alkyl acrylate cross-polymer in an amount of about 0.05% by weight”)</td>
</tr>
<tr>
<td>V</td>
<td>water,</td>
<td>water,</td>
</tr>
<tr>
<td>VI</td>
<td>and castor oil in an amount of</td>
<td>and castor oil in an amount of</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Item</th>
<th>Claim 1</th>
<th>Claim 13</th>
</tr>
</thead>
<tbody>
<tr>
<td>VII</td>
<td>about 1.25% by weight; and</td>
<td>about 1.25% by weight; and</td>
</tr>
<tr>
<td></td>
<td>wherein the first topical ophthalmic emulsion is therapeutically effective in treating dry eye disease; and</td>
<td>wherein the first topical ophthalmic emulsion is therapeutically effective in treating dry eye disease and</td>
</tr>
<tr>
<td>VIII</td>
<td>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.</td>
<td>wherein the first topical ophthalmic emulsion achieves at least as much therapeutic effectiveness as 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.</td>
</tr>
</tbody>
</table>
The following explanation shows where each element of each Item of the above table is found in Ding ’979 for independent claims 1 and 13. The same analysis addresses the corresponding dependent claims in the above table.

Regarding Item I from the table above, Ding ’979 discloses non-irritating CsA-in-castor oil emulsions “for treatment of keratoconjunctivitis sicca (dry eye) syndrome” that are “suitable for topical application to ocular tissue.” EX1006, 5:9-11; id. at 6:3-7; EX1025, ¶¶61, 94. Moreover, Ding ’979 teaches that CsA increases tear production in the eye and has been found effective in “the enhancement or restoring of lacrimal gland tearing” and in treating immune-mediated dry eye disease/KCS. EX1006, 1:10-16, 37-39. By teaching the topical administration of the CsA-containing emulsions of Ding ’979 to a human eye to increase tear production and to treat dry eye disease, Ding ’979 satisfies “first topical ophthalmic emulsion for treating an eye of a human” (Item I) of claims 1-10 and 12-13. EX1025, ¶94. Ding ’979 also thereby teaches the “emulsion is therapeutically effective in treating dry eye disease” (Item VII), as recited in of claims 1-10 and 12-13. EX1025, ¶101.

The emulsions disclosed in Ding ’979 contain every ingredient of the emulsion recited in claims 1-20 as shown in Items II- VI in the table above. The emulsion ingredients in Example 1 of Ding ’979 are shown below:
EX1006, 4:32-43. Examples 1A-E of Ding '979 illustrate the castor oil and CsA percentage ranges recited in claims 7 and 8 of Ding '979. As explained by Dr. Chambliss, Examples 1A-E would be effective in treating dry eye disease and indeed at least examples 1A-D are said in Ding '979 to be effective. EX1006, 5:18-28; EX1025, ¶71; EX1005, 0435-37 (applicants conceding that its argument that Example 1E would not be effective at treating dry eye “is in error”).

Ding '979 not only discloses each ingredient but also the percentage of each ingredient in the emulsion of claims 1-20 of the ’556 patent. The 1.0% polysorbate 80 ingredient in Ding '979 (e.g., Example 1) meets the polysorbate 80 limitation of claims 1-20, and is the precise percentage recited in claim 7 (Item III). EX1025, ¶¶96-97. Pemulen® is an “acrylate[ ]/C10-30 alkyl acrylate cross-polymer” (EX1006, 4:4-5), and thus Ding '979 (Example 1, at 0.05%) teaches the acrylate/C-10-30 alkyl acrylate cross-polymer as recited in claims 1-20 and the 0.05% weight percentage limitation in claim 8 (Item IV). EX1025, ¶¶96-97. Glycerine satisfies the tonicity/demulcent agent/component or glycerine elements
as recited in claims 2-3, 6, 9, and dependent claims of the ’556 patent (EX1001, 12:45-47), and the 2.2% percentage of claims 9-10 is shown in each emulsion of Example 1. EX1006, 4:32-43. Sodium hydroxide of e.g., the Ding ’979 Example 1 emulsions, satisfies the buffer and sodium hydroxide elements recited in claims 4-6 and 9-10. Id. The water ingredient in Ding ’979 satisfies the water in claims 1-20 (Item V). Id.

Example 1 of Ding ’979 discloses that the emulsions have a pH of 7.2-7.6, thereby satisfying the pH range element of claim 12. EX1025, ¶96. Ding ’979 also satisfies the weight percentages of CsA and castor oil claimed in claims 1-20 of the ’556 patent. Example 1 specifies that the percentage of CsA may be 0.05% (Item II) and that the percentage of castor oil may be 1.25% (Item VI). EX1006, 4:32-43. A person of ordinary skill in the art would have at once envisaged the CsA/castor oil amounts in the claimed combination, i.e., 0.05% CsA and 1.25% castor oil. EX1025, ¶97. Ding ’979 provides four castor oil emulsion vehicles, Examples 2A-D. Example 2C discloses each ingredient of the claimed emulsion, with the sole exception of the CsA concentration.
Ding '979 also teaches preferred CsA concentrations for particular castor oil emulsions. Ding '979 teaches that the preferred ratio of CsA to castor oil is below 0.16, and more preferably between 0.02 and 0.12. EX1006, 3:16-20. Example 1 presents five example emulsions (A-E) that include CsA in the four castor oil vehicles disclosed in Example 2. The emulsions each have a CsA-caster oil ratio within the more preferred range as taught at 3:16-20 of EX1006. EX1025, ¶64. Based on the four castor oil vehicles of Example 2, only two additional emulsions with the CsA percentages of Example 1 are possible within the “more preferred” range: an emulsion having 0.05% CsA / 1.25% castor oil, and an emulsion having 0.1% CsA / 2.5% castor oil. Id. As explained by Dr. Chambliss, the skilled artisan would at once envisage these two emulsions as being taught by Ding '979, and would reasonably expect them to be non-irritating and therapeutically effective for treating dry eye disease as discussed below. EX1025, ¶71.
Example 1 further defines an even narrower range of ratios of CsA to castor oil, as Examples 1A-E have ratios of either 0.08 or 0.04. EX1025, ¶97. As discussed by Dr. Chambliss, a person of ordinary skill in the art would have expected that any of the CsA amounts disclosed in Example 1, in combination with any of the vehicles disclosed in Example 2, would be non-irritating and effective in the treatment of dry eye disease if the ratios of CsA to castor oil and castor oil to polysorbate 80 fall within the preferred ranges taught by Ding ’979. EX1025, ¶71.

For Ding ’979 Example 2C, only two CsA percentages from Example 1 fall within both the preferred and Example 1 ratio range: 0.05% CsA and 0.10% CsA. The 0.10% CsA was combined with the 1.25% castor oil vehicle in Example 1 (emulsion D), and the other, 0.05% CsA (Composition II), the Patent Owner previously conceded, “is \textit{squarely within the teaching of the Ding reference}, and the Office should disregard any statements by the applicants suggesting otherwise[.]” EX1005, 0435 (emphasis added); EX1025, ¶¶18, 98.

Claim 1 further recites that the first (0.05% CsA) emulsion provides “overall efficacy substantially equal to a second emulsion” comprising CsA at 0.1% and castor oil at 1.25%. Claim 13 recites that the first emulsion “achieves at least as much therapeutic effectiveness as a second emulsion comprising CsA at 0.1% and castor oil at 1.25%.” The ’556 patent states that the “overall efficacy of the present compositions, for example in treating dry eye disease, \textit{is} substantially equal to an
identical composition in which the cyclosporin component is present in an amount of 0.1% by weight.” EX1001, 2:38-42 (emphasis added). As explained by Dr. Chambliss, both of the therapeutic efficacy elements (Item VIII) merely recite a property that results intrinsically from topical ophthalmic administration of the claimed emulsion to the human eye, which emulsion is identical to the emulsion disclosed in Ding ’979. EX1025, ¶102. Prior art publications provide additional evidence confirming Dr. Chambliss’s conclusion. EX1007, 631, 634-35 (0.05% CsA-in-castor oil emulsion at least as effective as 0.10% CsA-in-castor oil emulsion and exhibited no “dose-response effect”); EX1015, 967 (“Cyclosporin A 0.05% and 0.1% were deemed the most appropriate formulations.”). Thus, Ding ’979 anticipates claims 1-10 and 12-13. A claim chart which identifies the relevant teachings of Ding ’979 to each element of these claims is provided below.

ii. Claim 14

As discussed above with respect to claim 1, Ding ’979 anticipates the emulsion of claim 1. This applies equally to independent claim 14 because this claim merely further recites that the claimed emulsion “breaks down more quickly in the eye ... thereby reducing vision distortion ... as compared to a second emulsion that contains only 50% as much castor oil.”

As explained by Dr. Chambliss, the relative rate of emulsion “break down,” and its subsequent effects on visual distortion, is simply a known property intrinsic
to the emulsion, which is identical to the emulsion disclosed in Ding ’979. EX1025, ¶104. The ’556 patent and prior art publications provide additional evidence confirming Dr. Chambliss’s conclusion. EX1009, 10:66—11:3 (increasing oil concentration speeds up the rate of emulsion differentiation, reducing blurred vision); EX1001, 2:42-48 (same). Thus, Ding ’979 anticipates claim 14.

iii. Claims 15-17

As discussed above with respect to claim 1, Ding ’979 anticipates the emulsion of claim 1. This applies equally to claim 15 because each ingredient of the emulsion recited in claim 15 is the same as that recited in claim 1. Claim 15 further recites that the first emulsion “demonstrates a reduction in adverse events in the human” relative to a second emulsion comprising 0.1% CsA and 1.25% castor oil. Claim 16 depends from claim 15 and recites that the adverse events are side effects. Claim 17 depends from claim 16 and recites that the side effects are selected from the group consisting of visual distortion and eye irritation.

As explained by Dr. Chambliss, the relative amount of adverse effects and side effects is simply a property intrinsic to the claimed emulsion, which is identical to the emulsion disclosed in Ding ’979. EX1025, ¶107. The ’556 patent and prior art publications provide additional evidence confirming Dr. Chambliss’s conclusion. EX1001, 2:48-51 (“[U]sing reduced amounts of the active cyclosporin
component mitigates against undesirable side effects and/or potential drug interactions.”); EX1007, 631, 636-37 (finding reduced undesirable side effects, including eye irritation following administration of a 0.05% CsA-in-castor oil emulsion as compared to a 0.10% CsA-in-castor oil emulsion). Thus, Ding ’979 anticipates claims 15-17.

iv. Claims 11 and 18-20

As discussed above with respect to claims 1 and 13-15, Ding ’979 anticipates the emulsion of claims 1 and 13-15. This applies equally to claims 11 and 18-20 because they depend respectively from claims 1 and 13-15. Claims 11 and 18-20 further recite that “when the topical ophthalmic emulsion is administered to an eye of a human, the blood of the human has substantially no detectable concentration of cyclosporin A.”

As explained by Dr. Chambliss, the “substantially no detectable concentrations of cyclosporin A” resulting from administration of the claimed emulsion to an eye of a human is simply a known property intrinsic to the claimed emulsion, which is identical to the emulsion disclosed in Ding ’979. EX1025, ¶¶108-09. Prior art publications provide additional evidence confirming Dr. Chambliss’s conclusion. EX1021, 411 (“No patient receiving 0.05% CsA [in-castor oil emulsion] had any quantifiable CsA in the blood.”); EX1007, 637 (same); EX1008 at 1004 (same). Thus, Ding ’979 anticipates claims 11 and 18-20.
As discussed above, all ingredients of the claimed emulsion are identified in Ding ’979 for use together in the same emulsion for the same therapeutic indication, with percentages for each ingredient taught expressly by Ding ’979. The claim chart below shows how Ding ’979 discloses each element of claims 1-20 using exemplary claims 1, 7-10, and 12, and includes reference to the supporting explanation by Dr. Chambliss (EX1025). “Item” numbers are those from the table above, comparing independent claims 1 and 13. The teachings which anticipate claims 1, 7-10, and 12 also anticipate claims 2-6, 11, and 13-20. Accordingly, claims 1-20 are unpatentable under 35 U.S.C. § 102(b).

<table>
<thead>
<tr>
<th>Exemplary Claims</th>
<th>Anticipated by Ding ’979</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. A first topical ophthalmic emulsion for treating an eye of a human,</td>
<td>“[A] non-irritating emulsion ... suitable for topical application to ocular tissue.” EX1006, 6:3-7; EX1002, ¶¶61-64, 70, 94.</td>
</tr>
<tr>
<td>wherein the first topical ophthalmic emulsion comprises cyclosporin A in an amount of about 0.05% by weight [Item II], polysorbate 80 [Item III],</td>
<td>Example 1E and claims 7-8 (0.05% cyclosporin A, polysorbate 80, an acrylate/C10-30 alkyl acrylate cross-polymer, and water) EX1006, 4:33-</td>
</tr>
<tr>
<td>Exemplary Claims</td>
<td>Anticipated by Ding '979</td>
</tr>
<tr>
<td>------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>acrylate/C10-30 alkyl acrylate cross-polymer [Item IV], water [Item V].</td>
<td>43; EX1002, ¶63-71, 96-100.</td>
</tr>
<tr>
<td>and castor oil in an amount of about 1.25% by weight; and [Item VI]</td>
<td>“More preferably ... ratio of cyclosporin to castor oil is between 0.12 and 0.02.” EX1006, 3:17-20.</td>
</tr>
<tr>
<td>Example 2C (1.25% castor oil). EX1006, 4:33-54; EX1002, ¶63-71, 96-100.</td>
<td>Example 1B, 1D (0.04-0.08 ratio of CsA-to-castor oil). EX1006, 4:33-43; EX1002, ¶63-71, 96-100.</td>
</tr>
<tr>
<td>0.04-0.08 ratio for Example 2C is 0.05-0.10% CsA. EX1002, ¶97.</td>
<td>Intrinsic property of the formulation.</td>
</tr>
<tr>
<td>wherein the first topical ophthalmic emulsion is therapeutically effective in treating dry eye disease; and [Item VII]</td>
<td>“The formulations set forth in Examples 1-4 were made for treatment of keratoconjunctivitis sicca (dry eye) syndrome.” EX1006, 5:9-11; EX1002, ¶69, 94.</td>
</tr>
<tr>
<td>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</td>
<td>“Cyclosporins [are] effective in treating immune medicated [sic: mediated] keratoconjunctivitis sicca (KCS or dry eye disease)” EX1006, 1:10-16; EX1002, ¶61, 101.</td>
</tr>
<tr>
<td></td>
<td>Intrinsic property of the formulation. Discussed above.</td>
</tr>
<tr>
<td>Exemplary Claims</td>
<td>Anticipated by Ding ’979</td>
</tr>
<tr>
<td>----------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>amount of about 1.25% by weight.</td>
<td>EX1006, 4:33-43 (1.0% polysorbate 80); EX1002, ¶¶64, 70, 94-96.</td>
</tr>
<tr>
<td>[Item VIII]</td>
<td></td>
</tr>
<tr>
<td>7. The first topical ophthalmic emulsion of claim 1, wherein the first topical</td>
<td>EX1006, 4:33-43 (0.05% Pemulen®); EX1002, ¶¶64, 70, 95-96.</td>
</tr>
<tr>
<td>ophthalmic emulsion comprises polysorbate 80 in an amount of about 1.0% by</td>
<td></td>
</tr>
<tr>
<td>weight.</td>
<td></td>
</tr>
<tr>
<td>[Item III]</td>
<td></td>
</tr>
<tr>
<td>8. The first topical ophthalmic emulsion of claim 1, wherein the first topical</td>
<td>EX1006, 4:33-43 (2.2% glycerine and sodium hydroxide); EX1002, ¶¶64, 70, 95-96.</td>
</tr>
<tr>
<td>ophthalmic emulsion comprises acrylate/C10-30 alkyl acrylate cross-polymer in</td>
<td></td>
</tr>
<tr>
<td>an amount of about 0.05% by weight.</td>
<td></td>
</tr>
<tr>
<td>[Item IV]</td>
<td></td>
</tr>
<tr>
<td>9. The first topical ophthalmic emulsion of claim 1, wherein the first topical</td>
<td>EX1006, 4:33-43 (2.2% glycerine and sodium hydroxide); EX1002, ¶¶64, 70, 95-96.</td>
</tr>
<tr>
<td>ophthalmic emulsion further comprises glycerine in an amount of about 2.2% by</td>
<td></td>
</tr>
<tr>
<td>weight and a buffer.</td>
<td></td>
</tr>
<tr>
<td>10. The first topical ophthalmic emulsion of claim 9, wherein the buffer is</td>
<td>EX1006, 4:33-43 (pH 7.2-7.6); EX1002, ¶¶64, 96.</td>
</tr>
<tr>
<td>sodium hydroxide.</td>
<td></td>
</tr>
<tr>
<td>12. The first topical ophthalmic emulsion of claim 6, wherein the first topical</td>
<td></td>
</tr>
<tr>
<td>ophthalmic emulsion has a pH in the range of about 7.2 to about 7.6.</td>
<td></td>
</tr>
</tbody>
</table>
B. [Ground 2] Claims 1-20 are Obvious under 35 U.S.C. § 103 over Ding ’979 and Sall

Each of claims 1-20 would have been obvious to a person of ordinary skill in the art based on Ding ’979 further in view of Sall (EX1007). An artisan would look to Ding ’979 together with Sall because both describe non-irritating, therapeutically effective, topical, ophthalmic, castor oil emulsions suitable for delivery of 0.05% and 0.10% CsA for increasing tear production and treating dry eye disease/KCS. EX1025, ¶115.

i. Claims 1-10, 12-13

The teachings of Ding ’979 are discussed above. Sall provides further motivation to make the 0.05% CsA / 1.25% castor oil topical ophthalmic emulsion of Ding ’979, and expressly describes the properties of the emulsion claimed in claims 1-20 when administered to a human eye to treat dry eye disease.

Sall describes a “multicenter, randomized, double-masked” Phase 3 clinical trial. EX1007, 632; EX1025, ¶115. The trial involved the parallel assessment of the efficacy and safety of a 0.05% CsA-in-castor oil emulsion and a 0.10% CsA-in-castor oil emulsion as compared to a control vehicle (the same castor oil emulsion that did not contain CsA). EX1007, 632. One of the CsA/castor oil emulsions, or the control vehicle, was administered twice daily to patients. Id. Sall concluded that both the 0.05% and the 0.10% CsA emulsions “were safe and effective in the treatment of moderate to severe dry eye disease yielding improvements in both
objective and subjective measures.” Id. at 631; EX1025, ¶116. Sall reported that
treatment with either percentage of CsA provided “significantly (p≤0.05) greater
improvements than vehicle” for treating dry eye disease, when measured by
corneal staining and Schirmer values, and further noted that there was “no dose-
response effect” between the two percentages of CsA. EX1007, 637. Thus, Sall
teaches the 0.05% CsA emulsion “provides overall efficacy substantially equal to”
and “achieves at least as much therapeutics effectiveness as” a second topical
emulsion containing 0.1% CsA (Item VIII) of claims 1-13.

In addition to teaching that the 0.05% CsA emulsion is at least as effective
as the 0.10% CsA emulsion, Sall also provides a strong rationale to deliver 0.05%
CsA using the 1.25% castor oil vehicle taught by Ding ’979 (Example
2C).EX1007, 632; EX1025, ¶¶81, 120-21. Sall uses the same vehicle for delivering
both 0.05% and 0.10% CsA. EX1007, figs. 1-4 (each showing a single vehicle
control group for comparison to both the 0.05% and 0.10% CsA emulsion), 632
(“compare two concentrations of CsA ophthalmic emulsion to its vehicle”), 638
(stating that “the vehicle,... contributed to the overall improvements observed in all
treatment groups in this study”); EX1025, ¶¶120-21. Of the castor oil vehicles
disclosed in Example 2 of Ding ’979, only vehicle C (1.25% castor oil) and vehicle
D (0.625% castor oil) are used with emulsions in Example 1 having either 0.05%
or 0.10% CsA. EX1006, 4:32-54.
The 1.25% castor oil vehicle is the only vehicle from Ding ’979 Example 2 for which both 0.05% and 0.10% CsA have a ratio of CsA-to-castor oil inside the more preferred range of between 0.12 and 0.02 (EX1006, 3:17-20) and also within the ratio range found with each of the Example 1 emulsions (0.04-0.08). Id. Ding ’979 teaches that a 0.625% castor oil emulsion is not preferred for use with 0.10% CsA because the ratio of CsA to castor oil would be 0.16, and Ding ’979 teaches that “[p]referably, the ... weight ratio of the cyclosporin to castor oil is below 0.16.” EX1006, 4:15-17 (emphasis added); EX1025, ¶121. In contrast, a 1.25% castor oil emulsion would have been suitable for use with both the 0.05% and 0.10% CsA emulsions, having CsA-to-castor oil ratios of 0.04 and 0.08, respectively. Id. A person of ordinary skill would have formulated the 0.05% CsA / 1.25% castor oil emulsion of Ding ’979 and administered it ophthalmically twice-daily based on Sall and Ding ’979. Moreover, selecting the 0.05% CsA percentage over the 0.10% CsA percentage would also decrease the cost of production of the emulsion and reduce the potential for crystallization. EX1006, 3:58-63; EX1025, ¶118.

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; EX1025, ¶116. As explained by Dr. Chambliss, 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. EX1025, ¶¶99, 114; EX1001, 14:65-67 (“These compositions are produced in accordance with well known techniques[.]”).

ii. **Claim 14**

Claim 14 recites the same emulsion as in claims 1 and 13, and merely further recites that the claimed emulsion “breaks down more quickly in the eye ... thereby reducing vision distortion ... as compared to a second emulsion that contains only 50% as much castor oil.” As discussed above in Ground 1, the relative rate of emulsion “break down,” and its subsequent effects on visual distortion, is a property intrinsic to the claimed emulsion, which is identical to the emulsion disclosed in Ding ’979. EX1025, ¶122. Thus, claim 14 is obvious in view of Ding ’979 and Sall.

iii. **Claims 15-17**

Independent claim 15 recites the same emulsion as in independent claims 1 and 13, discussed above, and merely further recites that the claimed emulsion demonstrates a reduction in adverse events. Dependent claims 16 and 17 additionally recite the claimed emulsion demonstrates a reduction of side effects
and vision distortion or eye irritation in the human, relative to a second emulsion 0.10% CsA.

Sall expressly teaches that a 0.05% CsA-in-castor oil emulsion demonstrated a reduction in adverse events, side effects, and eye irritation or vision distortion as compared to the 0.10% CsA-in-castor oil emulsion. EX1025, ¶123. Sall states: “Overall, 25.3% (74/293) of patients treated with CsA 0.05%, 29.1% (85/292) of patients treated with CsA 0.10%, and 19.5% (57/292) of patients treated with the vehicle experienced one or more treatment-related adverse events.” EX1007, 636. Sall also teaches that patients receiving the 0.05% CsA treatment experienced fewer occurrences of burning eye, stinging eye, visual disturbances, and eye pain, as compared to the 0.10% CsA treatment group. Id.; EX1025, ¶124. Further, Sall reported superior results for the 0.05% CsA emulsion with regard to three parameters (including blurred vision and need for artificial tears). EX1007, 631; EX1025, ¶117.

The reduced burning eye, stinging eye, eye pain, and need for artificial tears of the 0.05% CsA solution as compared to the 0.10% CsA solution taught in Sall each satisfy the “eye irritation” limitation of claim 17, thereby obviating each of claims 15-17. The reduced visual disturbance and blurred vision each satisfy the reduced “visual distortion” limitation of claim 17, also thereby obviating each of claims 15-17. The reduced burning eye, stinging eye, conjunctival hyperemia, eye
pain, visual disturbances, and blurred vision each satisfy the “side “effects” and “adverse events” limitations of claims 15 and 16, respectively. In view of the express teachings of Sall, it would have been obvious that the 0.05% CsA / 1.25% castor oil emulsion would demonstrate a reduction in adverse events, side effects, and vision distortion or eye irritation in a human, as recited in claims 15-17.

iv. Claims 11 and 18-20

Claims 11 and 18-20 depend from claims 1 and 13-15, respectively and simply recite that there is “substantially no detectable concentration of” CsA in the blood when the emulsion is administered to the eye.

Sall expressly teaches that when the 0.05% CsA-in-castor oil emulsion was administered to the human eye twice a day, it resulted in substantially no detectable concentration of CsA in the blood: “Trough blood concentrations of CsA ... below the limit of quantitation (of 0.1 ng/ml) in all samples.” EX1007, 637; EX1025, ¶126. Sall’s teachings are confirmed by numerous other background references. EX1021, 411 (“No patient receiving 0.05% CsA [in castor oil emulsion] had any quantifiable CsA in the blood.”); EX1008 at 1004 (same). Thus, based on Ding ’979 and Sall, it would have been obvious to a person of skill in the art at the time of the earliest claimed priority date that when the 0.05% CsA / 1.25% castor oil emulsion is administered to the eye the result would be substantially no detectable concentration of CsA in the blood.
The claim chart below details teachings of Ding '979 and Sall that render claims 1-20 of the '556 patent obvious using exemplary claims 1, 11, and 15-17, along with reference to the supporting explanation in the declaration of Dr. Chambliss (EX1025). Accordingly, claims 1-20 are unpatentable as obvious under 35 U.S.C. § 103.

<table>
<thead>
<tr>
<th>Exemplary Claims</th>
<th>Obvious Over Ding '979 and Sall</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. A first topical ophthalmic emulsion for treating an eye of a human, [Item I]</td>
<td>“[A] non-irritating emulsion ... suitable for topical application to ocular tissue.” EX1006, 6:3-7; EX1002, ¶113. “Patients were treated twice daily with either CsA, 0.05% or 0.1%, or vehicle.” EX1007, 6:31; EX1002, ¶115.</td>
</tr>
<tr>
<td>wherein the first topical ophthalmic emulsion comprises cyclosporin A in an amount of about 0.05% by weight [Item II], polysorbate 80 [Item III], acrylate/C10-30 alkyl acrylate cross-polymer [Item IV], water [Item V].</td>
<td>See claim chart for claim 1 in Ground 1. EX1006, 3:16-20, 4:33-43, Example 1, and claims 7-8; EX1002, ¶113-14. “Patients were treated twice daily with either CsA, 0.05% or 0.1% or vehicle.” EX1007, 6:31; EX1002, ¶115.</td>
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<tr>
<td>and castor oil in an amount of</td>
<td>See claim chart for claim 1 in Ground 1.</td>
</tr>
<tr>
<td>Exemplary Claims</td>
<td>Obvious Over Ding '979 and Sall</td>
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<tr>
<td>about 1.25% by weight [Item VI]; and</td>
<td>“Both the CsA emulsions and vehicle were sterile, nonpreserved castor oil in water emulsions.” EX1007, 632; EX1002, ¶115.</td>
</tr>
<tr>
<td>wherein the first topical ophthalmic emulsion is therapeutically effective in</td>
<td>See claim chart for claim 1 in Ground 1.</td>
</tr>
<tr>
<td>treating dry eye disease [Item VII]; and</td>
<td>“The novel ophthalmic formulations CsA 0.05% and 0.1% were safe and effective in the treatment of moderate to severe dry eye disease.” EX1007, 631 &amp; n.1; EX1002, ¶116.</td>
</tr>
<tr>
<td>wherein the first topical ophthalmic emulsion provides overall efficacy</td>
<td>See claim chart for claim 1 in Ground 1.</td>
</tr>
<tr>
<td>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 [Item VIII].</td>
<td>“Treatment with CsA, 0.05% or 0.1%, gave significantly (P≤0.05) greater improvements than vehicle in two objective signs of dry eye disease (corneal staining and categorized Schirmer values). CsA 0.05% treatment also gave significantly greater improvements (P&lt;0.05) in three subjective measures of dry eye disease.” EX1007, 631; EX1002, ¶116.</td>
</tr>
<tr>
<td>11. The first topical ophthalmic emulsion of claim 1, wherein, when the first topical ophthalmic emulsion is administered to an eye of a human in an effective amount in treating dry eye disease, the blood of the human has substantially no detectable concentration of cyclosporin A.</td>
<td>See discussion of claim 1, above.</td>
</tr>
<tr>
<td>15. A first topical ophthalmic</td>
<td>See discussion of claim 1 above.</td>
</tr>
<tr>
<td>Exemplary Claims</td>
<td>Obvious Over Ding ‘979 and Sall</td>
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<tr>
<td>emulsion for treating an eye of a human... wherein the first topical ophthalmic emulsion, when administered to the eye of a human, demonstrates a reduction in adverse events in the human, relative 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.</td>
<td>25.3% adverse events in CsA 0.05 group vs. 29.1% in CsA 0.10%. EX1007, 636.</td>
</tr>
<tr>
<td>16. The first topical ophthalmic emulsion of claim 15, wherein the adverse events are side effects.</td>
<td>0.05% CsA treatment experienced fewer occurrences of burning eye, stinging eye, conjunctival hyperemia, visual disturbances, and eye pain, as compared to the 0.10% CsA treatment group. <em>Id.</em> at 536, Table 3.</td>
</tr>
<tr>
<td>17. The first topical ophthalmic emulsion of claim 16, wherein the side effects are selected from the group consisting of visual distortion and eye irritation.</td>
<td>EX1007, 631(reduced blurred vision and need for concomitant artificial tears in 0.05% CsA group); EX1002, ¶79.</td>
</tr>
</tbody>
</table>

C. [Ground 3] Claims 14 and 19 are Obvious under 35 U.S.C. § 103 over Ding ’979, Sall, and Glonek

Every element of claims 14 and 19 of the ’556 patent is taught through Ding ’979 (EX1006), Sall (EX1007), and Glonek (EX1009). As discussed above with respect to Ground 2, claim 14 further recites that the first emulsion “breaks down more quickly in the eye ... thereby reducing vision distortion ... as compared to a second emulsion that contains only 50% as much castor oil.” A person of ordinary skill would have looked to Glonek because Glonek teaches the impact of increasing oil percentage in oil-in-water emulsions for the treatment of dry eye.
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.” EX1009, 3:3-7; EX1025, ¶132. Glonek teaches that “an emulsion over the surface of the eye is expected to cause blurring. The duration of the blurring is dependent upon the time required for the emulsion to differentiate and form separate layers.” EX1009, 6:37-40; EX1025, ¶132. Glonek teaches that “it is preferred that the emulsion be stable for long term storage, but rapidly differentiate in the eye.” EX1009, 6:48-50 (emphasis added); EX1025, ¶¶132-33.

Increasing oil concentration in an emulsion, while holding surfactant concentration constant, results in an increase in emulsion instability, i.e., an increased rate of differentiation. EX1009, 10:66—11:3; EX1025, ¶¶132-34. Based on Glonek, a skilled artisan would have reasonably expected a 1.25% castor oil emulsion to break down faster than a 0.625% castor oil emulsion because of the increased instability from the higher oil concentration, and that the faster differentiation would result in a reduction of blurring. Id., ¶¶132-35. Further, one would not expect the 0.05% CsA / 1.25% castor oil formulation to cause undue blurring because it is within the preferred ranges disclosed by Ding and because other prior art ophthalmic emulsions comprising castor oil in amounts up to 2% did
not cause blurring. EX1025, ¶58; EX1017, p.2032. Thus, claim 14 of the ’556 patent is obvious based on Ding ’979, Sall, and Glonek.

Claim 19, which depends from claim 14, further recites that “when the topical ophthalmic emulsion is administered to an eye of a human, the blood of the human has substantially no detectable concentration of cyclosporin A.” As discussed above in Ground 2 with respect to claims 11 and 18-20, Sall expressly teaches that when the 0.05% CsA-in-castor oil emulsion is administered to the eye there is substantially no detectable concentration of CsA in the blood. EX1007, 637; EX1025, ¶126. Thus, based on Ding ’979, Sall, and Glonek, it would have been obvious to a person of skill in the art that when the 0.05% CsA / 1.25% castor oil emulsion of claim 14 is administered to the eye there is substantially no detectable concentration of CsA in the blood.

In view of the forgoing, claims 14 and 19 of the ’556 patent are obvious based on Ding ’979, Sall, and Glonek.

D. [Ground 4] Claims 11, 18, and 20 are Obvious under 35 U.S.C. § 103 over Ding ’979, Sall, and Acheampong

Every element of claims 1, 13, and 15 of the ’556 patent is taught through Ding ’979 (EX1006), Sall (EX1007), and Acheampong (EX1008). As discussed above, claims 11, 18, and 20 each further recite that “when the topical ophthalmic emulsion is administered to an eye of a human, the blood of the human has substantially no detectable concentration of cyclosporin A.”
As explained in Ground 2, Sall states that humans receiving ophthamlic administrations of 0.05% CsA emulsions containing castor oil twice a day had, “[t]rough blood concentrations of CsA ... below the limit of quantitation (of 0.1 ng/ml) in all samples.” EX1007, 637; EX1025, ¶138. Acheampong adds to these teachings by describing a months-long study which evaluated both peak and trough concentrations of CsA in the blood of humans receiving ophthamlic administrations of CsA/caster oil emulsions: “[S]ubjects with KCS received an eyedrop of vehicle or 0.05%, 0.10%, 0.20% or 0.40% cyclosporine emulsion twice daily.... Blood samples were collected ... at morning troughs ... [and] after the last dose [(trough levels)].” EX1008 at 1002; EX1025, ¶139. As presented in Table 1 of Acheampong, patients receiving ophthamlic emulsions of 0.05% CsA had no detectable concentration of CsA in the blood at both peak and trough levels. Id.

<table>
<thead>
<tr>
<th>Cyclosporine emulsion</th>
<th>Range of blood cyclosporine A concentration (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Trough level</td>
</tr>
<tr>
<td>0.05%</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>0.1%</td>
<td>&lt;0.1 to 0.102</td>
</tr>
<tr>
<td>0.2%</td>
<td>&lt;0.1 to 0.108</td>
</tr>
<tr>
<td>0.4%</td>
<td>&lt;0.1 to 0.157</td>
</tr>
</tbody>
</table>

EX1008 at 1004. Thus, Acheampong and Sall together provide one of ordinary skill in the art with a reasonable expectation of success that the 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. EX1025, ¶140.

In view of the forgoing, each of dependent claims 11, 18 and 20 of the ’556 patent is obvious and unpotentable under 35 U.S.C. § 103 based on Ding ’979, Sall, and Acheampong.

E. [Ground 5] Claim 19 is Obvious under 35 U.S.C. § 103 over Ding ’979, Sall, Glonek, and Acheampong

Claim 19 depends from independent claim 14. When the emulsion of claim 14 is administered to the eye, claim 19 recites that the blood has “substantially no detectable cyclosporin A” concentration. Every element of claim 19 is taught through Ding ’979 (EX1006), Sall (EX1007), Glonek (EX1009), and Acheampong (EX1008). As discussed in Ground 3, Sall states that humans receiving ophthalmic administrations of 0.05% CsA emulsions containing castor oil twice a day had, “[t]rough blood concentrations of CsA ... below the limit of quantitation (of 0.1 ng/ml) in all samples.” EX1007, 637; EX1025, ¶¶126, 138, 143. As discussed in Ground 4, Acheampong adds to these teachings by evaluating both peak and trough concentrations of CsA in the blood of humans receiving ophthalmic administrations of CsA/castor oil emulsions and finding that when the 0.05% CsA emulsion is administered to the eye there is no detectable concentration of CsA in the blood at either peak or trough levels. EX1008 at 1002; EX1025, ¶¶139, 143. Thus, based on Ding ’979, Sall, Glonek, and Acheampong, it would have been
obvious to a person of skill in the art at the time of the earliest claimed priority date that when a 0.05% CsA / 1.25% castor oil emulsion is administered to the eye, there would have been substantially no detectable concentration of CsA in the blood. EX1025, ¶144.

X. **NO OBJECTIVE INDICIA OF NON-OBSVIOUSNESS**

During prosecution of the ’556 patent, Allergan argued that objective indicia supported patentability. EX1004, 0194-0207. To determine whether claims would have been obvious, one must consider “all evidence of obviousness and nonobviousness before reaching a determination.” *Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC*, 683 F.3d 1356, 1365, fn. 5 (Fed. Cir. 2012). However, a strong case of *prima facie* obviousness may outweigh any objective indicia of nonobviousness. *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010).

Allergan submitted four declarations, two of which alleged “unexpected results” (EX1004, Schiffman Declaration 1, 0216, Attar Declaration, 0242), one alleged commercial success of the FDA-approved drug Restasis® (EX1004, Mottiwala Declaration, 0261), and one alleged a long-felt, unmet need existed prior to the alleged invention. EX1004, 0271.

A. **No Unexpected Results**

The data provided during prosecution failed to demonstrate unexpected results because it failed to provide parameters necessary for scientific
interpretation, including raw data values and error rates. Without these parameters, it is impossible to reach a scientific conclusion of unexpected results because it is not known whether the reported data are statistically significant or material. EX1025, ¶¶150-58, 162-68 (discussed in more detail below). Moreover, much of the data relied upon as demonstrating unexpected equivalent efficacy of the 0.05% CsA and 0.10% CsA emulsion appear identical to graphs published more than one year before the earliest alleged priority date. EX1025, ¶¶149-50. Results that were published before the 102(b) bar date cannot properly be deemed “unexpected.” The discussion below uses identifiers from the first Schiffman Declaration because these include the Attar declaration exhibits.

Allergan argued during prosecution that it had changed course regarding the obviousness of the claimed emulsion because, “[s]ince these comments have been filed, the Applicants have collected evidence that supports the patentability of the pending claims.” EX1004, 0007. However, it appears that Allergan repackaged the previously published graphs from Sall. Figures 1-4 of Schiffman Exhibit D line up squarely with Figures 1-4 of Sall, as exemplified below with side-by-side comparisons of Figures 1-4:
Each of Figures 1-4 of Sall are shown to be comparable to those in Schiffman Exhibit D in the Chambliss Declaration. EX1025, ¶¶152-55.

According to Schiffman, Figures 1-4 of Schiffman Exhibit D are from Allergan’s Phase 3 trials comparing the efficacy and safety of the 0.10% CsA / 1.25% castor oil emulsion to the 0.05% CsA/ 1.25% castor oil, “and to a vehicle containing 1.25% by weight castor oil [Ding ’979 Example 2C].” EX1004, 0217. Dr. Attar similarly references the Phase 3 clinical trial. Id. at 0243-44. Drs. Schiffman and Attar appear to be referring to the Phase 3 trials described in Sall. EX1007, 631, 638 (reporting results of Allergan’s Phase 3 clinical trials. EX1025, ¶149.

Consistent with standard scientific practices, Sall presents these data by providing the error bars that are missing from the versions presented in the later Schiffman and Attar declarations. EX1025, ¶¶150, 154. Though lacking parameters necessary to reach a scientific conclusion, Schiffman interpreted the data as “surprisingly exhibit[ing] a **comparable** or greater decrease in corneal staining” EX1004, 0219 (emphasis added). However, Sall had previously reported that the decrease in corneal staining and the increase in Schirmer score were comparable between the 0.05% CsA and 0.10% CsA emulsions:

Treatment with CsA, 0.05% or 0.1% gave significantly (P ≤ 0.05) greater improvements than vehicle in two objective signs of dry eye disease (corneal staining and categorized Schirmer values).…. **There was no dose-response effect.** Both CsA treatments exhibited an
excellent safety protocol. EX1007, 638; id. (In this study, the most important overall finding was that topical treatment with either CsA 0.05% or 0.1% resulted in significantly greater improvements....”) (emphases added). An assertion that a composition is at least as effective as another composition cannot constitute surprising or unexpected results when the prior art teaches such efficacy. This same analysis applies to Figures 3 and 4 of Schiffman Exhibit D. EX1025, ¶155.

Moreover, Stevenson had previously determined that the 0.05% CsA and 0.10% CsA emulsions were the “most appropriate formulations” because no “additional benefits were observed with the higher concentrations.” EX1015, 967; EX1025, ¶165. At best, Schiffman Exhibit D merely confirms the teachings of the prior art that the 0.05% and 0.10% CsA emulsions had similar results.

Schiffman Exhibits B-C and E-F also fail to establish unexpected results because they again do not provide necessary parameters to permit a scientific conclusion of unexpected results. EX1025, ¶¶150-58; 162-68. As can be seen in the reproduction below, Exhibit B contains brackets suggesting that the Phase 2 results indicated that the 0.10% CsA emulsion was significantly more effective than the 0.05% CsA emulsion. Id. at 0231. However, such an interpretation is not supported by Exhibit B, for several reasons. EX1025, ¶164.
For example, Exhibit B contains no error bars. EX1025, ¶¶162-63. Without error bars it is impossible to determine whether the results shown in Exhibit B are statistically significant. If not statistically significant, the observed results may simply be the result of chance variation due, for example, to sampling error. *Id.* Because of the absence of error bars, Dr. Schiffman’s assertion, based on Exhibit B, that “the 0.1% by weight cyclosporin A/ 1.25% by weight castor oil formulation demonstrated a greater increase in Schirmer Score (tear production) at week 12 than any other formulation tested,” (EX1004, 0217, formatting in original) lacks support.

In addition to being unsupported, Dr. Schiffman’s conclusion may be incorrect. As explained by Dr. Chambliss, the Stevenson publication reported the Phase 2 results of the CsA clinical trial for dry eye. EX1025, ¶165. Stevenson concluded that ophthalmic CsA emulsions containing 0.05%, 0.10%, 0.20%, and
0.40% CsA all “significantly improved the ocular signs and symptoms of moderate-to-severe dry eye disease, and decreased the effect of the disease on vision-related functioning,” and that “Cyclosporin A 0.05% and 0.1% were deemed the most appropriate formulations for future clinical studies because no additional benefits were observed with the higher concentrations.” EX1015, 967; EX1025, ¶165.

With respect to the Schirmer tear tests, Stevenson reports that the results of the Schirmer test in the Phase 2 CsA trials “only approached statistical significance” for the 0.10% CsA emulsion. EX1015, 971 (emphasis added). This indicates that the change in Schirmer score of 2 units for the 0.10% CsA group in Fig. 2 of Schiffman Exhibit B is not even statistically significantly different from 0 (baseline). EX1025, ¶167. Thus, the approximately 1.5 unit bracket drawn between the 0.05% and 0.10% CsA groups, even if fully attributable to the difference in CsA%, is also small enough to be statistically insignificant in this study. As explained by Dr. Chambliss, errors of this size are not unexpected because of the small sample. EX1025, ¶167; EX1015, 970.

Similarly, regarding Schiffman’s Exhibit B, Figure 1, for the results of the corneal staining tests used to measure Superficial Punctate Keratitis (“SPK”), Stevenson also published a graph of the SPK corneal staining results, which is shown below (right) adjacent to the corneal staining results from Figure 1 of
Schiffman Exhibit B (left). Stevenson stated that “[n]o statistically significant among-group differences in [SPK] were observed.” EX1025, ¶166; EX1015, 970.

Although there are some differences between the graphs, Stevenson demonstrates how the absence of error bars in Schiffman Exhibit B renders a scientific conclusion as to the significance of the 0.10% CsA emulsion impossible. Moreover, even if statistically significant, the differences in Phase 2 results between the 0.05% and 0.10% CsA emulsions cited by Dr. Schiffman appear to be immaterial. Despite what appears to be a large gap between the 0.05% and 0.10% CsA emulsions in the Stevenson figure, Stevenson concluded that CsA emulsions “0.05% and 0.1% were deemed the most appropriate formulations for future clinical studies because no additional benefits were observed with the higher concentrations.” EX1015, 967; EX1025, ¶165.

Schiffman’s Exhibit C, which addresses the concentration of CsA found in the cornea and conjunctiva tissues following the administration of the claimed
emulsion versus one which comprises half as much castor oil, similarly fails to establish any significant or material difference between the tested emulsions. Schiffman Exhibit C again lacks error bars (EX1004, 0233), which prevents any conclusion of statistical significance. EX1025, ¶168. Further, Schiffman Exhibit C fails to establish materiality of any observed differences, even if significant. Well prior to the earliest priority date of the ’556 patent, the minimal concentration of CsA needed in ocular tissues for therapeutic effectiveness was already known. Id.; EX1011, 652. It was also known that topical ophthalmic CsA in castor oil provided therapeutic concentrations, and that the 0.05% CsA emulsions in particular was sufficient to “significantly decrease[]”markers associated with dry eye disease/KCS. EX1025, ¶¶51, 168; EX1014, 496. However, instead of comparing the tissue CsA concentrations measured in Exhibit C to the known threshold for therapeutic efficacy, Exhibit C compares them to the level observed with 0.1% CsA in a 1.25% castor oil emulsion. Because Exhibit C reports no raw values, it is impossible to conclude that any observed increase in delivery is material. EX1025, ¶168.

Schiffman Exhibits E and F are a table and a graph of data said to originate from the Phase 2 and Phase 3 trials of Restasis®. EX1004, 0237-40. These exhibits allege efficacy of the claimed emulsion (0.05% CsA / 1.25% castor oil) relative to two other emulsions: 0.1% CsA/1.25% castor oil (Ding 1D) and 0.05%
CsA/0.625% castor oil (Ding 1E). EX1025, ¶156. Schiffman states there was an “8-fold increase” in the performance of the claimed emulsion over Ding ’979’s 1E formulation. Stevenson and Sall, however, reported results of Phase 2 and Phase 3 trials of Restasis® respectively, and both reported that variations between emulsions containing 0.05% and 0.10% CsA were not significant. EX1007, 631; EX1015, 967; EX1025, ¶¶ 74, 160, 165-67.

In contrast to Stevenson’s and Sall’s reports, Schiffman’s analysis is misleading and fraught with scientific inaccuracies. Instead of raw data and error
bars, Exhibits E and F report only “ratios” of the test scores for 0.05% CsA in either 0.625% castor oil or 1.25% castor oil. EX1025, ¶¶156-57. The ratios were purportedly derived by dividing the actual test results for the two 0.05% CsA emulsions by the actual results for the 0.10% CsA / 1.25% castor oil emulsion. However, using ratios instead of raw numbers can exaggerate the importance of very small and immaterial differences. EX1025, ¶¶156-57. Coupled with the failure to report error rates, it is impossible to say that the reported ratio differences are either statistically significant or material. Id.

Exhibits E and F indicate that the same Phase 3 study was performed twice. In both, the decrease in corneal staining with the 0.05% CsA/1.25% castor oil emulsion was essentially equivalent to the result with the 0.10% CsA/1.25% castor oil emulsion (reflected in the ratio values of “1” in the corneal staining row of Exhibit E, and as shown graphically in Exhibit F). EX1025, ¶¶156-57. In contrast, the results for the Schirmer Tear Test (STT) varied by as much as 100% across the two Phase 3 studies (reflected in the ratio values of “1” and “2” in the STT row of Exhibit E as reflected graphically in Exhibit F). This suggests a high degree of error in the test and indicates that a difference of “1” in Exhibit E is not statistically significant. It follows that the difference in the STT score of 0.25 and 1 (described in Exhibit E as a 4-fold increase) is not a statistically significant result. EX1025, ¶¶158. In other words, the difference between a “1” and a “0.25” may simply be due
to chance variation, and there may be no real difference between the two 0.05% CsA emulsions in Exhibits E and F, despite the appearance of a large difference. Further, the fact that the “8-fold Improvement” in STT was not repeatable, and that no 8-fold improvement was observed in corneal staining indicates that this value is unreliable. EX1025, ¶¶159-61.

As such, Exhibits E and F do not demonstrate that increasing the castor oil concentration from 0.625% to 1.25% resulted in any real improvement. Moreover, some improvement based on an increase in castor oil would be expected (EX1014; EX1015), and therefore cannot be attributed to an unexpected benefit resulting from the specific CsA concentration and the specific castor oil concentration claimed. EX1025, ¶¶160-61.

B. No Evidence of Commercial Success

During prosecution, the examiner concluded there was no evidence of commercial success because Allergan failed to establish a nexus between sales and the claims that ultimately issued in the ’556 patent. EX1004, 0417-18. “For objective evidence of secondary considerations to be accorded substantial weight, its proponent must establish a nexus between the evidence and the merits of the claimed invention.” Wyers v. Master Lock Co., 616 F.3d 1231, 1246 (Fed. Cir. 2010) (quotation omitted). Allergan failed to compare the commercial performance of Restasis® to any alternatives because it defined all alternatives out of the
relevant market. EX1004, 0261 (“Restasis® owns 100% of the market share.”).

Further, the required nexus was lacking because the sales were not attributable to using the 0.05% CsA emulsion. “Where the offered secondary consideration actually results from something other than what is both claimed and novel in the claim, there is no nexus to the merits of the claimed invention.” In re Kao, 639 F.3d 1057, 1070 (Fed. Cir. 2011).

In addition, Ding ’979 was listed in the Orange Book for Restasis® and thus presumably blocked the entry of both the claimed emulsion and comparable emulsions until 2014. EX1024, 0007. Thus, any sales of Restasis® that can be attributed to the medication (as opposed to what Allergan conceded was its decade-long marketing efforts (EX1004, 0367) and to the narrow definition of the relevant market) cannot be attributed to the 0.05% CsA emulsion because the 0.10% CsA emulsion was also safe and effective, and was as substantially effective as the 0.05% CsA emulsion. For example, the patent itself allegedly teaches the claimed emulsion is as substantially therapeutically effective as the prior art 0.10% CsA/1.25% castor oil emulsion, which is Example 1D of Ding ’979. EX1001, 14:14-44; EX1006, 4:32-43. Sall also taught that the 0.05% CsA emulsion was as substantially therapeutically effective as the 0.10% CsA emulsion. Section VIII.B.i, supra.
Because Allergan failed to provide relevant comparisons and did not permit sales of comparable emulsions, its evidence of sales of Restasis® lacks the required nexus to the claimed invention to support patentability.

C. **No Industry Praise**

Dr. Schiffman asserted in his second declaration that “Restasis® has been well received by the medical community.” EX1004, 0273. However, Allergan cited no industry praise during prosecution that related to the claims of the ’556 patent specifically or that would distinguish the claimed emulsion from the prior art 0.10% CsA emulsion of Ding ’979 Example 1D. *Id.* at 0273, 363 (referring to the use of topical CsA without differentiating between Restasis® and the topical CsA treatment of Ding ’979’s Example 1D). Thus, no nexus was shown to exist between the claims and alleged praise.

D. **No Long-Felt, Unmet Need**

Allergan similarly failed to demonstrate any nexus between the alleged long-felt need and the claims of the ’556 patent. As discussed above, Allergan’s Ding ’979 patent prevented sales of alternative comparable emulsions, including a 0.10% CsA emulsion that was as substantially therapeutically effective as a 0.05% emulsion. Furthermore, topical ophthalmic products were already available for those suffering from dry eye disease/KCS, including GenTeal®, Hypotears® PF, Moisture Eyes®, Refresh® Plus, Refresh® Tears, Tears Naturale Free®, and
TheraTears®. EX1020, 0002. There was no long-felt need established, nor a nexus shown between an alleged long-felt need and how it was adequately addressed by the claimed invention.

E. No Failure of Others

Dr. Schiffman asserted: “Other companies have tried to develop prescription treatments for dry-eye, but none have been FDA approved as of this date.”

EX1004, 0274. However, no evidence of failure on a technical or scientific level was presented, and such general assertions without supporting evidence are insufficient to demonstrate a failure of others. Perfect Web Technologies, Inc. v. InfoUSA, Inc., 587 F.3d 1324, 1332 (Fed. Cir. 2009). Indeed, as the owner of Ding ’979, only Allergan could have obtained FDA approval of Example 1D of Ding ’979. Thus, the failure to obtain FDA approval of Example 1D appears to be a self-inflicted failure of Allergan’s own design. Moreover, as discussed above in Section D, there were other topical ophthalmic products available for patients suffering from dry eye diseases. Allergan failed to establish a nexus between what was claimed in the ’556 patent and any purported failure of others.

XI. Conclusion

For the reasons set forth above, claims 1-27 of the ’556 patent are unpatentable over the asserted prior art. Petitioners therefore request that an inter
partes review of these claims be instituted and that they be found by the Board to be unpatentable and canceled.

Respectfully submitted,

Dated: January 6, 2017

/s/Gary J. Speier
Gary J. Speier, Lead Counsel
Reg. No. 45,458
Mark D. Schuman, Back-Up Counsel
Reg. No. 31,197
CARLSON, CASPERS, VANDENBURGH, LINDQUIST & SCHUMAN, P.A.
XII. Certificate of Compliance

Pursuant to 37 C.F.R. §42.24(d), the undersigned certifies that this Petition complies with the type-volume limitation of 37 C.F.R. §42.24(a). The word count application of the word processing program used to prepare this Petition indicates that the Petition contains 12,862 words, excluding the parts of the brief exempted by 37 C.F.R. §42.24(a).

Respectfully submitted,

Dated: January 6, 2017

/s/Gary J. Speier
Gary J. Speier, Lead Counsel
Reg. No. 45,458
XIII. PAYMENT OF FEES UNDER 37 C.F.R. §§ 42.15 (A) AND 42.103

The required fees are submitted herewith. If any additional fees are due at any time during this proceeding, the Office is authorized to charge such fees to Deposit Account No. 502880.
### XIV. Appendix – List of Exhibits

<table>
<thead>
<tr>
<th>Exhibit No.</th>
<th>Description</th>
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<tbody>
<tr>
<td>1001</td>
<td>U.S. Patent No. 8,624,556 to Acheampong <em>et al.</em></td>
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<tr>
<td>1002</td>
<td>Declaration of Dr. Mansoor Amiji</td>
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<tr>
<td>1003</td>
<td><em>Curriculum Vitae</em> of Dr. Mansoor Amiji</td>
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<td>1004</td>
<td>File history of U.S. Patent No. 8, 624,556 to Acheampong <em>et al.</em></td>
</tr>
<tr>
<td>1006</td>
<td>U.S. Patent No. 5,474,979 to Ding <em>et al.</em>, filed May 17, 1994</td>
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<tr>
<td>1007</td>
<td>K. Sall, <em>et al.</em>, <em>Two Multicenter, Randomized Studies of the Efficacy and Safety of Cyclosporine Ophthalmic Emulsion in Moderate to Severe Dry Eye Disease</em>, 107 OPHTHALMOLOGY 631 (2000)</td>
</tr>
<tr>
<td>1008</td>
<td>A. Acheampong <em>et al.</em>, <em>Cyclosporine distribution into the conjunctiva, cornea, lacrimal gland, and systemic blood following topical dosing of cyclosporine to rabbit, dog, and human eyes</em>, 2 LACRIMAL GLAND, TEAR FILM, AND DRY EYE SYNDROMES 1001 (1998)</td>
</tr>
<tr>
<td>1009</td>
<td>U.S. Patent No. 5,578,586 to Glonek <em>et al.</em>, filed February 4, 1994</td>
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<tr>
<td>1010</td>
<td>U.S. Patent No. 5,981,607 to Ding <em>et al.</em>, filed January 20, 1998</td>
</tr>
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<td>1011</td>
<td>R. Kaswan, <em>Intraocular Penetration of Topically Applied</em></td>
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<tr>
<td>Reference</td>
<td>Description</td>
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<td>1012</td>
<td><em>Cyclosporine</em> 20 <em>TRANSPL. PROC.</em> 650 (1988)</td>
</tr>
<tr>
<td>1013</td>
<td>K. Kunert <em>et al.</em>, <em>Analysis of Topical Cyclosporine Treatment of Patients with Dry Eye Syndrome</em> 118 <em>ARCH OPHTHALMOL</em> 1489 (2000)</td>
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<tr>
<td>1014</td>
<td>Physicians’ Desk Reference for Ophthalmic Medicines, 1999</td>
</tr>
<tr>
<td>1015</td>
<td>K. Turner <em>et al.</em>, <em>Interleukin-6 Levels in the Conjunctival Epithelium of Patients with Dry Eye Disease Treated with Cyclosporine Ophthalmic Emulsion</em> 19 <em>CORNEA</em> 492 (2000)</td>
</tr>
<tr>
<td>1016</td>
<td>D. Stevenson <em>et al.</em>, <em>Efficacy and Safety of Cyclosporin A Ophthalmic Emulsion in the Treatment of Moderate-to-Severe Dry Eye Disease</em> 107 <em>OPHTALMOL.</em> 967 (2000)</td>
</tr>
<tr>
<td>1019</td>
<td>A. Kanpolat <em>et al.</em>, <em>Penetration of Cyclosporin A into the Rabbit Cornea and Aqueous Humor after Topical Drop and Collagen Shield Administration</em> 20 <em>CLAO J</em> 119 (1994)</td>
</tr>
<tr>
<td>1020</td>
<td>A. Vieira <em>et al.</em>, <em>Effect of ricinoleic acid in acute and subchronic experimental models of inflammation,</em> 9 <em>MED. INFLAMM.</em> 223 (2000)</td>
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<tr>
<td>1021</td>
<td>R. Murphy, <em>The Once and Future Treatment of Dry Eye,</em> REVIEW OF OPTOMETRY 1 (2000)</td>
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<td>1021</td>
<td>D. Small et al., <em>Blood concentrations of Cyclosporin A During Long-Term Treatment with Cyclosporin A Ophthalmic Emulsions in Patients with Moderate to Severe Dry Eye Disease</em> 18 J. Oc. Pharm. Therap. 411 (2002)</td>
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<td>1024</td>
<td>Approved Drug Products with Therapeutic Equivalence Evaluations (34th Ed.) (2014) (Excerpts)</td>
</tr>
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<td>1025</td>
<td>Declaration of Dr. Walter Chambliss</td>
</tr>
<tr>
<td>1026</td>
<td><em>Curriculum Vitae</em> of Dr. Walter Chambliss</td>
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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105(a), this is to certify that I caused to be served a true and correct copy of the foregoing Petition for inter partes review of U.S. Patent No. 8,642,556 (and accompanying Exhibits 1001-1026) on this 6th day of January, 2017, on the Patent Owner at the correspondence address of the Patent Owner as follows:

by FedEx Priority Overnight® on the Patent Owner at the correspondence address of the Patent Owner as follows:

ALLERGAN, INC.
2525 Dupont Drive, T2-7H
Irvine, CA 92612-1599

and by FedEx Priority Overnight® on counsel of record for Allergan in IPR2016-01129 for U.S. Patent No. 8,642,556:

Dorothy P. Whelan
Michael Kane
FISH & RICHARDSON P.C.
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Respectfully submitted,

Dated: January 6, 2017
/s/Gary J. Speier
Gary J. Speier, Lead Counsel
Reg. No. 45,458