Paper No. _____

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AKORN INC.
Petitioner

v.

ALLERGAN, INC.
Patent Owner

Case No. IPR2017-00599
Patent No. 8,633,162

PETITION FOR INTER PARTES REVIEW OF U.S. PATENT NO. 8,633,162

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I. INTRODUCTION

On December 8, 2016, the Board instituted IPR2016-01130, stating that there was a reasonable likelihood that claims 1-24 of U.S. Patent No. 8,633,162 to Acheampong *et al.* ("the '162 patent," EX1001) are obvious. *Mylan Pharm., Inc. v. Allergan, Inc.*, IPR2016-01130, slip op. at 22 (PTAB December 8, 2016) (Paper 8). The present Petition presents the same grounds of unpatentability and the same arguments and evidence as the Petition in IPR2016-01130. The present Petitioner has received permission from Mylan Pharmaceuticals, Inc., the petitioner in IPR2016-01130, to rely upon the same expert. The present Petition is substantially identical to the Petition filed in IPR2016-01130. Accordingly, it is believed that the present Petition should be granted for the same reasons that the Board instituted IPR2016-01130.

In particular, Akorn Inc. ("Petitioner") requests review of the '162 patent that issued on January 21, 2014. PTO records indicate the '162 patent is assigned to Allergan, Inc. ("Patent Owner"). This Petition demonstrates that there is a reasonable likelihood that claims 1-24 of the '162 patent are unpatentable for failing to distinguish over 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 '162 patent claims concern conventional methods of treating dry eye disease by the "twice a day" topical ophthalmic administration of an emulsion containing cyclosporin A ("CsA"), castor oil, and other standard ingredients, as generally claimed in U.S. Patent No. 8,685,930. Each element of the emulsion, including the claimed CsA and castor oil percentages and methods for administering them to treat dry eye disease, were disclosed in a single prior art reference (Ding '979). During prosecution of a parent application, applicants admitted 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; EX1002, ¶18. A second 102(b) prior art reference, Sall, discloses twice-daily administration of a 0.05% CsA-in-castor oil emulsion for the same purpose.

In prosecuting the '162 patent as a continuation application, applicants changed course and attempted to withdraw the admissions regarding Ding '979. 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, 0253; EX1002, ¶¶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 the 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 expected in view of and were already disclosed in the prior art.

A. Brief Overview of the '162 Patent

The '162 patent has an earliest claimed priority date of September 15, 2003. Independent claim 1 recites a method of treating dry eye disease, comprising administering an emulsion of 0.05% CsA in 1.25% castor oil, polysorbate 80, acrylate/C10-30 alkyl acrylate cross-polymer ("cross-polymer") and water, twice-daily. 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, which comprises glycerine and a buffer. 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 13-16 compare the therapeutic effect of the claimed emulsion with emulsions with different percentages of CsA or castor oil. Claims 13-14 and 16-17 respectively compare the therapeutic efficacy or adverse events of the claimed emulsion verses one with 0.10% CsA. Claim 15 compares the breakdown rate of the claimed with a second emulsion containing half as much castor oil.

Claim 18 recites a method of reducing side effects in a human being treated for dry eye syndrome using an emulsion incorporating the ingredients and/or weight percentage limitations of claims 1 and 7-9, and the pH value recited in claim 12. Dependent claims 19-21 further specify sodium hydroxide as the buffer and glycerine as the tonicity/demulcent agent, and that the blood of the human has substantially no detectable concentration of CsA. Dependent claim 22 incorporates the limitation of claim 1 that the emulsion is effective in treating dry eye disease.

Independent claim 23 recites a method of treating dry eye disease in a human being treated for dry eye syndrome using an emulsion incorporating the ingredients and weight percentage limitations of claims 1 and 7-9 and the

limitation of claim 1 that the emulsion is effective in treating dry eye disease. Dependent claim 24 simply recites a pH range for the emulsion.

B. Brief Overview of the Prosecution History

U.S. Patent Application No. 13/967,179 ("the '179 application") was filed on August 14, 2013, and issued five months later on January 21, 2014, as the '162 patent. The '179 application is a continuation, via U.S. applications 13/961,818 and 11/897,177, of U.S. application 10/927,857 ("the '857 application," EX1005), which 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 '162 patent (EX1002, ¶¶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 '179 application, the applicants acknowledged their prior admissions, but claimed that they had collected evidence to support the patentability of the claims "[s]ince these comments have been filed." EX1004, 0007. The examiner then rejected the claims as obvious over Ding '979. *Id.* at 0126-43. 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 nonobvious based on objective indicia. *Id*. at 0189-93. It also

filed a terminal disclaimer for the applications or parent applications that resulted in the '930, '111, '556, '048, and '191 patents. *Id.* at 0115-16.

In remarks accompanying a Notice of Allowance (*id.* at 0393; EX1002, ¶23) the examiner concluded that applicants had failed to demonstrate commercial success or long-felt need. EX1004, 0403-05. However, relying on declarations submitted by Drs. Schiffman and Attar, the examiner stated 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 0407.

The alleged "unexpected results" are addressed in the declaration of Dr. Mansoor Amiji that accompanies this Petition. EX1002, ¶¶128-52. As noted by Dr. Amiji, 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 that made them

unreliable, which are discussed in this Petition. As such, and because of the new information presented herein and supported by Dr. Amiji'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. Amiji'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. Amiji'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. EX1002, ¶¶97-98, 114.

Further, this Petition presents new arguments based on expert testimony as to why the claims are obvious under Ding '979 and other references that were not substantively analyzed during prosecution. Among other things, Dr. Amiji 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

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; EX1002, ¶62. 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; EX1002, ¶65. Ding '979 teaches that CsA is effective in treating dry eye disease/KCS "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; EX1002, ¶66. 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; EX1002, ¶¶67-68. 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; EX1002, ¶68. 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; EX1002, ¶¶68, 99. Ding '979 does not expressly discuss twice-daily administration of the emulsions.

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; EX1002, ¶¶74-75. Sall states 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, 634-36; EX1002, ¶¶74-78, 81. 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; EX1002, ¶74.

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 KCS twice a day for a period of three months. EX1008 at 1002; EX1002, ¶¶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; EX1002, ¶¶85-86.

iv. U.S. Patent No. 5,578,586 to Glonek *et al.* ("Glonek," EX1009)

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; EX1002, ¶¶88-89. Glonek discloses topical emulsions for the treatment of dry eye disease, "whereby blurred vision is reduced." EX1009, 3:5-6; EX1002, ¶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; EX1002, ¶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. EX1002, ¶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.

Petitioner's expert, Dr. Mansoor Amiji, is the Bouvé College Distinguished Professor in the Department of Pharmaceutical Sciences at Northeastern University in Boston, Massachusetts. EX1002, ¶1; EX1003 (CV). Dr. Amiji is also an affiliate faculty member in the Departments of Chemical Engineering and Biomedical Engineering at Northeastern, as well as a Distinguished Adjunct Professor of Pharmacy at King Abdulaziz University. EX1002, ¶1; EX1003. Dr. Amiji has authored or co-authored more than 200 peer-reviewed journal articles and 43 book chapters. EX1002, ¶6; EX1003. He has served on the editorial board of 13 peer-reviewed journals, including *Drug Design: Development and Therapy, Expert Opinion on Drug Delivery, Pharmaceutical Formulations and Quality, and Tissue Barriers.* EX1002, ¶5; EX1003.

Dr. Amiji 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. EX1002, ¶¶3-4; EX1003. Dr. Amiji 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. EX1003.

II. GROUNDS FOR STANDING

Petitioner certifies that, under 37 C.F.R. § 42.104(a), the '162 patent is available for *inter partes* review, and Petitioner is not barred or estopped from requesting *inter partes* review of the '162 patent on the grounds identified in view of the Motion for Joinder submitted herewith.

III. MANDATORY NOTICES UNDER 37 C.F.R. § 42.8

Real Parties-in-Interest (37 C.F.R. § 42.8(b) (1)): The following real party-in-interest is identified: Akorn, Inc.

Related Matters (37 C.F.R. § 42.8(b) (2)): IPR2016-01130, discussed above, involves the '162 Patent, and that IPR was instituted on December 8, 2016. In addition, an IPR petition for the '162 patent was previously filed by Apotex Corp. and Apotex Inc. as IPR2015-01278, as were petitions for related U.S. Patent Nos. 8,648,048 (IPR2015-01284), 8,629,111 (IPR2015-01282), 8,642,556 (IPR2015-01286), and 8,685,930 (IPR2015-01283), but all were terminated prior to institution decisions. IPR petitions for the related patents 8,685,930, 8,629,111, 8,642,556, 8,648,048 and 9,248,191 were also filed by the petitioner in IPR2016-01130 as IPR2016-01127, IPR2016-01128, IPR2016-01129, IPR2016-01131 and

IPR2016-01132, respectively. U.S. Application No. 15/011,159, filed January 29, 2016, claims the benefit of U.S. Application No. 14/222,478 (now the '191 patent), which is a continuation, via U.S. Application Nos. 13/961,828 and 11/897,177, of the '857 application.

Petitioner and other entities are involved in litigation over the '162 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). A complaint asserting the '162 patent against Petitioner was served no earlier than August 24, 2015. Petitioner also identifies the following pending actions involving the '162 patent: *Allergan, Inc., v. Innopharma, Inc. and Pfizer, Inc.*, No. 2:15-cv-1504; *Allergan, Inc., v. DEVA Holding A.S.*, No. 2:16-cv-01447; *Allergan, Inc*., *v. Twi Pharmaceuticals, Inc. et al.*, No. 2:16-cv-00820; and *Allergan, Inc. v. Famy Care Ltd.,* No. 2:16-cv-00401, all in the Eastern District of Texas. Petitioner also identifies the following terminated action involving the '162 patent: *Allergan, Inc. v. Actavis et al.*, No. 2: 14-cv-00638, in the Eastern District of Texas.

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

Lead Counsel: Michael R. Dzwonczyk (Reg. No. 36,787)

Back-Up Counsel: Azy S. Kokabi (Reg. No. 58,902)

Back-Up Counsel: Travis B. Ribar (Reg. No. 61,446)

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

Petitioner hereby consents to electronic service.

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IV. STATEMENT OF THE PRECISE RELIEF REQUESTED

Petitioners request review of claims 1-24 of the '162 patent under 35 U.S.C. § 311 and AIA § 6 and that each of the claims be canceled as unpatentable:

Ground	Claims	Obvious Under § 103 over
1	1-10, 12-14, 16-20, and 22-24	Ding '979 and Sall
2	11 and 21	Ding '979, Sall, and Acheampong
3	15	Ding '979, Sall, and Glonek

V. STATEMENT OF NON-REDUNDANCY

Each of the Grounds raised in this Petition is meaningfully distinct. Ground 1 asserts obviousness of claims 1-10, 12-14, 16-20, and 22-24 based on Ding '979

and Sall. Ground 2 challenges dependent claims 11 and 21, based Ding '979, Sall, and Acheampong. Acheampong expressly teaches the property intrinsic to the claimed emulsion results in substantially no detectable blood concentration at trough and peak levels. Ground 3 challenges dependent claim 15 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.

VI. 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, and 18-19 of the '162 patent. Claims 5, 10, and 19 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, 12:25-27. In light of the specification, the broadest reasonable interpretation of the term "buffer" includes sodium hydroxide. EX1002, ¶38.

B. "substantially no detectable concentration"

The term "substantially no detectable concentration" appears in claims 11 and 21 of the '162 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, 5:64–6:3. A skilled artisan could measure blood concentration at either peak or trough levels. EX1002, ¶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," "substantially therapeutically effective as," and "as

much therapeutic effectiveness as"

Independent claims 1 and 23 and dependent claim 22 state the emulsion is "effective 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); EX1002, ¶¶40, 47. The '162 patent teaches that CsA "acts to enhance or restore lacrimal gland tearing in providing the desired therapeutic effect." EX1001, 9:14-17. 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; EX1002, ¶40. Thus, in the context of the '162 patent, an emulsion that is effective in increasing tear production is an example of an emulsion therapeutically effective in treating dry eye disease.

Claims 13 and 14 respectively describe the emulsion of claim 1 as being "as substantially therapeutically effective as" and having "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. EX1002, ¶¶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"

Claims 16 recites that the emulsion of the claimed method has fewer "adverse events" relative to a second emulsion, and claim 17 further recites that the "adverse events" are "side effects." The specification also defines adverse events to include "undesirable side effects." EX1001, 15:9-16. 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, stinging, and general eye pain. EX1002, ¶43; EX1007, 636, Table 3.

E. "breaks down"

Claim 15 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 '162 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, 2:43-49. As explained

by Dr. Amiji, a person of ordinary skill would understand the term "breaks down" as used in claim 15 to include that the emulsion differentiates into separate aqueous and oil layers on the eye. EX1002, ¶45.

VII. 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. OPHTHALMOL. 1489 (2000) ("Kunert," EX1012); EX1002, ¶48. CsA, a known anti-inflammatory agent, had been shown to significantly reduce inflammation markers associated with dry eye upon topical ophthalmic administration. EX1012,

1489; EX1002, ¶49. 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 [KCS]." *Medications for Dry Eye* (1999) In PHYSICIANS' 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; EX1002, ¶50.

Clinical trials establishing the efficacy and safety of CsA-in-castor oil emulsions for treatment of dry eye disease/KCS were known prior to September 2003. EX1002, ¶49. 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-in-castor 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; EX1002, ¶¶49, 52. 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 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; EX1002, ¶52. 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, 0262, 0286-87; EX1002, ¶¶129-30.

Castor oil vehicles were used for topical ophthalmic administration of highly lipophilic compositions, like CsA, that must be formulated in a water-solubilized form. U.S. Patent No. 5,981,607 to Ding *et al.*, filed January 20, 1998 ("Ding '607," EX1010); EX1002; ¶51 discussing REMINGTON'S 20TH EDITION: THE SCIENCE AND PRACTICE OF PHARMACY (A. Gennaro ed. 2003) ("Remington," EX1016); E. Goto *et al., Low-Concentration Homogenized Castor Oil Eye Drops for Noninflamed Obstructive Meibomian Gland Dysfunction* 109 OPHTHALMOL. 2030 (2002) ("Goto," EX1017).

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; EX1002, ¶¶54-55. 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; EX1002, ¶55.

Clinical trials conducted prior to September 2003, also established that castor oil provided a "large therapeutic effect" to patients suffering from KCS. *E.g.*, EX1014, 492; EX1015, 973; EX1002, ¶56. 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. *E.g., A. Vieira et al., Effect of ricinoleic acid in acute and subchronic experimental models of inflammation*, 9 MED. INFLAMM. 223 (2000) ("Vieira," EX1019); EX1002, ¶56. Vieira states, "topical application of ricinoleic acid (RA), the main

component of castor oil, exerts remarkable analgesic and anti-inflammatory effects." EX1019, 223; EX1002, ¶56.

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. EX1002, ¶57; 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/KCS by significantly reducing inflammation and increasing tear production. EX1002, ¶58, 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. EX1002, ¶¶53, 59, 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.

VIII. DETAILED EXPLANATION OF GROUNDS FOR UNPATENTABILITY

A. [Ground 1] Claims 1-10, 12-14, 16-20, and 22-24 are Obvious under 35 U.S.C. § 103 over Ding '979 and Sall

Ground 1 establishes by a preponderance of the evidence the obviousness over Ding '979 (EX1006) and Sall (EX1007) of methods for treating dry eye disease recited in claims 1-10, 12-14, 16-20, and 22-24 of the '162 patent.

i. Claims 1-10, 12, 18-20, and 22-24

Each of independent claims 1, 18, and 23 recites a method comprising topically administering to the eye of a human, twice-daily, an emulsion which comprises 0.05% CsA and 1.25% castor oil, and other excipients. Claims 1 and 23 each recite that the emulsion is effective in treating dry eye disease. The preamble

of claim 18 recites that it is a method of reducing side effects in a human being treated for dry eye syndrome. The discussion that follows uses the elements and organization recited in claims 23 and 24 because they are narrower than, and contain limitations from, independent claims 1 and 18. Thus, the teachings that render claims 23 and 24 obvious also render claims 1-10, 12, 18-20 obvious. *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 preamble phrase "[a] method of reducing side effects" in claim 18 is not limiting. However, to the extent it is deemed limiting, this feature is discussed below in Section VIII.A.iii.

The elements of claims 1-10, 12, 18-20, and 22, that are comparable to the elements of claims 23 and 24, are shown in the comparative table below (EX1002, ¶93), where particular clauses and elements have been given item numbers for convenient reference:

Item	Claim 23	Claim 18	Claim 1
I.A	A method of treating dry eye disease, the method comprising the step of topically	A method of reducing side effects in a human being treated for dry eye syndrome, the method	A method of treating dry eye disease, the method comprising topically

Item	Claim 23	Claim 18	Claim 1
	administering to an eye of a human in need thereof an emulsion..., the emulsion comprising:	comprising the step of topically administering to the eye of the human in need thereof an emulsion..., wherein the emulsion comprises:	administering to the eye of a human in need thereof an emulsion..., wherein the emulsion comprises
I.B	at a frequency of twice a day	at a frequency of twice a day	at a frequency of twice a day
II	cyclosporin A in an amount of about 0.05% by weight;	cyclosporin A in an amount of about 0.05% by weight;	cyclosporin A in an amount of about 0.05% by weight,
III	castor oil in an amount of about 1.25% by weight;	castor oil in an amount of about 1.25% by weight;	**Item IX** below
IV	polysorbate 80 in an amount of about 1.0% by weight;	polysorbate 80 in an amount of about 1.0% by weight;	polysorbate 80, **Claim 7** (1.0%)
V	acrylate/C10-30 alkyl acrylate cross-polymer in an amount of 0.05% by weight;	acrylate/C10-30 alkyl acrylate cross-polymer in an amount 25 of about 0.05% by weight;	acrylate/C10-30 alkyl acrylate cross-polymer, **Claim 8** (0.05%)
VI	glycerine in an amount of about 2.2% by weight;	a tonicity component or a demulcent component in an amount of about 2.2% by weight; **Claim 20** (glycerine)	**Claims 2** (tonicity/ demulcent agent); **3, 6** (glycerine); and **9-10** (2.2%)
VII	sodium hydroxide; and	a buffer; and **Claim 19** (sodium hydroxide)	**Claims 4, 6, 9** (buffer) and **5, 10** (sodium hydroxide)

Item	Claim 23	Claim 18	Claim 1
VIII	water;	water;	water;
IX	**Item III** above	**Item III** above	and castor oil in an amount of about 1.25% by weight; and
X	wherein the emulsion is effective in treating dry eye disease.	**Claim 22** (wherein the emulsion is effective in treating dry eye disease.)	wherein the topical ophthalmic emulsion is effective in treating dry eye disease.
XI	**Claim 24** (pH in the range of about 7.2 to about 7.6)	wherein the topical ophthalmic emulsion has a pH in the range of about 7.2 to about 7.6.	**Claim 12** (pH in the range of about 7.2 to about 7.6)

The following explanation shows where each element of each Item of the above table is found in Ding '979 for independent claims 1, 18, and 23. The same analysis addresses the corresponding dependent claims in the above table.

Regarding **Item I.A** 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; EX1002, ¶¶62, 94. Moreover, Ding '979 teaches that CsA increases tear production in the eye and has been found effective in treating KCS or dry eye disease. 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/KCS, Ding '979 satisfies the elements of "topically administering to the [an] eye of the [a] human in need thereof an emulsion," (**Item I.A**) of claims 1, 18, and 23. EX1002, ¶95. Ding '979 also thereby teaches the "emulsion is effective in treating dry eye disease" (Item X), as recited in of claims 1, 22, and 23. EX1002, ¶95.

The emulsions disclosed in Ding '979 contain every ingredient of the emulsion recited in claims 1-24 as shown in Items II-IX and XI in the table above. The emulsion ingredients in Example 1 are shown below:

	Example 1				
	A	B	C	D	E
Cyclosporin A	0.40%	0.20%	0.20%	0.10%	0.05%
Castor oil	5.00%	5.00%	2.50%	1.25%	0.625%
Polysorbate 80	1.00%	1.00%	1.00%	1.00%	1.00%
Pemulen ®	0.05%	0.05%	0.05%	0.05%	0.05%
Glycerine	2.20%	2.20%	2.20%	2.20%	2.20%
NaOH	qs	qs	qs	qs	qs
Purified water	qs	qs	qs	qs	qs
pH	7.2–7.6	7.2–7.6	7.2–7.6	7.2–7.6	7.2–7.6

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. Amiji, based on Ding '979, a skilled artisan would reasonably expect that each of Examples 1A-E would be effective in treating dry eye disease/KCS (Item X) and indeed at least examples 1A-D are said in Ding '979 to be effective. EX1006, 5:18-

28; EX1002, ¶72; 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 1-24 of the '162 patent. The 1.0% polysorbate 80 ingredient in Ding '979 (e.g., Example 1) meets the polysorbate 80 limitation of claim 1-24, and is the precise percentage as recited in claims 7, 18, and 23 (and dependent claims) (**Item IV**). EX1002, ¶¶97-98. 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 (**Item V**) as recited in claims 1-24 and the 0.05% weight percentage limitation in claims 8, 18, and 23. EX1002, ¶¶97-98. Glycerine satisfies the tonicity/demulcent agent/compound or glycerine elements as recited in claims 2-3, 6, 9, 18, 20, 23 and dependent claims of the '162 patent (EX1001, 11:61—12:3), and the 2.2% percentage of claims 9-10 and 18-24 (**Item VI**) is shown in each emulsion of Example 1. *Id*. Sodium hydroxide of e.g., the Ding 979 Example 1 emulsions satisfies the buffer and sodium hydroxide elements recited in claims 4-6, 9-10, and 18-24 (**Item VII**). *Id.* The water ingredient in Ding '979 Example 1 emulsions satisfies the water elements of claims 1-24 (**Item VIII**). *Id.* Example 1 of Ding

'979 also discloses that the emulsions have a pH of 7.2-7.6, thereby satisfying the pH range element (**Item XI**) of claims 12, 18, and 24. EX1002, ¶98.

Ding '979 also satisfies the weight percentages of CsA and castor oil claimed in claims 1-24 of the '162 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% (**Items III and IX**). EX1006, 4:32-43; EX1002, ¶91. 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. EX1002, ¶99. 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:

Example 2

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

EX1006, 4:44-53.

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-castor oil ratio within the more preferred range as taught at 3:16-20 of EX1006. EX1002, ¶65. 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. Amiji, the skilled artisan would at once envisage these two emulsions as being taught by Ding '979, and would reasonably expect them to be effective for increasing tear production and treating dry eye disease/KCS as discussed below. EX1002, ¶72.

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. EX1002, ¶99. As noted by Dr. Amiji, 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 effective in the treatment of dry eye disease/KCS if the ratio of CsA to castor oil falls within the preferred range taught by Ding '979. EX1002, ¶72. 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 ***squarely within the teaching of the Ding reference***, and the Office should disregard any statements by the applicants suggesting otherwise[.]" EX1005, 0435 (emphasis added); EX1002, ¶¶18, 108. 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.

Sall teaches that twice-daily topical ophthalmic administration of 0.05% CsA in a castor oil emulsion vehicle is safe and effective, and that the 0.05% emulsion was at least as effective as the 0.10% CsA emulsion. Sall describes a "multicenter, randomized, double-masked" Phase 3 clinical trial. EX1007, 632; EX1002, ¶100. 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 to patients twice a day and parameters such as corneal staining, Schirmer tear values, blurred vision, and artificial tear use were tracked and

recorded. *Id*. In describing the methods of the clinical trial, Sall notes, "patients were treated twice daily with either CsA, 0.05% or 0.10%, or vehicle" (EX1007, 631), thereby teaching the "at a frequency of twice a day" element (**Item 1.B**) of claims 1-24.

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 [(keratoconjunctivitis sicca)] yielding improvements in both objective and subjective measures." *Id.* at 631; EX1002, ¶101. Sall reported that treatment with either percentage of CsA provided "significantly ($p \leq 0.05$) greater improvements than vehicle" for treating dry eye disease/KCS 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. As the Schirmer Tear Test measures tear production, the results of the Schirmer test in Sall confirm that the 0.05% CsA-castor oil emulsion increased tear production in patients with KCS. *Id.* ("The mean categorized Schirmer values ... with the CsA 0.05% group [were] significantly greater than the vehicle group.") Sall also reported that the 0.05% CsA emulsion was statistically significantly better than vehicle for blurred vision and artificial tear use. EX1007, 636; EX1002, ¶¶79-80. Based on the express teachings of Sall, one of ordinary skill in the art would have expected the castor oil

emulsion vehicle containing 0.05% by weight CsA to be at least as safe and effective at treating dry eye disease/KCS and increasing tear production as the castor oil emulsion containing 0.10% by weight CsA.

In addition to teaching that the 0.05% CsA emulsion was at least as effective as the 0.10% CsA emulsion, Sall also provided reasons to select the 0.05% CsA emulsion over the 0.10% emulsion. EX1002, ¶82. For example, Sall reported superior results for the 0.05% CsA emulsion with regard to three parameters, but reported no such results for the 0.10% CsA emulsion:

> CsA 0.05% treatment also gave significantly greater improvements ($P < 0.05$) in three subjective measures of dry eye disease (blurred vision, need for concomitant artificial tears, and the physician's evaluation of global response to treatment).

EX1007, 631; EX1002, ¶102.

Sall further teaches that treatment with 0.05% CsA resulted in a decrease of adverse side effects as compared to the 0.10% CsA emulsion. EX1002, ¶103. 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, conjunctival hyperemia, visual disturbances, and eye pain, as compared to the 0.10% CsA treatment group. *Id*.; EX1002, ¶79. Sall also describes a significant decrease in the use of artificial tears for the 0.05% treatment group as compared to the vehicle at month 6. *Id*. at ¶80. As Sall described both emulsions as effective at increasing tear production and treating dry eye disease/KCS, the decrease in adverse side effects provided additional reasons to formulate the emulsion with 0.05% CsA instead of 0.10% CsA.

In addition, Sall also provides a strong rationale to deliver 0.05% CsA using the 1.25% castor oil vehicle taught by Ding '979 (Example 2C). 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"); EX1002, ¶¶83, 106. 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 Ding '979's more preferred range of between 0.12 and 0.02 (id. at 3:17-20) and also within the ratio range found with each of the Example 1 emulsions (0.04-0.08). *Id.* 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); EX1002, ¶107. 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, as taught by Sall. 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; EX1002, ¶104.

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. EX1002, ¶109. As explained by Dr. Amiji, it would have been a routine matter for a skilled artisan to make and then confirm the efficacy of the

emulsion comprising 1.25% castor oil and 0.05% CsA. EX1002, ¶109; EX1001, 14:14-16 ("These compositions are produced in accordance with well known techniques[.]").

Thus, Ding '979 and Sall, along with the knowledge of the skilled artisan, render claims 1-10, 12, 18-20 and 22-24 obvious. The following claim chart shows in further detail how Ding '979 and Sall render claims 1-10, 12, 18-20, and 22-24 obvious using exemplary claims 23 and 24, along with reference to supporting explanation in the declaration of Dr. Amiji (EX1002).

Exemplary Claim	**Obvious Over Ding '979 and Sall**
23. A method of treating dry eye disease, the method comprising the step of topically administering to an eye of a human in need thereof an emulsion..., **[Item I.A]**	"The formulations set forth in Examples 1-4 were made for treatment of keratoconjunctivitis sicca (dry eye) syndrome." EX1006, 5:9-11; EX1002, ¶95. "The activity of cyclosporins, as hereinabove noted, is as an immunosuppressant and in the enhancement or restoring of lacrimal gland tearing." EX1006, 1:37-39; EX1002, ¶94. "[A] non-irritating emulsion ... suitable for topical application to ocular tissue." EX1006, 6:3-7; EX1002, ¶¶63, 69-70. "Cyclosporins [have] ... known immunosuppressant activity ... effective in treating immune [mediated] keratoconjunctivitis sicca (KCS or dry eye disease)." EX1006, 1:10-16; EX1002, ¶¶94-95. "[F]ormulations of topical CsA ophthalmic emulsion" EX1007, 638.

Exemplary Claim	Obvious Over Ding '979 and Sall
	"[T]he mean categorized Schirmer values ... with the CsA 0.05% group [were] significantly greater than the vehicle group." EX1007, 635; EX1002, ¶102.
at the frequency of twice a day, **[Item I.B]**	"[T]reated twice daily." EX1007, 631; EX1002, ¶100.
the emulsion comprising: cyclosporin A in an amount of about 0.05% by weight; **[Item II]**	"The pharmaceutical emulsion ... wherein the cyclosporin "[CsA] is present in an amount of between about 0.05 to about 0.40%, by weight." EX1006, 6:27-29 and claims 7-8. Example 1E (0.05% CsA). Id. at 4:33-43. "More preferably ... the weight ratio of cyclosporin to castor oil is between 0.12 and 0.02." *Id*. at 3:17-20. Example 1B (0.04 ratio of CsA-to-castor oil). *Id*. at 4:33-43; EX1002, ¶¶96, 98-99. "CsA, 0.05% or 0.1%, or vehicle." EX1007, 631; EX1002, ¶100.
castor oil in an amount of about 1.25% by weight; **[Items III & IX]**	"The pharmaceutical emulsion ... [wherein] the castor oil is present in an amount of between about 0.625%, by weight, and about 5.0% by weight." EX1006, 6:27-31 and claims 7-8. Examples 1D and 2C (1.25% castor oil). *Id*. at 4:33-54. "More preferably ... the weight ratio of cyclosporin to castor oil is between 0.12 and 0.02." *Id*. at 3:17-20. Example 1B (0.04 ratio of CsA-to-castor oil). *Id*. at 4:33-43. "CsA, 0.05% or 0.1%, or vehicle." EX1007,

Exemplary Claim	Obvious Over Ding '979 and Sall
	631. "The objective of the studies to compare 0.05% and 0.1 % CsA emulsions to vehicle." *Id*. at 632, 635-36; *id*. at figs. 1-4. Castor oil in water emulsions. *Id*. at 632; EX1002, ¶¶96, 98-100.
polysorbate 80 in an amount of about 1.0% by weight; **[Item IV]**	EX1006, 4:33-43 (Examples 1A-E) and claims 7-8 (1.00% polysorbate 80); EX1002, ¶¶97-98.
acrylate/C10-30 alkyl acrylate cross-polymer in an amount of about 0.05% by weight; **[Item V]**	EX1006, 4:33-43 (Examples 1A-E) and claims 7-8 (0.05% Pemulen®); EX1002, ¶¶97-98. "Pemulens are Acrylates/C10-30 Alkyl Acrylate Cross-Polymers." EX1006, 4:4-5; EX1002, ¶65.
glycerine in an amount of about 2.2% by weight; **[Item VI]**	EX1006, 4:33-43, Examples 1A-E and claims 7-8 (2.20% glycerine); EX1002, ¶¶97-98.
sodium hydroxide; and **[Item VII]**	EX1006, 4:33-43, Examples 1A-E (sodium hydroxide); EX1002, ¶¶97-98. "The pH of the emulsions can be adjusted in a conventional manner using sodium hydroxide to a near physiological pH level." EX1006, 4:14-16; EX1002, ¶98.
water; and **[Item VIII]**	EX1006, 4:33-43, Examples 1A-E (water); EX1002, ¶¶97-98. "CsA emulsions ... were sterile, nonpreserved castor oil in water emulsions." EX1007, 632; EX1002, ¶100.
wherein the emulsion is effective in treating dry eye	"The formulations set forth in Examples 1-4 were made for treatment of keratoconjunctivitis

Exemplary Claim	Obvious Over Ding '979 and Sall
disease. **[Item X]**	sicca (dry eye) syndrome." EX1006, 5:9-11; EX1002, ¶72. "The activity of cyclosporins, as hereinabove noted, is as an immunosuppressant and in the enhancement or restoring of lacrimal gland tearing." EX1006, 1:37-39; EX1002, ¶94. "Cyclosporins [have] ... known immunosuppressant activity ... effective in treating immune medicated [sic: mediated] keratoconjunctivitis sicca (KCS or dry eye disease) in a patient suffering therefrom." EX1006, 1:10-16; EX1002, ¶94. "CsA 0.05% and 0.1% were safe and effective in the treatment of moderate to severe dry eye disease." EX1007, 631 & n.1; EX1002, ¶101. "[T]he mean categorized Schirmer values ... with the CsA 0.05% group [were] significantly greater than the vehicle group." EX1007, 635; EX1002, ¶102.
24. The method of claim 23, wherein the emulsion has a pH in the range of about 7.2 to about 7.6. **[Item XI]**	Examples 1A-E and claim 8, each having pH values of 7.2 – 7.6. EX1006, 4:33-43; EX1002, ¶98.

ii. <u>Claims 13 and 14</u>

Claim 13 depends from claim 1, and merely further recites, "the emulsion is as substantially therapeutically effective as a second emulsion administered to a human in need thereof at a frequency of twice a day, the second emulsion comprising cyclosporin A in an amount of 0.1% by weight and castor oil in an

amount of 1.25% by weight." Claim 14 similarly depends from claim 1, and further recites, "the emulsion achieves at least as much therapeutic effectiveness as a second emulsion administered to a human in need thereof at a frequency of twice a day, the second emulsion comprising cyclosporin A in an amount of 0.1% by weight and castor oil in an amount of 1.25% by weight."

As discussed above, Sall teaches the twice-daily administration of topical, ophthalmic emulsions comprising 0.05% or 0.10% CsA in castor oil. EX1007, 632; EX1002, ¶¶110-11. In assessing the relative efficacies of the CsA emulsions, Sall measured corneal staining and Schirmer values, two clinical tests described in the prior art (EX1010, 6:34—7:23) and identified during prosecution of the '162 patent by Allergan's Dr. Schiffman as, "key objective testing measures for dry eye or KCS." EX1004, 0261. Sall reported:

> "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 (corneal staining and categorized Schirmer values).... ***There was no dose-response effect.*** Both CsA treatments exhibited an excellent safety profile, and there were no significant topical or systemic adverse safety findings.

EX1007, 631. Because there was no dose-response effect with regard to the efficacy of a 0.05% CsA emulsion versus a 0.10% CsA emulsion, Sall established that the 0.05% CsA emulsion was "as substantially therapeutically effective as" and had "at least as much therapeutic effectiveness as" the 0.10% CsA emulsion, as recited in claims 13 and 14 of the '162 patent. EX1002, ¶113. These claim limitations thus fail to patentably distinguish the emulsion and method discussed above with respect to claim 1, which would have been obvious to a skilled artisan at the time.

The following claim chart compares the teachings of Ding '979 (EX1006) and Sall (EX1007) to the elements recited in claims 13-14:

Claims	Obvious Over Ding '979 and Sall
13. The method of claim 1, wherein the emulsion is as substantially therapeutically effective as a second emulsion administered to a human in need thereof at a frequency of twice a day, the second emulsion comprising cyclosporin A in an amount of 0.1% by weight and castor oil in an amount of 1.25% by weight.	*See* discussion of claim 1 and claim chart for claim 23 above. "[T]reatment with either CsA 0.05% or 0.1% resulted in significantly greater improvements than vehicle treatment in two objective signs of dry eye disease (corneal staining and categorized Schirmer values)." EX1007, 637; EX1002, ¶¶112-13.
14. The method of claim 1, wherein the emulsion achieves at least as much therapeutic effectiveness as a second emulsion administered to a human in need thereof a frequency of twice a day, the second emulsion comprising cyclosporin	"[N]o dose-response effect ... excellent safety profile." EX1007, 631; EX1002, ¶¶112-13. "At month 6, there was a statistically significant improvement [in the STT] from baseline within both CsA

Claims	Obvious Over Ding '979 and Sall
A in an amount of 0.1% by weight and castor oil in an amount of 1.25% by weight.	groups." EX1007, 635; EX1002, ¶¶112-13. "[T]reated twice daily with either CsA, 0.05% or 0.1%." EX1007, 631; EX1002, ¶74.

iii. Claims 16-18

Claim 16 depends from claim 1, and merely further recites that the emulsion: when administered to the eye of a human, demonstrates a reduction in adverse events in the human, relative to a second emulsion administered to a human in need thereof at a frequency of twice a day, the second emulsion comprising cyclosporin A in an amount of 0.1% by weight and castor oil in an amount of 1.25% by weight.

Claim 17 further specifies that the adverse events are side effects. Claim 18 is an independent claim containing the preamble phrase "[a] method of reducing side effects in a human being treated for dry eye syndrome...."

As discussed above, Sall reports the occurrence of adverse events and side effects in the context of a clinical trial, evaluating the safety of both 0.05% CsA and 0.10% CsA emulsions in castor oil. EX1007, 632; EX1002, ¶114. Sall teaches, "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 vehicle

experienced one or more treatment-related adverse events." EX1007, 636-37; EX1002, ¶115. Sall also discusses the relative occurrence of specific adverse side effects, teaching that patients treated with the 0.05% CsA emulsion experienced fewer side effects such as burning, stinging, or eye pain, than the 0.10% CsA treatment group. EX1007, 636; EX1002, ¶116. Moreover, Sall teaches that CsA blood concentration levels were below the limit of detection (EX1007, 637), and therefore no side effects resulting from elevated CsA blood concentration would be expected after treatment with the 0.05% CsA emulsion. Based on Sall, a person of ordinary skill would have understood that treatment with the ophthalmic emulsion with 0.05% CsA would result in fewer adverse events and side effects as treatment with a 0.10% CsA emulsion.

The following claim chart compares the teachings of Ding '979 (EX1006) and Sall (EX1007) to the elements recited in claims 16-18, respectively:

Claims	**Obvious Over Ding '979 and Sall**
16. The method of claim 1, wherein the emulsion, when administered to the eye of a human, demonstrates a reduction in adverse events in the human, relative to a second emulsion administered to a human in need thereof a frequency of twice a day, the second emulsion comprising cyclosporin A in an amount of 0.1% by weight and	*See* discussion of claim 1 above and claim chart for claim 23. "25.3% (74/293) of patients treated with CsA 0.05% [and] 29.1% (85/292) of patients treated with CsA 0.1% [had] one or more treatment-related adverse events." EX1007, 636-37; EX1002, ¶¶114-15. "[O]nly 19 of the 877 (2.2%) patients

Claims	Obvious Over Ding '979 and Sall
castor oil in an amount of 1.25% by weight. 17. The method of claim 16, wherein the adverse events are side effects. 18. A method of reducing side effects in a human being treated for dry eye syndrome	enrolled were discontinued because of burning and stinging (5 [1.7%] in the CsA 0.05% group, 9 [3.1%] in the CsA 0.1% group, and 5 [1.7%] in the vehicle group." EX1007, 637; EX1002, ¶¶115-16. EX1007, 636, Table 3 (fewer adverse events in 0.05% CsA group than CsA 0.1% group for burning eye, stinging eye, visual disturbance, and eye pain, among others); EX1002, ¶¶115-16. EX1007, 631(reduced blurred vision and need for concomitant artificial tears in 0.05% CsA group); EX1002, ¶80.

In view of the forgoing, each of claims 1-10, 12-14, 16-20, and 22-24 of the '162 patent is obvious and unpatentable under 35 U.S.C. § 103 based on Ding '979 and Sall.

B. [Ground 2] Claims 11 and 21 are Obvious under 35 U.S.C. § 103 over Ding '979, Sall, and Acheampong

Every element of claims 11 and 21 is taught through Ding '979 (EX1006), Sall (EX1007), and Acheampong (EX1008). Claims 11 and 21 each further recite "when the emulsion is administered to an eye of a human in an effective amount ... the blood of the human has substantially no detectable concentration of cyclosporin A." Claims 1 and 18, from which claims 11 and 21 depend, respectively, have been addressed in greater detail above in Ground 1 based on Ding '979 and Sall.

As explained in Ground 1, Sall teaches 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; EX1002, ¶¶118-19. Acheampong adds to these teachings by describing a study which evaluated peak and trough concentrations of CsA in the blood of humans receiving ophthalmic administrations of CsA/castor 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; EX1002, ¶120.

As presented in Table 1 of Acheampong, patients receiving ophthalmic emulsions of 0.05% CsA had no detectable concentration of CsA in the blood at both peak and trough levels. EX1008 at 1002; EX1002, ¶120.

Table 1. Human blood trough and maximum cyclosporin A concentrations over 12 weeks

Cyclosporine emulsion	Range of blood cyclosporine A concentration (ng/ml)	
	Trough level	Maximum level
0.05%	<0.1	<0.1
0.1%	<0.1 to 0.102	<0.1
0.2%	<0.1 to 0.108	<0.1 to 0.144
0.4%	<0.1 to 0.157	<0.1 to 0.158

EX1008 at 1004; EX1002, ¶120. Thus, Acheampong and Sall together provide one of ordinary skill in the art with a reasonable expectation of success that when the 0.05% CsA emulsion is administered to the eye there is "substantially no detectable concentration of cyclosporin A" in the blood. EX1002, ¶121.

In view of the forgoing, each of dependent claims 11 and 21 of the '162 patent is obvious and unpatentable under 35 U.S.C. § based on Ding '979, Sall, and Acheampong.

C. [Ground 3] Claim 15 is Obvious under 35 U.S.C. § 103 over Ding '979, Sall, and Glonek '586

Every element of dependent claim 15 of the '162 patent is taught through Ding '979 (EX1006), Sall (EX1007), and Glonek (EX1009). Claim 15 depends from claim 1 and merely further recites, "the emulsion breaks down more quickly in the eye of a human, once administered to the eye of the human, thereby reducing vision distortion in the eye of the human as compared to a second emulsion that contains only 50% as much castor oil." EX1002, ¶124. The obviousness of claim 1 has been addressed above in Ground 1 based on Ding '979 and Sall. EX1002,¶123.

The '162 patent teaches that the increased break down rate and concomitant decrease in visual distortion is a property intrinsic to an emulsion with an increased oil percentage. EX1001, 2:43-49 ("[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 reduced vision distortion"). This feature of the claimed emulsion would have been apparent from Glonek's teachings.

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; EX1002, ¶125. 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; EX1002, ¶125. 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); EX1002, ¶126.

Increasing the oil concentration in an emulsion, while holding the surfactant concentration constant, results in an increase in instability, *i.e.*, an increase in rate of differentiation. EX1009, 10:66—11:3; EX1002, ¶¶125-26. 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.*, ¶¶125-27. Further, one would not

expect the 0.05% CsA / 1.25% castor oil formulation to cause undue blurring because it is within the preferred ranges disclosed by Ding and because other prior art ophthalmic emulsions comprising castor oil in amounts up to 2% did not cause blurring. EX1002, ¶59; EX1017, p.2032.

Thus, claim 15 of the '162 patent is obvious based on Ding '979, Sall, and Glonek.

IX. NO OBJECTIVE INDICIA OF NON-OBVIOUSNESS

During prosecution of the '162 patent, Allergan argued that objective indicia supported patentability. EX1004, 0194-0205. 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, 0207, Attar Declaration, 0233), one alleged commercial success of the FDA-approved drug Restasis® (EX1004, Mottiwala Declaration, 0251), and one alleged a long-felt, unmet need existed prior to the alleged invention. EX1004, 0262.

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. EX1002, ¶¶135-38; 145-49 (discussed in more detail below). Moreover, much of the data relied upon as demonstrating unexpected equivalent efficacy of the 0.05% CsA emulsion and the 0.10% CsA emulsion appear identical to graphs published more than one year before the earliest alleged priority date. EX1002, ¶¶132-33. 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:

Figure 1
of Schiffman Exhibit D

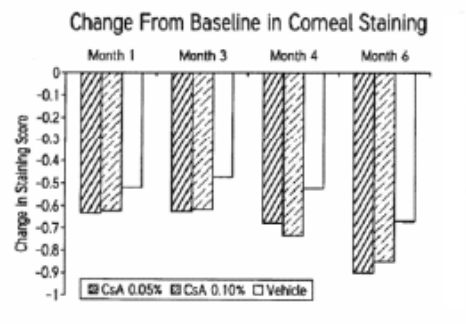


Figure 1
of Sall, Ex. 1007

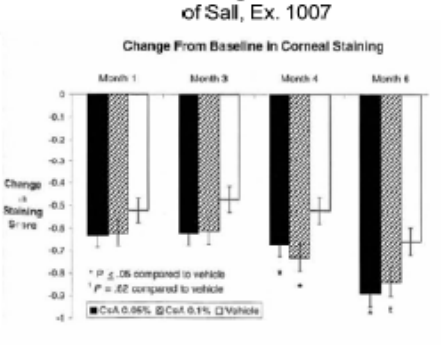


Figure 2
of Schiffman Exhibit D
Change From Baseline in Categorized Schirmer Values Measured With Anesthesia

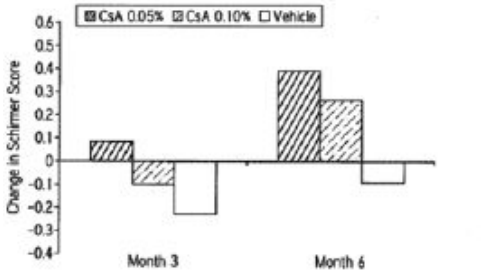


Figure 2
of Sall. Ex. 1007

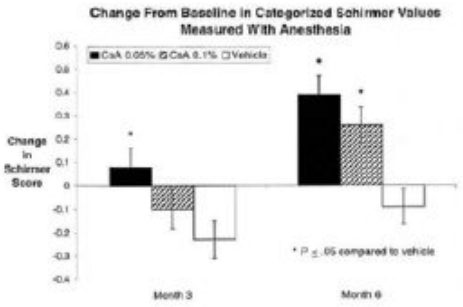


Figure 3
of Schiffman Exhibit D

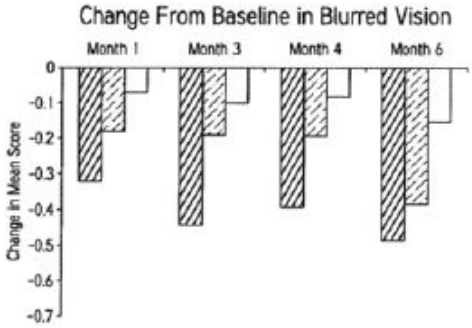


Figure 3
of Sall, Ex. 1007

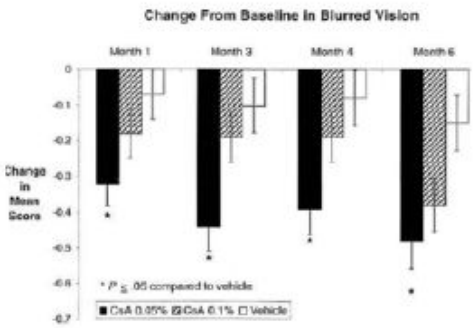


Figure 4
of Schiffman Exhibit D

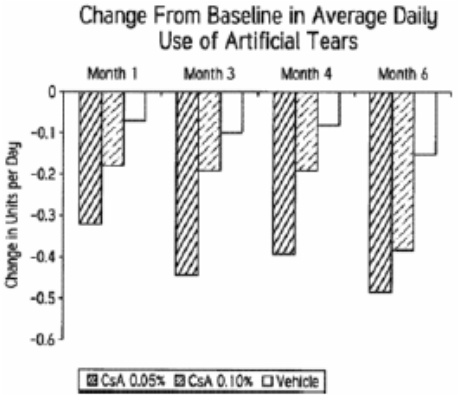
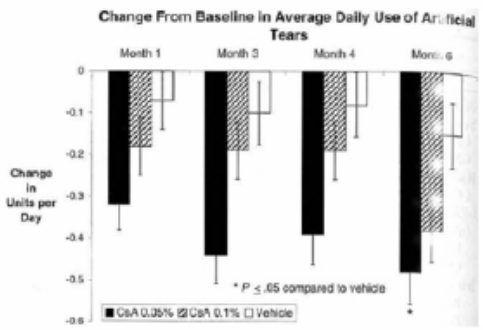


Figure 4
of Sall, Ex. 1007



Each of Figures 1-4 of Sall are shown to be comparable to those in Schiffman Exhibit D in the Amiji Declaration. EX1002, ¶¶135-38.

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, 0208. Dr. Attar similarly references the Phase 3 clinical trial. *Id.* at 0234-35. Drs. Schiffman and Attar appear to be referring to the Phase 3 trials described in Sall. EX1007, 631, 638 (reporting results of Allergan's "multicenter, randomized, double-masked" Phase 3 clinical trials. EX1002, ¶132.

Consistent with standard scientific practices, Sall presents these data by providing the error bars that are lacking from the versions presented in the Schiffman and Attar declarations. EX1002, ¶133. 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, 0210 (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 ($P \leq 0.05$) 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. EX1002, ¶138.

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;

EX1002, ¶148. 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. EX1002, ¶¶139, 145, 147, 151. 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 0222. However, such an interpretation is not supported by Exhibit B, for several reasons. EX1002, ¶146.

Schiffman Declaration Exhibit B

Phase 2 Results - Phase 3 Target Subpopulation

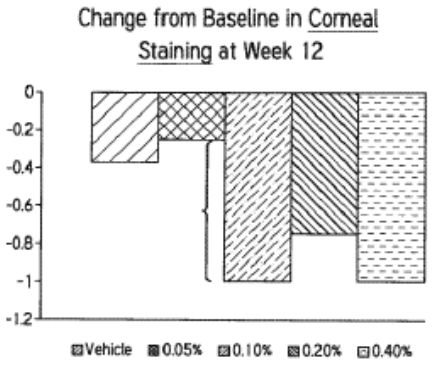


FIG. 1

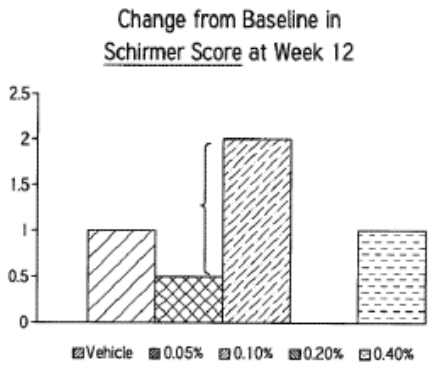


FIG. 2

For example, Exhibit B contains no error bars. EX1002, ¶¶146-47. 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. EX1002, ¶¶146-47. 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, 0208, formatting in original) lacks support.

In addition to being unsupported, Dr. Schiffman's conclusion may be incorrect. As explained by Dr. Amiji, the Stevenson publication reported the Phase 2 results of the CsA clinical trial for dry eye disease. EX1002, ¶148. 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; EX1002, ¶149.

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). EX1002, ¶150. 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. Amiji, errors of this size are not unexpected because of the small sample. EX1002, ¶¶148, 150; 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). EX1002, ¶149. Stevenson stated that "[n]o statistically significant among-group differences in [SPK] were observed." EX1002, ¶149; EX1015, 968, 971.

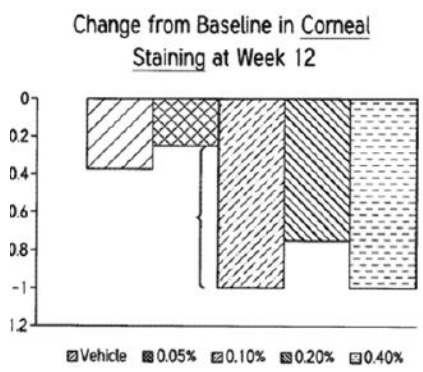
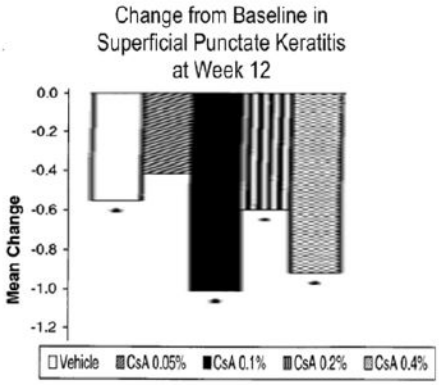


FIG. 1



Week 12 data, extracted from, Figure 2 of Stevenson; Ex. 1015

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; EX1002, ¶149.

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, 0224), which prevents any conclusion of statistical significance. EX1002, ¶151. Further, Schiffman Exhibit C fails to establish materiality of any observed differences, even if significant. Well to the earliest priority date of the '111 patent, the minimal concentration of CsA needed in ocular tissues for therapeutic effectiveness was already known. EX1002, ¶151; 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. EX1002, ¶151; 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 levels 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. EX1002, ¶151.

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%

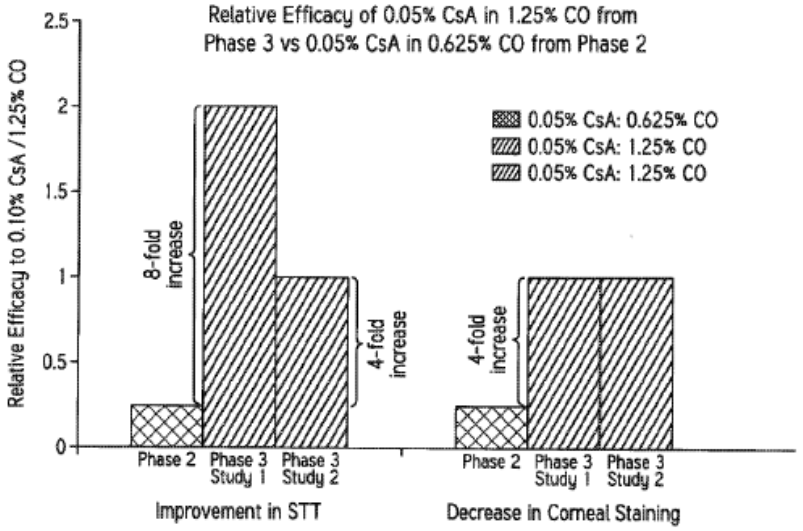
CsA/0.625% castor oil (Ding 1E). EX1002, ¶139. Schiffman states there was an "8-fold increase" in the performance of the claimed emulsion over Ding '979's 1E formulation. Stevenson and Sall, however, reported results of Phase 2 and Phase 3 trials of Restasis® respectively, and both reported that variations between emulsions containing 0.05% and 0.10% CsA were not significant. EX1007, 631; EX1015, 967; EX1002, ¶¶ 75, 143, 148-50.

Schiffman Declaration Exhibit E

	Phase 2 001	Phase 3 (1st study)	Phase 3 (2nd study)
	0.05% CsA in 0.625% CO	0.05% CsA in 1.25% CO	0.05% CsA in 1.25% CO
	Compared with 0.1% CsA in 1.25% CO		
Improvement in STT	0.25	2 (8-Fold Improvement*)	1 (4-Fold Improvement*)
Decrease in Corneal Staining	0.25	1 (4-Fold Improvement*)	1 (4-Fold Improvement*)

*Compared to the 0.05% CsA/0.625% CO Phase 2 formulation (disclosed in Ding)

Schiffman Declaration Exhibit F



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. EX1002, ¶¶139-40. 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. EX1002, ¶¶139-40. 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). EX1002, ¶¶139-40. 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. EX1002, ¶141. 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. EX1002, ¶¶142-43.

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. EX1002, ¶¶143-44.

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 '162 patent. EX1004, 0403-04. "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, 305 ("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 also 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, 0358) 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, *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, 0264. However, Allergan cited no industry praise during prosecution that related to the claims of the '162 patent specifically or that would distinguish the claimed emulsion from the prior art 0.10% CsA emulsion of Ding '979 Example 1D. Id. at 0264, 354 (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 '162 patent. As discussed above, Allergan's Ding '979 patent prevented sales of alternative comparable emulsions, including a 0.1% 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, 0265. 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 '162 patent and any purported failure of others.

X. CONCLUSION

For the reasons set forth above, claims 1-24 of the '162 patent are unpatentable over the asserted prior art. Petitioners therefore request that an *inter partes* review of these claims be instituted and joined with IPR2016-01130.

Respectfully submitted,

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XI. CERTIFICATE OF COMPLIANCE

As required by 37 C.F.R. § 42.24(d), the undersigned certifies that the present Petition contains 13,463 words, as calculated in Microsoft Word®, which is less than the 14,000 word limit set by 37 C.F.R. §§ 42.24(a)(1)(i). As noted in 37 C.F.R. § 42.24(a)(1), this does not include "a table of contents, a table of authorities, mandatory notices under § 42.8, a certificate of service or word count, or appendix of exhibits or claim listing."

Respectfully submitted,

Dated: January 6, 2017

/ Travis B. Ribar /
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XII. 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. 19-4880.

XIII. APPENDIX – LIST OF EXHIBITS

Exhibit No.	Description
1001	U.S. Patent No. 8,633,162 to Acheampong et al.
1002	Declaration of Dr. Mansoor Amiji
1003	*Curriculum Vitae* of Dr. Mansoor Amiji
1004	File history of U.S. Patent No. 8,633,162 to Acheampong *et al*.
1005	File history of U.S. Patent Application No. 10/927,857, filed on August 27, 2010 to Acheampong et al.
1006	U.S. Patent No. 5,474,979 to Ding et al., filed May 17, 1994
1007	K. Sall, et al., Two Multicenter, Randomized Studies of the Efficacy and Safety of Cyclosporine Ophthalmic Emulsion in Moderate to Severe Dry Eye Disease, 107 OPHTHALMOLOGY 631 (2000)
1008	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)
1009	U.S. Patent No. 5,578,586 to Glonek *et al*., filed February 4, 1994
1010	U.S. Patent No. 5,981,607 to Ding *et al*., filed January 20, 1998
1011	R. Kaswan, *Intraocular Penetration of Topically Applied Cyclosporine* 20 TRANSPL. PROC. 650 (1988)
1012	K. Kunert *et al*., *Analysis of Topical Cyclosporine Treatment of Patients with Dry Eye Syndrome* 118 ARCH OPHTHALMOL 1489 (2000)
1013	Physicians' Desk Reference for Ophthalmic Medicines, 1999

Exhibit No.	Description
1014	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)
1015	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)
1016	REMINGTON'S 20TH EDITION: THE SCIENCE AND PRACTICE OF PHARMACY (A. Gennaro ed. 2003)
1017	E. Goto *et al*. *Low-Concentration Homogenized Castor Oil Eye Drops for Noninflamed Obstructive Meibomian Gland Dysfunction* 109 OPHTHALMOL. 2030 (2002)
1018	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)
1019	A. Vieira *et al*., *Effect of ricinoleic acid in acute and subchronic experimental models of inflammation*, 9 MED. INFLAMM. 223 (2000)
1020	R. Murphy, *The Once and Future Treatment of Dry Eye*, REVIEW OF OPTOMETRY 1 (2000)
1021	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)
1022	STEDMAN'S MEDICAL DICTIONARY 27TH EDITION (M.B. Pugh ed. 2000)
1023	Complaint; *Allergan, Inc. v. Teva Pharmaceuticals USA, Inc., Teva Pharmaceutical Industries Ltd., Apotex, Inc., Apotex Corp., Akorn, Inc., Mylan Pharmaceuticals Inc., and Mylan Inc.,* No. 2:15-cv-01455
1024	Approved Drug Products with Therapeutic Equivalence Evaluations

Exhibit No.	Description
	(34th Ed.) (2014) (Excerpts)

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. 8,633,162 (and accompanying Exhibits 1001-1024) by overnight courier (Federal Express or UPS), on this 6th day of January, 2017, 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 at other addresses also likely to affect service:

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Respectfully submitted,

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