

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ARGENTUM PHARMACEUTICALS LLC,
Petitioner

v.

ALLERGAN, INC.
Patent Owner

Case IPR2016-01232
Patent 8,629,111

**PATENT OWNER ALLERGAN, INC.'S
PRELIMINARY RESPONSE**

TABLE OF CONTENTS

I. INTRODUCTION	1
II. BACKGROUND OF THE ‘111 PATENT	7
A. Dry Eye Disease is a Serious Disease	7
B. Palliative Treatments Only Alleviate the Symptoms of Dry Eye Disease.....	8
C. Allergan’s Development of RESTASIS®	9
III. THE ‘111 PATENT	9
A. It was counterintuitive to combine 0.05% cyclosporin with a vehicle containing 1.25% castor oil	10
1. Castor oil is cytotoxic and an irritant.....	11
2. Increasing the amount of castor oil in the emulsion would be expected to reduce the thermodynamic activity of the emulsion	12
3. PK data predicted 0.05% cyclosporin/1.25% castor oil would be less effective than 0.05% cyclosporin/0.625% castor oil and 0.10% cyclosporin/1.25% castor oil.....	13
B. During prosecution the Examiner agreed that the performance of the claimed emulsion relative to the Ding ‘979 patent emulsions was unexpected	17
IV. ARGUMENT	19
A. An emulsion that is “therapeutically effective” must treat the underlying disease	21
B. The Ding ‘979 patent does not anticipate claims 1-27	23
C. Claims 1-27 would not have been obvious over Ding ‘979 plus Sall.....	29
1. The inventors proceeded contrary to the teachings of the prior art and developed an emulsion that has surprising therapeutic efficacy against dry eye disease.....	29
2. Sall would not have motivated a person of ordinary skill to prepare an emulsion containing 0.05% cyclosporin and 1.25% castor oil	33
3. There was no reasonable expectation that increasing castor oil concentration would increase therapeutic efficacy	34

4. The differences between the claimed emulsion and the Ding ‘979 emulsions are differences in kind, not degree	36
D. Claims 11 and 16 would not have been obvious over Ding ‘607/Ding ‘979 plus Sall plus Acheampong	38
V. CONCLUSION	38

LIST OF EXHIBITS

Exhibit No.	Description
EX. 2001	NDA 21-023 Cyclosporine Ophthalmic Emulsion 0.05%, Original NDA Filing, Vol. 1 (Feb. 24, 1999)
EX. 2002	U.S. Pat. No. 4,839,342
EX. 2003	Said et al., Investigative Ophthalmology & Visual Science, vol. 48, No. 11 (Nov. 2007):5000-5006
EX. 2004	Alba et al., Folia Ophthalmol. Jpn. 40:902-908 (1989)
EX. 2005	Stedman's Medical Dictionary, definition of therapeutic
EX. 2006	Dorland's Illustrated Medical Dictionary, definition of therapeutic
EX. 2007	Stedman's Medical Dictionary, definition of palliative
EX. 2008	RESTASIS® label
EX. 2009	Murphy, R., "The Once and Future Treatment of Dry Eye," Review of Optometry, pp. 73-75 (Feb. 15, 2000)

TABLE OF AUTHORITIES

	Page(s)
Cases	
<i>Allergan, Inc. v. Sandoz Inc.</i> , 796 F.3d 1293 (Fed. Cir. 2015)	<i>passim</i>
<i>Arkie Lures, Inc. v. Gene Larew Tackle, Inc.</i> , 119 F.3d 953 (Fed. Cir. 1997)	38
<i>Atofina v. Great Lakes Chem. Corp.</i> , 441 F.3d 991 (Fed. Cir. 2006)	24
<i>Cuozzo Speed Techs., LLC v. Lee</i> , 136 S. Ct. 2131 (2016).....	22
<i>In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.</i> , 676 F.3d 1063 (Fed. Cir. 2012)	35
<i>Galderma Laboratories L.P. v. Tolmar, Inc.</i> , 737 F.3d 731 (Fed. Cir. 2013), explained.....	31, 39
<i>Sanofi-Synthelabo v. Apotex, Inc.</i> , 550 F.3d 1075 (Fed. Cir. 2008)	24
<i>In re Translogic Tech., Inc.</i> , 504 F.3d 1249 (Fed. Cir. 2007)	22
<i>Verdegaal Bros. v. Union Oil Co. of California</i> , 814, F.2d 628, 631 (Fed. Cir. 1987)	24
Other Authorities	
37 C.F.R.	22
37 CFR §§ 42.6(e)(4) and 42.205(b)	43

I. INTRODUCTION

U.S. Patent No. 8,629,111 (“the ‘111 patent”) covers Allergan’s RESTASIS® medication for treating a serious eye condition known as dry eye disease. Keratoconjunctivitis sicca (“KCS”) is a type of dry eye disease. Allergan has five other Orange Book-listed patents that cover RESTASIS® and its use, each of which is the subject of an IPR petition that Argentum filed.¹

RESTASIS® is the only prescription medication indicated for treating the underlying disease itself, as opposed to relieving symptoms of the disease. *See* EX. 2008 (RESTASIS® label), p. 1; EX. 1007 (Sall), p. 8 (“[T]here is currently no therapeutic treatment for dry eye disease. The only treatments available are palliative in nature and provide insufficient relief for many patients”).

RESTASIS® is a therapeutic emulsion that contains 0.05% by weight cyclosporin A in a liquid vehicle that includes 1.25% by weight castor oil, polysorbate 80, and other excipients. EX. 2008, pp. 3-4; EX. 2001, p. 256. Cyclosporin is an immunosuppressant that, when delivered to the eye, suppresses the inflammatory processes underlying dry eye disease. EX. 1007 (Sall), pp. 1-2. The distinction between treating the disease itself—*i.e.*, therapeutic treatment—versus merely relieving symptoms—*i.e.*, palliative treatment—is important for purposes of this

¹ The other 5 patents are U.S. Patent Nos. 8,633,162; 8,642,556; 8,648,048; 8,685,930; and 9,248,191.

IPR proceeding.

Although Argentum refers to the “therapeutic effect” of castor oil in the petition, *see, e.g.*, Petition at p. 21, castor oil has no therapeutic effect because it does not treat the disease itself. Cyclosporin is the only therapeutic agent present in RESTASIS®. However, because cyclosporin has limited solubility in water, it is necessary to combine it with a lipophilic material, such as castor oil, in a vehicle to deliver it to the eye. *See* EX. 1006 (Ding ‘979), 1:40-53.

Castor oil was known to irritate the sensitive tissues of the eye and the conventional teaching was to limit its use in ophthalmic formulations. *See, e.g., id.*, 3:43-48. Allergan’s prior art Ding ‘979 patent, however, disclosed that combining castor oil with an emulsifier and dispersing agent such as polysorbate 80, along with other excipients, could reduce the irritation potential of an emulsion vehicle using castor oil. *Id.*, 3:49-53. When cyclosporin was added to a vehicle formulated in this way, the resulting composition exhibited reasonably high thermodynamic activity, yet avoided the cyclosporin crystallizing and precipitating out of the vehicle. *Id.*, 3:21-28; 3:58-63. But even in these emulsions, the castor oil remains a component in the vehicle used to deliver the therapeutic agent—the cyclosporin—to tissues of the eye.

The claims of the ‘111 patent recite the specific combination of 0.05% cyclosporin/1.25% castor oil/polysorbate 80 found in RESTASIS®. This

particular combination is unique and has unexpected therapeutic effect against dry eye disease relative to emulsions containing 0.05% cyclosporin/0.625% castor oil/polysorbate 80 and 0.10% cyclosporin/1.25% castor oil/polysorbate 80. The latter two emulsions are disclosed in Allergan's Ding '979 patent (EX. 1006, 4:30-45, Example 1, compositions D and E), over which the Examiner rejected the claims during the original prosecution of the '111 patent.

The Ding '979 patent is the closest prior art to the '111 patent. During prosecution of the '111 patent, Allergan presented the results of pharmacokinetic ("PK") experiments comparing the claimed emulsion to the two emulsions disclosed in the Ding '979 patent. EX. 1004, pp. 229-290 (Response to Office Action dated 10/17/13; Declaration of Dr. Rhett Schiffman, pp. 248-50, ¶¶ 9-20; Declaration of Dr. Mayssa Attar, pp. 272-75, ¶¶ 6-14). The PK experiments predicted that on the basis of bioavailability, the claimed emulsion would have been *less effective* than the two emulsions disclosed in the Ding '979 patent. *Id.* Surprisingly, however, the claimed emulsion was *more effective* than the 0.05%/0.625%/1.00% emulsion and *at least as effective* as the 0.1%/1.25%/1.00% emulsion. *Id.*

The claimed emulsion cut the amount of cyclosporin in half without loss of efficacy. This feature is particularly advantageous because cyclosporin has been known to cause serious liver and kidney damage. *See* EX. 2002, 3:59-66.

Moreover, it was achieved by doubling the amount of castor oil relative to the composition in the Ding '979 patent that contained 0.05% cyclosporin, a choice that was counterintuitive given that castor oil was cytotoxic and known to irritate patients' eyes. *See, e.g.*, EX. 2003 (Said et al.), p. 1 ("Castor oil is the commonly used lipophilic vector but has been shown to be cytotoxic"); EX. 2004 (Alba et al.), p. 7 (describing "significant corneal edema" associated with castor oil when used as a vehicle for cyclosporin).

The natural inclination of a person of skill in the art would have been to use the minimum amount of castor oil necessary to dissolve the cyclosporin. In the case of 0.05% cyclosporin, that amount would have been no greater than the 0.625% amount of castor oil that the Ding '979 patent used and described as reducing the irritation associated with the cyclosporin while maintaining reasonably high thermodynamic activity. Using more castor oil would be expected to possibly increase irritation and reduce thermodynamic activity.

The Examiner allowed the claims over the Ding '979 patent on the basis of these surprising results. EX. 1004, pp. 441-443. Argentum now asks the Board to re-visit the patentability of the '111 patent claims over the very same Ding '979 patent. But Argentum offers no credible evidence to rebut the surprising results on which the Examiner relied when she allowed the claims. Neither Argentum nor its expert, Dr. Bhagwat, compares the observed results with what the PK experiments

would have predicted based upon bioavailability. These PK experiments provide the baseline for judging unexpected results.

Argentum wrongly argues that any improvement would have been expected due to the “therapeutic benefits” of castor oil. *See* EX. 1002 (Bhagwat Decl’n), ¶¶ 56, 138; Petition, pp. 21-22, 60. But castor oil has no **therapeutic** effect on dry eye disease. Cyclosporin is responsible for the therapeutic effect and must be delivered from the lipophilic vehicle into the ophthalmic tissue.

Argentum further alleges that the Sall paper (EX. 1007) would have motivated a person of ordinary skill to combine 0.05% cyclosporin with 1.25% castor oil. *See* EX. 1002 (Bhagwat Decl’n), ¶¶ 106-109; Petition, pp. 38-40. Sall concludes that emulsions containing both 0.05% and 0.1% cyclosporin were “safe and effective.” EX. 1007 (Sall), p. 1. However, Sall does **not** disclose the amount of castor oil, polysorbate 80, and other excipients in each “proprietary” vehicle with which the cyclosporin was combined.

Argentum admits that Sall does not disclose the amount of castor oil, polysorbate 80, and other excipients in each “proprietary vehicle.” *See* EX. 1002 (Bhagwat Decl’n), ¶ 11; Petition, pp. 9. However, Argentum argues that because Sall discloses both 0.05% cyclosporin and 0.10% cyclosporin in a common vehicle, each vehicle necessarily contained the same amount of castor oil. EX. 1002 (Bhagwat Decl’n), ¶ 112; Petition, p. 39. Argentum then argues both the

0.05% cyclosporin emulsion and the 0.10% cyclosporin emulsion would have contained 1.25% castor oil because “[t]he 1.25% castor oil vehicle is the only vehicle from Ding ‘979 Example 2 for which both 0.05% and 0.10% CsA have a ratio of CsA-to-castor oil inside Ding ‘979’s more preferred range of between 0.12 and 0.02 ... and also within the ratio range found with each of the Example 1 emulsions (0.04-0.08).” Petition, p. 40; EX. 1002 (Bhagwat Decl’n), ¶ 113.

Argentum’s argument fails. The art, including the Ding ‘979 patent itself, would have taught persons of ordinary skill that the emulsions in Sall would have had the same *ratio* of cyclosporin to castor oil, rather than the same *amount* of castor oil. A person of ordinary skill would have recognized that using the same ratio would achieve the goal of selecting the minimum amount of cytotoxic castor oil needed to dissolve the cyclosporin. This means that the 0.05% cyclosporin emulsion would have contained 0.625% castor oil and the 0.10% cyclosporin emulsion would have contained 1.25% castor oil because in both cases the cyclosporin to castor oil ratio is 0.08. Example 1 of the Ding ‘979 patent describes these very two emulsions. Nowhere does the Ding ‘979 patent describe an emulsion having 0.05% cyclosporin and 1.25% castor oil.

The PK data that the Examiner considered during prosecution predicted that emulsions with 0.05% cyclosporin/0.625% castor oil would be more effective than emulsions with 0.05% cyclosporin/1.25% castor oil. Moreover, as noted above,

castor oil was known to be cytotoxic and irritating. Both points are consistent with the Ding '979 patent, where the only example of an emulsion with 0.05% cyclosporin included 0.625% castor oil. Therefore, a person of ordinary skill reading Sall logically would have used 0.05% cyclosporin with 0.625% castor oil—not 1.25%. The inventors' decision to use 1.25% castor oil was counterintuitive and produced an emulsion that was surprisingly effective.

Argentum's petition merely recycles references and grounds raised during the original prosecution, but offers no credible new evidence that would compel a different conclusion. Argentum's petition, therefore, fails to establish a reasonable likelihood that at least one claim of the '111 patent is unpatentable. Accordingly, Allergan requests that the Board deny the petition.

II. BACKGROUND OF THE '111 PATENT

A. Dry Eye Disease is a Serious Disease

Dry eye disease is a serious ocular disease that afflicts millions of patients. Indeed, it is one of the most common patient complaints treated by ophthalmologists. It is estimated that it affects millions of people worldwide. EX. 1007 (Sall), pp. 1-2; EX. 1015 (Stevenson), pp. 1-2. Dry eye disease is not simply occasionally feeling eye dryness; it is a serious condition that can substantially impact the quality of life in patients who have it. Patients who suffer from dry eye disease generally experience symptoms such as ocular discomfort, which can

include a dry, gritty feeling in the eye and foreign body sensation; burning; irritation; photophobia; and blurred vision. *Id.* Severe dry eye disease can also lead to an inability to produce tears and an increased risk of ocular surface damage and ocular infection. *Id.*

B. Palliative Treatments Only Alleviate the Symptoms of Dry Eye Disease

Dry eye disease is the result of an underlying inflammatory process. Conventional medications for dry eye disease, though, do not affect these underlying processes, and thus do not treat dry eye. Rather, they merely provide palliative relief in the form of tear replacement or eye lubrication. EX. 1007 (Sall), pp. 1-2; EX. 1015 (Stevenson), pp. 2-3.

Prior to the filing date of the ‘111 patent, a number of palliative treatments for dry eye were known. Examples included artificial tear formulations, punctal plugs, and topical steroids. EX. 2009, pp. 2-3. Emulsions comprising admixtures of polysorbate 80 and oils such as castor oil, corn oil, sunflower oil, and light mineral oil were also known to provide palliative relief. EX. 1010 (Ding ‘607), 3:41-48. For example, the Ding ‘607 patent describes the ability of these emulsions, when applied to the surface of the eye, to form a film that remained in place and “retard[ed] water evaporation from the eye which alleviates dry eye symptoms.” *Id.*, 3:66 to 4:3. As the Ding ‘607 patent notes, these treatments were palliative—they alleviated dry eye symptoms, but did not treat the disease itself.

C. Allergan's Development of RESTASIS®

RESTASIS® is formulated as an emulsion of 0.05% by weight cyclosporin A, 1.25% by weight castor oil, and 1% by weight polysorbate 80, along with other excipients. EX. 2008, pp. 3-4; EX. 2001, p. 256. RESTASIS® is different from any other drug prescribed for dry eye disease. Its active ingredient, cyclosporin A, is a drug with immunomodulatory and anti-inflammatory properties. EX. 1007 (Sall), pp. 1-2. Unlike other dry eye medications—which relieve the symptoms of dry eye disease, but do not treat it—RESTASIS® actually affects the underlying processes that are thought to lead to dry eye disease. In other words, it treats the disease rather than just relieving the symptoms. *See* EX. 2008, p. 1.

In late 2002, FDA approved RESTASIS®, the first prescription ophthalmic emulsion ever approved, “to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca.” EX. 2008, p. 1. RESTASIS® remains the only product approved by FDA that increases the eye’s production of natural tears, even 12 years after its original approval and despite a substantial commercial incentive for developing dry eye treatments. *See id.*

III. THE ‘111 PATENT

The ‘111 patent is one of several patents covering Allergan’s RESTASIS® medication and its use to treat conditions such as dry eye disease. It contains 27

claims, each directed towards an ophthalmic emulsion that includes 0.05% by weight cyclosporin A, 1.25% by weight castor oil, and polysorbate 80. Claim 1 is representative. It recites:

1. A topical ophthalmic emulsion for treating an eye of a human comprising cyclosporin A in an amount of about 0.05% by weight, polysorbate 80, acrylate/C10-30 alkyl acrylate cross-polymer, water, and castor oil in an amount of about 1.25% by weight, wherein cyclosporin A is the only peptide present in the topical ophthalmic emulsion.

This is the formulation of RESTASIS®. Claims 20-27 recite that the ophthalmic emulsions be “therapeutically effective” in treating dry eye, keratoconjunctivitis sicca, or increasing tear production, which are the FDA-approved uses for RESTASIS®.

A. It was counterintuitive to combine 0.05% cyclosporin with a vehicle containing 1.25% castor oil

The claims reflect the inventors’ discovery that emulsions containing 0.05% cyclosporin A in a vehicle containing 1.25% castor oil, polysorbate 80, and acrylate/C10-30 alkyl acrylate cross-polymer were surprisingly effective, measured by standard ophthalmic criteria, for treating dry eye disease relative to emulsions containing twice as much cyclosporin or half as much castor oil described in the prior art Ding ‘979 patent. These results were surprising for a number of reasons.

1. Castor oil is cytotoxic and an irritant

Prior to the filing date of the ‘111 patent, castor oil was known to be cytotoxic and an irritant. For example, one group of researchers wrote (EX. 2003 (Said et al.), p. 1):

Castor oil, which mainly contains ricinoleic acid (90% of total fatty acid content), is one of the lipophilic vehicles used in cyclosporine eye drops. However, it presents both a low-stability and an epithelial and conjunctival toxicity as well as systemic adverse effects such as purgative effects, hypersensitivity, nephrotoxicity, and neurotoxicity. Since castor oil is presumed to be responsible for cytotoxic effects in the eye, its replacement by another lipophilic vector could result in better tolerance of the drops.

These researchers then investigated 4 other vegetable oils as replacements for castor oil. *Id.* Similarly, a different group noted that there was “significant corneal edema” associated with castor oil when used as a vehicle for cyclosporin, causing the group to discard it in favor of other lipophilic carriers. EX. 2004 (Alba et al.), p. 7. And Ding ‘979 states that “conventional teaching in the art is away from a formulation which utilizes a higher fatty acid glyceride, such as castor oil, and cyclosporine.” EX. 1006 (Ding ‘979), 3:46-48.

Because of the cytotoxic and other undesirable properties of castor oil, a person of ordinary skill looking for a lipophilic vehicle in which to dissolve the

highly lipophilic cyclosporin either would have chosen a carrier other than castor oil or, if he chose castor oil, would have used the minimum amount necessary to dissolve cyclosporin. Given that the Ding ‘979 patent described emulsions containing 0.05% cyclosporin in a vehicle with 0.625% castor oil and polysorbate 80, a person of ordinary skill would have recognized that a concentration of 0.625% was sufficient to dissolve cyclosporin and would not have selected a higher amount—certainly not 1.25% castor oil, which was twice as high.

2. Increasing the amount of castor oil in the emulsion would be expected to reduce the thermodynamic activity of the emulsion

A person of ordinary skill would know the basic thermodynamic principles governing diffusion, and that increasing the amount of castor oil in the emulsion would reduce the diffusion of the lipophilic cyclosporin out of the lipophilic castor oil and into the hydrophilic tissues of the eye. The Ding ‘979 patent discussed using enough oil to maintain a stable composition that did not cause the cyclosporin to precipitate, but not too much to reduce the necessary thermodynamic activity necessary for the cyclosporin to diffuse out of the emulsion and into the eye. EX. 1006 (Ding ‘979), 2:46-57; 3:7-38; 5:18-25. The Ding ‘979 patent discloses emulsions containing 0.05% cyclosporin/0.625% castor oil and 0.10% cyclosporin/1.25% castor oil. *Id.*, Ex. 1 at 4:32-43. The Ding ‘979

patent explains that when formulated in the way instructed, “the drug has reasonably high thermodynamic activity.” *Id.*, 3:25-27.

Neither Argentum nor Dr. Bhagwat explains why the Ding ‘979 patent would not cause a person of skill to prepare an emulsion by combining 0.05% cyclosporin with 0.625% castor oil. A person of ordinary skill would expect an emulsion containing 0.05% cyclosporin and 0.625% castor oil to have better thermodynamic properties than an emulsion containing the same amount of cyclosporin but twice as much of the lipophilic castor oil vehicle. The inventors’ decision to combine 0.05% cyclosporin with a vehicle containing 1.25% castor oil and polysorbate 80 was counterintuitive and not obvious.

3. PK data predicted 0.05% cyclosporin/1.25% castor oil would be less effective than 0.05% cyclosporin/0.625% castor oil and 0.10% cyclosporin/1.25% castor oil

Allergan performed PK studies on animal eyes that compared the PK properties of 3 different ophthalmic emulsions:

- (1) 0.05% cyclosporin/1.25% castor oil/1.00% polysorbate 80,
- (2) 0.05% cyclosporin/0.625% castor oil/1.00% polysorbate 80, and
- (3) 0.10% cyclosporin/1.25% castor oil/1.00% polysorbate 80.

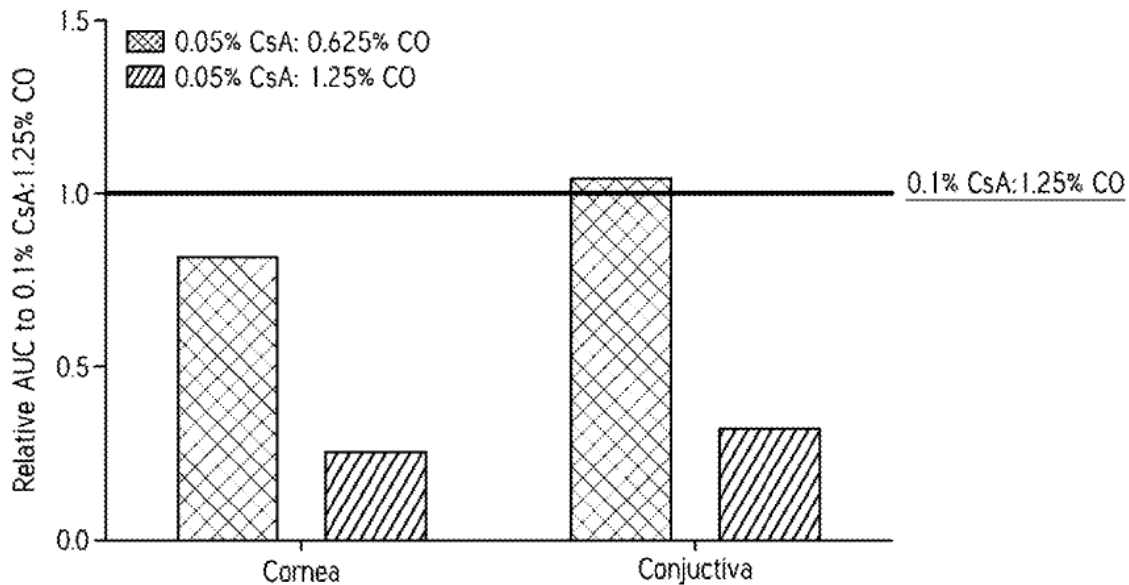
The latter two emulsions are described in the Ding ‘979 patent. Dr. Mayssa Attar, in her declaration submitted during prosecution of the ‘111 patent, described these experiments. EX. 1004, pp. 272-73 (Decl’n of Dr. Mayssa Attar, ¶¶ 6-8).

Argentum fails to consider the PK studies and what they would have predicted with respect to emulsion performance.

Dr. Attar explained in her declaration that in order to obtain cyclosporin's anti-inflammatory and anti-apoptotic therapeutic effects, cyclosporin must be delivered to ocular tissues such as the cornea, conjunctiva, and lacrimal gland. *Id.* (¶ 6)). The more cyclosporin that reaches these tissues, the more therapeutically effective the drug will be in treating dry eye. *Id.*

PK studies involving animal eyes are used to evaluate the amount of drug absorbed in ocular tissues. Allergan performed PK studies comparing the extent to which the cyclosporin in the 3 above-described emulsions was absorbed in two ocular tissues: the cornea and the conjunctiva. *Id.* (¶ 7). As shown in the graph, reproduced below, and explained by Dr. Attar, the results show that in both the cornea and conjunctiva, the amount of cyclosporin delivered to the ocular tissue was greater in emulsions containing 0.05% cyclosporin/0.625% castor oil and 0.1% cyclosporin/1.25% castor oil than in the claimed emulsion containing 0.05% cyclosporin/1.25% castor oil. *Id.*

Exhibit B to Attar Declaration



Based upon these results, according to Dr. Attar, a person of ordinary skill would have expected that both a 0.05% cyclosporin/0.625% castor oil emulsion and a 0.1% cyclosporin/1.25% castor oil emulsion would have been more therapeutically effective for treating dry eye disease than the claimed emulsion having 0.05% cyclosporin/1.25% castor oil. *Id.*, p. 273 (¶ 8). In other words, one would expect that increasing the amount of castor oil relative to the amount of cyclosporin would decrease bioavailability and thus therapeutic effectiveness.

But the actual results, based upon standard ophthalmic measures of efficacy, tell a different story. During prosecution, Allergan presented the results of experiments comparing the claimed emulsion to the two emulsions disclosed in the Ding '979 patent, measured according to two key objective testing parameters for

dry eye: Schirmer Tear Testing and decrease in Corneal Staining. Exhibit E, attached to the Declaration of Dr. Rhett Schiffman, shows the results of two studies comparing the performance of a 0.05% cyclosporin/0.625% castor oil emulsion to that of a 0.05% cyclosporin/1.25% castor oil emulsion. EX. 1004, pp. 249-50 and 267-68 (Decl'n of Dr. Rhett Schiffman, ¶¶ 17-19 and Exhibit E). In both studies, the 0.05% cyclosporin/1.25% castor oil emulsion performed significantly better than the 0.05% cyclosporin/0.625% castor oil emulsion—contrary to what the PK experiments predicted. *See id.*

Allergan also presented results comparing the performance of a 0.10% cyclosporin/1.25% castor oil emulsion with the claimed 0.05% cyclosporin/1.25% castor oil emulsion with respect to 4 parameters: Corneal Staining, Schirmer Tear Testing, blurred vision, and decrease in the number of artificial tears (palliative treatment) used by patients. The results are shown in Exhibit D attached to the Declaration of Dr. Rhett Schiffman. EX. 1004, pp. 247-49 and 264-65 (Decl'n of Dr. Rhett Schiffman, ¶¶ 8 and 14-16 and Exhibit D). The claimed 0.05% cyclosporin/1.25% castor oil emulsion performed better than the 0.10% cyclosporin/1.25% castor oil emulsion with respect to Schirmer Tear Testing, blurred vision, and use of artificial tears, and was comparable with respect to Corneal Staining. *Id.* Again, these results were contrary to what the PK experiments predicted. *See id.*

The test results depicted in Exhibit D correspond to Phase 3 clinical testing Allergan conducted, which is also described in the Sall paper (EX. 1007). The important distinction between the two is that Sall does not describe the composition of the vehicles, instead noting that their formulations were proprietary. Sall merely recites emulsions containing either 0.05% cyclosporin or 0.10% cyclosporin. Thus, a person of ordinary skill reading the Sall paper would not have known the materials in the vehicles and certainly not the castor oil content of the vehicles tested. Based upon the Ding '979 patent, which described emulsions containing 0.05% cyclosporin/0.625% castor oil/1.00% polysorbate 80 and 0.10% cyclosporin/1.25% castor oil/1.00% polysorbate 80, it would have been entirely logical for a person of ordinary skill to conclude that Sall was testing those two emulsions, rather than the claimed emulsion.

B. During prosecution the Examiner agreed that the performance of the claimed emulsion relative to the Ding '979 patent emulsions was unexpected

The Examiner rejected the '111 patent claims as obvious over the Ding '979 patent during prosecution. The Examiner agreed to withdraw the rejection and allow the claims on the basis of Allergan's evidence of unexpected results. In her reasons for allowance, the Examiner stated (EX. 1004, p. 443) (emphasis added):

Taking the results of the studies and data presented in the EXHIBITS 1 and 2 together, *it is clear that the specific combination of 0.05% by weight cyclosporin A with 1.25% castor oil is*

surprisingly critical for the therapeutic effectiveness in the treatment of dry eye or keratoconjunctivitis sicca.

Accordingly, the Declarations in EXHIBIT 1 and EXHIBIT 2, together with the data presented in those declarations, provide ***clear and convincing objective evidence*** that establishes that the claimed formulations, including 0.05% by weight cyclosporin A and 1.25% by weight castor oil, demonstrate surprising and unexpected results, including improved Schirmer Tear Test scores and corneal staining scores (key objective measures of efficacy for dry eye or keratoconjunctivitis sicca) and improved visual blurring and reduced artificial tear use as compared to the prior art, for example, emulsion formulations disclosed in Ding et al., including formulations with 0.05% by weight cyclosporin A and 0.625% castor oil (Ding et al. 1E) and formulations with 0.10% by weight cyclosporin A and 1.25% castor oil (Ding et al. 1D) which are the closest prior art formulations. The unexpected results are commensurate in scope with the claims (MPEP 716.02(d)).

Thus, the obviousness rejection in view of Ding et al. is herein withdrawn.

Argentum now resurrects the Ding '979 patent in its IPR petition. But Argentum ignores evidence presented during prosecution regarding what the PK studies predicted and presents no new evidence to demonstrate that the Examiner was wrong.

IV. ARGUMENT

Argentum alleges that claims 1-27 of the ‘111 patent are unpatentable as anticipated by the Ding ‘979 patent or, alternatively, obvious over the combination of the Ding ‘979 patent plus the Sall paper. In the case of claims 11 and 16, Argentum further includes Acheampong (EX. 1008) in the obviousness mix. However, despite including an 84-page declaration to support a 60 page petition, Argentum fails to demonstrate a reasonable likelihood that at least one claim of the ‘111 patent is unpatentable.

Argentum mischaracterizes and overstates the role of castor oil for treating dry eye disease, as opposed to relieving its symptoms. Argentum offers no credible reason why a person of ordinary skill would combine 0.05% cyclosporin with twice the amount of castor oil described in the Ding ‘979 patent, given that castor oil was a known cytotoxic agent, increasing the amount of castor oil would decrease the thermodynamic activity of the emulsion, and PK data predicted that the lower amount of castor oil resulted in an emulsion that was more therapeutically effective. Argentum also misconstrues the term “therapeutically effective” appearing in claims 20-27.

Argentum further misinterprets Sall. Sall describes emulsions containing both 0.05% and 0.10% cyclosporin, but does does *not* disclose the amount of castor oil, polysorbate 80, and other excipients in each “proprietary” vehicle with

which the cyclosporin was combined. Argentum’s argument that a person of ordinary skill would assume that both emulsions used the same ***amount*** of castor oil is wrong. A person of ordinary skill looking at the art would have believed that the two emulsions would have had the same ***ratio*** of cyclosporin to castor oil. This means that the 0.05% cyclosporin emulsion would have contained 0.625% castor oil and the 0.10% cyclosporin emulsion would have contained 1.25% castor oil because in both cases the cyclosporin to castor oil ratio is 0.08. This is consistent with the Ding ‘979 patent, which describes these very two emulsions.

Contrary to the Sall reference, the Schiffman declaration, while disclosing the same clinical results as Sall, provides the key information—including the make-up of the “proprietary” vehicle. The Schiffman declaration, relying on the Attar declaration, goes on to explain why, with knowledge of the proprietary vehicle, the claimed formulation was counterintuitive and the results unexpected. Argentum’s argument that the Schiffman and Attar declarations cannot be properly used to support the examiner’s conclusion “that the claimed formulations, including the 0.05% by weight cyclosporine A and 1.25% by weight castor oil, demonstrate surprising and unexpected results, . . .” ignores the information in the declarations that is missing from Sall.

A. An emulsion that is “therapeutically effective” must treat the underlying disease

Claims are interpreted using the “broadest reasonable construction in light of the specification of the patent in which [they] appear[.]” 37 C.F.R. § 42.100(b); *see also* *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2142 (2016). Under the broadest reasonable construction standard, claim terms are given their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007).

Claims 20-27 depend on either claim 1, 13, or 18. Each recites that the topical ophthalmic emulsion is “therapeutically effective in treating” keratoconjunctivitis sicca or dry eye, or increasing tear production. Properly construed, these claims require that the emulsion treat the underlying disease. This construction is consistent with the dictionary definition of “therapeutic”: “Relating to therapeutics or to the treatment, remediating, or curing of a disease or disorder.” EX. 2005 (Stedman’s Medical Dictionary (27th Ed.)); *see also* EX. 2006 (Dorland’s Illustrated Medical Dictionary (31st Ed.))². It is also consistent with the

² In contrast, palliative treatments do not treat the underlying disease. *See, e.g.*, EX. 2007 (Stedman’s Medical Dictionary (27th Ed.)) (“palliative” defined as

specification of the ‘111 patent. Throughout the specification, the ‘111 patent uses the word “therapeutic” in connection with the action of cyclosporin. For example, the ‘111 patent states at 5:10-12:

The present methods are useful in treating any condition which is therapeutically sensitive to or treatable with cyclosporin components.

Cyclosporin is the active agent in the emulsion and responsible for treating the underlying cause of the disease itself. In contrast, the ‘111 patent specification does not use the word “therapeutic” to refer to the activity of the other components of the emulsion, including castor oil.

This construction is also consistent with the way in which persons of ordinary skill used the word “therapeutic” in conjunction with ophthalmic compositions. For example, Sall (EX. 1007) describes vehicles for cyclosporin emulsions as providing “palliative benefits.” EX. 1007 (Sall), p. 8. However, Sall then distinguishes these palliative compositions from “therapeutic” compositions (*id.*):

[I]t is important to keep in mind that there is currently no therapeutic treatment for dry eye disease. The only treatments available are

“Reducing the severity of; denoting the alleviation of symptoms without curing the underlying disease.”).

palliative in nature and provide insufficient relief for many patients, particularly those with chronic moderate to severe disease.

Sall also refers to the development of “therapeutic treatments for dry eye disease [being] hampered by a limited understanding of the underlying pathophysiologic processes.” *Id.*, p. 1.

Argentum proposes construing “therapeutically effective” to include both palliative treatments and curative treatments. Petition, p. 16. This construction is inconsistent with the ordinary meaning of the word “therapeutic,” as well as the specification of the ‘111 patent and the way in which persons of ordinary skill understood the term. Accordingly, the Board should reject Argentum’s construction and adopt Allergan’s construction of the term “therapeutically effective.”

B. The Ding ‘979 patent does not anticipate claims 1-27

“A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.” *Verdegaal Bros. v. Union Oil Co. of California*, 814, F.2d 628, 631 (Fed. Cir. 1987). “It is well established that the disclosure of a genus in the prior art is not necessarily a disclosure of every species that is a member of that genus.” *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006). In *Atofina*, the court held that a reference disclosing a broad temperature range did

not anticipate a claim reciting a narrower range falling within that broad genus.

Id.; see also *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1083 (Fed. Cir. 2008) (reference disclosing a genus did not anticipate a species where the reference provided no “specific preferences” for the species).

The ‘111 patent claims cover a specific composition—one having 0.05% by weight cyclosporin A, 1.25% by weight castor oil, as well as polysorbate 80 and an acrylate/C10-30 alkyl acrylate polymer. The Ding ‘979 patent does not disclose this specific composition.

The Ding ‘979 patent generally describes compositions containing cyclosporin A and castor oil for treating dry eye disease. With respect to the relative amounts of these two agents, the patent merely states that the weight ratio of cyclosporin to castor oil is below 0.16 and preferably between 0.12 and 0.02. EX. 1006, 3:15-20. This is very broad. Even in the narrower range, the end points differ by a factor of six. With respect to specific amounts of the two agents, the Ding ‘979 patent discloses in claims 7 and 8 that cyclosporin is present in an amount “of between about 0.05 to and about 0.40% by weight,” and that castor oil is present in an amount “of between about 0.625% by weight, and about 5.0%, by weight.” *Id.*, 6:27-42. Both of these ranges are continuous; thus they include an almost infinite number of points between the two end points. The Ding ‘979 patent also includes examples of only 5 specific compositions having the following

cyclosporin/castor oil ratios: 0.40%/5.00% (Sample A), 0.20%/5.00% (Sample B), 0.20%/2.50% (Sample C), 0.10%/1.25% (Sample D), and 0.05%/0.625% (Sample E). *Id.*, 4:30-45. Notably absent is a composition containing 0.05% cyclosporin/1.25% castor oil.

If the continuous ranges set forth in claims 7 and 8 are read in conjunction with the preferred cyclosporin/castor oil ratio of 0.12 to 0.02, the number of possible combinations is enormous. Even using the 5 compositions in Example 1 as a baseline yields a large number of compositions. Each of the 5 different recited cyclosporin amounts theoretically could be paired with an amount of castor oil satisfying a ratio of 0.12 to 0.02 cyclosporin to castor oil. This yields the following possible combinations:

Cyclosporin	Castor oil
0.40%	3.33% to 20%
0.20%	16.66% to 10%
0.10%	0.83% to 5.0%
0.05%	0.42% to 2.5%

Similarly, each of the 5 different recited castor oil amounts could be paired with an amount of cyclosporin satisfying the 0.12 to 0.02 ratio. This yields the following possible combinations:

Castor oil	Cyclosporin
5.00%	0.6% to 0.1%
2.50%	0.3% to 0.05%
1.25%	0.15% to 0.025%
0.625%	0.075% to 0.0125%

Buried within these possible combinations is the 0.05% cyclosporin/1.25% castor oil combination claimed in the ‘111 patent. But there is nothing in the Ding ‘979 patent that points to this specific combination among the many possible combinations. If anything, the Ding ‘979 patent would point to combining 0.05% cyclosporin with 0.625% castor oil and combining 1.25% castor oil with 0.10% cyclosporin.

Argentum focuses only on the 5 specific formulations disclosed in Example 1 and then treats these compositions as a matrix in which a finite set of cyclosporin concentrations is paired with a finite set of castor oil concentrations. Argentum then pairs 0.05% cyclosporin with 1.25% castor oil, arguing that a person of ordinary skill “would have at once envisaged” this particular combination. *See* Petition, p. 28. In support, Argentum offers the testimony of Dr. Bhagwat, who summarily argues that “Example 1 provides what amounts to interchangeable

amounts of CsA and castor oil, so long as they fall within the more preferred ratio specified.” EX. 1002 (Bhagwat Decl’n), ¶ 94.

Argentum’s argument is flawed because it ignores the rest of the disclosure of the Ding ‘979 patent. Argentum offers no explanation as why a person of ordinary skill would mix and match only the specific amounts disclosed in Example 1 when the disclosure of the patent itself is far broader. In this regard, Dr. Bhagwat’s testimony is wholly conclusory and merely a proxy for attorney argument. Dr. Bhagwat offers no reasoned explanation regarding why the Ding ‘979 patent would direct a person of ordinary skill to a specific emulsion having 0.05% cyclosporin and 1.25% castor oil.

Both Argentum and Dr. Bhagwat also rely upon an alleged admission that Allergan made during prosecution to the effect that the 0.05% cyclosporin/1.25% castor oil emulsions were not patentable. *See* Petition, pp. 1, 63-64; EX. 1002 (Bhagwat Decl’n), ¶ 95. However, both Argentum and Dr. Bhagwat fail to mention that Allergan subsequently expressly retracted these statements.

Argentum’s statement that “Allergan cannot now disclaim its earlier admission of obviousness” is ~~incorrect~~inaccurate. Allergan is not “now” disclaiming its admission—Allergan properly disclaimed its admission during prosecution. In remarks accompanying a Preliminary Amendment in USSN 13/961,828, which is

the parent of the application from which the '111 patent issued, Allergan wrote (EX. 1004, p. 7):

The claims of the present application may vary in scope from the claims pursued in the parent applications. To the extent any prior amendments or characterizations of the scope of any claim, or the specification, or referenced art could be construed as a disclaimer of any subject matter supported by the present disclosure, the Applicants hereby rescind and retract such disclaimer.

Specifically, the Applicants would like to bring to the Examiner's attention comments made in the Response filed on June 15, 2009 in U.S. Patent Application Serial No. 10/927,857 (now abandoned) and comments made in the Amendment filed on June 15, 2009 in U.S. Patent Application Serial No. 11/897,177 (currently pending) regarding U.S. Patent No. 5,474,979 and the present application specification. Since these comments have been filed, the Applicants have collected evidence that supports the patentability of the pending claims.

The Examiner never relied on Allergan's alleged admissions that preceded the above-quoted retraction. Instead, the Examiner relied upon evidence of unexpected results Allergan presented, to which the above-quoted passage refers. Because Allergan expressly retracted any alleged admissions and the Examiner properly ignored them, they are irrelevant to the issues currently before the Board. See New Hampshire v. Maine, 532 U.S. 742, 750 (2001). (stating that for judicial

estoppel to apply, a party's later position must be "clearly inconsistent" with its earlier position).

For at least the reasons discussed above, Argentum has failed to demonstrate that the Ding '979 patent anticipates claims 1-27. Accordingly, Argentum's proposed Ground No. 1 for unpatentability should be denied.

C. Claims 1-27 would not have been obvious over Ding '979 plus Sall

Argentum asserts that claims 1-27 would have been obvious over the Ding '979 patent plus Sall. Each of these references was of record during prosecution of the '111 patent. As discussed above, Allergan overcame rejections based upon the Ding '979 patent by showing surprising results relative to the emulsions disclosed in the Ding '979 patent. In its petition, Argentum adds nothing to what the Examiner considered during the original prosecution.

1. The inventors proceeded contrary to the teachings of the prior art and developed an emulsion that has surprising therapeutic efficacy against dry eye disease

In *Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1304-05 (Fed. Cir. 2015), the Federal Circuit, quoting its decision in *Galderma Laboratories L.P. v. Tolmar, Inc.*, 737 F.3d 731 (Fed. Cir. 2013), explained the framework for evaluating obviousness in the context of a claimed invention falling within a broad range disclosed in the prior art:

[W]here there is a range disclosed in the prior art, and the claimed invention falls within that range, a relevant inquiry is whether there would have been a motivation to select the claimed composition from the prior art ranges In those circumstances, “the burden of production falls upon the patentee to come forward with evidence that (1) the prior art taught away from the claimed invention; (2) there were new and unexpected results relative to the prior art; or (3) there are other pertinent secondary considerations.” [*Galderma*] at 738.

In *Allergan*, the claims at issue recited a composition containing specific amounts of two agents: 0.01% w/v bimatoprost and 200 ppm benzalkonium chloride (“BAK”). *Allergan*, 796 F.3d at 1304. A single prior art reference disclosed a composition containing 0.001%-1% bimatoprost and 0-1000 ppm of a preservative, including BAK. *Id.* A prior art commercial embodiment contained 0.03% bimatoprost and 50 ppm BAK. *Id.*

The court held that the claims would not have been obvious because “the claimed amounts of the two different ingredients could and did materially and unpredictably alter the property of the claimed formulation.” *Id.* at 1305. In particular, the court found that the prior art taught that BAK should be minimized to avoid safety problems, and thus taught away from using 200 ppm BAK, “especially when 50 ppm BAK was known to be an adequate preservative in Lumigan 0.03%.” *Id.*

The court also held that evidence of unexpected results supported nonobviousness. *Id.* at 1307. The evidence showed that while the prior art suggested that 200 ppm BAK would either have no impact on the permeability of bimatoprost or would have decreased it, the inventors unexpectedly discovered that it enhanced permeability. *Id.* Additional evidence showed that the claimed formulation unexpectedly retained efficacy while reducing certain side effects, even though the prior art taught that reducing bimatoprost from 0.03% to 0.01% decreased efficacy and that BAK could cause such side effects at high concentrations. *Id.* The court concluded (*id.*):

Those results exhibited by the claimed formulation thus constitute an unexpected difference in kind, *viz.*, the difference between an effective and safe drug and one with significant side effects that caused many patients to discontinue treatment.

The Federal Circuit's decision in *Allergan* squarely applies to the present case. The claimed emulsions surprisingly cut the amount of cyclosporin in half without loss of efficacy relative to the emulsions disclosed in the Ding '979 patent, which is the closest prior art. The emulsions achieved this result by doubling the amount of castor oil relative to the composition in the Ding '979 patent that contained 0.05% cyclosporin, a choice that was counterintuitive for a number of reasons.

First, castor oil was cytotoxic and known to irritate patients' eyes. *See, e.g.*, EX. 2003 (Said et al.), p. 1 (“Castor oil is the commonly used lipophilic vector but has been shown to be cytotoxic”); EX. 2004 (Alba et al.), p. 7 (describing “significant corneal edema” associated with castor oil when used as a vehicle for cyclosporin). Therefore, the logical choice would have been to use the minimum amount of castor oil to dissolve the cyclosporin, especially when treating patients with dry eye disease, whose eye were already inflamed. In the case of 0.05% cyclosporin, the Ding ‘979 patent taught that this amount was 0.625% castor oil.

Second, basic thermodynamic principles governing diffusion out of the emulsion would lead one of skill to use the least amount of oil necessary to prevent precipitation and create an emulsion with higher thermodynamic activity and more bioavailability of the cyclosporin. Consistent with the governing thermodynamics, the PK data Allergan presented during prosecution suggested that emulsions containing 0.05% cyclosporin/1.25% castor oil would be less effective than compositions containing 0.05% cyclosporin/0.625% castor oil, providing yet another reason *not* to combine 0.05% cyclosporin and 1.25% castor oil.

Argentum has identified no reason, other than hindsight, to combine 0.05% cyclosporin with 1.25% castor oil and 1.00% polysorbate 80. *See In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d

1063, 1070-71 (Fed. Cir. 2012) (cautioning against “hindsight claims of obviousness”).

2. **Sall would not have motivated a person of ordinary skill to prepare an emulsion containing 0.05% cyclosporin and 1.25% castor oil**

Sall describes emulsions containing 0.05% and 0.10% cyclosporin, and concludes that both were “safe and effective.” EX. 1007 (Sall), p. 1. Sall does *not* disclose the amount of castor oil, polysorbate 80, and other excipients in each “proprietary” vehicle with which the cyclosporin was combined. Nevertheless, Argentum argues that Sall would have motivated a person of ordinary skill to combine 0.05% cyclosporin with 1.25% castor oil. *See* EX. 1002 (Bhagwat Decl’n), ¶¶ 111-113; Petition, pp. 38-41.

Argentum contends that both the 0.05% cyclosporin emulsion and the 0.10% cyclosporin emulsion would have contained 1.25% castor oil because “[t]he 1.25% castor oil vehicle is the only vehicle from Ding ‘979 Example 2 for which both 0.05% and 0.10% CsA have a ratio of CsA-to-castor oil inside Ding ‘979’s more preferred range of between 0.12 and 0.02 ... and also within the ratio range found with each of the Example 1 emulsions (0.04-0.08).” Petition, p. 40; EX. 1002 (Bhagwat Decl’n), ¶¶ 112-113.

Argentum’s argument is flawed. It is true that the vehicles for both the 0.05% cyclosporin emulsion and the 0.10% cyclosporin emulsion contained the

same chemical ingredients, including castor oil. However, that does not mean that one of ordinary skill would assume that both emulsions contained the same **amount** of castor oil. Rather, a person of ordinary skill would have expected the emulsions to have had the same **ratio** of cyclosporin to castor oil. This means that the 0.05% cyclosporin emulsion would have contained 0.625% castor oil and the 0.10% cyclosporin emulsion would have contained 1.25% castor oil, leading to a cyclosporin to castor oil ratio in both emulsions of 0.08. This is consistent with Example 1 of the Ding ‘979 patent, which describes these very two emulsions.

Nothing in Sall supports Argentum’s argument. The Ding ‘979 patent points to a different conclusion, *i.e.* that Sall used the two the emulsions described in Example 1 of the Ding ‘979 patent, one of which contained 0.05% cyclosporin/0.625% castor oil and the other of which contained 0.10% cyclosporin/1.25% castor oil. Nowhere does the Ding ‘979 patent describe an emulsion containing 0.05% cyclosporin and 1.25% castor oil.

3. **There was no reasonable expectation that increasing castor oil concentration would increase therapeutic efficacy**

Sall (EX. 1007) expressly distinguishes between compositions having palliative effect that merely treat symptoms and compositions having therapeutic effect that treat the disease itself. EX. 1007 (Sall), p. 1. Sall acknowledges that the vehicle “provided substantial palliative benefits” *Id.*, p. 8. However, Sall further states (*id.*) (emphasis added):

[I]t is important to keep in mind that ***there is currently no therapeutic treatment for dry eye disease. The only treatments available are palliative in nature*** and provide insufficient relief for many patients, particularly those with chronic moderate to severe disease. These patients are at increased risk of ocular surface damage and ocular infection, as well as being subjected to chronic ocular discomfort and visual difficulties. ***The data presented here demonstrate improvements in objective and subjective measures of dry eye disease that are beyond what can be expected with other existing treatments and therefore are clinically significant.*** Moreover, the changes in objective measures suggest the possibility that treatment with topical CsA may also result in clinically significant changes in the progression of the disease and its sequelae.

In other words, Sall distinguishes between therapeutic and palliative treatments, and suggests that the vehicle itself is not responsible for the “clinically significant” effects observed. A person of ordinary skill reading Sall would not have expected to achieve this level of efficacy by increasing the amount of castor oil relative to the amounts disclosed in the Ding ‘979 patent.

There is no dispute that the castor oil/polysorbate 80 vehicle provides some palliative effect. As the Ding ’607 patent describes, when the vehicle is applied to the surface of the eye, it can form a film that remains in place and “retard[s] water evaporation from the eye which alleviates dry eye symptoms.” EX. 1010 (Ding ’607), 3:66 to 4:3. However, that in no way would have suggested to a person of

ordinary skill that increasing the castor oil in the vehicle would have improved the ability of the emulsion to treat dry eye disease itself—especially when there were a number of countervailing considerations teaching minimizing the castor oil concentration relative to the cyclosporin concentration. *See Allergan*, 796 F.3d 1293 at 1306 (claimed invention not obvious where prior art “‘criticize[d], discredit[ed], or otherwise discouraged[d]’ the use of 200 ppm BAK in a bimatoprost formulation”), quoting *In re Mouttet*, 686 F.3d 1322, 1334 (Fed. Cir. 2012); *Arkie Lures, Inc. v. Gene Larew Tackle, Inc.*, 119 F.3d 953, 958 (Fed. Cir. 1997) (“[C]onventional wisdom that a combination should not be made is evidence of unobviousness.”).

4. The differences between the claimed emulsion and the Ding ‘979 emulsions are differences in kind, not degree

“Unexpected results that are probative of nonobviousness are those that are different in kind and not merely in degree from the results of the prior art.” *Galderma Laboratories, L.P. v. Tolmar, Inc.*, 737 F.3d 731, 739 (Fed. Cir. 2013). In *Allergan*, the Federal Circuit held that the ability of 200 ppm BAK to enhance permeability of bimatoprost, when the prior art taught that it would either have no effect or would reduce permeability, constituted “an unexpected difference in kind that supports nonobviousness.” *Allergan*, 796 F.3d at 1306, citing *In re Applied Materials, Inc.*, 692 F.3d 1289, 1298 (Fed. Cir. 2012) (“Evidence that the variables

interacted in an unpredictable or unexpected way could render the combination nonobviousness”).

In the present case, Allergan submitted data during prosecution showing that the claimed emulsions containing 0.05% cyclosporin/1.25% castor oil performed better than the Ding ‘979 emulsions containing 0.05% cyclosporin/0.625% castor oil, and at least as well as the Ding ‘979 emulsions containing 0.10% cyclosporin/1.25% castor oil, despite PK data that predicted the opposite should have been true.

Here, PK data predicted that the claimed emulsion would be less effective than either of the prior art Ding ‘979 emulsions. Argentum does not, and cannot, dispute this point. But the opposite occurred. Relative to the 0.10% cyclosporin/1.25% castor oil prior art emulsion, the comparable performance meant that half the amount of cyclosporin could be used without loss of efficacy. This was surprising based upon the PK predictions. Equally surprising was the improved performance relative to the 0.05% cyclosporin/0.625% castor oil prior art emulsion. Just as in *Allergan*, both represent a difference in kind when judged against the PK predictions. Both, therefore, are evidence of unexpected results that supports the nonobviousness of the claims.

**D. Claims 11 and 16 would not have been obvious over
Ding '607/Ding '979 plus Sall plus Acheampong**

Claims 11 and 16 depend on claims 1 and 13, respectively. Accordingly, claims 11 and 16 are patentable for at least the same reasons as independent claims 1 and 13.

V. CONCLUSION

For at least the foregoing reasons, Allergan requests that the Board deny Argentum's petition.

Please apply any fees or any credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: October 7, 2016/

/Dorothy P. Whelan/

Dorothy P. Whelan, Reg. No. 33,814

Michael J. Kane, Reg. No. 39,722

Attorneys for Allergan, Inc.

Customer Number 26171
Fish & Richardson P.C.
Telephone: (612) 337-2509
Facsimile: (612) 288-9696

61341541.doc

CERTIFICATION UNDER 37 CFR § 42.24(d)

Under the provisions of 37 CFR § 42.24(d), the undersigned hereby certifies that the word count for the foregoing Patent Owner's Preliminary Response totals 8,011, which is less than the 14,000 allowed under 37 CFR § 42.24(b)(1).

Respectfully submitted,

Date: October 7, 2016/

/Dorothy P. Whelan/

Dorothy P. Whelan, Reg. No. 33,814

Michael J. Kane, Reg. No. 39,722

Attorneys for Allergan, Inc.

Customer Number 26171

Fish & Richardson P.C.

Telephone: (612) 337-2509

Facsimile: (612) 288-9696

CERTIFICATE OF SERVICE

Pursuant to 37 CFR §§ 42.6(e)(4) and 42.205(b), the undersigned certifies that on October 7, 2016 a complete and entire copy of this Patent Owner Allergan, Inc.'s Patent Owner Preliminary Response with supporting exhibits were provided via electronic service, to the Petitioner by serving the correspondence address of record as follows:

Matthew J. Dowd
John Murray
Andrews Kurth, LLC
1350 I Street NW, Suite 1100
Washington, D.C. 20005
MatthewDowd@andrewskurth.com
JohnMurray@andrewskurth.com

/Jessica K. Detko/
Jessica K. Detko
Fish & Richardson P.C.
60 South Sixth Street, Suite 3200
Minneapolis, MN 55402
(612) 337-2516