IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

INTENDIS GMBH, INTRASERV GMBH & CO. KG and BAYER HEALTHCARE PHARMACEUTICALS INC.,	)	
Plaintiffs,	)	
v.	)	Civ. No. 13-421 (SLR)
GLENMARK PHARMACEUTICALS LIMITED and GLENMARK PHARMACEUTICALS INC., USA.,	)	
Defendants.	)	

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MEMORANDUM OPINION

Dated: July 31, 2015
Wilmington, Delaware

ROBINSON, District Judge

I. INTRODUCTION

This action arises out of the filing of an Abbreviated New Drug Application ("ANDA") by defendant Glenmark Pharmaceuticals Limited[1] ("Glenmark Pharmaceuticals") seeking to market a generic azelaic acid hydrogel. Plaintiff Bayer Healthcare Pharmaceuticals Inc. ("Bayer") is the holder of approved New Drug Application ("NDA") No. 21-470 for Finacea® Gel, 15%, indicated for topical treatment of inflammatory papules and pustules of mild to moderate rosacea. Plaintiff Intraserv GmbH & Co., KG ("Intraserv") is the assignee of U.S. Patent No. 6,534,070 ("the '070 patent") ("the patent-in-suit") entitled "Composition with Azelaic Acid." (D.I. 118, ex. 1 at ¶ 13) The '070 patent is listed in the Food and Drug Administration's ("FDA's") publication titled "Approved Drug Products with Therapeutic Equivalence Evaluations" (known as the "Orange Book") for Finacea®.[2] (*Id.* at ¶ 16) Plaintiff Intendis GmbH ("Intendis") (together with Bayer and Intraserv, "plaintiffs") holds an exclusive license under the '070 patent. (*Id.* at ¶ 14) Bayer is the exclusive distributor of Finacea®. (*Id.* at ¶ 22)

On July 27, 2012, pursuant to 21 U.S.C. § 355(j), Glenmark Pharmaceuticals submitted ANDA No. 204637, seeking approval to commercially manufacture, use, sell, offer for sale and/or import a generic Azelaic Acid Gel, 15% formulation with a paragraph IV certification stating that the '070 patent is not infringed and is invalid. (D.I.

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[1] Formerly Glenmark Generics Limited.

[2] The expiration date of the '070 patent, as listed in the Orange Book, is November 18, 2018. (D.I. 118, ex. 1 at ¶ 17)

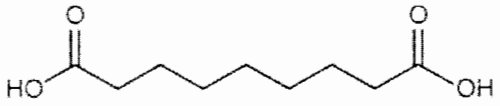
1 at ¶¶ 18-20) On January 30, 2013, defendant Glenmark Pharmaceuticals Inc., U.S.A.[3] (together with Glenmark Pharmaceuticals, "defendants") informed plaintiffs that an ANDA had been filed and alleged that the ANDA product would not infringe the '070 patent. (D.I. 118, ex. 1 at ¶ 39) Plaintiffs responded on March 14, 2013 by filing this suit for infringement of the '070 patent. The court held a Markman hearing and a final pretrial conference on January 21, 2015. The court held a five-day bench trial from February 5 - 11, 2015 on the issues of infringement and validity, and the parties have since completed their post-trial briefing. The 30-month stay of FDA final approval on Glenmark Pharmaceutical's ANDA expires on July 31, 2015. The court has jurisdiction over this matter pursuant to 28 U.S.C. §§ 1331, 1338(a), and 1400(b). Having considered the documentary evidence and testimony, the court makes the following findings of fact and conclusions of law pursuant to Federal Rule of Civil Procedure 52(a).

II. FINDINGS OF FACT AND CONCLUSIONS OF LAW

A. The Technology at Issue

1. Azelaic acid

Azelaic acid has the following chemical structure:



By the year 1998, azelaic acid formulations were being used as topical treatments for various skin disorders, including acne vulgaris, melisma, and rosacea. (D.I. 126 at

[3] Glenmark Pharmaceuticals, formerly named Glenmark Generics Inc., U.S.A., is a wholly-owned subsidiary of Glenmark Generics. (D.I. 118, ex. 1 at ¶ 6)

300:17-301:4; D.I. 127 at 524:18-20, 525:1-8; D.I. 128 at 695:23-696:1; D.I. 125 at 60:5-13; '070 patent, col. 1:24-26) Prior to Finacea®, Bayer marketed and sold a topical 20% azelaic acid cream, marketed abroad as Skinoren®[4] and in the United States as Azelex. (D.I. 125 at 60:2-10; D.I. 127 at 525:1-8; D.I. 128 at 761:7-18)

2. Bayer's Finacea® Gel

Finacea® Gel is a composition that contains azelaic acid as the therapeutically active ingredient as well as at least one triacylglyceride, propylene glycol, at least one polysorbate,[5] at least one polyacrylic acid,[6] lecithin, purified water, edetate disodium and benzoic acid. (D.I. 118, ex. 1 at ¶¶ 24-37) Bayer's development of Finacea® Gel unfolded as follows:

a. Skinoren® Cream

Prior to developing Finacea® Gel, Schering[7] marketed and sold azelaic acid in the form of Skinoren®, a facial cream containing 20% azelaic acid.[8] (D.I. 125 at 59:20-60:13) Dr. Patrick Franke ("Dr. Franke"), one of the named inventors on the '070 patent, testified that Skinoren® cream suffered from unwanted agglomeration and phase separation. (D.I. 125 at 60:22-25) Because the "cream formulation has a pretty

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[4] Skinoren®, Azelex, and Fenevin creams all have the same formulation. (D.I. 127 at 466:19-23)

[5] The azelaic acid, triacylglyceride, propylene glycol, and polysorbate are in an aqueous phase that further comprises water and salts. (D.I. 118, ex. 1 at ¶ 28)

[6] Carbopol® 980, which acts as a gelling agent. (D.I. 118, ex. 1 at ¶¶ 29, 33)

[7] Schering is a "German-based international pharma company that was [later] taken over by Bayer." (D.I. 125 at 57:14-16)

[8] Skinoren® cream is a topical formulation containing: (1) 20% azelaic acid; (2) triacylglycerides; (3) propylene glycol; (4) polysorbates; and (5) water and salts. ('070 patent, col. 1:16-26)

high load of azelaic acid, 20 percent, there was a risk and a problem that certain particles concentrated in so-called agglomerates, so there was . . . an inhomogeneity within th[e] cream emulsion" that caused a patient to "feel particles or agglomerates on the skin." (D.I. 125 at 61:4-18) Dr. Franke testified that the agglomeration "caused some stability problems due to . . . liquid separation . . . so we had to reject batches." (D.I. 125 at 61:14-18) As for phase separation, Dr. Franke explained that it "may occur when you have an emulsion and one of the phases separates, so liquid may not disperse anymore and it's what we saw partly connected with the agglomeration." (D.I. 125 at 62:5-8)

b. Formulation of Finacea® Gel

Dr. Karin Hoffman ("Dr. Hoffman"), defendants' non-infringement and invalidity expert, testified that Schering opted to develop a gel formulation because it "had Skinoren® cream on the market and a gel formulation was a line extension." (D.I. 128 at 760:24-761:4) Dr. Hoffman explained that "[t]o develop the brand further [through a line extension], it's usual to come up with a second formulation on the market" in order "to increase sales." (D.I. 128 at 761:3-6) In contrast, Dr. Franke opined that the decision to reformulate Skinoren® was based on a desire to solve the "agglomerate instability problem" and to cure "disadvantages of the cream regarding the . . . application properties and cosmetic properties" such as a whitening effect, while still "maintain[ing] the same efficacy of the cream." (D.I. 125 at 63:8-15, 77:4-10)

Because an azelaic acid concentration of 20 percent carried a risk of agglomeration, Dr. Franke and his colleagues first "thought of reducing the azelaic acid in content" to 15 percent. (*Id.* at 61:4-7, 63:19-64:6) Dr. Franke testified that the

researchers "discussed on the one hand to keep close to the cream emulsion, Skinoren® cream, and reformulate the cream in terms of thinking of how we can modify ingredients in quantity or quality, and on the other side we also thought about a hydrogel formulation type." (*Id.* at 64:18-22) Between the cream emulsion and the hydrogel, "[t]here was certainly preference towards the cream formulation." (*Id.* at 65:13-17) The clinicians on the team "were afraid . . . that reformulated or new formulation would lose efficacy," and the team "thought that we might have to cope with an efficacy problem." (*Id.* at 66:2-9) Specifically, "there [was] the possibility that active ingredients are held back through this [hydrogel] matrix and interact." (D.I. 125 at 66:12-18) Dr. Franke testified that the team ultimately selected the hydrogel formulation for further testing because the hydrogel solved the "agglomeration problem and phase separation" and it also offered "an improvement of the cosmetic properties" regarding the "whitening effect and spreadability problems with the cream." (*Id.* at 66:19-21)

After settling on a hydrogel formulation, the researchers initially "concentrated on being very similar to the cream" and later "switched to other ingredients and left out ingredients from the cream composition." (*Id.* at 68:4-21) In order to narrow down the list of potential formulations, the team began "characterizing and analyzing the stability of the compounds . . . also taking care of the rheological behavior" and additionally "assess[ing] the [cosmetic] application properties." (*Id.* at 70:21-71:5) According to Schering's formulation development report, "[a] framework recipe based on a polyacrylate gel was available from an earlier acne therapeutic development using a related active ingredient," and "[t]he gel has already been clinically tested as placebo control in the indication acne and should be changed as little as possible . . . because of

its high acceptance and tolerance." (JTX 20 at BAYER0434130) The report stated that "[f]urther development work concentrated on the choice and optimization of the moisture-retaining/regreasing complex." (*Id.*) Dr. Franke explained that after "we saw that we [were] successfully on the track of solving the problems," the question remained of whether "there [was] still efficacy having now reduced azelaic acid and taken care of all other formulation parameters." (D.I. 125 at 71:8-12) Eventually, the researchers selected two 15% azelaic acid hydrogels, hydrogel A and hydrogel B, for further testing "[b]ased on the results in our lab." (*Id.* at 71:13-20, 72:17-22)

Dr. Franke agreed that the two gel formulations "were based on the same formulation concept" and they differed only in the kind of moisture-retaining/regreasing complex that was used. (D.I. 125 at 97:2-7; JTX 20 at BAYER0434141) Dr. Franke further agreed that hydrogel A "took . . . ingredients from the cream formulation but made it into a gel." (D.I. 125 at 97:2-5) Specifically, the moisture-retaining/regreasing complex of the hydrogel A formulation included arlatone and cetearyl octonoate while the hydrogel B formulation – which would later become Finacea® – contained lecithin, triglycerides and polysorbate 80. (*Id.* at 95:11-17, 153:2-3; D.I. 128 at 757:4-10; JTX 20 at 9) Dr. Franke testified that lecithin was chosen for the hydrogel B formulation because of its "amphiphilic structure" that allowed it to "interact in the skin layers," and because it "fit in" with "oils and active ingredients." (D.I. 125 at 69:3-23) Triglycerides were selected because they have "a caring effect on the skin" and "in terms of its polarity as an oil, [it is] very suitable being together with lecithin." (*Id.* at 70:4-10)

c. Franz diffusion cell test

In the next phase of Finacea® development, Dr. Clemens Günther ("Dr. Günther), a named inventor on the '070 patent, "performed in vitro percutaneous penetration studies," otherwise referred to as Franz diffusion cell tests or Franz cell tests. (D.I. 125 at 142:16-21; D.I. 127 at 518:2-519:18; JTX 16 at BAYER0384907) Defendants' expert, Dr. Bozena Michniak-Kohn ("Dr. Michniak-Kohn"), testified that Franz cell tests are popular for ethical reasons as well as for the reason that researchers "don't want a complicated screening method" in the initial stages of testing. (D.I. 127 at 518:21-519:16) Insofar as the goal is to ultimately use the product on living human skin, Franz cell testing is "just a model" that is "used to predict what might happen when a drug is given to humans." (D.I. 125 at 183:20-25; *see also id.* at 184:24-185:5; D.I. 127 at 516:18-518:19; D.I. 128 at 764:22-765:10) The ability to use Franz cell testing to predict the efficacy in vivo on human skin is limited by the fact that in vitro skin is dead, it is "treated in some way" such as cutting the fat layer, and "there's no blood supply." (D.I. 127 at 517:13-518:8; *see also* D.I. 129 at 998:25-999:5)

The goal of the Franz cell test was to assess the "distribution of azelaic acid in the skin and the absorption across the skin" after treatment with the two hydrogel formulations and Skinoren® cream. (D.I. 125 at 142:24-143:1, 143:17-20) To measure absorption, Dr. Günther used a "Franz diffusion cell consist[ing] of a donor chamber and a receptor chamber, which both are separated by the [mouse] skin sample acting as a membrane." (*Id.* at 145:17-20) Mouse skin was the "established routine skin" used in the laboratory, and they "did not have access at that time to human skin vivo," the "gold standard" for Franz cell testing. (D.I. 125 at 146:1-8, 156:20-24; D.I. 127 at 515:14) Because "hairless mouse skin is much thinner than human skin . . . [it] overexaggerates

the numbers you see when you use chemical penetration enhancers." (D.I. 127 at 516:18-517:9; *see also* D.I. 125 at 146:9-13)

After selecting skin type and assembling the apparatus, "a thin layer of formulation [is] placed on the skin" and "the drug enters the stratum corneum[9] and diffuses across the skin" then "partitions . . . into the receptor chamber" and "excess flow-through" is captured and studied.[10] (D.I. 125 at 148:1-149:4) Dr. Günther explained that "[t]he concentrations in the receptor fluid resembled systemic absorption and thus might correlate or indicate systemic side effects." (*Id.* at 156:20-24) At the end of the 24-hour period, Dr. Günther measured "the distribution of azelaic acid in various skin layers" including the stratum corneum and the underlying layers. (D.I. 125 at 151:10-16; JTX 16 at BAYER384907, -23)

Dr. Günther performed two experiments for the Skinoren® cream and two experiments for each of the hydrogel formulations, with four samples apiece for a total of eight data points per formulation. (D.I. 125 at 178:9-17; JTX 16 at BAYER0384916) However, Dr. Günther decided to only "use the results of the second [hydrogel] experiment" as the "results of both experiments were not in agreement." (D.I. 125 at 179:1-25) Dr. Günther "did not perform any statistical analysis of the results of [the] study," although he testified that it is not "standard practice in this type of pharmacokinetic investigation" to perform statistical analysis. (D.I. 125 at 174:25-175:2; D.I. 126 at 371:5-372:21)

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[9] Skin consists of three layers: the stratum corneum, the epidermis and the dermis. (D.I. 126 at 290:10-292:4) The site of action for the active ingredient is "somewhere in the living skin past the stratum corneum." (D.I. 126 at 292:2-11)

[10] The diffusion test was run for 24 hours, with sampling of the flow-through taken at 2-hour time intervals. (D.I. 125 at 149:12-29)

Dr. Franke was "surprised to see such a good penetration behavior into living skin tissue with one of our gel candidates" containing lecithin and triglycerides (hydrogel B). (D.I. 125 at 73:2-21) Dr. Franke testified that they did not "see similar results with the hydrogel formulation containing the arlatone and cetearyl octonoate ingredients [hydrogel A] that had been carried over from the cream." (D.I. 125 and 73:22-5, 95:1-17, 152:9-153:4; JTX 16 at BAYER384923) More specifically, Dr. Günther explained that, "after account[ing] for the fact that there was only 15 percent azelaic acid in the hydrogels and 20 percent in the cream to begin with," the azelaic acid remaining in the skin after treatment with hydrogel B was five times higher than compared to Skinoren® cream. (D.I. 125 at 154:16-155:16; 174:15-22) Dr. Günther "expected that the concentration in the skin and receptor fluid would point in the same . . . direction," but "[i]n this case, it appeared to be vice-versa, meaning that the fraction of dose present at the end of experiment in the skin was lower for Skinoren® cream versus the hydrogel B." (D.I. 125 at 158:14-19) In the words of plaintiffs' expert, Dr. Norman Weiner ("Dr. Weiner"), "the inventive formulation had more of the . . . azelaic acid going into the skin, but the prior art had more formulation going out of the skin." (D.I. 128 at 917:23-918:13)

Dr. Franke testified that, following the Franz diffusion cell test, "we again collected our data from the pharmaceutical technology lab and took the results of Dr. Günther, and . . . proposed this new candidate" for clinical trials. (D.I. 125 at 74:3-7) Defendants propose that finances were the true motivator behind the decision to pursue hydrogel B, citing Schering's formulation development report which stated that the "decisive" difference leading to a preference for hydrogel B over hydrogel A was that "[t]he components of the moisture-retaining/regreasing complex in [hydrogel B] can be

processed cold, melting is unnecessary and makes large-scale production cheaper." (JTX 20 at BAYER0434146)

d. Clinical tests

Next, a double-blind scarification test was performed "to detect small differences in irritation potential," wherein hydrogel A and hydrogel B and Skinoren® cream "were applied once daily for 4 days in 20 [healthy human] subjects" and skin reactions were assessed (hereinafter "the scarification test"). (DTX 92; DTX 111 at BAYER0384619) Prior to application, the subject's skin is "predamaged" by scarification to "mimic[] the situation found in lesional skin." (DTX 111 at BAYER0384630) The reaction score for hydrogel B was significantly higher than that for Skinoren® (DTX 111 at BAYER384644; DTX 93; D.I. 129 at 1037:17-1039:8), thus "confirm[ing] the results of the hairless mouse Franz flow-through diffusion cell study" (D.I. 129 at 1038:23-1039:3).

Following the scarification test, an 8-week double-blind pilot study measuring percutaneous absorption was conducted to directly compare the initial clinical effect of hydrogel B to Skinoren®. (D.I. 125 at 162:22-25; D.I. 129 at 1003:14-17; JTX 11 at BAYER154358) According to the Schering clinical study report, "[t]he aim of this exploratory pilot study was to investigate the effect of [hydrogel B] on acne lesions during an 8-week treatment period, as compared with that of [Skinoren®]." (JTX 11 at BAYER0154358) The study looked at "the relative decrease in the sum of facial papules and pustules," as well as "the amounts of [azelaic acid] excreted with the urine." (JTX 11 at BAYER0154358) Dr. Günther testified that "there was no significant treatment difference between the Skinoren® cream and Finacea® or later on Finacea® hydrogel with regard to the efficacy in reducing the number of acne lesions." (D.I. 125

at 167:19-22; D.I. 126 at 193:19-24, 373:23-374:1; JTX 11 at BAYER154393) Additionally, Dr. Weiner admitted that "the progression of the efficacy over time was similar for both treatments." (D.I. 127 at 443:23-444:4) According to Dr. Günther, there was also "no statistical significance in urinary excretion of azelaic acid . . . and this is certainly positive in terms of the point that this does not give rise to concerns related to systemic safety." (D.I. 125 at 166:2-6; JTX 11 at BAYER0154360) Dr. Günther opined that a study with only 30 patients (15 per treatment group) means it is "likely that such [a] study does not bring statistical power." (D.I. 125 at 165:4-7; JTX 11 at BAYER0154370)

The company proceeded with full-scale clinical trials comparing Finacea® to placebo formulations as "required by regulator purpose for submission." (D.I. 126 at 206:3-8) In 2002, Dr. Franke gave a presentation to the marketing and management members of the project team detailing the benefits of Finacea® over Skinoren®. (JTX 3) In the presentation, Dr. Franke identified three benefits of hydrogel B: (1) no agglomeration or phase separation; (2) good results in the clinics and maintenance of efficacy; and (3) cosmetic benefits. (D.I. 125 at 76:2-22; JTX 3 at BAYER6527-530) Eventually, FDA approval was sought and Finacea® gel was approved and indicated for treating rosacea. (D.I. 125 at 74:8-15, 168:18-25)

3. The asserted patent

The '070 patent issued on March 18, 2003, and claims priority to U.S. Provisional Application No. 60/074,850 ("the '850 provisional"), filed on February 12, 1998. Plaintiffs assert independent claim 1 and dependent claims 2-12. The '070 patent

claims azelaic hydrogel compositions, including Finacea®, as well as methods for treating rosacea and other skin conditions. ('070 patent, cols. 6:27-8:9)

Independent claim 1 reads:

> 1. A composition that comprises:
>
> (i) azelaic acid as a therapeutically active ingredient in a concentration of 5 to 20% by weight,
>
> (iii) at least one triacylglyceride[11] in a concentration of 0.5 to 5% by weight,
>
> (iv) propylene glycol, and
>
> (v) at least one polysorbate, in an aqueous phase that further comprises water and salts, and the composition further comprises
>
> (ii) at least one polyacrylic acid, and
>
> (vi) lecithin,
>
> wherein the composition is in the form of a hydrogel.

(*Id.* at col. 6:28-38)

The specification of the '070 patent identifies Skinoren® cream and EP 0 336 880 as relevant prior art cream formulations that contain azelaic acid. ('007 patent, col. 1 at 16-36) Skinoren® cream is described as "the closest prior art." (*Id.* at col. 1:36) The specification also identifies non-azelaic acid prior art "emulsions" or "nanoemulsions" such as the composition disclosed in International Application WO 96/11700. ('070 patent, col. 1:37-49)

[11] The term "triacylglyceride" means "triglyceride." (D.I. 118, ex. 1 at ¶ 18)

Example 1 describes the formulation and processing steps for producing the claimed hydrogel.[12] ('070 patent, col. 5:20-39) Specifically, a "pre-emulsion" is formed from a mixture of benzoic acid, EDTA, triglycerides, polysorbate 80, lecithin, and propylene glycol. (*Id.* at col. 5:20-32) The "pre-emulsion" is homogenized, and then polyacrylic acid and azelaic acid are added. ('070 patent, col. 5:32-34) Finally, a gel is formed by adding sodium hydroxide, which raises the pH of the solution. (*Id.* at col. 5:34-36) The specification emphasizes that "[t]he presence of polyacrylic acid[13] is essential" and "decisive for the production of the hydrogel." (*Id.* at col. 2:51:52) The specification defines polyacrylic acid as "an anion-active polymerizate of acrylic acid, which is only partially water-soluble" where "[t]he one-percent aqueous suspension has a pH of 3 and approximately the same viscosity as water." (*Id.* at col. 3:42-45) The specification states that "gel formation and the production of highly viscous products" only occurs during neutralization (raising the pH) of polyacrylic acid. (*Id.* at col. 3:46-48)

One named advantage of the claimed composition is that it "allows a larger amount of pharmaceutical active ingredient to penetrate into living skin layers and/or cutaneous organs." (*Id.* at col. 2:29-40) Dr. Weiner, Dr. Michniak-Kohn and Dr. Günther all testified that the claim of "increased bioavailability" is solely supported by the results from the Franz diffusion cell test, as described in example 2 of the specification.[14] (D.I. 125 at 170:21-717:8; D.I. 128 at 932:2-8; D.I. 129 at 1013:4-6; '070 patent, 5:40-6:26)

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[12] The same processing steps are used to make Finacea®. (JTX 25 at BAYER536793-95; D.I. 126 at 303:2-305:5)

[13] The trade name for polyacrylic acid is Carbopol®.

[14] The advantage of increased bioavailability was referenced by the patent examiner in the "reasons for allowance," in which the examiner wrote that "[t]he prior art of record

Another named advantage of the claimed composition is that when lecithin is 1% or less by weight, the composition "does not form any standard nanoemulsion" but rather forms a gel "that comprises a homogenous mass with virtually no vesicles" as detected by a scanning electron microscope. ('070 patent, cols. 2:61-3:3) Dr. Franke testified that the electron microscopy was performed on Finacea® by Dr. Rolf Schubert ("Dr. Schubert") at the Albert Ludwig Universitat. (D.I. 125 at 111:1-19) In a report submitted to Dr. Hoffman, Dr. Schubert wrote that "the examinations have proven to be particularly difficult" as "the processing methods you recommended for us were not optimally suited to separate and identify structures to a sufficient extent." (D.I. 125 at 112:22-113:3; DTX 16 at BAYER0524392) Dr. Schubert stated that "[f]urther examinations will have to be performed," although no further examinations were conducted following the initial report. (D.I. 125 at 113:7-114:4; DTX 16 at BAYER0524392) Dr. Schubert concluded that, given the heterogeneity of the samples, "more images must be used for interpretation." (D.I. 125 at 115:5-9; DTX 16 at BAYER0524404)

4. The accused ANDA product

a. Overview

Defendants' ANDA product ("the accused product" or "the accused formulation") is a composition for topical administration to treat rosacea that contains azelaic acid as the therapeutically active ingredient at a concentration of 15% by weight, isopropyl

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neither teaches nor suggests an azelaic acid hydrogel composition containing instant amount of azelaic acid in the form of a hydrogel and said hydrogel enabling over four times higher bioavailability and penetration of azelaic acid . . . compared to conventional creams/emulsions of the prior art." (JTX 2.2 at BAYER 547)

myristate at a concentration of 2% by weight, propylene glycol at a concentration of 12% by weight, at least one polysorbate,[15, 16] at least one polyacrylic acid[17] at a concentration of 0.85% by weight, purified water, benzoic acid at a concentration of 0.10% by weight, and edetate disodium at a concentration of 0.10% by weight. (D.I. 118, ex. 1 at ¶¶ 44-59)

b. Formulation of the accused product

Mr. Kamal Mehta ("Mehta"), defendants' corporate witness, testified that defendants used, *inter alia*, "details about Finacea® [that] are available in the public domain" such as the Finacea® label to develop the accused formulation. (D.I. 126 at 214:11-16; PTX 214 at GMG_710) For the first experimental batch, Mehta agreed that defendants used "the formulation that was listed in the patent." (D.I. 126 at 220:12-19; *see also* JTX 54 at GMG_VP1266-67) Like the procedure described in example 1 of the '070 patent, defendants' manufacturing process involved dissolving EDTA and benzoic acid in water, adding additional excipients to create a homogenized "pre-emulsion," adding polyacrylic acid and azelaic acid, and finally neutralizing with sodium hydroxide to achieve "orientation of the gel." (JTX 39 at GMG_0014878; JTX 53 at GMG_VP798-800; '070 patent, col. 5:22-39)

In their original ANDA submission, defendants detailed experimental trials in which triglyceride and lecithin were swapped for alternate excipients, with the goal of "match[ing] the appearance . . . and chemical stability of the [experimental] gel with the

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[15] Polysorbate 80.

[16] The azelaic acid, propylene glycol, and polysorbate are in an aqueous phase that further comprises water and salts. (D.I. 118, ex. 1 at ¶ 51)

[17] Carbopol® 980, which acts as a gelling agent. (D.I. 118, ex. 1 at ¶¶ 52, 56)

reference-listed drug Finacea® Gel 15%." (JTX 53 at GMG_VP000776; D.I. 126 at 220:21-227:10) Defendants' overall "[o]bjective was to develop a formulation which doesn't fall in the [scope of] the patent claims." (D.I. 126 at 217:14-23) Defendants determined that batch 540/03-08/036 ("batch 036") and batch 540/03-08/041 ("batch 041") were "satisfactory" formulations. (JTX 53 at GMG_VP000776) In batch 036, PPG-20-Methyl glucose ether distearate was substituted for triglyceride and lecithin. (*Id.*) In batch 041 – which would later become the accused formulation – isopropyl myristate was substituted for triglyceride and lecithin "to improve the penetration." (*Id.*; JTX 54 at GMG_VP001272; D.I. 126 at 225:14-226:13) In their original ANDA submission, defendants listed the "function" of isopropyl myristate, lecithin and medium chain triglyceride as "penetration enhancer." (JTX 53 at GMG_VP000775) With the exception of the substitution of isopropyl myristate for triglyceride and lecithin, all other excipients in the accused product remained "exactly the same" as those in Finacea®. (D.I. 126 at 313:18-21; JTX 53 at GMG_VP000775; JTX 54 at GMG_VP001266)

c. Franz diffusion cell and clinical testing

Defendants performed Franz diffusion cell tests with human cadaver skin, comparing the rate of penetration of azelaic acid across the skin layers between batch 036, batch 041 and Finacea® gel. (D.I. 126 at 233:18-235:12; JTX 54 at GMG_VP1271-73; JTX 38 at GMG_12942-45, -949) In the Franz diffusion cell test, defendants applied a finite dose of product, then measured penetration and absorption of azelaic acid over a period of 48 hours. (JTX 38 at GMG_12942, 44-49) For both batch 041 and Finacea®, "more azelaic acid stayed in the epidermis skin layer than what went through to the reservoir." (D.I. 128 at 720:9-12; JTX 38 at GMG_0012948)

Compared to one another, nearly twice as much azelaic acid remained in the epidermis following treatment with Finacea® than following treatment with batch 041. (JTX 38 at BMB_0012947) Both batch 041 and Finacea® reached a peak flux between 1 to 5 hours after application, although the absorption levels declined more rapidly for batch 041 than for Finacea®. (JTX 38 at BMB_0012947; D.I. 127 at 581:9-17) Mehta admitted that defendants selected batch 041 over batch 036 because it was "close[r] to the reference product, Finacea®." (D.I. 126 at 214:8-11, 241:8-10)) The study concluded that "there were no statistically significant differences" across the parameters, and "the flux profiles suggest that the test formulations are similar to, but not identical to, the Finacea® reference formulation." (JTX 38 at GMG_0012949) Mehta agreed that "once [defendants] got the results from the cadaver study with the isopropyl-myristate containing formulation, [they] didn't investigate . . . any other alternative formulations." (D.I. 126 at 227:6-11) Defendants then performed a large-scale clinical trial comparing batch 041 to Finacea®, and concluded that "the test product was bioequivalent" to Finacea® and superior to placebo. (*Id.* at 259:13-20, 261:7-11; PTX 219 at GMG_002365-68, 2412)

B. Claim Construction

1. Standard

Claim construction is a matter of law. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1330 (Fed. Cir. 2005) (en banc). Claim construction focuses on intrinsic evidence – the claims, specification, and prosecution history – because intrinsic evidence is "the most significant source of the legally operative meaning of disputed claim language." *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996); *Markman v.*

Westview Instruments, Inc., 52F.3d 967, 979 (Fed. Cir. 1995) (en banc), *aff'd*, 517 U.S. 370,116 S.Ct. 1384, 134 L.Ed.2d 577 (1996). Claims must be interpreted from the perspective of one of ordinary skill in the relevant art at the time of the invention. *Phillips*, 415 F.3d at 1313.

Claim construction starts with the claims, *id.* at 1312, and remains centered on the words of the claims throughout. *Interactive Gift Express, Inc. v. Compuserve,Inc.*, 256 F.3d 1323, 1331 (Fed. Cir. 2001). In the absence of an express intent to impart different meaning to claim terms, the terms are presumed to have their ordinary meaning. *Id.* Claims, however, must be read in view of the specification and prosecution history. Indeed, the specification is often "the single best guide to the meaning of a disputed term." *Phillips*, 415 F.3d at 1315.

2. Issues at bar

The parties agree that a "hydrogel" is a semi-solid dosage form wherein the gel structure contains water and a gelling agent to form a gel, which may contain dispersed particles such as undissolved azelaic acid.[18] The crux of the parties' disagreement is whether, as defendants propose, hydrogels may also contain insoluble liquids. Regarding the term "lecithin," the parties dispute whether construction of the term is necessary given that the construction may not alter the outcome of the court's validity or infringement analysis. Substantively, the parties dispute whether lecithin is equivalent to phosphatidylcholine or whether lecithin is a complex mixture of compounds that is characterized by the presence of phosphatidylcholine.

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[18] Azelaic acid is poorly soluble in water at 20° Celsius (0.24%). (D.I. 118, ex. 1 at ¶ 21)

3. "Hydrogel"[19]

Plaintiffs admit that claim 1 calls for the addition of a small amount of oil – triacylglyceride in a concentration of 0.5 to 5% by weight – which is insoluble in liquid water. ('070 patent, claim 1) Plaintiffs also recognize that example 1 of the '070 patent describes a homogenized mixture containing liquid water and triacylglycerides as a "pre-emulsion." (*Id.* at col. 5:20-32) Plaintiffs contend, however, that no more than a trace amount of triacylglyceride would remain in the solution following addition of polyacrylic acid and neutralization of the solution to form a gel, arguing that droplets of triacylglyceride would be adsorbed[20] onto the surface of any solid azelaic acid particles. Although the issue is most narrowly framed as whether the claimed hydrogel contains insoluble liquid vesicles, the parties somewhat confusingly present the issue as whether the claimed hydrogel "contains" a nanoemulsion. Plaintiffs argue that defendants blur the line between a gel and an emulsion in order to advance their invalidity position, while defendants respond that they do not blur any lines insofar as they do not argue that gels are equivalent to emulsions. As such, the parties appear to accept the premise that a gel differs from an emulsion in that, at least on the macro level, a gel is a single-phase semisolid and an emulsion is a mixture of two liquids. With this framework in mind, the court considers the following intrinsic evidence:

Under the heading of "advantages," the specification states that

> [i]t has unexpectedly proven that the composition according to the invention in the case of concentrations in lecithin of 1% by weight and less does not form any standard

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[19] The term "hydrogel" appears in independent claim 1 of the '070 patent.

[20] According to Hawley's Condensed Chemical Dictionary, "adsorption" is the "[a]dherence of the atoms, ions, or molecules of a gas or liquid to the surface of another substance, called the adsorbent." (D.I. 91, ex. 13 at 25)

> nanoemulsions according to the prior art. Rather a gel is present that comprises a homogenous mass with virtually no vesicles, but does have membrane fragments. The fact that azelaic acid and the remainder of the solution do not form any nanoemulsions was not expected. Only with the aid of scanning electron microscope recordings was it possible to provide clarity. It turned out that no nanoemulsions could be identified in microscopic examination.

('070 patent, cols. 2:61-3:7) By stating that the claimed hydrogel "unexpectedly" fails to form a "standard nanoemulsions" as in the prior art, the drafters belie an expectation that gel compositions will typically form nanoemulsions. Moreover, in using the word "nanoemulsion," it is evident that the drafters envisaged a "gel" present as a "homogenous mass" that contains vesicles. Indeed, as explained in the final two sentences of the passage, the inventors imaged samples of the claimed composition[21] with a scanning electron microscope for the purpose of verifying the absence of a nanoemulsion (a.k.a. vesicles).

Importantly, the absence of a nanoemulsion was only observed in formulations containing less than 1% lecithin by weight.[22] Although the embodiment disclosed in example 1 and claimed in dependent claim 4 contains lecithin in the vesicle-free range of 0-1%, independent claim 1 does not specify a concentration and dependent claim 11 claims a concentration in the range of 0-3%. Interpreting claim 1 as being limited to the vesicle-free embodiment would run afoul of the doctrine of claim differentiation and

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[21] Dr. Franke's testimony confirms that electron microscopy was indeed performed on Finacea® gel, not on the "pre-emulsion" intermediate. (D.I. 125 at 111:1-19)

[22] The court is skeptical of this observation given the heterogeneity of the samples submitted for electron microscopy and the lack of follow-up imaging. (D.I. 125 at 113:7-115:9)

would improperly read a single embodiment from the specification into the claims. *See Phillips*, 415 F.3d at 1323.

The court's construction is further bolstered by the prosecution history. The '850 provisional application, to which the '070 patent claims priority, describes a method of making a "nanoemulsion gel" wherein the gel is made in the same manner as the method disclosed in example 1 of the '070 patent. (DTX 15 at 11-14) The concentrations disclosed in the two methods are not identical, but are overlapping. (DTX 15 at 11; '070 patent, col. 5:26-40) For example, the '850 application calls for 1-5 parts lecithin, whereas the '070 patent calls for 1 part lecithin. (DTX 15 at 11; '070 patent, col. 5:30-31) The '850 application goes on to state that "detection of the nanoemulsion" is achieved by measuring "vesical [sic] sizes using zeta sizers." (DTX 15 at 11) The issued '070 patent substitutes the phrase "nanoemulsion gel" with "gel," and omits the language regarding detection of vesicles, presumably because at a lecithin concentration of less than 1%, no vesicles were detected. Nonetheless, the example provided by the '850 application reinforces the concept that, when lecithin is in a range of 1-5%, a "nanoemulsion gel" will form that contains measurable nanovesicles. For the foregoing reasons, the court construes "hydrogel" as "a semisolid dosage form that contains water and a gelling agent to form a gel, which may contain dispersed particles and/or insoluble liquids."

4. "Lecithin"[23]

[23] The term "lecithin" appears in independent claim 1 and dependent claims 3, 4 and 11 of the '070 patent.

The parties do not dispute the meaning of the term lecithin in the context of literal infringement, nor do plaintiffs allege that defendants' generic product contains lecithin. (D.I. 91, ex. 15 at 230:15-232:23) Moreover, defendants do not allege that the construction of lecithin impacts the court's analysis regarding validity. (*See* D.I. 97 at 18-28) Rather, defendants propose that the construction of lecithin is relevant to the court's analysis of infringement under the doctrine of equivalents. Specifically, defendants object to the portion of plaintiffs' proposed construction[24] equating lecithin with phosphatidylcholine. Defendants' counsel argues that limiting what is allegedly a mixture of compounds to a single pure compound makes lecithin appear more like isopropyl myristate, the compound allegedly substituted for lecithin and triglycerides in the generic compound. However, this non-infringement posture is not adopted by defendants' expert, who stated that the difference between the two proposed constructions "doesn't make any difference to my opinion" as to whether the accused composition meets the limitations of the claims. (D.I. 91, ex. 15 at 236:17-237:7) Because construing "lecithin" will not impact the court's analysis, the court declines to issue a construction. *See Jang v. Boston Sci. Corp.*, 532 F.3d 1330, 1336-37 (Fed. Cir. 2008) (cautioning that "[t]he Supreme Court has explicitly held that Article III does not permit the courts to resolve issues when it is not clear that the resolution of the question will resolve a concrete controversy between interested parties.").

C. Infringement

1. Standard

[24] "Phosphatidylcholine, or a mixture, extracted from biological material, characterized by the presence of phosphatidylcholine."

A patent is infringed when a person "without authority makes, uses or sells any patented invention, within the United States . . . during the term of the patent." 35 U.S.C. § 271(a). To prove direct infringement, the patentee must establish, by a preponderance of the evidence, that one or more claims of the patent read on the accused device literally or under the doctrine of equivalents. *See Advanced Cardiovascular Sys., Inc. v. Scimed Life Sys., Inc.*, 261 F.3d 1329, 1336 (Fed. Cir. 2001). A two-step analysis is employed in making an infringement determination. *See Markman*, 52 F.3d at 976. First, the court must construe the asserted claims to ascertain their meaning and scope. *See id.* Construction of the claims is a question of law subject to de novo review. *See Cybor Corp. v. FAS Techs.*, 138 F.3d 1448, 1454 (Fed. Cir. 1998). The trier of fact must then compare the properly construed claims with the accused infringing product. *See Markman*, 5 2 F.3d at 976. This second step is a question of fact. *See Bai v. L & L Wings, Inc.*, 160 F.3d 1350, 1353 (Fed. Cir. 1998).

"Direct infringement requires a party to perform each and every step or element of a claimed method or product." *Exergen Corp. v. Wal-Mart Stores, Inc.*, 575 F.3d 1312, 1320 (Fed. Cir. 2009) (internal quotation marks omitted). "If any claim limitation is absent from the accused device, there is no literal infringement as a matter of law." *Bayer AG v. Elan Pharm. Research Corp.*, 212 F.3d 1241, 1247 (Fed. Cir. 2000). If an accused product does not infringe an independent claim, it also does not infringe any claim depending thereon. *See Wahpeton Canvas Co. v. Frontier, Inc.*, 870 F.2d 1546, 1553 (Fed. Cir. 1989). However, "[o]ne may infringe an independent claim and not infringe a claim dependent on that claim." *Monsanto Co. v. Syngenta Seeds, Inc.*, 503 F.3d 1352, 1359 (Fed. Cir. 2007) (quoting *Wahpeton Canvas*, 870 F.2d at 1552)

(internal quotations omitted). A product that does not literally infringe a patent claim may still infringe under the doctrine of equivalents if the differences between an individual limitation of the claimed invention and an element of the accused product are insubstantial. *See Warner–Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 24 (1997). One test used to determine "insubstantiality" is whether the element performs substantially the same function in substantially the same way to obtain substantially the same result as the claim limitation. *Graver Tank & Mfg. Co. v. Linde Air Products Co.*, 339 U.S. 605, 608 (1950). This test is commonly referred to as the "function-way-result" test. The mere showing that an accused device is equivalent overall to the claimed invention is insufficient to establish infringement under the doctrine of equivalents. The patent owner has the burden of proving literal infringement and/or infringement under the doctrine of equivalents by a preponderance of the evidence. *See SmithKline Diagnostics, Inc. v. Helena Lab. Corp.*, 859 F.2d 878, 889 (Fed. Cir. 1988) (citations omitted).

The doctrine of equivalents is limited by the doctrine of prosecution history estoppel. In *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., Ltd.*, 535 U.S. 722 (2002) ("*Festo I*"), the Supreme Court stated:

> Prosecution history estoppel ensures that the doctrine of equivalents remains tied to its underlying purpose. Where the original application once embraced the purported equivalent but the patentee narrowed his claims to obtain the patent or to protect its validity, the patentee cannot assert that he lacked the words to describe the subject matter in question. The doctrine of equivalents is premised on language's inability to capture the essence of innovation, but a prior application describing the precise element at issue undercuts that premise. In that instance the prosecution history has established that the inventor turned his attention to the subject matter in question, knew the words for both

> the broader and narrower claim, and affirmatively chose the latter.

Id. at 734–735. In other words, the prosecution history of a patent, as the public record of the patent proceedings, serves the important function of identifying the boundaries of the patentee's property rights. Once a patentee has narrowed the scope of a patent claim as a condition of receiving a patent, the patentee may not recapture the subject matter surrendered. In order for prosecution history estoppel to apply, however, there must be a deliberate and express surrender of subject matter. *See Southwall Techs., Inc. v. Cardinal IG Co.*, 54 F.3d 1570, 1580 (Fed. Cir. 1995).

Once a court has determined that prosecution history estoppel applies, it must determine the scope of the estoppel. *See id.* at 1580. This requires an objective examination into the reason for and nature of the surrendered subject matter. *Id.; see also Augustine Med., Inc. v. Gaymar Indus., Inc.*, 181 F.3d 1291, 1299 (Fed. Cir. 1999). If one of ordinary skill in the art would consider the accused product to be surrendered subject matter, then the doctrine of equivalents cannot be used to claim infringement by the accused product; i.e., prosecution history estoppel necessarily applies. *Augustine Med.*, 181 F.3d at 1298. In addition, a "patentee may not assert coverage of a 'trivial' variation of the distinguished prior art feature as an equivalent." *Id.* at 1299 (quoting *Litton Sys., Inc. v. Honeywell, Inc.*, 140 F.3d 1449, 1454 (Fed. Cir. 1998)).

"[A] narrowing amendment made to satisfy any requirement of the Patent Act" creates a presumption that "the patentee surrendered all subject matter between the broader and the narrower language" and bars any equivalents. *Festo I,* 535 U.S. 722, 736, 740 (2002); *see also Honeywell Int'l, Inc. v. Hamilton Sundstrand*, 370 F.3d 1131, 1139 (Fed. Cir. 2004) (prosecution history estoppel "bar[s] the patentee from asserting

equivalents if the scope of the claims has been narrowed by an amendment during prosecution."). Thus, a presumption of prosecution history estoppel is established by showing that the patentee made a narrowing amendment and that "the reason for that amendment was a substantial one relating to patentability." *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 344 F.3d 1359, 1366 (Fed. Cir. 2003) (en banc) ("*Festo II*"). There are three exceptions to this presumption: (1) the equivalent was "unforeseeable at the time of the narrowing amendment"; (2) the rationale for the amendment "bore no more than a tangential relation to the equivalent in question"; or (3) "some other reason suggested that the patentee could not reasonably have been expected to describe the alleged equivalent." *Festo I.*, 535 U.S. at 740–41.

To establish indirect infringement, a patent owner has available two theories: active inducement of infringement and contributory infringement. *See* 35 U.S.C. § 271(b) & (c). To establish active inducement of infringement, a patent owner must show that an accused infringer "knew or should have known [their] actions would induce actual infringements." *DSU Med. Corp. v. JMS Co., Ltd.*, 471 F.3d 1293, 1306 (Fed. Cir. 2006). To establish contributory infringement, a patent owner must show that an accused infringer sells "a component of a patented machine ... knowing the same to be especially made or especially adapted for use in an infringement of such patent, and not a staple article or commodity of commerce suitable for substantial noninfringing use." *Golden Blount, Inc. v. Robert H. Peterson Co.*, 365 F.3d 1054, 1061 (Fed. Cir. 2004) (quoting 35 U.S.C. § 271(c)). Liability under either theory, however, depends on the patent owner having first shown direct infringement. *Joy Technologies, Inc. v. Flakt, Inc.*, 6 F.3d 770, 774 (Fed. Cir. 1993).

2. Doctrine of equivalents[25]

Plaintiffs allege that defendants infringe claims 1-12 of the '070 patent ("the asserted claims") under the doctrine of equivalents. Defendants do not dispute that the accused product meets the azelaic acid, propylene glycol, polysorbate, aqueous phase with water and salts, and polyacrylic acid limitations, as well as the concentration ranges specified in claims 1, 5, 6 and 10. Defendants also do not dispute that the accused product meets the additional limitations recited in dependent claims 2, 7, 8, 9 and 12. (D.I. 118, ex. 1 at ¶¶ 53, 57, 58) Defendants contend, however, that the accused product does not fully satisfy the limitations of the asserted claims insofar as the accused product does not physically contain triacylglycerides, lecithin or soybean lecithin. (*Id.* at ¶¶ 46-47) Plaintiffs argue that defendants' substitution of isopropyl myristate for triglycerides and lecithin raises a question of legal equivalency under the "function-way-result" test.

a. Function

(1) Evidence

Dr. Weiner testified that lecithin and triglycerides function as penetration enhancers in the claimed formulation. (D.I. 126 at 320:15-323:16) In support of this conclusion, Dr. Weiner examined the results of the Franz diffusion study and found that "the inventive formulation was much more effective than the prior art in allowing the

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[25] Defendants also argue that, "[t]o the extent 'hydrogel' is construed to exclude the presence of emulsions, [defendants'] ANDA product does not infringe the asserted claims." (D.I. 134 at 33) Because the court adopted defendants' construction – which allows for the presence of insoluble liquids in the hydrogel – the court does not address defendants' argument as to whether the accused product literally meets the 'hydrogel' limitation.

penetration of the azelaic acid into . . . the skin." (D.I. 126 at 321:19-21) Dr. Weiner explained that, because "the amount of propylene glycol in [Skinoren® cream and Finacea®] were [sic] essentially the same," the increased penetration could not be explained by differing amounts of azelaic acid and, therefore, must be explained by the addition of lecithin and triglycerides. (*Id.* at 323:4-17) Dr. Michniak-Kohn agreed that "a person of ordinary skill in the art [would] understand that lecithin contributed to the reportedly better results for the claimed gel function." (D.I. 127 at 563:9-12) Indeed, Dr. Franke testified that he originally selected lecithin for its "penetration enhancement" qualities in that it could "interact in the skin layers" which are "also double membrane structures with a similar chemistry" to lecithin. (D.I. 126 at 69:11-19) Dr. Franke testified that he selected triglycerides due, in part, to their "polarity as an oil" which makes them "suitable being together with lecithin." (*Id.* at 70:2-10)

Defendants argue that Dr. Weiner's analysis should be disregarded because he was mistaken in concluding that Skinoren® cream does not contain triglycerides (D.I. 127 at 453:22-455:20), and he did not offer an opinion as to whether lecithin alone could act as a penetration enhancer. Defendants also argue that the Franz diffusion test is unreliable because one of the experimental data sets was discarded (JTX 16 at BAYER0384920; D.I. 125 at 178:9-179:17) and because Dr. Günther "did not perform any statistical analysis of the results of [the] study" (D.I. 125 at 174:25-175:2; D.I. 126 at 371:5-372:21).

Plaintiffs argue that in defendants' ANDA filings and formulation development report, defendants repeatedly stated that the function of lecithin and triglyceride in the claimed formulation and isopropyl myristate in the accused formulation is identical; to

wit, all three excipients enhance penetration of the skin. (JTX 53 at GMG_VP765, -774-76; JTX 54 at GMG_VP1241, -252, -253, -272; PTX 312 at GMG_137769; D.I. 126 at 217:1-10, 226:2-5, 228:19-229:4, 323:25-325:22) As detailed *supra*, defendants performed Franz cell diffusion tests comparing the accused product to Finacea® and found that the two formulations have statistically similar penetration profiles in terms of the amount and rate of skin penetration. (JTX 38 at GMG_0012947-49) In response to a query by the FDA regarding defendants' selection of penetration enhancer in the accused product, defendants wrote that the penetration studies "demonstrate the equivalence" between Finacea® and the accused product. (PTX 312 at GMG_0137769)

Defendants respond that plaintiffs are in the best position to understand the function of lecithin and triglycerides in the claimed formulation. (*See* D.I. 126 at 369:24-370:5) In this vein, defendants cite several documents from plaintiffs suggesting that an increased percentage of dissolved azelaic acid, not the presence of lecithin and triglycerides, is responsible for the increased penetration observed in the claimed hydrogel.[26] (JTX 3 at BAYER0006537 (a marketing presentation by Dr. Franke reports the percentage of dissolved azelaic acid as ~25% for Finacea® and ~3% for Skinoren® cream); DTX 92 (a poster from two scientists involved in clinical development of Finacea® states that the hydrogel "contains a higher dissolved fraction of azelaic acid

[26] Dr. Weiner testified that the documents cited by defendants, including the Finacea® promotional materials, were all incorrect in attributing increased penetration to increased dissolution of azelaic acid. (D.I. 127 at 463:3-5, 467:18-20, 471:23-472:1) However, Dr. Weiner agreed that "if the solubility explanation were correct," he would "certainly have to reconsider" his position that lecithin and triglycerides function as penetration enhancers. (D.I. 127 at 458:3-8)

than the cream, leading to improved drug release and bioavailability")) Indeed, Dr. Franke admitted that none of plaintiffs' documents describes the function of lecithin and triglycerides as penetration enhancers. (D.I. 125 at 88:23-89:10; *see also* D.I. 126 at 369:7-11) Instead, plaintiffs' development reports and NDA submissions affirmatively describe the function of lecithins and triglycerides as either moisturizers, emollients or emulsifiers. (*See* JTX 20 at BAYER0434132; DTX 19 at BAYER0157202; JTX 11 at BAYER0154373) Defendants also cite various publications to support the conclusion that lecithin or triglycerides are not penetration enhancers, including a publication by Dr. Weiner[27] in which he wrote that "when phospholipid based liposomes are incorporated in an emulsion, the delivery of the drug is greatly diminished because phospholipids do not function as permeation enhancers." (D.I. 126 at 430:9-19; *see also* JTX 49 (the Handbook of Pharmaceutical Excipients does not identify either lecithin or triglycerides as being a penetration enhancer);[28] JTX 29 at BAYER0544905; D.I. 126 at 395:14-396:1) The '070 patent itself is silent on the question of whether lecithins or triglycerides function as penetration enhancers. (D.I. 126 at 368:3-6)

Plaintiffs offer that their failure to include "penetration enhancer" as a potential function of lecithin and triglycerides is not fatal given that an excipient may have multiple relevant functions. In support of this position, plaintiffs cite Dr. Weiner's testimony that "lecithin can be an emollient . . . and the triglyceride can act as a humectant or emollient [skin softener]" in addition to acting as penetration enhancers. (D.I. 126 at 320:7-18)

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[27] Not admitted into evidence.

[28] Plaintiffs note that the Handbook of Pharmaceutical Excipients states that triglycerides have "good penetration properties." (JTX 49 at GMG_136959; D.I. 128 at 707:23-708:19)

Additionally, Dr. Michniak-Kohn testified that isopropyl myristate may act as an emollient or as a penetration enhancer. (D.I. 127 at 552:15-553:4) Plaintiffs also cite Mehta's testimony that isopropyl myristate, lecithin and triglycerides each perform multiple functions, and that they share at least the qualities of penetration enhancer and emulsifying agent. (D.I. 126 at 229:24-230:4, 232:24-233:10)

(2) Discussion

The parties agree that two factors could contribute to the increased penetration observed in plaintiffs' Franz cell study: (1) increased dissolution of azelaic acid; or (2) the presence of chemical penetration enhancers. The '070 patent does not specify the role of lecithin and triglycerides in the claimed composition, and plaintiffs' Franz cell test was not designed to control for the potential contribution of either factor. As such, Dr. Weiner artificially held one variable constant by assuming that the amount of dissolved azelaic acid did not differ between samples, and he was then able to attribute the observed increase in penetration to the presence of lecithin and triglycerides. (D.I. 126 at 323:4-17) The court is troubled by Dr. Weiner's method of deduction, especially given that Dr. Weiner did not realize that Skinoren® cream also contains triglycerides and given that plaintiffs' scientific representatives twice reported an increased percentage of dissolved azelaic acid in Finacea® as compared to Skinoren® cream. (JTX 3 at BAYER0006537; DTX 92) Nonetheless, although plaintiffs' position lacks scientific rigor, the court discerns nothing in the record that indicates that lecithin and triglycerides cannot act as penetration enhancers. Indeed, Dr. Michaniak-Kohn admitted that a person of ordinary skill in the art would understand that lecithin contributed to the better results of the claimed gel (D.I. 127 at 563:9-12), and Mehta

acknowledged that lecithin and triglycerides could function as penetration enhancers (D.I. 126 at 232:24-233:10). Additionally, Dr. Franke testified that he initially selected lecithin for its "penetration enhancement" properties and triglyceride for its compatibility with lecithin. (*Id.* at 70:2-10)

Similarly, the fact that plaintiffs did not identify lecithin and triglycerides as penetration enhancers in their own filings and internal documents does not exclude the possibility that they function as such in the claimed composition. Plaintiffs provided testimony from both sides' witnesses to support the common-sense proposition that a given excipient may perform more than one function. (D.I. 126 at 320:7-18; D.I. 127 at 552:15-553:4) It logically follows that listing the function of lecithin and triglyceride as "moisturizer" or "emollient" does not mean that the excipients cannot also act as penetration enhancers.

The court is also swayed by defendants' repeated statements in their ANDA filings that lecithin, triglyceride and isopropyl myristate function as penetration enhancers. (*See, e.g.*, JTX 53 at GMG_VP765, -774-76) The Federal Circuit has held that, "[b]ecause drug manufacturers are bound by strict statutory provisions to sell only those products that comport with the ANDA's description of the drug, an ANDA specification defining a proposed generic drug in a manner that directly addresses the issue of infringement will control the infringement inquiry." *Abbott Labs. v. TorPharm, Inc.*, 300 F.3d 1367, 1373 (Fed. Cir. 2002). Moreover, "[i]f an ANDA specification defines a property of a compound such that it must meet a limitation of an asserted claim, then there will almost never be a genuine dispute of material fact that the claim is infringed with respect to that limitation." *Id.* Here, the infringement inquiry hinges on the

question of whether the claimed[29] and accused excipients both act as penetration enhancers. Throughout their ANDA filings, defendants repeatedly answered that question in the affirmative. Defendants should not be permitted to liken their product to the claimed composition to support their bid for FDA approval, yet avoid the consequences of such a comparison for purposes of infringement.

b. Way

(1) Evidence

At trial, Dr. Weiner opined that lecithin, triglyceride, and isopropyl myristate enhance penetration by "temporarily altering the structural properties of the lipid bilayers in the stratum corneum." (D.I. 126 at 332:7-336:25) For support, Dr. Weiner relied on a 1987 article entitled "Mode of Action of Penetration Enhancers in Human Skin" by B.W. Barry ("Barry"). (JTX 29) Barry proposed that penetration enhancers "interact[] in some way with the stratum corneum lipid structure, disrupting its organization and increasing its fluidity." (D.I. 126 at 334:12-21; JTX 29) Barry reported that non-polar materials, such as oleic acids, "enter the lipid regions . . . where they disrupt the structure." (JTX 29 at BAYER0544916) Dr. Weiner admitted that Barry discloses a "general theory of skin accelerant activity" in which it does not directly "identify lecithin or triglyceride as penetration enhancers."[30] (D.I. 126 at 395:15-396:1) Dr. Weiner opined that Barry is

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[29] The claimed composition in the '070 patent is identical to the commercialized embodiment insofar as they both contain triglycerides and lecithin. (D.I. 126 at 303:2-305:5)

[30] Defendants argue that Dr. Weiner's testimony should be rejected because he did not personally test the relevant excipients, but Dr. Weiner is not obligated to perform such tests where the law provides that "[d]irect infringement can be proven by circumstantial evidence." *Molecular Research Corp. v. CBS, Inc.*, 793 F.2d 1261, 1272 (Fed. Cir. 1986).

nonetheless applicable to the instant case because – like oleic acid – lecithin, triglycerides, and ispropyl myristate[31] are large non-polar materials. (D.I. 127 at 481:19-23) Dr. Weiner explained that lecithin, triglycerides, isopropyl myristate, and the lipids in the stratum corneum are all hydrophobic and, as such, are "very soluble in oils." (D.I. 126 at 335:5-17) Like the lipids in the stratum corneum, lecithin and isopropyl myristate are amphiphilic[32] and, therefore, are likely to "enter into the lipid portion of the . . . stratum corneum." (D.I. 128 at 715:23-716:2) Triglycerides are compatible with the lipids in the stratum corneum by virtue of being insoluble and "extremely compatible with lecithin." (D.I. 126 at 335:22-335:20) Plaintiffs argue that the exact location of integration is irrelevant as Dr. Michniak Kohn agreed that a disruptive "interaction of a penetration enhancer can be with the polar heads of the lipid, in between those lipid heads, or between the hydrophobic tails of the lipids in the stratum corneum." (D.I. 128 at 715:23-716:2)

Although Dr. Weiner did not opine on the relationship between chemical class and penetration ability, defendants' expert acknowledged that lecithin, triglyceride, and isopropyl myristate contain a fatty ester group (*id.* at 705:2-706:1), a feature that defendants linked to absorption capacity in their ANDA submission. (JTX 53 at GMG_VP774 (isopropyl myristate was selected "as [a] penetration enhancer instead of lecithin and medium chain triglyceride because isopropyl myristate has a good absorption capacity due to [its] fatty ester group . . . .); D.I. 126 at 275:9-276:20; D.I. 128

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[31] Dr. Michniak-Kohn does not dispute that isopropyl myristate causes "fluidization of the stratum corneum lipids." (D.I. 127 at 567:20-568:23)

[32] The parties agree that "amphiphilic" is defined as containing both hydrophilic and lipophilic groups. (D.I. 128 at 714:11-25; D.I. 126 at 335:9-11)

at 706:2-23) Moreover, defendants do not dispute that an article cited by Dr. Michniak-Kohn[33] categorizes chemical penetration enhancers and their mechanism of action by class. (DTX 83 at GMG_137198 (listing isopropyl myristate under the category of "fatty acid esters")

Although Dr. Michniak-Kohn relied on several publications to support her opinions at trial,[34] defendants' post-trial briefing focuses on a single article entitled "An Attempt to Clarify the Mechanism of the Penetration Enhancing Effects of Lipophilic Vehicles with Differential Scanning Calorimetry (DSC)" by Claudia S. Leopold et al. ("Leopold"). (DTX 84) Leopold used DSC to test the ability of various excipients to "alter the structure of the stratum corneum," including caprylic/capric acid triglycerides and phospholipids[35] and isopropyl myristate. (DTX 84 at GMG_0136577-78) Leopold concluded that "the observed decrease of only the phase-transition enthalpy by the . . . caprylic/capric acid triglycerides with phospholipids is due to dissolution or extraction of the stratum corneum lipids." (DTX 84 at GMG_0136581) However, "[v]ehicles which cause both a reduction of the enthalpy and a decrease of the phase-transition temperatures" such as isopropyl myristate, "are thought to fluidize the lamellar-gel phase of the stratum corneum lipids, and possibly also partially dissolve the lipids." (*Id.*; D.I. 127 at 568:19-23) Defendants argue that fluidization of the stratum corneum lipids

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[33] "Skin penetration enhancers" by Majella E. Lane ("Lane").

[34] *Inter alia*, Lane, and a 2004 article titled "An attempt to clarify the influence of glycerol, propylene glycol, isopropyl myristate and a combination of propylene glycol and isopropyl myristate on human stratum corneum," by I. Brinkmann and C.C. Muller-Goymann.

[35] Dr. Michniak-Kohn testified that the combination of caprylic/capric acid triglycerides and phospholipids is equivalent to the claimed combination of triglycerides and lecithin. (D.I. 127 at 567:20-568:23)

is materially different from dissolution of the stratum corneum lipids. The court disagrees, given that Leopold itself concedes that "[t]he observed enthalpy decrease caused by dissolution or extraction of the intercellular lipids cannot be distinguished from enthalpy changes caused by fluidization of the lipid bilayers." (DTX 84 at GMG_0136580) Plaintiffs argue that, even if DSC could distinguish between fluidization and dissolution, such a difference is insignificant where Dr. Michniak-Kohn agreed that both types of penetration enhancers are "lipophilic liquids" that may enhance drug penetration by causing a "specific alteration of the stratum corneum lipids." (D.I. 128 at 709:9-710:2; DTX 84 at GMG-136577)

The parties agree that defendants' Franz cell study demonstrated no statistically significant differences in the flux profiles between batch 041, batch 036 and Finacea®. (JTX 38 at GMG_0012949) The parties also agree that batch 041 was selected for further development because its flux profile was "more similar to Finacea®." (*Id.*; JTX 38 at BMB_0012949; JTX 41 at GMG_0015047) Defendants propose two somewhat incongruous interpretations of the data: (1) lecithin and triglyceride enhance penetration differently than isopropyl myristate because the flux curves are not "very, very close or overlapping" (D.I. 127 at 581:18-582:2); and (2) a penetration enhancer cannot be responsible for increased absorption because the flux curve for batch 036, which defendants allege does not contain a penetration enhancer,[36] is statistically similar to the flux curves for batch 041 and Finacea®. (D.I. 134 at 22-23)

[36] Dr. Weiner agreed that the Handbook of Pharmaceutical Excipients does not list PPG-20 methyl glucose ether distearate, the substituted ingredient in batch 036, as a penetration enhancer. (D.I. 126 at 418:13-16) On cross, Dr. Weiner opined that PPG 20 might be acting as a penetration enhancer or a combination enhancer. (D.I. 126 at 418:24-419:8)

(2) Discussion

As discussed, *supra*, the '070 patent does not directly attribute enhanced penetration to a specific excipient, nor does it discuss the "way" in which enhanced penetration is achieved. Having determined that isopropyl myristate, lecithin, and triglycerides all function as penetration enhancers, the court is charged with determining whether isopropyl myristate enhances penetration in substantially the same way as lecithin and triglycerides. Defendants rely primarily on Leopold to support the proposition that the excipients-at-issue increase penetration differently; to wit, lecithin and triglycerides increase penetration through dissolution of the stratum corneum lipids, while isopropyl myristate increases penetration through fluidization of the stratum corneum lipids. For the reasons stated above, the court does not find that Leopold adequately supports drawing such a distinction. Even if the court were to accept the conclusions in Leopold as fact, distinguishing between dissolution and fluidization of the stratum corneum lipids would not impact the court's ultimate conclusion. The '070 patent does not specify a mechanism for penetration enhancement, and requiring a particular sub-mechanism is unnecessary where the parties accept that disruption of stratum corneum lipids is sufficient to enhance penetration. *See Abraxis Bioscience, Inc. v. Mayne Pharma (USA) Inc.*, 467 F.3d 1370, 1380 (Fed. Cir. 2006) (holding that "the district court properly assessed the 'way' [the claimed ingredient] works by referring to the patent and the evidence presented at trial," despite infringer's argument that "way" should be interpreted more narrowly).

Moreover, requiring a high degree of mechanistic similarity would not comport with the court's duty to determine whether the accused product "performs substantially

the same function in substantially the same way" as the claimed limitation. *Graver Tank & Mfg. Co. v. Linde Air Prods. Co.*, 399 U.S. 605, 508 (1950). The court was presented with ample evidence to support the conclusion that all of the excipients-at-issue increase penetration in a substantially similar way; namely, disruption of the stratum corneum lipids. The court found Dr. Weiner's testimony regarding the applicability of Barry to the claimed excipients to be credible and well-supported, and the court is also influenced by defendants' admission that all three excipients contain a fatty acid ester group, a feature associated with increased absorption. Regarding defendants' Franz cell study results, the court is unpersuaded that the flux profiles from batch 041 and Finacea® must overlap exactly where there is no statistically significant difference between the curves. Defendants' final theory regarding the flux curve for batch 036 was unsupported by expert testimony and weakened by uncertainty over the true function of substituted excipient, PPG-20. Altogether, the court concludes that the excipients-at-issue enhance penetration in a substantially similar way.

c. Result

(1) Evidence

Plaintiffs propose that the proper articulation of the "results" prong is "to have a therapeutically effective azelaic acid composition able to penetrate the stratum corneum so as to deliver the active ingredient, which is azelaic acid." (D.I. 126 at 340:21-341:8) For support, plaintiffs cite the '070 patent, which claims a composition that "allows a larger amount of pharmaceutical active ingredient to penetrate into living skin layers and/or cutaneous organs" as demonstrated by Franz cell diffusion tests. ('070 patent, col. 2:29-37) The '070 patent specifies that "the living skin layers and/or cutaneous

organs are the desired target sites for azelaic acid." (*Id.* at col. 2:37-40) Finally, the specification describes "[t]he composition of the invention [as being] suitable for the treatment of various indications" including rosacea. (*Id.* at col. 4:46-51)

Plaintiffs also reference defendants' Franz cell study and clinical trial comparing the penetration and efficacy of the accused product and Finacea®. As detailed, *supra*, defendants' Franz study reported slight differences in flux profiles between batch 041 and Finacea®, including differing rates of decline in absorption levels and differences in the amount of azelaic acid remaining in the epidermis following treatment. (JTX 38 at BMB_0012947) However, "there were no statistically significant differences" across the parameters (JTX 38 at GMG_0012949), and defendants admittedly selected batch 041 over batch 036 due to its similarity to Finacea® (D.I. 126 at 214:8-11). Defendants' subsequent large-scale clinical trial comparing batch 041 to Finacea® prompted the conclusion that "the test product was bioequivalent" to Finacea® and superior to placebo. (PTX 219 at GMG_002365-68, 002412)

Finally, defendants filed a patent application in which the drafters stated that "the composition according to the invention has the advantage that it allows a larger amount of pharmaceutical active ingredient to penetrate into living skin layers and/or cutaneous organs." (JTX 42 at ¶ 23, GMG_0111203; D.I. 126 at 340:21-342:15) The patent application also stated that "[t]he resulting gel has approximately about four times higher availability of azelaic acid in living skin layers and/or cutaneous organs." (JTX 42 at ¶ 35, GMG_0111204) Plaintiffs point out that the language used in defendants' patent application copies or closely mirrors the language used in the '070 patent. (Compare JTX 42 at ¶ 23, 35 to '070 patent, cols. 2:29-32, 5:36-38)

(2) Discussion

The court agrees that the proper "result" by which to evaluate the evidence is "to have a therapeutically effective azelaic acid composition able to penetrate the stratum corneum so as to deliver the active ingredient." Unlike the "function" and "way" prongs, the '070 patent directly addresses the "result" of treatment with the claimed composition. Specifically, the '070 patent claims increased penetration of azelaic acid into the skin, resulting in treatment of various skin conditions such as rosacea. Defendants do not deny that their own patent application attributes an identical result to the accused product. Defendants' Franz cell study and clinical trial provide further evidence of the similar penetration and treatment results of the claimed and accused compositions.

Defendants' sole response is to criticize plaintiffs' attempt to attribute enhanced penetration to the presence of lecithin and triglycerides, arguing that only an element-by-element comparison is appropriate. However, because the court has already concluded that enhanced penetration may be properly attributed to lecithin and triglycerides, defendants' argument must fail. Accordingly, the court finds that plaintiffs have demonstrated that the claimed and accused products have substantially similar results. As a whole, the court finds that plaintiffs have carried their burden of proving infringement under the doctrine of equivalents by a preponderance of the evidence. Because defendants do not dispute any particular limitation present in any of the dependent claims (other than the physical absence of lecithin and triglycerides), the court's finding of infringement extends to all of the asserted claims.[37]

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[37] Defendants do not dispute that method claims 8 and 9 are infringed under 35 U.S.C. § 271(b). Claim 8 recites "[a] method for treating rosacea, presbyderma, melisma, acne and/or skin irritations in a patient, comprising administering to the patient

3. Defenses to Doctrine of Equivalents

a. Ensnarement

Ensnarement is a legal limitation on the doctrine of equivalents that "bars a patentee from asserting a scope of equivalency that would encompass, or 'ensnare,' the prior art." *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1322 (Fed. Cir. 2009). The Federal Circuit has cautioned that "[t]he ensnarement inquiry is separate and distinct from the . . . element-by-element equivalence analysis, and has no bearing on the validity of the actual claims." *Id.* at 1323. When conducting an ensnarement analysis, the court is first charged with "construct[ing] a hypothetical claim that literally covers the accused device." *Id.* at 1324. Here, the parties disagree on the proper construction of the hypothetical claim: Defendants argue that the triglyceride and lecithin limitations of claim 1 of the '070 patent should be substituted with "penetration enhancer," and plaintiffs argue that isopropyl myristate should be added as an alternative ingredient to triglyceride and lecithin. Mindful of the Federal Circuit's guidance to construct a hypothetical claim that "literally" covers the accused product, the court declines to adopt defendants' broad construction. Instead of claiming a class of compounds with similar characteristics (for example, fatty acid esters), plaintiffs elected to claim two very specific penetration enhancers. Although plaintiffs strenuously argued that all three compounds are penetration enhancers in the context of infringement, broadening the scope of the claim to include all penetration enhancers – a

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in need thereof a therapeutically effective amount of the composition according to claim 1." Claim 9 recites "[t]he method of claim 8, wherein the composition is administered topically." Plaintiffs presented unrebutted evidence that defendants' proposed label instructs patients to apply the accused product to affected areas "topically to treat rosacea." (D.I. 118, ex. 1 at ¶ 53; PTX 213 at GMG_677)

group which the court understands to include numerous compounds with varying characteristics – would be inconsistent with the careful and limited language of the claim. Accordingly, the court adopts plaintiffs' hypothetical claim in which isopropyl myristate is added as an alternative penetration enhancer to lecithin and triglycerides.

The next step in the court's ensnarement analysis is to "assess the prior art introduced by the accused infringer and determine whether the patentee has carried its burden of persuading the court that the hypothetical claim is patentable over the prior art." *DePuy Spine*, 567 F.3d at 1325. The court considers patentability under 35 U.S.C. §§ 102 and 103. *Id.* Defendants argue that the hypothetical claim is anticipated and rendered obvious by a prior art article entitled "In vitro permeation of azelaic acid from viscosized microemulsions" by M.R. Gasco et al. ("Gasco"). (DTX 59) Gasco discloses a microemulsion containing azelaic acid as the active ingredient and DMSO as an "enhancer." (DTX 59 at GMG_0006360) The parties agree that Gasco does not disclose isopropyl myristate, lecithin or triglycerides. ('070 patent, claim 1; D.I. 126 at 339:5-7; D.I. 127 at 652:2-6; D.I. 128 at 731:22-24, 922:22-25) As the court's hypothetical claim requires, at a minimum, the presence of either triglycerides and lecithin or isopropyl myristate, the court need not consider the remaining limitations in order to conclude that Gasco does not anticipate either hypothetical claim[38] under 35 U.S.C. § 102.

Regarding 35 U.S.C. § 103, the Federal Circuit has held that "to make the hypothetical claim obvious, the court must find that 'the differences between the subject

[38] Because Gasco does not anticipate the hypothetical independent claim, any hypothetical dependent claims are also not anticipated.

matter sought to be patented [i.e., the hypothetical claim] and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.'" *Abbott Labs. v. Dey, L.P.*, 287 F.3d 1097, 1106 (Fed. Cir. 2002) (emphasis omitted) (quoting 35 U.S.C. § 103(a) (1994)). Plaintiffs argue that a skilled artisan would not substitute a different penetration enhancer for DMSO given that the DMSO microemulsion tested in Gasco outperformed the non-DMSO microemulsion. (DTX 59 at GMG_0006362) Plaintiffs argue that, even if a skilled artisan desired to substitute DMSO for another penetration enhancer, lecithin and triglyceride were not known penetration enhancers in 1998, the priority date of the '070 patent. (D.I. 127 at 556:15-18) Dr. Weiner added that, based on their chemical properties, a skilled artisan would not substitute lecithin and triglycerides, which "hardly [have] any water solubility at all," with DMSO, which is "a very water-soluble chemical."[39] (D.I. 126 at 338:18-339:1; D.I. 128 at 923:17-924:13) Plaintiffs cite Dr. Weiner's testimony that "excipients [and] the active ingredient interact with each other . . . differently from formulation to formulation" to support the argument that a skilled artisan would not have an expectation of success when swapping excipients. (D.I. 126 at 296:9-14) Finally, Dr. Weiner testified that defendants did not, to his knowledge, "consider using DMSO in the ANDA formulation." (D.I. 126 at 339:2-4)

In contrast, Dr. Michniak-Kohn testified that a skilled artisan would be motivated to substitute a different chemical penetration enhancer for DMSO because DMSO is

[39] Plaintiffs also argue that a skilled artisan would not substitute penetration enhancers of different classes for one another, but offers no expert testimony to support this position.

"metabolized in the body, and when you used it topically, you didn't smell very nice." (D.I. 127 at 575:7-17) Defendants argue that plaintiffs did not provide adequate testimony to explain why a skilled artisan would consider water solubility when substituting excipients. Finally, Dr. Michniak-Kohn testified that "[t]here would be no reason to believe that the formulation [with a new penetration enhancer] would not be successful." (*Id.* at 605:12-18)

Although both sides present on-point expert testimony, the court finds that plaintiffs have met their burden to prove that the range of equivalents does not ensnare the prior art. *See Wilson Sporting Goods Co. v. David Geoffrey & Associates*, 904 F.2d 677, 685 (Fed. Cir. 1990) ("the burden is on [the patent owner] to prove that the range of equivalents which it seeks would not ensnare the prior art."). The parties dispute whether a skilled artisan would attempt to substitute another penetration enhancer for DMSO: in particular, plaintiffs urge that efficacy would be the primary concern, and defendants argue that cosmetic concerns would dominate. Without further guidance, the court is unable to assign greater weight to either seemingly legitimate priority. However, the court is persuaded that a skilled artisan would not necessarily substitute a large hydrophobic molecule with as-yet-unknown penetration capabilities with a known, water soluble penetration enhancer. In light of defendants' own substantial efforts to develop a bioequivalent generic formulation (chronicled *supra*) and Dr. Weiner's testimony that different excipients behave differently depending on the surrounding milieu, the court is persuaded that a skilled artisan would not have a reasonable expectation of success when swapping the penetration enhancers at issue.

Accordingly, the court finds that infringement under the doctrine of equivalents is not barred by ensnarement of the prior art.

b. Estoppel

As set forth in greater detail *supra*, a presumption of prosecution history estoppel is established by showing that the patentee made a narrowing amendment and that "the reason for that amendment was a substantial one relating to patentability." *Festo II,* 344 F.3d at 1366. During prosecution, the applicant altered the language in two dependent claims from "lecithin . . . at a concentration of up to 1% [or 3%] by weight" to "more than 0 to 1% [or 3%] by weight." (JTX 2.2 at BAYER526; D.I. 127 at 562:7-24) Prior to making the amendment, the applicant stated that the examiner's criticism that the use of "up to" would include no lecithin was "not well taken" as "[t]hese recitations are only in claims dependent on independent claims, which clearly require the recited components. Since the dependent claims must limit the independent claims, the meaning is clear that zero amounts are not included." (JTX 2.2 at BAYER510-511) Defendants do not dispute that the independent claim from which both dependent claims depend included a "lecithin" limitation before and after this amendment. (JTX 2.1 at BAYER374; '070 patent, col. 6:27-39)

The court discerns no "clear and unmistakable surrender" of a lecithin-free compound through either claim amendment or attorney argument. *See Cordis Corp. v. Medtronic Ave. Inc.,* 511 F.3d 1157, 1177 (Fed. Cir. 2008). Neither party disputes that the independent claim at issue contains a "lecithin" limitation that is necessarily incorporated by reference into the dependent claims. *See* 35 U.S.C. § 112 ¶ 4 (2006). When taken in context, the court agrees that the applicant's amendment was made for

the purpose of clarifying that "zero amounts [of lecithin] are not included" (JTX 2.2 at BAYER510-511), not to disclaim formulations with zero lecithin. *See Cordis Corp.*, 511 F.3d at 1177 (The disputed amendment did not "disclaim any subject matter that was otherwise within the scope of the claim language, but merely explained, in more explicit terms, what the claims already covered."). Accordingly, the court finds that infringement under the doctrine of equivalents is not barred by prosecution history estoppel.

4. Exceptional case under 35 U.S.C. § 285

In *Octane Fitness, LLC v. ICON Health & Fitness, Inc.*, the Supreme Court described § 285 as imposing "one and only one constraint on district courts' discretion to award attorney's fees in patent litigation: The power is reserved for 'exceptional' cases." 134 S.Ct. 1749, 1755-56 (2014). Because the Patent Act does not define "exceptional," the Court construed it "'in accordance with [its] ordinary meaning.'" *Id.* at 1756 (citation omitted). "In 1952, when Congress used the word in § 285 (and today, for that matter), "'[e]xceptional' meant 'uncommon,' 'rare,' or 'not ordinary.'" *Id.* (citation omitted). In support of its interpretation, the Court referred to an earlier interpretation of the term "'exceptional' in the Lanham Act's identical fee-shifting provision, 15 U.S.C. § 1117(a), to mean 'uncommon' or 'not run-of-the-mill.'" *Id.* The Court concluded that

> an "exceptional" case is simply one that stands out from others with respect to the substantive strength of a party's litigating position (considering both the governing law and the facts of the case) or the unreasonable manner in which the case was litigated. District courts may determine whether a case is "exceptional" in the case-by-case exercise of their discretion, considering the totality of the circumstances. As in the comparable context of the Copyright Act, "'[t]here is no precise rule or formula for making these determinations,' but instead equitable discretion should be exercised 'in light of the considerations we have identified.'"

Id. at 1756 (citing *Fogerty v. Fantasy, Inc.*, 510 U.S. 517, 534 (1994)). In addressing Rule 11 of the Federal Rules of Civil Procedure, the Court expressly held that "sanctionable conduct is not the appropriate benchmark" for § 285 cases. Under the standard announced in *Octane*, "a district court may award fees in the rare case in which a party's unreasonable conduct – while not necessarily independently sanctionable – is nonetheless so 'exceptional' as to justify an award of fees" or "a case presenting either subjective bad faith or exceptionally meritless claims." *Id.* at 1757. A party seeking attorney fees under § 285 must prove the merits of their contentions by a preponderance of the evidence. *Id.* at 1758.

Plaintiffs allege that fee-shifting is appropriate here because defendants copied the '070 formulation and defendants repeatedly shifted positions on key issues throughout litigation, thereby unnecessarily compounding the number of disputed issues. Regarding the copying of the '070 patent, plaintiffs argue that defendants could have copied one of many generic non-azelaic acid formulations (PTX 299) or an off-patent azelaic acid cream (*see* D.I. 129 at 1079:4-20), but they instead decided to pursue a Finacea® generic without first asking its legal team about liability implications. (D.I. 126 at 279:17-280:13) Regarding defendants' "moving target" litigation practices, plaintiffs allege that defendants repeatedly took positions that were contrary to expert testimony and its own prior statements.

Regardless of whether defendants "cleared" the generic 15% azelaic acid composition with their legal department, the court accepts that defendants demonstrated an intent to develop a non-infringing substitute. (*See* JTX 54 at GMG_VP001238; D.I. 127 at 217:14-218:2) Moreover, as evidenced by the

considerable efforts expended by the court in reaching its infringement determination, the court is not persuaded that defendants were so lacking a good faith belief of non-infringement as to merit awarding exceptional case status under § 285. To the extent that some of defendants' arguments were unsupported or contradictory, the court does not find that defendants' conduct in the case was so one-sided or unreasonable as to rise to the level of "exceptional." Accordingly, the court does not find that this is an exceptional case under 35 U.S.C. § 285.

D. Obviousness

Defendants argue that the asserted claims are obvious in view of Skinoren® cream in combination with (1) references disclosing hydrogel formulations containing the claimed excipients and (2) references disclosing hydrogel formulations containing azelaic acid.[40]

1. Standard

"A patent may not be obtained . . . if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. § 103(a). Obviousness is a question of law, which depends on underlying factual inquiries.

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[40] Plaintiffs do not rebut Dr. Michniak-Kohn's conclusions that a person of ordinary skill in the art (hereinafter, "POSITA") as of February 12, 1998 is a scientist with a Master's or Ph.D., or its equivalent, in pharmaceutical science or its equivalent, or a medical degree. (D.I. 127 at 528:3-14) A skilled artisan would additionally have been involved in the research and development of pharmaceutical formulations and would have several years of experience in the field of topical pharmaceutical formulations, with the amount of post-graduate level experience dependent upon the level of formal education. (*Id.*)

> Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented.

KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 406 (2007) (quoting *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17-18 (1966)).

"[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR*, 550 U.S. at 418. Likewise, a defendant asserting obviousness in view of a combination of references has the burden to show that a person of ordinary skill in the relevant field had a reason to combine the elements in the manner claimed. *Id.* at 418-19. The Supreme Court has emphasized the need for courts to value "common sense" over "rigid preventative rules" in determining whether a motivation to combine existed. *Id.* at 419-20. "[A]ny need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." *Id.* at 420. In addition to showing that a person of ordinary skill in the art would have had reason to attempt to make the composition or device, or carry out the claimed process, a defendant must also demonstrate that "such a person would have had a reasonable expectation of success in doing so." *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1360 (Fed. Cir. 2007).

A combination of prior art elements may have been "obvious to try" where there existed "a design need or market pressure to solve a problem and there [were] a finite

number of identified, predictable solutions" to it, and the pursuit of the "known options within [a person of ordinary skill in the art's] technical grasp" leads to the anticipated success. *Id.* at 421. In this circumstance, "the fact that a combination was obvious to try might show that it was obvious under § 103." *Id.*

A fact finder is required to consider secondary considerations, or objective indicia of nonobviousness, before reaching an obviousness determination, as a "check against hindsight bias." *See In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1079 (Fed. Cir. 2012). "Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented." *Graham*, 383 U.S. at 17–18.

"Because patents are presumed to be valid, see 35 U.S.C. § 282, an alleged infringer seeking to invalidate a patent on obviousness grounds must establish its obviousness by facts supported by clear and convincing evidence." *Kao Corp. v. Unilever U.S., Inc.*, 441 F.3d 963, 968 (Fed. Cir. 2006) (citation omitted). In conjunction with this burden, the Federal Circuit has explained that,

> [w]hen no prior art other than that which was considered by the PTO examiner is relied on by the attacker, he has the added burden of overcoming the deference that is due to a qualified government agency presumed to have properly done its job, which includes one or more examiners who are assumed to have some expertise in interpreting the references and to be familiar from their work with the level of skill in the art and whose duty it is to issue only valid patents.

PowerOasis, Inc. v. T-Mobile USA, Inc., 522 F.3d 1299, 1304 (Fed. Cir. 2008) (quoting *Am. Hoist & Derrick Co. v. Sowa & Sons*, 725 F.2d 1350, 1359 (Fed. Cir. 1984)).

2. Disclosure of non-azelaic acid prior art references[41]

a. '752 PCT

The '752 PCT is entitled "Topical and Transdermal Delivery System Utilizing Submicron Oil Spheres." (DTX 72) The '752 PCT was published on September 30, 1993, and the parties agree that it is prior art to the '070 patent. (D.I. 118, ex. 1 at ¶ 60) Dr. Michniak-Kohn testified that the '752 PCT was not considered by the Patent Office when examining the '070 patent. (D.I. 127 at 625:2-5) The '752 PCT discloses a composition that may be used to "reduce or prevent dermatological conditions and diseases." (DTX 72 at GMG_0006401; D.I. 127 at 627:2-10) The following table compares the ingredients disclosed in the '752 PCT with those in the claimed composition:[42]

'070 Claimed Formulation	**'752 PCT Formulation**	**'163 PCT Formulation**
Azelaic Acid	Insoluble drugs or cosmetically active substances. (DTX 72 at GMG_0006402; D.I. 127 at 627:16-20)	A "wide variety" of drugs. (DTX 73 at BMB_006442)
Triacylglyceride (0.5 - 5%)	Medium chain triglycerides at a concentration of "0.5 to 30%." (DTX 72 at GMG_0006399; D.I. 127 at 626:13-18)	Triglycerides (4.0 - 20%). (DTX 73 at GMG_0006451; '070 patent, col. 1:57-60)

[41] PCT Application Pub. No. WO 93/18752 ("the '752 PCT") and PCT Application Pub. No. WO 95/05163 ("the '163 PCT").

[42] The various concentration ranges recited next to the claimed excipients were taken from the broadest range recited in the dependent claims.

Propylene Glycol (5 to 15%)	Glycerol[43]	Glycerol (1%)[44]
Polysorbate (0.5 - 3%)	TWEEN (~0.2 – 5%). (DTX 72 at GMG_0006405; D.I. 127 at 627:25-628:6)	Polysorbate (1%). (DTX 73 at GMG_0006451-53; '070 patent, col. 1:58-60)
Aqueous phase containing salts	Aqueous phase containing salts. (DTX 72 at BMB_0006495-06; D.I. 127 at 628:20-25)	Aqueous phase containing salts. (DTX 73 at GMG_0006451-53; '070 patent, col. 1:61)
Polyacrylic acid (0.5 - 2%)	Carbopol® as a "gelling agent" (~0.2 - 15%). (DTX 72 at GMG_0006406; D.I. 127 at 629:7-630:4; D.I. 127 at 983:4-12)	Carbopol® (0.1%). (DTX 73 at GMG_0006451-53; '070 patent, col. 1:57)
Lecithin (>0 - 3%)	Lecithin (~0.2 - 5%). (DTX 72 at GMG_0006399-400; D.I. 127 at 626:21-627:1)	Lecithin (0.65 or 0.06%). (DTX 73 at GMG_0006451; '070 patent, col. 1:60-61)
Pharmacological adjuvant or vehicle[45]	Conventional additives and preservatives and EDTA. (DTX 72 at GMG_0006406, -18; D.I. 127 at 629:1-633:1)	Various suitable chelating agents. (DTX 73 at GMG_0006446)
Benzoic acid[46]	None. (D.I. 128 at 882:7-12)	None. (D.I. 128 at 894:22-23)

In place of azelaic acid, the '752 PCT discloses "[i]nsoluble drugs or cosmetically active substances" such as antibacterial agents. (DTX 72 at GMG_0006402; D.I. 127 at 627:16-20) Dr. Michniak-Kohn testified that azelaic acid is an insoluble drug. (*Id.*) In

[43] Dr. Michniak-Kohn testified that a POSITA would have understood that propylene glycol and glycerol were interchangeable. (D.I. 127 at 631:5-13)

[44] The '070 patent credits the '163 PCT with the disclosure of propylene glycol, a disclosure that both experts agree was in error. (D.I. 128 at 894:24-896:6; D.I. 127 at 662:5-12)

[45] Recited only in dependent claim 7 of the '070 patent.

[46] Recited only in dependent claim 12 of the '070 patent.

contrast, Dr. Weiner opined that none of the active ingredients disclosed in the '752 patent are "structurally related to azelaic acid." (D.I. 128 at 882:7-12)

The critical dispute between the parties is whether the '752 PCT discloses a hydrogel or an emulsion. Dr. Michniak-Kohn explained that the '752 PCT discloses two ways to form a "viscous composition:" (1) "the oily liquid may be present in an amount of about 20 to 30%;" or (2) "one or more adjuvants such as gelling agents or thickening agents may be included." (DTX 72 at GMG_0006399; D.I. 127 at 629:7-630:4) Example 30 of the '762 PCT describes adding Carbopol® and neutralizing the solution, which defendants argue is consistent with gel formation. (DTX 72 at GMG_0006420-21) Plaintiffs argue that the '752 PCT describes the composition as "oil spheres in an aqueous suspension or emulsion," not a gel. (*Id.* at GMG_0006395) Additionally, the '752 PCT describes the viscosized compositions as being "useful as creams or ointments" (*id.* at GMG_0006409), and the neutralized solution in example 30 as a "homogenous cream" (*id.* at GMG_0006421).

For all of the asserted prior art references, the parties' experts reach opposite conclusions concerning the disclosure of a hydrogel. The parties appear to agree on the fundamental concept that hydrogels (which have a three dimensional structure)[47] and emulsions (which contain two liquid phases)[48] are different dosage forms. (D.I. 127 at 673:6-674:19; D.I. 128 at 937:19-938:8; D.I. 126 at 295:16-21) As mentioned in the

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[47] Dr. Franke explained that, unlike emulsions, hydrogels are "basically a one phase aqueous system consisting of . . . a three-dimensional backbone system, which is made of polymers most of the time." (D.I. 125 at 64:24-65:9)

[48] Dr. Franke testified that an emulsion is "a minimum two-phase dispersed system consisting of a lipid, an oily phase and an aqueous phase, normally stabilized by modifiers" such as emulsifiers. (D.I. 125 at 62:9-17)

court's claim construction, *supra*, the oft-used description of a hydrogel "containing" an emulsion creates unnecessary confusion where the parties agree that an emulsion, by definition, does not have a three dimensional structure. The parties do accept that a low-viscosity liquid (potentially in the form of an emulsion) may be turned into a hydrogel. ('070 patent, col. 5:22-38; D.I. 129 at 1030:3-1031:7; D.I. 125 at 79:8-80:8) The parties disagree, however, as to how and when a hydrogel is formed given the excipients-at-issue. As set forth in a pharmaceutical bulletin for the properties of Lubrizol ("the Lubrizol Bulletin") (JTX 31), the concentration of the Carbopol® polymer, the type of Carbopol® polymer, and the pH of the solution all impact viscosity, with viscosity increasing along a parabolic curve in response to increased concentration or pH. (*See* JTX 31; D.I. 128 at 743:9-18) Neither expert was able to pinpoint the exact point at which the solution changes from merely "viscous" to a "hydrogel." (*See, e.g.*, D.I. 128 at 939:6-12; 951:4-7) Given the lack of a clear scientific threshold, the court considers the representation of the prior art authors to be the best authority regarding the "true" dosage form of the disclosed compositions.[49]

Here, although the '752 PCT discloses Carpobol® plus neutralization, the authors describe the resulting composition as an "emulsion," "cream" or "ointment," but never a "gel." Although the '752 PCT does disclose a large number of highly similar or identical excipients to the claimed composition, the court finds that it does not disclose a "hydrogel." Moreover, there is no dispute that the '752 PCT does not literally disclose

[49] The court is unpersuaded by defendants' arguments that a POSITA might refer to a gel as an emulsion given that gels can "contain" emulsions, as the parties agree on a fundamental level that gels and emulsions are different dosage forms.

azelaic acid, so court addresses, *infra*, whether a POSITA would modify the disclosure in the '752 PCT to include azelaic acid in a hydrogel form.

b. '163 PCT

The '163 PCT is entitled "Bioadhesive Emulsion Preparations for Enhanced Drug Delivery." (DTX 73) The '163 PCT was published on February 23, 1995, and is identified as prior art in the specification of the '070 patent. ('070 patent, col. 1:50-62) The '070 patent states that the '163 PCT discloses all of the limitations of the '070 claimed formulation, with the exception that it is in the form of an emulsion and does not contain azelaic acid. (*See* table, *supra*) The '163 PCT provides a list of potentially suitable drugs, stating that "[t]he pharmacological activity of a wide variety of drugs render them suitable for use in bioadhesive emulsion formulations, to treat a number of conditions." (DTX 73 at GMG_006442) Just as with the '752 PCT, Dr. Weiner opined that none of the disclosed drugs is structurally related to azelaic acid. (D.I. 128 at 893:15-22) The '163 PCT states that "[m]any of the drugs listed above are poorly soluble in water" and "[l]ow bioavailability of such drugs severely limits their applicability, usage and effectiveness. Incorporation of such drugs into mucoadhesive emulsions of the present invention increase their bioavailability." (*Id.*) Specifically, the '163 PCT reports more effective drug delivery into the eye using the Carbopol®-containing emulsion as compared to a Carbopol®-free emulsion. (DTX 73 at GMG_0006456) Dr. Weiner questioned the applicability of experiments done in mucus membranes such as the cornea of the eye to the stratum corneum, which is more difficult for drugs to penetrate. (D.I. 128 at 892:17-895:12)

Dr. Michniak-Kohn testified that the '163 PCT discloses a hydrogel because the composition combines water and the gelling agent Carbopol® along with a neutralization step. (D.I. 127 at 636:7-14; DTX 73 at GMG_0006432-33, 51 (example 4)) Plaintiffs respond that, by its very title, the '163 PCT characterizes the composition as an emulsion, not a gel. (DTX 73 at GMG_0006430; D.I. 128 at 896:16-897:19) Plaintiffs point out that in one example, addition of Carbopol® resulted in a drop in viscosity. (DTX 73 at GMG_6460-62; D.I. 128 at 897:13-22) Just as in the '752 PCT, the authors of the '163 PCT describe combining Carbopol® with neutralization, but characterize the resulting composition as an "emulsion," not a "gel." Accordingly, the court finds that the '163 PCT discloses a large number of highly similar or identical excipients to the claimed composition, but does not disclose such ingredients in "hydrogel" form.

3. Disclosure of azelaic acid prior art references

a. Maru

Defendants identify an article titled (in translation) "In Vitro Diffusion and Cutaneous Permeation of Azelaic Acid from Dermic Preparations: Research of Correlations" by U. Maru et al. ("Maru") as relevant prior art that discloses a hydrogel formulation containing azelaic acid. (DTX 64) Maru was published in 1982, and the parties agree that it is prior art to the '070 patent. (DTX 64 at GMG_0136983; D.I. 118, ex. 1 at ¶ 64) Maru discloses three azelaic acid formulations, including a "gel ointment" containing azelaic acid, Carbopol® 934, propylene glycol, ethyl alcohol and water. (DTX 64 at GMG_0136983) Maru compared the skin permeation of azelaic acid in the three compounds and concluded that "the gel formulation was revealed to be the most

active" in terms of permeability of azelaic acid as compared to the cream and the anhydrous ointment. (*Id.* at GMG_0136987; D.I. 127 at 645:22-646:10) Dr. Weiner opined that these results differ from the '070 penetration results in that the '070 patent reported both enhanced penetration and less flow-through as compared to the reference product. (D.I. 128 at 917:23-918:13)

Defendants argue that Maru discloses a hydrogel because it contains a gelling agent at a concentration of 5% and water, although defendants concede that no neutralization step is described. (D.I. 127 at 534:6-17; 645:8-14) Dr. Michniack-Kohn testified that "[b]y the broad definition of a three-dimensional structure being a gel, you do not need neutralization" of a polymer such as Carbopol® to form a gel.[50] (D.I. 128 at 743:15-20) Defendants argue that, by comparing figure 8 to figure 1 of the Lubrizol Bulletin, it is evident that a 5% Carbopol® 934 solution has a higher viscosity than is required for gel formation. (JTX 31 at BAYER0544944) Although Dr. Weiner maintained that neutralization of Carbopol® is required for gel formation, he agreed that Carbopol® 934 at 5% would yield "an extremely viscous product . . . [e]ven without neutralizing." (D.I. 126 at 304:20-305:5; D.I. 129 at 979:3-21; JTX 31 at BAYER0544944)

The court agrees with defendants that Maru discloses a hydrogel formulation containing azelaic acid. As explained, *supra*, the court gives weight to the authors' description of the disclosed composition. Here, the authors describe the composition as a "gel ointment," and even contrast the gel with the cream and anhydrous ointment.

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[50] Plaintiffs argue that Dr. Michniak-Kohn was impeached with her own deposition testimony in which she admitted that Carbopol® "certainly isn't gelling until you neutralize it." (D.I. 127 at 680:1-14)

The court finds the expert testimony regarding the necessity of neutralization to hydrogel formation to be largely unhelpful, with both experts offering conflicting views on the science and on the proper interpretation of the graphs in the Lubrizol Bulletin. Plaintiffs recognize that, while Maru does not disclose a neutralization step, Maru also does not disclose the pH of the composition. (DTX 64; D.I. 127 at 679:22-680:24) Even if the court were to accept that neutralization is required for gel formation, the court is again left guessing as to the "true" dosage form in the absence of any expert testimony regarding the likely pH of the disclosed solution and the predicted viscosity at that pH given the percentage of Carbopol®.[51] As such, the court relies on Maru's own characterization of the composition and determines that Maru discloses a hydrogel.

b. Gasco

Gasco was published in 1991, and the parties stipulate that it is prior art to the '070 patent. (DTX 59 at GMG_0006359; D.I. 188, ex. 1 at ¶ 66) Gasco reportedly improved on a prior art microemulsion that "could not be applied on the skin because of [its] fluidity" by viscosizing the microemulsion through the addition of Carbopol® 934. (DTX 59 at GMG_0006359; D.I. 127 at 682:10-22) Dr. Michniak-Kohn testified that Gasco disclosed a hydrogel because the composition contained Carbopol® 934 and water, although she agreed that the microemulsion had a pH of 3.0. (D.I. 127 at 602:19-603:22, 682:23-25) Plaintiffs respond that no hydrogel was formed because the Lubrizol Bulletin shows no gel formation below pH 4.0 for the grade of Carbopol® used in Gasco. (JTX 31 at BAYER549942-44) Gasco performed Franz cell penetration

[51] The court is instead presented with attorney argument that the pH is lower than that required for gel formation because there is no "room" for a neutralizing agent. (D.I. 133 at 16-17)

studies comparing the viscosized microemulsion against the "gel" disclosed in Maru, but did not measure the amount of azelaic acid remaining in the skin. (DTX 59 at GMG_6361; D.I. 128 at 690:7-12) Gasco reported increased permeation of azelaic acid in the viscosized microemulsion as compared to both the gel and the prior art fluid microemulsion. (DTX 59 at GMG_0006361-62)

As with the preceding references, the court first examines the representation of the prior art author regarding the dosage form of the disclosed composition. Here, the authors of Gasco describe the composition as a viscosized "microemulsion," although they readily identify the composition in Maru as a "gel." The Lubrizol Bulletin also supports the conclusion that the composition is a microemulsion in that it shows no gel formation at a pH of 3.0 given the particular grade of Carpobol® used in Gasco. Accordingly, the court concludes that Gasco does not disclose a hydrogel.

c. Pattarino

Defendants identify an article entitled "Topical delivery systems for azelaic acid: Effect of the suspended drug in microemulsion: by F. Pattarino et al. ("Pattarino") as a prior art reference. (DTX 67) Pattarino was published in 1994, and the parties stipulate that it is prior art to the '070 patent. (DTX 67 at GMG_0137017; D.I. 118, ex. 1 at ¶ 67) Dr. Michniak-Kohn testified that Pattarino improved upon the work of Gasco by adding an increased quantity of azelaic acid. (D.I. 127 at 670:6-671:7; DTX 67 at GMG_1037018) The composition with the smallest amount of azelaic acid showed the greatest penetration, but the results were difficult to interpret given the possibility of undissolved azelaic acid obstructing the flow-through. (DTX 67 at GMG_0137018) As the court has concluded that Gasco does not disclose a hydrogel and there is no

evidence that increasing the amount of azelaic acid alone would convert a microemulsion into a hydrogel, the court finds that Pattarino similarly does not disclose a hydrogel.

d. '943 patent

U.S. Patent No. 5,385,943 ("the '943 patent") is titled "Use of Topically Applicable Preparations for Treatment of Presbyderma" and issued on January 31, 1195. (DTX 71) The parties stipulate that the '943 patent is prior art to the '070 patent. (D.I. 118, ex. 1 at ¶ 62) The '943 patent describes using "topically applicable preparations" containing dicarboxylic acids to treat skin conditions. (DTX 71 at GMG_006391) In the preferred embodiment, the '943 patent describes using azelaic acid in a concentration of 5 to 30% as the dicarboxylic acid. (DTX 71 at GMG_0006392-93; D.I. 127 at 638:17-19) The excipients include a "fatty phase, oil/water emulsifier, aqueous phase and preservatives." (DTX 71 at GMG_0006392) The '943 patent also discloses "moisture-holding factors" such as propylene glycol and "emulsifiers" such as Carbopol®, but does not disclose lecithin. (*Id.* at GMG_0006392; D.I. 127 at 639:3-13; D.I. 127 at 651:8-13) Dr. Weiner opined that thousands of combinations of formulations could be created from the "laundry list" of named ingredients. (D.I. 128 at 905:7-23) Plaintiffs highlight the fact that the '943 patent discusses "milk, lotion or cream (oil/water emulsions)" and "ointments (water/oil emulsions)," but does not disclose a gel. (DTX 71 at GMG_0006392; D.I. 128 at 904:20-905:1)

The '943 patent suffers from the same deficiencies as several other prior art references at issue; namely, the authors describe various potential dosage forms including "lotion," "cream," or "ointment," but exclude any mention of gels. Additionally,

the '943 patent describes Carbopol® as an "oil/water emulsifier" and does not list a neutralization step or specify a baseline pH. (D.I. 118, ex. 3 at ¶ 70; DTX 71 at col. 2:48-57) As such, nothing in the record compels the court to conclude that the '943 patent discloses anything more than a composition in cream or ointment form.

e. '119 PCT

PCT Application Pub. No. WO 93/39119 ("the '119 PCT") is entitled "Topical Vehicles Containing Solubilized and Stabilized Azelaic Acid." (DTX 74) The '119 PCT was published on December 12, 1996, and is prior art to the '070 patent. (D.I. 118, ex. 1 at ¶ 63) The '119 PCT discloses "[a] completely solubilized topical composition of azelaic acid in a glycol base which is stable at normal temperatures and pressures." (DTX 74 at GMG_0006485) The '119 PCT achieves a solubilized composition by adding a glycol (such as propylene glycol), which "easily and completely dissolves the azelaic acid without affecting the stability of the azelaic acid." (*Id.* at GMG_0006491-92) Example 2 discloses a cream formulation that may alternatively be a "translucent gel" "by removing the glycol distearate therefrom." (*Id.* at GMG_0006494) Plaintiffs argue that Dr. Michniak-Kohn could not explain how removing glycol distearate would result in gel formation. (D.I. 127 at 642:5-655:2, 677:21-678:5) Plaintiffs also note that the '119 PCT does not disclose polysorbate, lecithin or polyacrylic acid, nor does it specifically mention triglycerides. (*Id.* at 651:14-19; D.I. 128 at 910:15-20; DTX 74 at GMG_0006492)

Although the authors of the '119 PCT described the formulation as a "translucent gel," the '119 PCT does not disclose how removal of glycol distearate would result in gel formation, and defendants' expert was similarly unable to explain the phenomenon. As

the transition from a cream to a "translucent gel" through removal of a single excipient is unsupported by any evidence of record, the court concludes that the '119 PCT does not disclose a hydrogel.

4. Motivation to combine

Dr. Michniak-Kohn opined that Skinoren® cream would be the "starting point" for a POSITA who had already identified the relevant disease and drug. (D.I. 127 at 621:17-622:14) From there, a person of ordinary skill working in industry would look for "an alternative product," considering "cream, gels, ointments" and "topically applied formulations." (*Id.*) Dr. Michniak-Kohn testified that a person of ordinary skill in the art would have questioned whether "to remain with a cream or . . . look at another formulation," considering "interesting data . . . that would have led [a POSITA] to . . . really consider hydrogels as a possible option." (*Id.* at 623:25-624:7) Defendants argue that the '163 PCT (DTX 73 at GMG_0006456), Maru (DTX 64 at GMG_0136987) and Gasco (DTX 59 at GMG_0006362) all demonstrate improved drug delivery with hydrogel formulations which would motivate a POSITA to reformulate Skinoren® cream as a hydrogel. Dr. Michniak-Kohn agreed that "a person of ordinary skill in the art as of 1998 [would] have had a reasonable expectation of success in making an azelaic acid gel formulation instead of a cream formulation." (D.I. 127 at 657:10-14) As additional motivation to develop Skinoren® into a hydrogel, defendants cite Hoffman's testimony that the developers of Finacea® hoped to "come up with a second formulation on the market . . . to increase sales." (D.I. 128 at 761:2-6)

For the reasons discussed, *supra*, the court finds that of all the named prior art references, only Maru discloses a hydrogel formulation. The court accepts that a

POSITA would consider developing an alternative product to Skinoren® in a different dosage form given the market forces (D.I. 128 at 761:2-6) and the agglomeration instability and cosmetic deficiencies of Skinoren® cream (D.I. 125 at 63:8-15, 77:4-10). Although the developers of Finacea® were skeptical about reformulating as a hydrogel given the possibility that the active ingredient would be trapped in the hydrogel matrix (D.I. 125 at 66:12-18), it is the court's opinion that such reservations would not prevent further development, especially given Maru's report of a successful azelaic acid-containing hydrogel formulation. The decision to pursue a hydrogel formulation would be further reinforced by Maru's report of increased permeability of azelaic acid with the gel formulation as compared to the cream and anhydrous ointment.[52] (DTX 64 at GMG_0136987; D.I. 127 at 645:22-646:10)

Having found that a POSITA would pursue a hydrogel formulation, the relevant question then becomes whether a POSITA would combine the disclosure of the azelaic-acid containing hydrogel from Maru[53] with the prior art in a manner that make obvious claim 1 of the '070 patent. At trial, Dr. Michniak-Kohn provided testimony regarding two prior art combinations: (1) Gasco and the '752 PCT; and (2) the '163 PCT with the '119 PCT. (D.I. 127 at 652:7-655:25) Defendants do not specifically address either combination in their post-trial briefing. Rather, defendants urge the court to consider the

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[52] Even though Gasco later reporter greater azelaic acid permeation with its viscosized microemulsion as compared to Maru's gel (DTX 59 at GMG_0006361), the court is not convinced that this report, in isolation, "teaches away" from pursuing a gel formulation.

[53] Although defendants argue that a POSITA could begin with an emulsion (such as those disclosed in Gasco or the '163 PCT), convert it to a hydrogel and then combine the hydrogel with either the '752 PCT or the '163 PCT, this method of combination was not addressed by defendants' expert and amounts to pure attorney argument. (D.I. 131 at 33)

combination of two "buckets" of references, namely, those that disclose formulations containing the claimed excipients in the form of a hydrogel (the '752 PCT and '163 PCT) with those that disclose azelaic acid in the form of a hydrogel, but that do not contain all of the claimed ingredients (Maru, Gasco, Pattarino, the '943 patent and the '119 PCT). As support for this group-wise combination, defendants apparently rely on Dr. Michniak-Kohn's statement at trial that a POSITA "could have put . . . information together from another two publications" to render obvious claim 1. (D.I. 127 at 656:7-17) Such a cursory statement, without more, cannot satisfy defendants' burden to demonstrate, by clear and convincing evidence, that a POSITA would be motivated to combine Maru with either the '752 PCT or the '163 PCT. Any attempt by the court to manufacture a motivation to combine the references-at-issue without guiding testimony or evidence would amount to pure speculation.

Even if the court were presented with a fully-developed record on motivation to combine, defendants have not carried their burden to demonstrate a reasonable expectation of success in making the combination. Contrary to defendants' representation, Dr. Michniak-Kohn never testified as to the "routine nature of optimizing a formulation," but instead provided pointed testimony regarding swapping particular excipients in two specific combinations. (*See* D.I. 127 at 653:22-654:1, 655:13-1, 659:19-660:10) Defendants' own substantial efforts to swap ingredients to create a bioequivalent formula, coupled with testimony from both experts that excipients and the active ingredient react differently depending on the formulation (D.I. 126 at 296:9-14; D.I. 128 at 693:18-694:2, 879:23-880:13), leads the court to understand that swapping ingredients in complex chemical formulations is anything but "routine." The court was

not presented with testimony or other evidence regarding the expectation of success in swapping ingredients in the specific combination(s)-at-issue and, therefore, cannot conclude that defendants have carried their burden in this regard.

5. Secondary considerations[54]

Plaintiffs argue that the patented composition is nonobvious in light of: (1) the unexpected Franz diffusion cell results; (2) the commercial success of Finacea®; and (3) defendants' copying of the hydrogel.

a. Unexpected results

Plaintiffs argue that the Franz diffusion cell test reported in example 2 of the '070 specification was unexpected in that more azelaic acid both penetrated and remained in the skin. (D.I. 125 at 158:14-19) In Dr. Günther's words, this finding was contrary to the expectation that "the concentration in the skin and receptor fluid would point in the same . . . relationship direction." (*Id.* at 158:3-5) Plaintiffs argue that the Franz cell study is predictive of clinical effectiveness to the extent that both plaintiffs and defendants used the data to select compounds for further clinical study. (D.I. 126 at 241:4-7, 311:15-22; JTX 41 at GMG_15047) Additionally, in its formulation comparison report that was submitted to the FDA, defendants wrote that "[t]he [Franz cell] method has historic precedent for accurately predicting in vivo percutaneous absorption kinetics." (JTX 38 at GMG_0012957) As detailed, *supra*, the Franz diffusion cell results were confirmed by the scarification test comparing the efficacy of Finacea® to Skinoren® in human

[54] The court reads *In re Cyclobenzaprine*, *supra*, as requiring a review of such evidence even where it is apparent that defendants cannot meet their burden to prove obviousness by clear and convincing evidence.

subjects.[55] (DTX 92; DTX 111 at BAYER0384619; D.I. 129 at 1038:23-1039:3) Plaintiffs admit that the 8-week double-blind pilot study comparing Finacea® and Skinoren® cream in patients with papulopustular facial acne did not yield statistically significant results, but argue that a population size of 30 would be unlikely to yield statistical significance. (D.I. 125 at 165:4-7; JTX 11 at BAYER0154370)

Although defendants express concern about the reliability of the Franz cell study given the study design and lack of statistical analysis (D.I. 125 at 178:10-15; 179:11-14; 175:1-3), the court is willing to accept the results of the study if for no other reason than that the results were confirmed by defendants' own Franz cell test comparing Finacea® and batch 041. (JTX 38 at GMG_0012949) Defendants do not dispute Dr. Günther's testimony that the penetration profile, as reported, shows an unexpected relationship between penetration and retention. To the extent that the unexpected in vitro results must be verified by in vivo clinical trials, the court is persuaded that the scarification test adequately confirmed the in vitro results. Although the scarification test did not gather data regarding absorption of azelaic acid, hydrogel B had higher reaction scores than Skinoren® (DTX 111 at BAYER384643-44), a difference that scientists involved in the development of Finacea® interpreted as "indicat[ing] higher release of azelaic acid from the type B AzA gel than from the azelaic acid 20% cream." (DTX 92; *see also* JTX 13 at

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[55] Defendants argue that the scarification test does not confirm the Franz cell results because plaintiffs produced no expert testimony at trial regarding the study. However, defendants themselves admitted into evidence a presentation by two scientists involved in the development of Finacea® in which the authors conclude that "[t]he differences in scores also indicate higher release of azelaic acid from the type B AzA gel than from the azelaic acid 20% cream, despite its lower nominal strength, **confirming the results of the hairless mouse Franz flow-through diffusion cell study**." (DTX 92) (emphasis added)

BAYER219860) Defendants also argue that the scarification study cannot support a finding of unexpected results because it demonstrated that Finacea® performed worse than Skinoren® in terms of skin irritation. (DTX 111 at BAYER0384621) In an article titled "The Rationale for Advancing the Formulation of Azelaic Acid Vehicles" (JTX 13), Dr. Zoe Diana Draelos wrote that "[b]ecause a higher drug concentration in the viable skin favors a higher therapeutic effectiveness, the type B formulation was selected for final clinical development even though it appeared to be more irritating than AzA gel type A." (JTX 13 at BAYER0219860) This statement indicates that the drug delivery benefits of Finacea® outweighed any undesirable increase in local skin irritation. Altogether, the court finds that unexpected results weigh in favor of nonobviousness.

b. Commercial success

Plaintiffs also claim that the success of Finacea® supports a finding of nonobviousness. Plaintiffs cite evidence that Finacea® is the number one prescribed branded topical treatment for rosacea in the United States with net sales exceeding $562 million. (D.I. 128 at 799:7-13; D.I. 129 at 1063:3-8; PTX 40 at BAYER138709; PTX 300) Mr. Ivan Hofman, defendants' rebuttal expert, agreed that "net sales have increased every year [since] Finacea® was introduced in 2003." (D.I. 129 at 1064:7-19; PTX 302; PTX 303) Although at the time of Finacea's® launch in March of 2003, there were no "other azelaic acid products on the market for the treatment of rosacea" (D.I. 128 at 778:21-24), it competed with "several other branded products" with metronidazole as the active ingredient (D.I. 128 at 832:14-834:14). Mr. John C. Jarosz, plaintiffs' expert on commercial success, testified that the composition of components in Finacea®, as a whole, delivered the benefits of increased bioavailability, greater

efficacy, and favorable cosmetic properties. (D.I. 128 at 843:11-844:1; *see also* JTX 19 at BAYER427623; PTX 140; PTX 13 at BAYER30453)

When a patentee offers objective evidence of nonobviousness, there must be a sufficient relationship between that evidence and the patented invention." *In re Paulsen*, 30 F.3d 1475, 1482 (Fed. Cir. 1994). "A prima facie case of nexus is made when the patentee shows both that there is commercial success, and that the product that is commercially successful is the invention disclosed and claimed in the patent." *Crocs, Inc. v. Int'l Trade Comm'n*, 598 F.3d 1294, 1310–11 (Fed. Cir. 2010). Commercial success must be "due to the merits of the claimed invention beyond what was readily available in the prior art." *J.T. Eaton & Co. v. Atl. Paste & Glue Co.*, 106 F.3d 1563, 1571 (Fed. Cir. 1997); *see also Dippin' Dots, Inc. v. Mosey*, 476 F.3d 1337, 1345 (Fed. Cir. 2007).

Defendants do not dispute that Finacea® embodies the product disclosed and claimed in the patent. (D.I. 118, ex. 1 at ¶¶ 24-37) Instead, defendants argue that plaintiffs have failed to establish a prima facie case of nexus because commercial success was driven by ingredients in the claimed composition that were known in the prior art. Specifically, defendants argue that azelaic acid was known to be effective at treating skin disorders (DTX 113 at BAYER0435023; D.I. 126 at 300:17-301:4; D.I. 129 at 1020:3-8) and hydrogel formulations were known to be effective and well tolerated (D.I. 129 at 1018:19-1019:6). The court finds defendants' rationale unpersuasive where, as here, no ingredient or element on its own demonstrates the desirable characteristics of the claimed composition such as increased bioavailability and favorable cosmetic properties. (*See, e.g.*, D.I. 129 at 1031:13-18 (Dr. Michniak-Kohn

admitted that azelaic acid powder cannot be applied directly on the skin)) The fact that Finacea® also causes increased skin irritation is further testament to the desirability of the positive attributes of the composition.

Defendants offer evidence to rebut plaintiffs' prima facie case of nexus including a third-party assessment of the market for Finacea®, which concluded that "the frequency of sampling [is] a significant factor in the prescribing decisions for Finacea®. (D.I. 129 at 1058:9-25; DTX 136 at BAYER0047118) In addition to sampling, defendants point to plaintiffs' marketing campaign (D.I. 129 at 1059:1-18) and use of discounts (*Id.* at 1061:1-1062:10) as the predominant drivers of commercial success. Plaintiffs respond that marketing did not drive sales given that Bayer's marketing budget is dependent on the prior year's sales. (D.I. 128 at 784:15-22) Plaintiffs also argue that Finacea's® sampling and coupon programs are designed to stay competitive with other products. (D.I. 128 at 789:13-791:11; D.I. 129 at 1087:13-19) Finally, plaintiffs argue that the third-party assessment concluded that Metrogel, not Finacea®, was one of the top 5 drugs prescribed nationally with a sample. (D.I. 128 at 1087:2-1088:6; DTX 158 at GMG_137607) The court concludes that, even if Finacea® is heavily marketed and sampling is a "significant factor" driving prescriptions, defendants have not negated the possibility that the merits of the claimed composition also drive prescriptions and sales. As such, the court concludes that commercial success weighs toward a finding of nonobviousness.

c. Copying

Finally, citing substantially the same facts set forth by the court in section II.A.3.b, *supra*, plaintiffs argue that defendants copied the '070 patent and Finacea® to make

their generic gel. Plaintiffs further argue that defendants' alleged copying was particularly egregious given the availability of non-infringing alternatives such as Skinoren® cream and various metronidazole-based formulations. The Federal Circuit, however, has held that it "do[es] not find compelling . . . evidence of copying in the ANDA context where a showing of bioequivalency is required for FDA approval." *Purdue Pharma Products LP v. Par Pharm., Inc.*, 377 Fed.Appx. 978, 983 (Fed. Cir. 2010); *see also Bayer Healthcare Pharm., Inc. v. Watson Pharm., Inc.*, 713 F.3d 1369, 1377 (Fed. Cir. 2013) ("[C]opying in the ANDA context is not probative of nonobviousness because a showing of bioequivalence is required for FDA approval."). Accordingly, the court finds that, even if the process of reverse-engineering Finacea® amounted to copying of the '070 patent, such conduct is not persuasive evidence of nonobviousnessness.

6. Conclusion on obviousness

The court finds that defendants have not met their burden to prove, by clear and convincing evidence, that claims 1-12[56] of the '070 patent are invalid for obviousness. The court also finds that the secondary considerations of unexpected results and commercial success, but not copying, support this finding of nonobviousness.

III. CONCLUSION

For the foregoing reasons, the court finds that defendants infringe the asserted claims of the '070 patent, and that the '070 patent is valid. An appropriate order shall issue.

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[56] Although the court's analysis focused on independent claim 1, dependent claims 2-12, which add additional limitations, are not obvious as a matter of law. *See Ortho-McNeil Pharm, Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1365 (Fed. Cir. 2008).