

NOT FOR PUBLICATION

**UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY**

BAUSCH HEALTH
IRELAND LIMITED, et al.,

Plaintiffs,

v.

PADAGIS ISRAEL
PHARMACEUTICALS LTD et al.,

Defendants.

**Civil Action No. 20-5426 (SRC)
(CONSOLIDATED)**

OPINION

CHESLER, U.S.D.J.

INTRODUCTION

Plaintiffs Bausch Health Ireland Limited, Bausch Health Americas Inc., and Bausch Health US, LLC (collectively, “Bausch”) bring this action for patent infringement against Defendants Padagis Israel Pharmaceuticals LTD and Padagis US LLC (collectively, “Padagis.”) This case concerns patents related to the pharmaceutical products Duobrii® and Bryhali®. Padagis is a pharmaceutical company which has filed ANDA Nos. 214285 and 214626 to produce generic versions of those pharmaceutical products. Bausch owns U.S. Patent Nos. 10,251,895 (“the ’895 patent”), 10,426,787 (“the ’787 patent,” and together with the ’895 patent, the “Combination Patents”), 8,809,307 (“the ’307 patent”) and 10,478,502 (“the ’502 patent,” and together with the ’307 patent, the “HP Patents”). All four patents are listed in the Orange Book as protecting Plaintiffs’ Duobrii® halobetasol propionate (“HP”)/tazarotene product. The HP Patents are listed in the Orange Book as protecting Plaintiffs’ Bryhali® HP product. Bausch

asserts claims 13, 16, and 20 of the '307 patent and claims 4 and 16 of the '502 patent against both Padagis's proposed HP ANDA Product and proposed HP and tazarotene ANDA Product. Bausch asserts claims 3 and 6 of the '895 patent and claims 4, 5, and 7 of the '787 patent against Padagis's proposed HP and tazarotene ANDA Product. Padagis contends that the asserted patent claims are invalid, pursuant to 35 U.S.C. § 103 and the definiteness requirement of 35 U.S.C. § 112. The parties have stipulated to infringement of the claims at issue. A bench trial on patent validity was held for 3 days, beginning on October 4, 2022, and ending on October 7, 2022. Upon hearing the evidence presented at trial, this Court finds that Padagis has failed to prove that the claims at issue are invalid.

Civil Action No. 20-5426 is a consolidated case. On May 1, 2020, Plaintiffs filed the Complaint in Civil Action No. 20-5426. On August 28, 2020, Plaintiffs filed the Complaint in Civil Action No. 20-11807. On September 3, 2020, this Court Ordered that the two cases be consolidated for all purposes, with Civil Action No. 20-5426 as the lead case.

STIPULATED FACTS

The parties stipulated to the following facts in the Final Pretrial Order ("FPO"):

23. IDP-118, as referred to in the '895 and '787 Patents, is the same formulation as Bausch's commercialized product, Duobrii®.

25. Clinical Study No. V01-118A-201 ("201 Study"), summarized in a report bearing Bates Nos. BAU00028944–29263, is the clinical study referred to in the specification of the '895 and '787 Patents. '895 Patent, at 11:30–20:10; '787 Patent, at 11:30–20:8.

26. On January 22, 2014, Bausch registered the 201 Study, a Phase II clinical trial involving IDP-118, to ClinicalTrials.Gov as Study No. NCT02045277 ("NCT Posting").

33. Diethyl sebacate is a dicarboxylic acid ester.

36. The '307 Patent claims priority to U.S. Provisional Application No. 61/458,339, filed on November 22, 2010.

42. The '502 Patent claims priority to U.S. Provisional Application No. 61/458,339 filed on November 22, 2010.

48. The '895 Patent claims priority to U.S. Provisional Application Serial No. 62/181,481 filed on June 18, 2015.

54. The '787 Patent claims priority to U.S. Provisional Application Serial No. 62/181,481, which was filed on June 18, 2015.

95. Japanese Patent Application Publication No. S63-255228 ("JP 228"), a copy of which has been produced at HALOBET0020443-0020459, published on October 21, 1988.

96. Indian Patent Application IN 2461/MUM/2009 ("Gandhi"), a copy of which has been produced at HALOBET0018559-0018590, published on March 30, 2012.

98. Gollnick et al., "Combination Therapy with tazarotene plus a topical corticosteroid for the treatment of plaque psoriasis," *British Journal of Dermatology* 1999: 140 (Suppl. 54): 18-23 ("Gollnick"), a copy of which has been produced at HALOBET0019240-19245, was published in 1999.

99. Blum et al.. "Multicenter, Double-Blind Comparative Observation of Application of 0.02%, 0.05% CGP 14 458 Ointments and Dermovate Ointment in the Treatment of Chronic Psoriasis," *Chinese J. Dermaol.* Vol. 19(3), 139-141 (1986) ("Blum"), a copy of which has been produced at HALOBET0020215-20221, was published in 1986.

THE ISSUES FOR TRIAL

1. Have Defendants proven, by clear and convincing evidence, that claims 13, 16, and 20 of the '307 patent, claims 4 and 16 of the '502 patent, claims 3 and 6 of the '895 patent, and claims 4, 5, and 7 of the '787 patent are invalid as obvious, pursuant to 35 U.S.C. § 103?
2. Have Defendants proven, by clear and convincing evidence, that claims 13, 16, and 20 of the '307 patent and claims 4 and 16 of the '502 patent are invalid as indefinite, pursuant to 35 U.S.C. § 112 ¶ 2?

THE EVIDENCE AT TRIAL

What follows are selected summaries of the testimony of the witnesses appearing in Court at trial:

A. Testimony of Linda Stein Gold

What follows is a summary of the witness's testimony. Dr. Stein Gold was qualified as an expert witness in the field of dermatology, clinical studies in dermatology, psoriasis, and treatment of psoriasis. (Tr. 38:10-18.) Dr. Stein Gold stated that corticosteroids are the mainstay of topical therapies for psoriasis; other topical therapies are vitamin A analogs (retinoids like tazarotene) and vitamin D analogs. (Tr. 41:6-10.) The nonsteroidal topical therapies provide many benefits but tend to be quite irritating. (Tr. 41:11-12.) Superpotent topical steroids cause worrisome side effects, including thinning of the skin, stretch marks, and systemic absorption that can lead to hormonal abnormalities. (Tr. 41:19-42:2.) The standard of care in psoriasis treatment is the use of superpotent topical steroids. (Tr. 42:15-18.) The potency of a corticosteroid is determined by a vasoconstrictor assay, which measures the skin-whitening effect of the steroid. (Tr. 42:19-25.) Both the active ingredient and the vehicle affect the potency of the drug in important ways. (Tr. 43:5-12.) Halobetasol is a superpotent topical corticosteroid that was first commercialized in 1990, with a .05% dose, under the brand name Ultravate®. (Tr. 43:13-44:3.) Only one topical retinoid has been used to treat psoriasis, tazarotene. (Tr. 44:8-22.)

Bryhali® is a superpotent topical corticosteroid containing halobetasol at a .01% concentration that can be used for up to eight weeks, unlike previous halobetasol medications, which could only be used for two weeks. (Tr. 45:3-22) Duobrii® is a combination of

halobetasol at .01% and tazarotene at .045% with no cap on the duration of use. (Tr. 46:9-21.) The problem with tazarotene as a monotherapy is that it is very, very irritating, so it was rarely used as a monotherapy. (Tr. 47:6-14.)

On cross-examination, Dr. Stein Gold stated that the FDA has limited treatment with Ultravate® to two weeks because of HPA axis suppression, and two weeks is generally not long enough to treat most patients' psoriasis. (Tr. 50:8-20.) Prior to 2015, tazarotene .05% was approved for topically treating psoriasis. (Tr. 51:16-19.) Bryhali® has a potency equal to Ultravate®. (Tr. 53:13-14.)

B. Testimony of Radhakrishnan Pillai

What follows is a summary of the witness's testimony. Dr. Pillai stated that he is vice president for R&D at Bausch Health. (Tr. 57:8-9.) He is a named inventor on one or more of the patents at issue in this case. (Tr. 57:21-23.) He was responsible for the overall management of the Bryhali® and Duobrii® projects. (Tr. 59:20-60:6.) At the time these development projects began, the primary products available for the treatment of psoriasis were the super-high or high potency corticosteroids, and tazarotene and calcipotriene. (Tr. 65:1-6.) These corticosteroid treatments were limited to use for two, sometimes four, weeks, and the tazarotene and calcipotriene were highly irritating compounds. (Tr. 65:9-20.) At the beginning of development, there were many active ingredients available for dermatologic use. (Tr. 66:11-19.) Development begins with preformulation, which involves choosing the two compounds to be combined and then evaluating their solubility in different solvents. (Tr. 68:18-69:4.) At first, they experimented with tazarotene at .09% and halobetasol propionate at .045%. (Tr. 69:6-13.) The evaluation of their solubility in different solvents is described in the IDP-118

development report (PTX-67). (Tr. 71:6-19.) The team conducted solubility studies. (Tr. 72:2-25.) The results of the solubility studies were not predictable. (Tr. 73:10-14.) The team then did simultaneous solubility studies of the two active ingredients together. (Tr. 74:2-15.) Then the team needed to assess compatibility of the two actives with the solvents. (Tr. 74:16-20.) The compatibility studies identified three compatible solvents. (Tr. 75:2-21.) Development then moved from preformulation to the formulation phase. (Tr. 76:17-25.) Multiple prototype formulations were developed and evaluated, with a subset selected primarily because of stability. (Tr. 77:3-15.) These selected formulations were then assessed with a vasoconstrictor assay ("VCA"). (Tr. 78:1-8.) The VCA studies showed surprising results: some formulations with a halobetasol concentration as low as 20% of the reference Ultravate®, produced the same level of skin blanching as Ultravate®. (Tr. 80:9-23.) Two concentrations of HP, .01% and .025%, were selected for a second VCA study, done with multiple formulations. (Tr. 81:5-82:23.) The second VCA study confirmed that the .01% concentration showed very similar vasoconstriction to the control. (Tr. 83:12-16.) Multiple formulations were then evaluated with in vitro skin penetration studies, looking for low penetration into the receptor phase of the skin, so as to minimize systemic side effects. (Tr. 84:10-86:14.) Based on these studies, they decided to replace propylene glycol with sorbitol, and cut the tazarotene concentration by half to .045%. (Tr. 87:6-19.) The formulation phase concluded with the selection of two lead formulations, both of which contained tazarotene at .045%, and HP at .01% or .025%. (Tr. 88:8-16.) After this came animal and clinical studies. (Tr. 88:22-89:2.) For IDP-118, Phase 1 of the clinical studies assessed cumulative irritation, sensitization, and systemic exposure; Phase 2 studies were of safety and efficacy; and then Phase 3, as well as a

long-term safety study. (Tr. 89:9-22.) Phase 2 also involved a combination study required by the FDA, called the “201 Study.” (Tr. 94:23-96:21.) The 201 Study results showed a surprising level of effectiveness for IDP-118. (Tr. 102:13-103:5.)

On cross-examination, Dr. Pillai admitted that his testimony that he was involved in formulating the Duobrii® product was inconsistent with his response at deposition, when he said he was not involved. (Tr. 104:4-105:24.) He agreed that it was known prior to 2011 that combining a corticosteroid and tazarotene would alleviate irritation from tazarotene. (Tr. 111:8-11.) He agreed that, in a 2011 FDA filing, Bausch cited Menter for the idea that combining tazarotene and a corticosteroid would provide a synergistic effect, which Dr. Pillai explained meant that the irritating effect of tazarotene would be reduced and allow for a longer treatment duration. (Tr. 111:22-113:8.) Dr. Pillai further explained that “synergistic” did not here mean “it will do it better,” but that it would allow for a longer duration of treatment. (Tr. 113:24-114:8.) He agreed that the filing also stated that clinical studies had shown that the combination of tazarotene and the corticosteroid gives a better result than either one of the monads. (Tr. 114:24-115:9.) It was known prior to 2011 that combining tazarotene and a high potent or superpotent corticosteroid would reduce the irritation of the tazarotene, though Dr. Pillai then stated that “combining” here meant applying them together, not putting them into a combination product. (Tr. 116:5-23.) Bausch’s concept was that the tazarotene would help with the skin atrophy adverse events from the corticosteroid, and the corticosteroid would help with the irritating effect of tazarotene. (Tr. 119:4-8.) Bausch stated in the 2011 filing that tazarotene .045% was comparable to the branded .05% tazarotene product. (Tr. 121:12-122:1.) The word “synergistic” is used in the literature in a number of different ways. (Tr. 126:16-25.) Duobrii®

and Bryhali® have the same vehicle. (Tr. 138:23-139:1.)

On redirect examination, Dr. Pillai explained that, when he said that he was not involved in the formulation of Duobrii®, he meant that he was not in the lab or directing the formulation group. (Tr. 143:11-18.) Neither the Lebwohl nor Menter references refer to a fixed-dose combination product. (Tr. 144:12-20.) In the Duobrii® patents, “synergistic” means “one plus one would be greater than two.” (Tr. 145:7-14.) As used in the FDA filing presented to him, “synergistic” means “there is mutual benefit . . . for each other.” (Tr. 145:15-18.) Prior to the publication of the results of the 201 Study, there was no literature that showed the kind of synergy claimed in the Duobrii® patents. (Tr. 145:19-23.)

C. Testimony of Robert Stern

What follows is a summary of the witness’s testimony. Dr. Stern stated that he had reviewed the halobetasol patents, the ’307 and ’502 patents, which are nearly identical. (Tr. 157:23-158:5.) With the use of corticosteroids, there is a risk of systemic side effects, which increases with the potency of the steroid, the amount applied, and the duration of use. (Tr. 162:10-16.) A POSA would have been motivated to lower the concentration of steroid applied, to as low as .01%, so as to reduce the risk of systemic side effects. (Tr. 162:17-163:6.) The 1986 Blum and Yawalker study showed that reducing the halobetasol dosage from .05% to .02% resulted in only a 9% reduction in efficacy for the treatment of psoriasis, compared to treatment with Dermovate, the most widely-used superpotent corticosteroid at the time. (Tr. 163:17-164:12.) There was no statistically significant difference between the outcomes of the three tested preparations. (Tr. 164:16-23.) Because two weeks of treatment is not sufficient for most psoriasis patients, the POSA would have been motivated to use .01% halobetasol for longer than

two weeks, since a lower dosage allows use for a longer period with lower risk of systemic and local side effects. (Tr. 165:13-166:1.) The Temovate® label teaches that it could be used for as long as four weeks by limiting the application to 5-10% of the body surface area. (Tr. 166:5-167:1.)

As to the '895 and '787 patents, the Combination Patents, they are obvious in view of three combinations of prior art references. (Tr. 167:21-168:5.) The '824 publication is a patent application which is substantively the same as the Halobetasol Patents. (Tr. 168:6-18.) A 1999 journal publication by Gollnick and Menter reports on two clinical studies using combinations of corticosteroids and tazarotene in psoriasis patients. (Tr. 168:19-169:4.) One reference is the label for Tazorac® cream, which contains .05% or .01% tazarotene, and reports a 12-week clinical trial. (Tr. 169:5-15.) One reference is the clinicaltrials.gov publication of the IDP-118 study. (Tr. 169:17-23.) One reference is an Indian patent application which describes the combination of halobetasol and tazarotene in single formulations, including lotions. (Tr. 190:3-5.)

The Gollnick reference describes two clinical studies, one in which tazarotene was applied at the start of the day, and then one of three different corticosteroids, or placebo, was applied at the end of the day; in the other, the tazarotene and the corticosteroid were applied on alternating days. (Tr. 177:15-178:11.) Both studies showed improved efficacy and reduced local skin effects; “Gollnik states that combination therapy with tazarotene and a topical corticosteroid is likely to have additive or synergistic effects.” (Tr. 178:14-19.) Gollnick would have motivated a POSA to consider combining tazarotene with stronger steroids, such as halobetasol, to improve efficacy and reduce skin irritation. (Tr. 179:1-4.) The Indian patent

application, referred to as “Gandhi,” describes formulations comprising halobetasol and tazarotene, and states that, when combined in a formulation, these compounds have synergistic effects, “which leads to more rapid clearing.” (Tr. 179:23-180:6.) The clinicaltrials.gov publication discloses the combination of .01% HP and .045% tazarotene. (Tr. 180:7-18.) Based on the halobetasol patents, the POSA would have been motivated to use .01% HP with little loss in efficacy, with the reduced concentration allowing for longer than two weeks of use. (Tr. 181:6-16.) The Tazorac® label calls for reducing tazarotene concentration to .01%-.045% to reduce irritation, and shows that a reduction from .1% to .05% has “rather little” impact on efficacy, so one would expect a further lowering to .045% should lower irritation and not substantially impact efficacy. (Tr. 181:24-182:22.) The ’824 publication, Gollnick, and Gandhi, tell us that a lotion of potent topical corticosteroids and tazarotene would be likely to lead to synergy, and Gandhi teaches that the actives can be combined in a lotion with an expectation of synergy. (Tr. 183:6-184:2.) Based on Gollnick and Gandhi, the POSA would have reasonably expected the combination of HP and tazarotene to provide synergistic efficacy and a synergistic reduction of an adverse event. (Tr. 185: 5-18.) If synergy is present, it is an inherent property of IDP-118, because applying IDP-118 to psoriasis patients inherently results in synergistic efficacy and synergistic reduction of adverse events. (Tr. 185:24-186:4.) Gollnick teaches that treatment for eight weeks is adequate for treating psoriasis with a tazarotene/corticosteroid combination with a high success rate. (Tr. 190:10-23.) Sustained relief from psoriasis from the use of IDP-118 is an inherent property of IDP-118, the natural reactions of the patient’s disease to IDP-118. (Tr. 192:5-17.)

On cross-examination, Dr. Stern agreed that the formulation can have a material effect on

the performance of a topical treatment. (Tr. 199:13-17.) He admitted that, in all of the prior art he had identified, he did not know whether the formulations had any effect on the performance of the various products. (Tr. 199:18-22.) He agreed that Ultravate® came out in 1990, containing .05% HP, and for twenty years after that, no one made an HP product with a lower concentration. (Tr. 207:13-19.) Blum said that HP .05% ointment would be a favorite treatment weapon for skin diseases, but made no such statement about the .02% ointment, which Blum described as less effective than Dermovate ointment. (Tr. 211:3-24.) The developers of Ultravate® did not evidence the motivation, based on Blum, to lower the concentration of HP to under .05%. (Tr. 213:4-15.) Rather, what these developers did was consistent with the express teaching of Blum that the .05% concentration was preferable. (Tr. 213:17-20.) The Temovate® label teaches a way to use a high potency steroid product for longer than two weeks without lowering the concentration. (Tr. 214:21-24.) Dr. Stern did not know of any HP products that have, similar to Temovate®, a four-week use exception based on application to a limited body area. (Tr. 214:25-215:4.) When asked about the inferences to be drawn from the selection of the formulation to undergo stability testing in the '824 Publication, Dr. Stern said that he was not sufficiently skilled in formulation to answer the question. (Tr. 225:2-226:6.) While the Lebwohl reference showed that tazarotene and corticosteroids were in most cases compatible, that is an issue for a formulation expert. (Tr. 277:19-24.) The compatibility of tazarotene with the '824 Publication formulations is an issue for a formulation expert. (Tr. 277:25-278:3.) Gollnick provides motivation to combine tazarotene and halobetasol, but does not disclose a combination product with those actives. (Tr. 278:18-279:9.) Gollnick does not talk about superpotent corticosteroids in combination with tazarotene, but only mid- or high-

potency steroids. (Tr. 280:15-281:25.) For first combination of prior art references, Dr. Stern did not rely on either the '824 Publication or the Tazorac® label to provide motivation to combine HP and tazarotene in a single product, but only Gollnick. (Tr. 283:6-14.) The Tazorac® label itself does not disclose the use of .045% tazarotene. (Tr. 284:1-4.) No one made a tazarotene product with less than .05% tazarotene in the 18 years between Tazorac® approval in 1997 and the priority date of the Duobrii® patents. (Tr. 284:18-21.) Nothing in the label suggests a .045% concentration. (Tr. 285:1-5.) Dr. Stern agreed that he had no evidence that .045% would be the optimal concentration of tazarotene in a combination with HP. (Tr. 285:6-21.) The IDP-118 study does not disclose the vehicle used with the actives. (Tr. 286:20-22.) The '824 Publication and Gollnick, without more, would not have led a POSA to the .045% concentration. (Tr. 288:14-22.) Gandhi would not have motivated a POSA to use the .045% concentration. (Tr. 289:9-12.) Gandhi does not disclose .01% HP, .045% tazarotene, or the formulations used in IDP-118. (Tr. 290:13-21.) Based on Gollnick and Gandhi, a POSA would have reasonably expected the combination of HP and tazarotene to provide synergistic efficacy and synergistic reduction of an adverse event. (Tr. 291:10-17.) The word “synergy” has been used incorrectly in the literature. (Tr. 293:9-13.) Dr. Stern did not know what either Gollnick or Gandhi meant when they used the terms “synergy” or “synergistic,” and there is no data in those publications to shed light on that question. (Tr. 293:14-24.) Thus, Dr. Stern had no way to know what Gollnick or Gandhi meant when they wrote that the combination is likely to have synergistic effects. (Tr. 293:25-294:3.)

On redirect examination, Dr. Stern stated that, prior to 2010, there were no references that disclosed a vehicle containing .01% HP. (Tr. 299:1-7.)

On re-cross examination, Dr. Stern agreed that the '824 Publication discloses multiple formulations that contain .01% HP. (Tr. 302:17-20.)

D. Testimony of Bozena Michniak-Kohn

What follows is a summary of the witness's testimony. Dr. Michniak-Kohn was admitted as an expert in the field of pharmaceutical science, particularly in the area of development and evaluation of dermatological formulations. (Tr. 306:9-12; 318:13-18.) Table 1 in the '307 patent lists five HP formulations with ingredients, four of which are embodiments of the invention. (Tr. 310:12-24.) Table 3 shows the VCA scores of those formulations, and the four formulations have VCA scores very similar to Ultravate®, the .05% HP product. (Tr. 311:4-24.) Dicarboxylic acid esters are lipophilic and are commonly used in topical formulations to dissolve corticosteroids, which are lipophilic too. (Tr. 320:12-18.) Diethyl sebacates are a subset of dicarboxylic acid esters that are known to be penetration enhancers. (Tr. 320:23-321:6.) The Gao and Po reference from 1994 studied fluocinolone acetonide at different concentrations and found no statistically significant difference between the VCA at three concentrations. (Tr. 321:22-322:13.) The 1986 Blum reference compared HP at .02% and .05% with Dermovate®. (Tr. 323:18-325:2.) The .02% HP treatment showed only a 9% decrease in efficacy compared to .05% HP, with a significantly cured (or better) rate of 81.4% vs. 90.2%. (Tr. 325:3-11.) While Blum concluded that .02% HP was less effective than both .05% HP and Dermovate®, the three treatments did not show any statistically significant difference. (Tr. 325:21-326:9.) The '295 patent, issued in 1980, teaches the use of sebacates, such as dialkyl sebacate, with corticosteroids, mentioning dialkyl sebacates, where the alkyl chain contains from 1 to 10 carbons; a POSA would know that diethyl sebacate is a dialkyl

sebacate with two carbons. (Tr. 328:11-25.) Selection of the diethyl sebacate would have been a matter of routine optimization based on the solubility of the corticosteroid. (Tr. 329:9-11.) Based on the '295 patent, a POSA would have had the reasonable expectation that solubilizing HP in a dialkyl sebacate would have improved the release of HP from the formulation and improved the penetration into the skin. (Tr. 330:15-19.) Blum would have motivated the POSA to further lower the HP concentration below Blum's .02% with an expectation of success. (Tr. 330:20-25.) Because the POSA would have understood the problem with systemic side effects, the POSA would have been motivated to formulate a lower concentration to minimize them, while still preserving efficacy. (Tr. 331:11-25.) Psoriasis is a chronic condition and needs treatment for longer than two weeks. (Tr. 333:4-6.) Decreasing the concentration of the active is an obvious approach to solving problems with its concentration. (Tr. 333:12-24.) Formulators have other solutions to these problems: they can optimize the level of drug saturation in the vehicle, for example, and can also improve the dissolution of the active in the formulation. (Tr. 334:1-12.) There are also compounds that allow the formulator to control the amount of drug that will go into the skin, known as penetration enhancers. (Tr. 334:13-17.) The vehicle in the HP Patents "has an action of both a vehicle and a chemical penetration enhancer." (Tr. 334:19-21.) Penetration enhancers work on the topmost layer of the skin to allow more drug to pass through it. (Tr. 335:11-14.) The '566 patent, issued in 1994, teaches that one can use dibutyl adipate (a dicarboxylic acid ester) or dibutyl adipate with isopropyl myristate, to enhance penetration of topical agents. (Tr. 336:8-337:6.) The '566 patent contains numerous examples of HP formulations. (Tr. 338:8-11.) It also teaches the advantages of preparing the formulations without petrolatum. (Tr. 338:25-339:7.)

The JP 228 reference was published in 1988 and teaches the formulation of topical preparations in which the steroid is dissolved by one or more solvents, including diethyl sebacate, among others. (Tr. 339:21-340:1.) The '566 and '295 patents, and JP 228, all teach the improvement of release or penetration of corticosteroids from topical formulations by completely dissolving the steroid in a liquid oil phase containing a dicarboxylic acid ester. (Tr. 342:15-343:1.) The POSA would have understood that these teachings were applicable to HP, given the knowledge in the art and the example HP formulations in the '566 patent. (Tr. 343:7-10.) Based on these three references, the POSA would have been motivated to use a liquid oil component comprising diethyl sebacate. (Tr. 345:7-13.) The three references teach dialkyl sebacates such as diethyl sebacate and dibutyl sebacate as the liquid oil solvent. (Tr. 346:15-18.) The Handbook of Pharmaceutical Excipients teaches the use of light mineral oil in topical pharmaceuticals. (Tr. 349:1-22.) The Temovate® label teaches use for four consecutive weeks when application is limited to less than 10% of the body surface area. (Tr. 354:3-23.)

The claim term “liquid oil component” in the halobetasol patents is indefinite. (Tr. 356:14-24.) Sorbitan monooleate (“SMO”) is an emulsifier that falls within the definition of “liquid oil component” in the patents. (Tr. 358:6-15.) The Handbook of Pharmaceutical Excipients confirms the properties of SMO. (Tr. 358:16-359:15.) SMO should be part of the liquid oil component, but the numbers in Table 2 in the patents appears not to include it. (Tr. 360:4-24.) “There’s a little bit of confusion here as to what the '307 patent teaches because the numbers should have been different there in Table 2 if the SMO had been included.” (Tr. 360:25-361:4.) Dr. Lane agrees that the POSA would not be able to reconcile this discrepancy,

this inconsistency in the patent. (Tr. 361:10-22.)

The '824 Publication teaches a corticosteroid dissolved in a formulation with a liquid oil component that includes a dicarboxylic acid ester, the addition of light mineral oil to the liquid oil component, and that the composition may be an oil-in-water emulsion. (Tr. 366:11-367:15.) It also describes a way of making a particular lotion formulation in which, at a certain point, light mineral oil and SMO are added. (Tr. 369:1-370:15.) The '716 patent, issued in 2014, teaches preparation of a tazarotene emulsion in which tazarotene is dissolved in diisopropyl adipate. (Tr. 373:6-21.) The formulation claims in the Combination Patents are obvious in view of the '824 publication. (Tr. 374:19-378:23.)

On cross-examination, Dr. Michniak-Kohn stated that “the formulation makes all the difference in the delivery of the drug.” (Tr. 382:1-17.) A corticosteroid formulation’s potency is influenced by numerous factors, including the concentration of the active, the type of formulation, and the ingredients used in the vehicle and their concentrations. (Tr. 386:7-387:4.) Dr. Michniak-Kohn agreed that both clobetasol .05% and HP .05% were sold commercially in 2010 and there was no specific reason for a POSA to select one over the other. (Tr. 388:6-390:4.) As of 2010, there were no commercial formulations for corticosteroids for treating psoriasis that contained diethyl sebacate. (Tr. 391:7-10.) The obviousness analysis for claim 4 of the '502 patent requires a POSA to select diethyl sebacate from the class of dicarboxylic acid esters. (Tr. 390:8-391:14.) Dr. Michniak-Kohn agreed that she did not know how many oily solvents existed before 2010 that a POSA could have chosen from. (Tr. 391:23-392:5.) There was no experimental evidence in the prior art that shows that diethyl sebacate is better at dissolving HP than other oleaginous solvents. (Tr. 393:2-5.) Light mineral oil was not in any

commercially available topical products for treatment of psoriasis as of 2010. (Tr. 395:25-396:4.) Ultravate® ointment contains white petrolatum. (Tr. 397:12-14.) The '295 patent teaches use of dialkyl sebacates, a class of compounds, in formulations with corticosteroids, but does not specifically disclose HP or limit the invention's utility to superpotent corticosteroids. (Tr. 401:8-22.) The '295 patent discloses only two species of dialkyl sebacates, dibutyl sebacate and diisopropyl sebacate. (Tr. 403:15-25.) The '295 patent teaches that white petrolatum can be used in the composition. (Tr. 404:14-16.) The Blum reference does not disclose anything about the formulations used except that they were ointments. (Tr. 406:10-12.) Dr. Michniak-Kohn agreed that Blum recommends the .05% concentration of HP, but a POSA would ignore that recommendation and rely on Blum as motivation to pick a lower concentration. (Tr. 408:2-12.) JP 228 was before the examiner during prosecution of the Bryhali® patents. (Tr. 409:18-20.) JP 228 discloses a cream preparation that can be used with any steroid, of which there are "quite a number." (Tr. 410:12-17.) JP 228 does not mention HP. (Tr. 411:10-12.) JP 228 discloses three solvents, diisopropyl adipate, diethyl sebacate, and triacetin, and contains no data showing that diethyl sebacate is preferable; none of the formulations given VCA testing contained diethyl sebacate. (Tr. 411:16-413:10.) The '566 patent was before the examiner during prosecution of the Bryhali® patents. (Tr. 414:25-415:2.) All the example formulations in the '566 patent which use HP use a .05% concentration; the patent does not refer to any HP formulation with a lower concentration. (Tr. 415:25-416:7.) The '566 patent contains nothing that would motivate a POSA to use HP at concentrations less than .05%. (Tr. 416:12-18.) As of 2010, no commercially available superpotent corticosteroid for the treatment of psoriasis used the vehicle disclosed in the '566 patent. (Tr. 417:8-11.) The '566 patent does not mention

diethyl sebacate, but does mention isopropyl myristate, which is not a sebacate. (Tr. 418:4-23.)

Dr. Michniak-Kohn agreed that a POSA would reasonably understand the components of the Court's construction of "liquid oil component." (Tr. 421:9-422:2.)

Dr. Michniak-Kohn agreed that she contends that, based on the '824 Publication, a POSA would have arrived at the formulation of IDP-118, and not that a POSA would have been motivated to arrive at all the compositions of the asserted claims of the Combination Patents. (Tr. 423:6-13.) The POSA would have considered all five formulations that have data reported in the '824 Publication. (Tr. 431:21-432:1.) No claim in the '824 Publication specifies .01% HP. (Tr. 432:10-12.)

E. Deposition Testimony of Binu Alexander

What follows is a summary of the witness's testimony. Mr. Alexander stated that he is employed by Bausch and has been designated to testify on behalf of Plaintiffs on the subject of its transactions with the clinicaltrials.gov website. (Tr. 437:21-439:3.) Information about study number NCT 02045277 was posted to clinicaltrials.gov; the first posted date is January 24, 2014, the date on which the study listing was first made public. (Tr. 441:20-444:15.) The study information first posted included the information that the experimental arm is IDP-118 lotion, which contained HP .01% and tazarotene .045%. (Tr. 448:21-449:20.)

F. Deposition Testimony of Sean Humphrey

What follows is a summary of the witness's testimony. Mr. Humphrey stated that he is employed by Bausch as director of regulatory affairs. (Tr. 454:14-24.) He said that, in an FDA filing connected to the Duobrii® IND, he certified that information on study number NCT 02045277 was posted to clinicaltrials.gov. (Tr. 459:10-462:2.)

G. Testimony of Majella Lane

What follows is a summary of the witness's testimony. Dr. Lane was admitted as an expert in the field of topical pharmaceutical formulations, including development and testing. (Tr. 468:21-469:8.) The asserted claims of the Bryhali® patents would not have been obvious to a POSA; Dr. Michniak-Kohn's analysis involves picking and choosing from old references. (Tr. 471:8-12.) Formulation science is unpredictable and requires trial and error experimentation. (Tr. 476:1-3.) A topical formulator must consider interactions among the drug, the vehicle, and the skin. (Tr. 476:7-19.) These four interactions are unpredictable, and require testing at every stage to determine how a particular group of actives and vehicle components work together. (Tr. 477:11-17.) Other factors to consider are crystallization on the skin, and the effect of evaporation. (Tr. 480:7-17.) None of the commercially available topical corticosteroid preparations, prior to 2010, contained a superpotent corticosteroid at a concentration less than .05%. (Tr. 482:13-20.) At that time, Ultravate® was the gold standard treatment using HP, and it did not have a vehicle containing a dicarboxylic acid ester. (Tr. 483:2-16.) Its use was limited to two weeks because of a side effect of all superpotent corticosteroids, HPA axis suppression. (Tr. 483:20-24.) Temovate® could be used for four weeks if body surface area was restricted, as an approach to managing HPA axis suppression. (Tr. 484:16-485:7.) There are five superpotent corticosteroids, as shown in Table 1 of the '307 patent. (Tr. 485:12-20.) At that time, the conventional wisdom was that reducing the concentration of an active in a formulation would reduce efficacy, so the POSA would not have been motivated to decrease concentration because of the concern for reducing efficacy. (Tr. 486:4-13.) For example, a tenfold drop in concentration of fluocinonide, from .1% to .01%

moves it from being a superpotent corticosteroid to being a mildly potent corticosteroid. (Tr. 486:20-487:15.) Blum also shows a decrease in efficacy with lower steroid concentration. (Tr. 487:18-488:3.) Contrary to the view of Dr. Michniak-Kohn, Gao shows that, when you lower concentration, there is a trend toward lesser activity. (Tr. 488:10-489:5.) Gao also says that that study's data was not reliable, due to problems in study design. (Tr. 489:6-20.) The '566 patent teaches the use of dibutyl adipate, alone or with isopropyl myristate, as a penetration enhancer. (Tr. 490:11-17.) The '295 patent sought to develop formulations for percutaneous delivery, all the way through the skin. (Tr. 490:18-20.) JP 228 addressed inadequate transdermal absorption. (Tr. 490:21-25.) These references reflect an old idea in the field that the way to succeed with a formulation is to push it all the way through the skin, but topical formulation science has moved on since then. (Tr. 491:2-18.) The approach in the Bryhali® patents is different, seeking to achieve localized delivery to the skin, not to push it all the way through. (Tr. 491:16-21.) In the Bryhali® patents, the vehicle delivers the drug preferentially into the skin rather than through the skin and into the systemic circulation. (Tr. 492:1-10.) For a disease like psoriasis, your target is in the skin, and you want the drug to stay in the skin. (Tr. 493:7-9.)

The '295 patent, 30 years prior to the priority date of the Bryhali® patents, does not mention HP or diethyl sebacate or light mineral oil, does not exclude formulations with white petrolatum, and seeks to achieve percutaneous absorption, delivery of the drug through the skin. (Tr. 496:12-497:2.) Dr. Michniak-Kohn viewed the Blum reference as teaching that .02% HP was effective in treating psoriasis. (Tr. 499:22-24.) But Blum does not disclose the formulations tested, other than saying they were ointments with particular actives at particular

concentrations. (Tr. 500:9-11.) Blum recommends the .05% corticosteroid preparation and teaches away from using the .02%. (Tr. 500:12-25.) The '566 patent, from 1994, focuses on using penetration enhancers to drive the drug through the skin – opposite to the approach taken in the Bryhali® patents. (Tr. 501:13-16.) The '566 patent teaches that one can improve dermal and transdermal penetration by using dibutyl adipate, alone or with isopropyl myristate, as a penetration enhancer. (Tr. 501:22-502:3.) The '566 patent does not teach more broadly about dicarboxylic acid esters. (Tr. 502:9-13.) The '566 patent teaches the use of penetration enhancers which will increase systemic absorption. (Tr. 503:8-15.) The goal of the '566 patent was increased systemic absorption and would not motivate a POSA to lower the concentration of the active. (Tr. 503:18-24.) In JP 228, the goal is improvement of transdermal absorption, and discloses only generic corticosteroid structures, which do not include HP. (Tr. 504:4-22.)

A POSA would not have been motivated to look to the '295 patent to select a solvent for use with a corticosteroid, and there is no basis to select diethyl sebacate from the broad class of sebacates disclosed in that patent. (Tr. 560:24-561:12.) Blum taught away from the lower HP concentration. (Tr. 561:9-12.) The combination of the '295 patent and Blum does not disclose .01% HP, diethyl sebacate, light mineral oil, or exclusion of white petrolatum, and there would not be a reasonable expectation of success as to efficacy or use longer than two weeks. (Tr. 561:18-562:2.) The '566 patent focuses on dibutyl adipate and isopropyl myristate, which are not sebacates; there is no reason to combine it with the '295 patent that describes dialkyl sebacate. (Tr. 563:5-13.) No one has ever used dibutyl adipate and isopropyl myristate in a commercial HP product. (Tr. 563:18-21.) Nor would there be a motivation to combine JP 228, which discloses formulations for corticosteroids generally, but not HP. (Tr. 564:19-22.) The

Ultravate® label does not disclose use of HP for four weeks, as the Temovate® label does. (Tr. 566:3-6.) The Temovate® label teaches away from the Bryhali® patents by providing a different solution to the two-week limitation problem. (Tr. 566:7-9.)

Combination products are more difficult to formulate, as the skin has a finite capacity to take in drugs. (Tr. 568:15-18.) There are even more interactions to consider in formulating a combination product. (Tr. 568:22-25.) The '824 Publication does not refer to a combination product, and there is no reason why a POSA would have been motivated to modify it. (Tr. 571:14-17.) The prior art does not provide a reasonable expectation that tazarotene could be dissolved in the liquid oil portion of the formulation in the '824 Publication; a POSA would have to test that. (Tr. 571:20-572:19.) Dr. Pillai said that, during formulation, they had a problem dissolving tazarotene in dibutyl sebacate; they did not know that would happen and discovered it by testing. (Tr. 573:1-12.) The '824 Publication describes a series of formulations, but only two of them fall with the scope of the Duobrii® patent claims. (Tr. 574:2-4.) The '824 Publication discusses a huge range of monocarboxylic and dicarboxylic acid esters, and the Duobrii® patents disclose only diethyl sebacate. (Tr. 574:13-19.) The '824 Publication discloses eight different lipophilic liquids, while the Duobrii® patents only refer to one, light mineral oil. (Tr. 574:20-575:2.) The '824 Publication discloses five superpotent corticosteroids; the Duobrii® patents refer to only one. (Tr. 575:3-8.) The '824 Publication discloses formulations of lotions, gels, creams, and ointments, while the Duobrii® patents refer only to a lotion. (Tr. 575:9-14.) A POSA would understand the Court's construction of "liquid oil component." (Tr. 575:23-576:13.) SMO falls within the Court's construction of "liquid oil component." (Tr. 577:5-7.) A POSA would understand the figures in Table 2 to reflect that

SMO is not a solvent for HP. (Tr. 579:3-8.)

On cross-examination, Dr. Lane agreed that Table 2 excludes SMO from the calculation of the “liquid oil component.” (Tr. 580:11-14.) At claim construction, Dr. Lane submitted a declaration stating that a POSA could not reconcile Table 2 with Perrigo’s proposed construction of “liquid oil component.” (Tr. 581:14-23.) Table 2 shows no express limitation to solvents. (Tr. 582:2-8.) The specifications of the ’307 and ’502 patents are not limited to only superpotent corticosteroids. (Tr. 586:7-16.) Blum states that, in order to develop a dermatological preparation, it is most important to conduct double-blind trials to find the right concentration in the treatment of patients with psoriasis. (Tr. 596:11-22.) Solvents do not always act as penetration enhancers; sometimes they do, other times they do not. (Tr. 602:6-10.) The vehicle in Table 4 of the ’824 Publication is the same as the vehicle in Duobrii®, and formula 4A describes the formulation of Bryhali®. (Tr. 611:3-17.) Solubility testing is a standard test for pharmaceutical scientists and important to conduct. (Tr. 612:10-20.)

On redirect examination, Dr. Lane stated that, in addition to dissolving a superpotent corticosteroid in an oily solvent, one could also formulate a product as a suspension. (Tr. 614:9-18.) All the experiments in the ’566 patent focus on measuring transdermal permeation, all the way through the skin into the blood stream. (Tr. 615:5-9.) Broad ranges do not teach a POSA to use any steroid at any concentration in the range; one has to experiment and do testing, as there are no routine outcomes. (Tr. 615:16-24.) In the Bryhali® patents, the vasoconstriction data in Table 3 supports the inventor’s hypothesis of preferential delivery: it clearly shows that the low-concentration formulations localize the drug in the skin, while Ultravate® has the same local score but the rest of the Ultravate® is going all the way through the skin. (Tr. 615:24-

616:16.)

On recross examination, Dr. Lane stated that the Bryhali® patents contain no measurement of systemic absorption. (Tr. 617:22-618:5.)

H. Additional Testimony of Linda Stein Gold

What follows is a summary of the witness's testimony. Dr. Stein Gold stated that a POSA reducing the concentration of a corticosteroid below .05% would not have any expectation that it would work, or that .01% HP would have similar efficacy to full-strength HP. (Tr. 619:25-620:6.) A POSA would not have expected to be able to use a superpotent steroid for any period approaching eight weeks. (Tr. 620:7-8.) A POSA would not have been motivated to make a fixed combination because of the difficulty. (Tr. 620:22-24.) Lotion formulations are among the least efficacious formulations. (Tr. 620:25-621:2.) Nothing in the prior art regarding HP and tazarotene taught anything about the synergy limitations being discussed here, and so a POSA would have had no motivation to try to achieve synergy. (Tr. 621:16-21.) As of 2010, the gold standard topical treatment for psoriasis was superpotent steroids. (Tr. 623:1-3.) But there were "a whole host" of other topical therapies, including one retinoid, tazarotene. (Tr. 623:9-25.) Tazarotene was so irritating that it was rarely prescribed. (Tr. 624:11-14.) In 2010, the POSA would have believed that the concentration of HP had been optimized. (Tr. 625:12-15.) A POSA would have believed that lowering the concentration of HP would have made it less efficacious as a treatment, and there was no evidence of good efficacy from using a concentration of HP lower than .05%. (Tr. 625:16-22.) Changing the vehicle can strengthen or weaken the potency of a drug. (Tr. 627:14-17.) For example, depending on the vehicle, a betamethasone propionate formulation can range in potency from Class 1 to Class 5. (Tr.

627:22-628:3.) Lotion formulations are often weaker than ointments because they are less occlusive. (Tr. 628:4-10.) The market has many weaker topical corticosteroids; there is no need for another. (Tr. 628:19-25.) The mainstream opinion in the art was to initially treat patients with the most potent drug, and to use a weaker one after the illness has been brought under control. (Tr. 629:22-24.) The Blum study was not conducted well or explained well. (Tr. 630:10-631:2.) Blum states that, for the severe psoriasis group in the study, the .02% HP was less effective, and one should look at that group to get the most reliable comparison of formulations. (Tr. 631:14-18.) Blum explains that the lower concentration produced a higher incidence of local side effects than the higher concentration did. (Tr. 632:5-12.) The effectiveness of Bryhali® was an unexpected result. (Tr. 634:5-9.) The safety of Bryhali®, which went up such that it could be used for 8 weeks, was unexpected; nothing like that had been seen before. (Tr. 637:6-22.) The Temovate® label warns that patients treated for 4 weeks with the body surface area limitation must be watched for the development of HPA axis suppression. (Tr. 637:23-638:4, 15-19.) The Bryhali® patents satisfied a long-felt need for a treatment that can be safely used for longer than two weeks. (Tr. 638:20-639:9.)

Blum would teach a POSA that there is no benefit to using the lower concentration of .02%. (Tr. 641:6-16.) The Temovate® label teaches that if you use it for longer than two weeks, you have to watch for HPA axis suppression. (Tr. 641:20-25.) Gollnick has two studies which look at combining tazarotene and corticosteroids through alternating administration, which teach that there is a reason not to use these drugs together. (Tr. 647:21-648:9.) The tazarotene package insert shows that reducing the dosage by half, from .1% to .05%, decreases the irritation profile by less than half a percent, which is not accomplishing much; one would not

expect a further 10% reduction to change the irritation profile at all. (Tr. 648:21-649:6.) If one is attempting to reduce the irritating effect of tazarotene, it does not make sense to use a steroid with a dose reduced by 80% to achieve that goal. (Tr. 650:22-651:2.) In the first Gollnick study, the mid- and high-potency steroids performed about the same, which teaches that it's a better idea to use a mid-potency topical corticosteroid. (Tr. 651:12-25.) The second study uses what would be considered low and mid-potency steroids, and would leave a POSA with confusion. (Tr. 652:1-11.)

None of the prior art references teach synergistic efficacy or synergistic reduction of adverse events. (Tr. 655:10-15.) The term "synergy" is used in the literature in two different ways: one meaning complementary or working in harmony together, and one is the meaning being used in this case, the efficacy of the combination is greater than the sum of the efficacies of the two actives. (Tr. 655:16-656:10.) While Gollnick uses the word "synergy," he gives no explanation or data, so a POSA would assume that there it has the meaning of "complementary." (Tr. 658:9-14.) Superpotent steroids produce an effect quickly, but the effect disappears quickly when you stop administering it, while tazarotene has a prolonged effect; so one would not know prior to testing the combination whether it will have a sustained effect. (Tr. 659:21-660:13.) Potent topical steroids can cause stinging and burning; 40% of patients have that with clobetasol spray. (Tr. 662:1-5.) Generally, increases in efficacy are likely to be associated with increases in side effects; you don't expect them to go together. (Tr. 662:18-24.) Gollnick teaches not to use HP and tazarotene at the same time. (Tr. 663:2-6.) Gandhi does not teach anything about synergy. (Tr. 663:7-14.) The Tazorac® label teaches that one would not expect a 10% reduction in concentration to make the irritation any different. (Tr. 663:15-19.)

On cross-examination, Dr. Stein Gold said that the '824 Publication has the same specification as the Bryhali® patents. (Tr. 669:24-670:1.) Nothing in the '307 patent describes using the composition for up to eight weeks. (Tr. 679:5-7.) Two reasons to combine HP and tazarotene are convenience and patient compliance, and could also solve issues relating to layering the products as separate ingredients in separate vehicles. (Tr. 681:15-23.) The Weigle reference teaches use of a corticosteroid to manage local irritation of tazarotene. (Tr. 682:2-24.) Two fixed combination drugs for the treatment of psoriasis show synergy: Duobrii® and Taclonex® (which is the same as Enstilar®). (Tr. 687:22-688:25.) Taclonex® was approved in 2006. (Tr. 689:4-9.) Taclonex® has three formulations, and only the one used in the scalp showed synergy. (Tr. 692:9-12.) It was known prior to 2015 that tazarotene treatment for psoriasis can produce a maintenance effect lasting up to four weeks. (Tr. 705:2-9.) A POSA reading Gollnick would note that the dropout rate for the high-potency steroid was quite high, but much lower for the mid-potency steroid, and conclude that they should use the mid-potency steroid, inasmuch as the two showed similar efficacy. (Tr. 712:19-713:1; 716:7-12.)

On redirect examination, Dr. Stein Gold said that the lack of a finding of statistically significant differences in Blum is not meaningful because it simply shows that the study was underpowered in terms of the number of subjects in each study arm. (Tr. 720:2-721:3.)

I. Testimony of Sean David Sheridan

What follows is a summary of the witness's testimony. Dr. Sheridan stated that Duobrii® was a commercially successful product, as evidenced in over \$30 million in sales in less than three years. (Tr. 733:11-14.) On cross-examination, Dr. Sheridan stated that, from the data he has seen, Bausch has not made a net profit from Duobrii®. (Tr. 747:24-748:4.) He

agreed that the net sales of Duobrii® have declined every year since launch. (Tr. 748:23-749:12.) In a market of three products, Duobrii® had the lowest market share for Q2 2019 through Q2 2021. (Tr. 751:21-24.) On redirect examination, Dr. Sheridan said that a major factor in the decline in sales between 2019 and 2021 was the pandemic. (Tr. 759:7-13.)

J. Testimony of Mickey Aron Ferri

What follows is a summary of the witness's testimony. Dr. Ferri was admitted as an expert in economics. (Tr. 762:19-22.) Duobrii® has had a negative net profit, its annualized sales are declining, sales have failed to meet Bausch's projections by significant margins, its sales are small relative to competitors, and it has a tiny market share. (Tr. 763:9-25.) Duobrii® shows a lack of commercial success. (Tr. 764:12-14.) It is losing money every year. (Tr. 765:8-12.) On cross-examination, Dr. Ferri stated that, in some cases, a product with a 1% market share could be a commercial success. (Tr. 779:11-13.)

K. Deposition Testimony of Arturo Angel

What follows is a summary of the witness's testimony. Dr. Angel stated that he is executive director of Bausch. (Tr. 794:6-10.) A routine step during preformulation involves assessing the solubility properties of compounds of interest in different ingredients. (Tr. 794:14-22.) During the development of Duobrii®, it was decided to reduce the tazarotene concentration from .09% to .045% with the objective of further lowering the prototype's irritation potential. (Tr. 796:21-25.)

DISCUSSION

The parties raised no disputes about the characteristics of the person of ordinary skill in the art ("POSA"); several witnesses testified that their opinions would not change if the

definition of the POSA was that offered by the other side.

I. Invalidity of the '307 and '502 patents

Bausch asserts claims 13, 16, and 20 of the '307 patent and claims 4 and 16 of the '502 patent. Claim 1 of the '307 patent is representative:

1. A pharmaceutical composition for topical application to the skin of an individual comprising halobetasol propionate at a concentration of 0.04% or less and a liquid oil component comprising one or more dicarboxylic acid esters, wherein the dicarboxylic acid esters are selected from diethyl sebacate, diisopropyl adipate, and dibutyl sebacate and wherein at least 25% of the halobetasol propionate is solubilized in the liquid oil component at 22.degree. C.

Claims 13, 16, and 20 from the '307 patent depend on claim 1 and are directed to compositions and methods of treatment using more narrowly-defined formulations. Claim 1 of the '502 patent states:

1. A pharmaceutical composition for topical application to the skin of an individual comprising: a liquid oil component comprising diethyl sebacate and a corticosteroid selected from the group consisting of halobetasol propionate . . . at a concentration less than 0.05%; and an aqueous component comprising water; wherein the composition is free of white petrolatum.

Claims 4 and 16 of the '502 patent depend on claim 1 and disclose a narrower composition and a treatment method using a narrower composition. Claim 16 discloses a method involving treatment for longer than two weeks.

A. Obviousness

The parties agree that the Priority Date for both the '307 and '502 patents is November 22, 2010. Certain fundamental facts about the state of the art as of the Priority Date are undisputed. HP was known in the art as a topical treatment for psoriasis and was commercially available as branded product Ultravate at a concentration of .05%. The category of the most potent corticosteroid topical medications was referred to as “superpotent,” and such medications

were known to have the potential to cause serious systemic side effects, including HPA axis suppression, if too much steroid penetrated a patient's skin and entered the bloodstream. As of 1995, the FDA-approved label for Ultravate warned that it should not be used for more than two weeks. Psoriasis is a chronic condition and there are many cases for which two weeks of treatment does not produce sufficient improvement.

Padagis begins with the problem to be solved, which is clear from these undisputed facts: many psoriasis patients need topical treatment for longer than two weeks, but, because of the systemic side effect of HPA axis suppression, Ultravate could not be used for longer than two weeks.¹ There is no dispute that, as of the Priority Date, the art viewed the SCD problem as an important problem to solve.

Padagis argues that the inventions disclosed in the HP Patent claims at issue are all obvious solutions to the SCD problem. Padagis contends that the parties agree that, as of the Priority Date, "a POSA would have known that the risk of systemic side effects with topical corticosteroids is reduced by lowering the concentration of the steroid." Bausch, however, does not agree. (See, generally, Pls.' Br. at 4-6.) In support of this proposition, Padagis cites the trial transcript as follows: "123:7-14, 166:9-167:10, 673:13-674:6; 794:20-795:4." (Defs.' Br. at 10.) These citations do not provide firm support for that proposition. Padagis cites a snippet of Dr. Pillai's testimony, but overlooks the context: "if you reduce the drug, there is a potential that you will reduce the adverse event in this case." (Tr. 123:7-14.) This was in the context of questions about Bausch's INDA submission to the FDA which, as will be discussed, is not prior

¹ This Opinion will call this the superpotent corticosteroid duration problem (the "SCD problem.")

art, and Dr. Pillai's quoted statement is an interpretation of that document, not a statement about the prior art. Dr. Stern opined that the Temovate E® label teaches lowering the concentration, but pointed only to the disclosure that one can use Temovate E® for longer if you apply much less of it. (Tr. 166:9-167:10.) Dr. Stern pointed to nothing on the Temovate E® label that addresses lowering the concentration of the active to reduce side effects. Dr. Stein Gold stated on cross-examination that "it has been seen with topicals" that lowering concentration would lead to greater safety, but she neither said when this was seen (before or after the Priority Date), nor whether "greater safety" meant "reduced systemic effects." (Tr. 673:13-674:6.) Dr. Angel testified that if you reduce the systemic absorption of corticosteroids, you can potentially reduce side effects. (Tr. 794:24-795:4.) Padagis did not cite any prior art reference in support of the key proposition that lowering the concentration of the corticosteroid was a known solution to the SCD problem. Nor did any witness state that, as of the Priority Date, a POSA would have thought that lowering the concentration of the steroid is a viable approach to solving the problem of systemic side effects with topical corticosteroids. The witness statements cited by Padagis at most may have been in the same ballpark as the key proposition, but none of the cited testimony clearly states that the prior art had the insight that lowering the concentration of a topical corticosteroid would lower the risk of systemic side effects. If this key proposition was truly common knowledge, why did Padagis not offer a reference that stated it? This appears to be the kind of insight that, from the perspective of hindsight, appears to be obvious, but the Court must prevent hindsight from substituting for evidence of what was known in the prior art. Cheese Sys. v. Tetra Pak Cheese & Powder Sys., 725 F.3d 1341, 1352 (Fed. Cir. 2013) ("Among the difficult challenges of applying the doctrine of obviousness is avoidance of even a hint of

hindsight.”)

This is a key point, because the contention that it would have been obvious to a POSA to solve the SCD problem by lowering the HP concentration is critical to Defendants’ theories of obviousness and, contrary to Defendants’ assertion, Bausch does not agree that lowering the concentration was an obvious solution to the SCD problem – Bausch disagrees strongly. Instead, Bausch contends that Dr. Michniak-Kohn “got it right” when she stated: “So the motivation to formulate a lower concentration, to minimize this risk of these side effects, while still maintaining efficacy, would have been a motivation for the POSA.” (Pls.’ Br. at 5; Tr. 331:22-25.) Bausch thus agrees with the proposition that a POSA would have been motivated to solve the SCD problem by lowering concentration *while preserving efficacy*. The problem with the Padagis version of the proposition is that it omits the POSA’s concern about the preservation of efficacy.

In support, Bausch cites the testimony of Drs. Stein Gold and Lane. Dr. Stein Gold testified that she would have expected that reducing the HP concentration from .05% to .01% would reduce the potency from superpotent to midpotent, because efficacy is usually linked to concentration. (Tr. 636:15-637:2.) Dr. Lane was asked about Table 1 in the ’307 patent, which shows five superpotent corticosteroids. (Tr. 485:12-20.) Dr. Lane stated:

Q. In your opinion, would a person of skill in the art in 2010 have thought to experiment with a lower concentration of corticosteroid in order to reduce the side effects that were associated with those high concentration formulations?

A. Yes. So the common wisdom at the time was if you decrease the concentration of a drug in a formulation, you would compromise the efficacy. So you would be worried that this would not be as effective as the formulation with the higher dose concentration. So if you decrease concentration, you decrease efficacy. And because of that, I do not believe that a person of skill in the art, in 2010, would have been motivated to decrease the concentration because we want our

medicines to work. We do not want to decrease their efficacy.

Q. What support do you have for the premise that decreasing the concentration will generally correspond with a decrease in efficacy?

(Tr. 485:25-486:16.) Dr. Lane then discussed Table 1 in the '307 patent and pointed out, in short, that Table 1 evidences a correlation between concentration and potency. (Tr. 486:17-487:14.) Dr. Lane observed that Table 1 shows that .10% fluocinonide is superpotent, .05% fluocinonide is in the potent category, and .01% fluocinonide is in the mild potency category. (Id.) Table 1 appears in the "Background of the Invention" section of the '307 specification. It depicts the state of the art, and it evidences a direct relationship between corticosteroid concentration and potency. Dr. Lane's testimony about Table 1 is persuasive and provides solid support for Bausch's contention that a POSA would have expected that a reduction in corticosteroid concentration would result in a reduction in potency. From this evidence, the Court determines that, before the Priority Date, a POSA would have believed that there was a direct relationship between corticosteroid concentration and potency, and that a reduction in concentration would be associated with a reduction in potency. Furthermore, faced with the SCD problem, a POSA would not have been motivated to create a less effective treatment.²

Defendants' theories do not incorporate this understanding of the efficacy/concentration relationship, nor the concern about preserving efficacy. Padagis writes:

Armed with Blum's teachings on the efficacy of 0.02% HP and the knowledge that reducing corticosteroid concentration lowers the risk of adverse events, a POSA would have been motivated to explore further reductions in HP concentration, including concentrations as low as 0.01%, to minimize the risk of adverse events.

² As Dr. Stein Gold explained, there were many less potent treatments available and it would not make sense to make a new, less potent drug. (Tr. 628:19-629:3.)

(Defs.' Br. at 12.) As the following analysis will show, the evidence offered by Padagis does not support this. The concern about the preservation of efficacy must be considered.

Padagis contends that the asserted claims in the HP Patents would have been obvious to a POSA as of November 2010 in view of four prior art combinations:

- (1) U.S. Patent No. 4,233,295 ("295 Patent") and Blum (all claims);
- (2) the '295 Patent, Blum, and U.S Patent No. 5,326,566 ("566 Patent") (all claims);
- (3) the '295 Patent, Blum, and Japanese Patent App. Pub. No. S63-255228 ("JP '228") (claims 13, 16, and 20 of the '307 patent and claim 4 of the '502 patent); and
- (4) the '295 Patent, Blum, and the Temovate E Label (claim 16 of the '502 patent).

(Defs.' Br. at 9.) All four combinations contain two of the references, Blum and the '295 patent.

Temovate E® (clobetasol priopionate) was another superpotent topical corticosteroid treatment. Like Ultravate, the FDA-approved label for Temovate E® contains a warning about the risk of systemic side effects if used for longer than two weeks: "Patients receiving super-potent corticosteroids should not be treated for more than two weeks at a time, and only small areas should be treated at any one time due to the risk of HPA suppression." (DX-006 at 1.)

Under "Dosage and Administration," the label states:

Temovate E Emollient is a super-potent corticosteroid; **therefore, treatment should be limited to two consecutive weeks and amounts greater than 50g/week should not be used.** In moderate to severe plaque-type psoriasis, TEMOVATE E Emollient applied to 5% to 10% of body surface area can be used up to 4 weeks. The total dosage should not exceed 50 g/week. When dosing for more than 2 weeks, any additional benefits of extending treatment should be weighed against the risk of HPA suppression. As with other highly active corticosteroids, therapy should be discontinued when control has been achieved. If no improvement is seen within 2 weeks, reassessment of diagnosis may be necessary. Treatment beyond 4 consecutive weeks is not recommended.

(Id. at 2.) Dr. Lane pointed out: “The Temovate E® Label actually teaches away from the Bryhali® patents by providing a different solution to the two-week limitation problem.” (Tr. 566:7-9.) Limiting total dosage is not the same as reformulating to lower the concentration of the active.

The Blum reference was published in 1986 in Chinese, with an abstract in English, in the Chinese Journal of Dermatology; Padagis supplied a translation for the Chinese text. (DX-002.)

The abstract states:

A double-blind, randomized multicentre clinical trial was carried out in 336 patients with chronic psoriasis by 21 dermatologists in Germany and Switzerland. The percentages of patients with severe chronic psoriasis showing cure (complete clearance) or marked improvement following treatment with 0.05% CGP 14 458 ointment, 0.02% CGP 14 458 ointment [sic] or Dermovate® ointment for up to 25 days were 90%, 77% and 80% respectively. Adverse effects were reported at the site of application in 4%, 5% and 6% of the patients treated with 0.05% CGP 14 458 ointment, 0.02% CGP 458 ointment and Dermovate® ointment, respectively. No clinically detectable systemic adverse effects were observed. Cosmetic acceptability and ease of application of the three trial preparations were practically identical. 0.05% CGP 14 458 proved more effective than Dermovate® ointment, the most potent corticosteroid topical presently used worldwide in clinical practice. Therefore, 0.05% CGP 14 458 ointment would be a welcome addition to the therapeutic armamentarium for chronic, localized, severe or recalcitrant dermatoses.

(DX-002 at 3.) The article, by way of introduction, states: “The efficacy of corticosteroid dermatological preparations mainly depends on the proportion of its active ingredient, its effectiveness and extent of its intradermal penetration.” (Id. at 4.) The study compared the efficacy of ointments containing .05% HP, .02% HP,³ and clobetasol propionate .05% (marketed as Dermovate®). (Id.) The results are summarized in the abstract, quoted above. Discussing the results, the article states that the HP .05% ointment was more effective than Dermovate®,

³ The article does not state that CGP 14 458 is HP, but the parties agree that this is the case.

and finishes with this paragraph:

Therefore the 0.05% CGP 14 458 ointment will provide a favorite treatment weapon for chronic, localized, severe, or refractory skin diseases that have effect with corticosteroids. In the treatment of severe chronic psoriasis vulgaris, the ointment with the lower concentration (i.e., 0.02% CGP 14 458) was less effective than that with concentration of 0.05% and Dermovate ointment. However, the difference among the 3 groups was not statistically significant. The severe chronic psoriasis is the most reliable measurement for comparing efficacy. Not only it can be compared for highly effective corticosteroids, but it is very reliable for comparing the efficacy of different concentrations of drugs in prescriptions as well. In order to get the best efficacy, a dermatological preparation needs to contain the appropriate concentration of active ingredient. Therefore, just like finding the dose for a systemic medication, in order to develop a dermatological preparation, it is most important to conduct double blind trials to find the right concentration in the treatment of patients with chronic plaque psoriasis.

(Id. at 5-6.)

Padagis views Blum as providing a cornerstone for its obviousness case, and sums up its view of Blum as follows:

Armed with Blum's teachings on the efficacy of 0.02% HP and the knowledge that reducing corticosteroid concentration lowers the risk of adverse events, a POSA would have been motivated to explore further reductions in HP concentration, including concentrations as low as 0.01%, to minimize the risk of adverse events. Given Blum's teaching that reducing the concentration of HP by 60%, from 0.05% to 0.02%, resulted in only a minor difference in efficacy, a POSA would have reasonably expected concentrations of HP as low as 0.01% to remain efficacious.

(Defs.' Br. at 12 (citations omitted)). This reading of Blum finds no support in the text and is contrary to what Blum wrote, as just quoted. Blum's conclusion emphasizes the importance of finding the "appropriate concentration of active ingredient" through double blind trials. Defendants' reading of Blum entirely negates this. There is nothing in the text of Blum that states that .02% is the appropriate concentration, and there is nothing that says or suggests that the difference in efficacy was "only a minor difference." The text supports neither that

characterization nor such an inference. The text, instead, supports the inference that .05% HP is “the right concentration.”

Defendants’ contention that Blum teaches that there is “only a minor difference” in efficacy between the .05% HP formulation and the .02% HP formulation – which this Court has just found entirely unsupported by the text – is fundamental to Defendants’ case for the obviousness of the HP Patents. There is nothing in the text of Blum that would have motivated a POSA to lower the concentration of HP below .05% in a formulation for the treatment of psoriasis.

In support, Padagis quotes and cites two cases which work against it:

Even if Blum expressed a preference for the 0.05% HP ointment, it is well established that “just because ‘better alternatives’ may exist in the prior art does not mean that an inferior combination is inapt for obviousness purposes.” Dome Patent L.P. v. Lee, 799 F.3d 1372, 1381 (Fed. Cir. 2015) (internal quotations omitted); In re Mouttet, 686 F.3d 1322, 1334 (Fed. Cir. 2012).

(Defs.’ Br. at 11-12.) In the cited sentence in Dome Patent, the Federal Circuit quotes Mouttet.

Here is the cited paragraph of Mouttet:

In *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994), we emphasized that “[a] reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant.” Thus, the “mere disclosure of alternative designs does not teach away.” *In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004). This court has further explained that just because better alternatives exist in the prior art does not mean that an inferior combination is inapt for obviousness purposes. *Gurley*, 27 F.3d at 553.

In re Mouttet, 686 F.3d 1322, 1333-34 (Fed. Cir. 2012). The point the Federal Circuit is making here is more clearly expressed in the sentence preceding the one quoted in Dome Patent: “mere disclosure of alternative designs does not teach away.” Thus, a reference that both discloses an

inferior design and also does not teach away from that design may not discourage a POSA from following that path. Here, in contrast, the Blum reference expressly teaches away from the .02% HP formulation and cannot be fairly described as a mere disclosure of an inferior design that does not teach away from that design. Padagis has built its case that the HP Patent claims are obvious on a reference that teaches away from the path Padagis contends is the obvious one.

Defendants' expert Dr. Stern was the first expert to testify about Blum, and the first to point out "only a 9% reduction in efficacy." (Tr. 164:1-5.) He then stated:

My opinion is that this work that shows one could reduce the concentration of halobetasol by 60 percent and lose very little, if any, efficacy in the treatment of psoriasis would have motivated an individual to further reduce the concentration with the expectation that all or most efficacy would be -- would be preserved.

(Tr. 165:4-9.) On cross-examination, Dr. Stern acknowledged Blum's preferential statements about the .05% HP treatment, leading to this exchange:

Q. Blum doesn't say that about the 0.02 percent concentration, does he?

A. He says that there's no difference in --

Q. Sir, I just want to know. He doesn't say that about the 0.02 --

A. You're right.

(Tr. 210:14-19.) Confronted with the text of Blum, Dr. Stern attempted to say that Blum found no difference between .05% HP and the .02% HP, which is unsupported by the text.⁴ In attempting to justify his view of Blum, Dr. Stern stated: "Blum, that says you don't lose that much in efficacy," which is unsupported by the text. (Tr. 212:15.) The Blum reference does not contain the statements that Dr. Stern attributes to it.⁵

⁴ Blum found no statistically significant difference, but the reference does not say there is no difference.

⁵ The facts of the Blum reference are different. In the concluding paragraph, Blum states, as already quoted: "The severe chronic psoriasis is the most reliable measurement for comparing efficacy." (DX-002 at 6.) Blum's data tables show that, for the severe psoriasis group, the

On direct examination, Dr. Michniak-Kohn made similar statements about Blum, looking at the experimental group that Blum said has the less reliable efficacy measurement, and saying that “it went down only to 81.4,” which was “a pretty good number” and “still effective.” (Tr. 324:20-325:15.) She stated:

As we saw from the last table, the absolute number was a little lower. However, what they found was that the difference among the three groups was not statistically significant. And that’s important to the POSA. He’s getting the message, or she’s getting the message, that going down in the concentration to 0.02 halobetasol propionate was effective in treating psoriasis in these patients and in this multicenter trial.

(Tr. 326:2-9.) The Court did not discern the same message in Blum that Dr. Michniak-Kohn did, and concludes that the text does not support her opinion about what message a POSA would have gotten from the Blum reference. She further stated:

[The POSA] would have also had Blum. And from that they would have known that 0.02 halobetasol was effective in treating psoriasis. We just saw that in the last few slides. And it would have provided the POSA a motivation to formulate a lower dose of halobetasol formulation with an expectation of success.

(Tr. 330:20-25.) On cross-examination, Dr. Michniak-Kohn acknowledged that Blum had recommended the .05% HP concentration, and Blum also said that the .02% HP formulation would be less effective. (Tr. 407:4-9.) She also agreed that “a POSA would ignore Blum’s recommendation and rely on the Blum article as a motivation to pick a lower concentration.”

(Tr. 408:8-12.) Dr. Michniak-Kohn provided no persuasive justification for this assertion.

significant or cured percentage for the .05% HP was 89.7%, and for the .02% HP was 76.8%. (DX-002 at 5.) The “9% difference” figure that Defendant points to does not derive from the severe psoriasis group that Blum says provides the most reliable efficacy measurement. Rather, the most reliable measurements, according to Blum, are roughly 77% and 90%. Nowhere in the reference does Blum characterize this as “no difference” or “you don’t lose that much in efficacy” or a “minor” reduction.

Plaintiff's expert Dr. Lane testified and responded to Dr. Michniak-Kohn's testimony. Dr. Lane opined that Blum teaches away from using the .02% HP ointment and recommends the .05% concentration. (Tr. 500:12-15; 560:9-10.) Dr. Lane described Blum as "effusive" in its findings about the .05% HP treatment. (Tr. 500:16.) The text of Blum supports Dr. Lane's opinions.

Plaintiff's expert Dr. Stein Gold testified and responded to the testimony she had heard. She stated that Blum was not a well-run study, that the reference does not explain the research procedures used, and that Blum recommends the .05% HP formulation. (Tr. 630:11-631:6.) Dr. Stein Gold noted that Blum stated that the severe category provides the most reliable measurement of efficacy, and it shows lower efficacy for the .02% formulation. (Tr. 631:7-20.) She stated that Blum discloses that the lower concentration had a higher rate of local side effects than the .05% HP had. (Tr. 632:2-12.) Dr. Stein Gold concluded that Blum gave her no reason to use a .02% HP concentration. (Tr. 632:21-22.) On redirect examination, Dr. Stein Gold stated that the finding of no statistically significant difference in efficacy between the treatment arms reflected the relatively small size of the study, with small numbers of patients in each treatment arm; it was an "underpowered" study. (Tr. 720:2-721:3.) Dr. Stein Gold stated that, for those reasons, the absence of statistically significant differences in efficacy was not meaningful to her, except insofar as it reflected that the study was underpowered. (Tr. 720:25-721:3.) The text of Blum supports Dr. Stein Gold's opinions.

Considering all the evidence, the Court finds that the opinions of Drs. Lane and Stein Gold are well-supported by the text of Blum and deserving of weight, while the opinions of Drs. Stern and Michniak-Kohn are poorly supported by Blum and deserving of little weight. The

Court concludes that the Blum reference taught away from using .02% HP for the treatment of psoriasis and would have motivated a POSA to use a .05% HP formulation for maximum efficacy. Blum would have discouraged a POSA from reducing the concentration of a HP treatment below .05%. Dr. Stern's contentions that Blum teaches no difference between the levels of efficacy or "you don't lose that much in efficacy" have no support in the text of the reference. Defendants' interpretation of the Blum reference attempts to contradict the clear, express teaching of the reference that the .05% HP formulation would be "a favorite treatment weapon" for psoriasis. (DX-002 at 5.) Similarly, Dr. Michniak-Kohn's attempt to frame the efficacy of the .02% HP formulation as "a little lower" is not supported by the text of the reference. Dr. Michniak-Kohn admitted that it was her opinion that a POSA would have ignored Blum's recommendation of the .05% HP formulation and instead would have been motivated by Blum to pick a lower concentration; the Court finds this reasoning unsupported and not credible.

The Court found the testimony of Drs. Lane and Stein Gold about the teachings of Blum much more persuasive. As these experts said, Blum would not have motivated a POSA to use the lower concentration of HP as a treatment for psoriasis; it is clear that Blum favored a more effective treatment over a less effective one. Dr. Lane was persuasive that Blum taught away from reducing the concentration of a HP treatment for psoriasis below .05%. As will be seen in the discussion that follows, Defendants' case for the obviousness of the HP Patents has Blum as one of its cornerstones, and none of Defendants' HP Patent obviousness theories or combinations of prior art can survive the Court's determinations about the teachings of Blum.

The next problem in Defendants' case for the obviousness of the HP Patents concerns the

selection of diethyl sebacate as a solvent. Padagis proposes three combinations of prior art that, it contends, render claims 13 and 16 of the '307 patent⁶ obvious: 1) Blum and the '295 patent; 2) Blum, the '295 patent and the '566 patent; and 3) Blum, the '295 patent, and JP 228. The '295 patent, the '566 patent, and JP 228 have in common an interest in solvents for use in topical formulations (collectively, the "Solvent References.")

The '295 patent, issued in 1980, discloses topical corticosteroid formulations in which the corticosteroid is dissolved in a dialkyl sebacate carrier, wherein the alkyl contains 1 to 10 carbon atoms. '295 patent, col.1 ll.40-44. Dr. Michniak-Kohn stated that diethyl sebacate is the dialkyl sebacate with two carbon atoms. (Tr. 328:20-25.) She also stated that "selection of the diethyl sebacate would have been a matter of routine optimization based on the solubility of the corticosteroid." (Tr. 329:9-11.) Dr. Michniak-Kohn cited a statement in the '295 patent about drug delivery:

To be therapeutically effective, the active ingredient preferably should be in a molecular dispersion to facilitate desired percutaneous absorption which is particularly important in achieving a therapeutic response for the management of psoriasis.

'295 patent, col.1 ll.12-16; (cited at Tr. 330:9-14.) Dr. Michniak-Kohn then stated:

So a POSA would have also had a reasonable expectation that solubilizing halobetasol in a dialkyl sebacate, as taught by the '295 patent, would have improved the release of halobetasol from the formulation and improved the penetration into the skin.

(Tr. 330:15-19.) A little later, she again stated that the '295 patent is "directed to improving

⁶ Claim 13 of the '307 patent requires, *inter alia*, a liquid oil component comprising diethyl sebacate. Claim 16 is a method claim requiring providing a composition comprising a liquid oil component comprising one or more dicarboxylic acid esters, wherein one of the esters are selected from diethyl sebacate, diisopropyl adipate, and dibutyl sebacate.

release and/or penetration of corticosteroids from topical formulations.” (Tr. 342:20-23.)

The abstract of the '566 patent states:

The present invention relates to composition and methods for enhancing and/or controlling epidermal, dermal and transdermal penetration of topically applied pharmacologically active agents by use of dibutyl adipate, or a mixture of dibutyl adipate and isopropyl myristate.

The specification of the '566 patent makes clear that penetration enhancers are valuable components of topical formulations aimed at delivery of the active to systemic circulation, as well as topical formulations aimed at delivery to various layers of the skin:

It is also an object of the present invention to provide a novel agent which will enhance and/or control epidermal and dermal absorption of dermatological agents (that is, drugs affecting skin to give a cosmetic or therapeutic benefit) and enhance and/or control delivery of *systemically active* therapeutic agents through the skin and *into the general circulation*.

'566 patent, col.4 ll.1-7 (italics added.)

Dr. Michniak-Kohn stated that dibutyl adipate is a dicarboxylic acid ester.⁷ (Tr. 337:4-5.) She noted that a number of examples in the '566 patent disclose formulations in which HP is the active, and that the corticosteroid is dissolved in a liquid oil phase containing dibutyl adipate or dibutyl adipate and isopropyl myristate, which solubilize the steroid. (Tr. 338:5-21.) Dr. Michniak-Kohn did not opine on aspects of the patent related to delivery of the active into systemic circulation.

⁷ Curiously, Padagis, in its opening post-trial brief, states: “The '566 Patent teaches that use of dicarboxylic acid esters, such as dibutyl adipate or dibutyl adipate and isopropyl myristate, ‘enhance and control the epidermal, dermal, and transdermal penetration of corticosteroids . . .’” (Defs.’ Br. at 14.) The '566 patent does not contain the phrase, “dicarboxylic acid esters.” To the extent that a POSA would understand the '566 patent to teach the use of that genus, dicarboxylic acid esters, as penetration enhancers, as Padagis contends, the '566 patent teaches that they enhance delivery into systemic circulation and thus teaches away from their use for the SCD problem.

JP 228 is a Japanese patent publication, published in 1988; Padagis submitted it with a translation into English. (DX-005.) JP 228 teaches the formulation of steroid creams that have good drug release behavior and transdermal absorption, containing a solvent selected from diisopropyl adipate, diethyl sebacate, and triacetin. (DX-005 at 10.) Dr. Michniak-Kohn, discussing JP 228, said that “transdermal” had different meanings in the art, but a POSA would know that JP 228 did not involve systemic absorption; the reference talks about delivery to the skin layers.⁸ (Tr. 341:3-20.)

Padagis contends that the prior art knew about the use of dicarboxylic acid esters, including diethyl sebacate, as solvents for corticosteroids in topical preparations. The Solvent References support this. On this foundation, Padagis proposes the combinations of Blum and the Solvent References, and argues that the combination of Blum, the ’295 patent, and one of the Solvent References would have motivated a POSA “to formulate a lower concentration HP composition with a ‘liquid oil component’ as claimed in claims 13 and 16 of the ’307 patent.” (Defs.’ Br. at 14.)

It is a big leap from the factual determination that the prior art knew about diethyl

⁸ Contrary to Dr. Michniak-Kohn’s testimony that a POSA would know that “transdermal” in JP 228 does not refer to systemic absorption, Defendants’ post-trial brief refers to “transdermal delivery through the skin and into systemic circulation.” (Defs.’ Br. at 23.) Defendants’ brief also states that the ’566 patent teaches the use of dicarboxylic acid esters to enhance transdermal penetration of corticosteroids. (Defs.’ Br. at 14.) The title of the ’566 patent includes the phrase, “transdermal products” and states: “many investigators have used the transdermal route to deliver the therapeutically active agent into systemic circulation.” ’566 patent, col.1 ll.49-51. Defendants’ brief also states: “JP ’228 teaches that the formulations of the invention exhibit ‘good drug release behavior and transdermal absorption. . .’” (Defs.’ Br. at 15.) JP 228 repeatedly refers to the “transdermal absorption” of the invention. (See, e.g., DX-005 at 15.) It is surprising, then, that, on the next page, Defendants’ brief states: “Padagis’s Prior Art Does Not Focus On Transdermal Delivery Through The Skin,” when the brief has just asserted that two of the Solvent References *do* teach transdermal delivery. (Defs.’ Br. at 16.)

sebacate as a solvent for corticosteroids in topical preparations to the conclusion that a POSA would have been motivated to formulate a lower concentration HP composition with a liquid oil component comprising diethyl sebacate. Setting aside for the moment the Court's determination that Blum would not motivate a POSA to make a HP formulation with a concentration lower than .05%, Padagis has offered no theory of how and why the POSA would have selected these prior art references from the other teachings in the prior art about solvents for corticosteroids in topical preparations. And there are more problems here than just that one, as Dr. Lane explained.

Dr. Lane discussed the three Solvent References and viewed them differently from Dr. Michniak-Kohn. One important difference was that Dr. Lane addressed the question of whether a POSA would have been motivated to consider and combine the references, whereas Dr. Michniak-Kohn did not opine on the question of how and why a POSA working to solve the SCD problem would have picked these references in searching for a solution. Dr. Lane stated that the '295 patent, the '566 patent, and JP228 taught the use of penetration enhancers for topical corticosteroids. (Tr. 490:5-10.) She said that the '566 patent taught the use of dibutyl adipate or dibutyl adipate and isopropyl myristate as penetration-enhancing agents. (Tr. 490:11-17.) Dr. Lane stated that the '295 patent aims "to develop formulations for percutaneous delivery, so delivery all the way through the skin." (Tr. 490:18-20.) She said that JP 228 addresses the problem that prior topical formulations of corticosteroids showed inadequate transdermal absorption, meaning "all the way through the skin." (Tr. 490:21-25.)

Dr. Lane then discussed the three Solvent References together and stated:

These are old references. Now, one reference was 1980, I think one of them was 1988 and the other was 1994. So that reflected the understanding in the field that

the way to succeed with your formulation is to push it all the way through the skin. But science moves on, especially the field of topical formulation. So since those 1980s and 1990s references, we understand that our goal is actually more subtle than that. To treat a skin disease, we have to try and localize the drug in the skin. We do not want to push it all the way through the skin. So the inventors of the Bryhali® patents have explained they want to achieve localized delivery. So to the skin, not through the skin.

(Tr. 491:6-21.) Thus, Dr. Lane opined, the three Solvent References share an outdated approach to improving the efficacy of a topical corticosteroid preparation: “back then, the field and scientists in the field thought if we push it all through, then we are making a super effective formulation.” (Tr. 493:5-7.) The inventors of the HP Patents, Dr. Lane stated, solved the SCD problem in a different way, not by pushing the active all the way *through* the skin, but by delivering it preferentially *to* the skin. (Tr. 492:1-10.)

Dr. Lane opined that there was no motivation for a POSA to look to a 30-year old reference, the '295 patent, to find an oily solvent “from the whole universe of other solvents disclosed in the art.” (Tr. 561:2-3.) There is also no motivation to select diethyl sebacate from the genus of sebacates disclosed in the '295 patent. (Tr. 561:11-12.) Nor is there any basis for a POSA to have a reasonable expectation of success in combining HP .01% with a sebacate solvent from the '295 patent to create a formulation that could be used for longer than two weeks. (Tr. 561:22-562:2.)

As to the '566 patent. Dr. Lane stated that it does not disclose a sebacate, and there is no motivation to combine it with the '295 patent, which does disclose sebacates. (Tr. 563:7-13.) Dr. Lane also noted that the '566 patent is discussed in the specifications of the HP Patents. (Tr. 501:10-11.) The specification of the '307 patent states:

Parab, U.S. Pat. No. 5,326,566, in contrast to the disclosure of Busse which discloses that a high concentration oily phase will decrease systemic absorption of

a corticosteroid when applied to the skin, discloses that, when a formulation contains a skin penetration enhancing amount of dibutyl adipate or a mixture of dibutyl adipate and isopropyl myristate at a concentration that is sufficient to dissolve the corticosteroid in the formulation but which is less than 1.5 times that which is required to dissolve the corticosteroid, the penetration of the corticosteroid through skin and into the systemic circulation is increased rather than decreased. Thus, Parab discloses that formulations containing a corticosteroid and an oily phase containing dibutyl adipate, alone or in combination with isopropyl myristate, at a concentration between 1 and 1.5 times that required to dissolve the corticosteroid are useful for increasing the systemic absorption of a topically applied corticosteroid.

'307 patent, col.3 ll.28-44. The inventors clearly state that the '566 patent discloses formulations that are useful for increasing the systemic absorption of a topically applied corticosteroid. As has been established, the inventors viewed systemic absorption of superpotent corticosteroids as undesirable and a key problem to be solved. This leads to the conclusion that the inventors would have understood the '566 patent to teach away from the inventions of the HP Patents, since it teaches ways to increase systemic absorption, which the inventors viewed as problematic.

As already discussed, because the Court concludes that Blum teaches away from the claims at issue in the HP Patents, none of Defendants' theories of obviousness can succeed. Nonetheless, the Court will consider the Solvent References in relation to Defendants' obviousness theories. The experts, Dr. Michniak-Kohn and Dr. Lane, offered essentially opposing testimony about whether a POSA would have been motivated to combine any of the Solvent References with Blum, leading to the inventions in the HP Patents, with a reasonable chance of success.

Dr. Lane raised a number of questions and objections to Dr. Michniak-Kohn's testimony. First, Dr. Lane questioned why a POSA would have picked the '295 patent and dialkyl sebacates

as solvents out of the universe of solvents for topical corticosteroids known in the art as of the priority date. (Tr. 560:21-561:3.) Plaintiffs' post-trial brief asserts "an incalculable number of references that describe solvents dissolving corticosteroids" – but offers nothing in support. Unfortunately, neither side provided evidence of how large or small the universe of solvents for topical corticosteroids, or references disclosing those solvents, actually was as of the Priority Date.

Plaintiffs aptly cite the Federal Circuit's decision in Unigene Labs., Inc. v. Apotex, Inc., 655 F.3d 1352, 1360 (Fed. Cir. 2011), which held:

Obviousness requires more than a mere showing that the prior art includes separate references covering each separate limitation in a claim under examination. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418, 127 S. Ct. 1727, 167 L. Ed. 2d 705 (2007). Rather, obviousness requires the additional showing that a person of ordinary skill at the time of the invention would have selected and combined those prior art elements in the normal course of research and development to yield the claimed invention.

This is right on point. Although Padagis did not find separate references covering each limitation in the HP Patent formulation claims, it did find references disclosing HP as a treatment for psoriasis, and JP 228 teaches the use of diethyl sebacate as a solvent for topical corticosteroid creams. Padagis has not, however, made the additional showing that a POSA at the time of the invention would have selected JP 228, and then selected diethyl sebacate out of the three solvents taught by JP 228, to combine with HP. Nor has Padagis shown that a POSA would have selected the '295 patent, and then diethyl sebacate out of the ten dialkyl sebacates disclosed, to combine with HP.⁹

⁹ As to the '566 patent, the evidence of record (from both Dr. Lane's testimony and the statements of the inventors in the specification of the HP Patents) demonstrates that a POSA would not have selected this reference to combine because of its teaching that its solvents

The third major problem with Defendants' case for the obviousness of the HP Patents is that it seems to wander off the track of the problem to be solved.¹⁰ As already established, the problem to be solved was the limitation on duration of treatment with superpotent corticosteroids due to the systemic effect of HPA suppression. The specification of the HP Patents makes clear that this is the problem that the inventors sought to solve, and Padagis builds its case for the obviousness of the HP Patents on this premise: "a POSA would have been motivated to reduce the concentration of HP below 0.05% to reduce the risk of systemic side effects and enable treatment for periods longer than two consecutive weeks." (Defs.' Br. at 10.) The next step for Padagis is to bring the Blum reference into the theory. Setting aside for the moment this Court's rejection of Defendants' reading of the Blum reference, the following step for Defendant involves finding diethyl sebacate in the Solvent References. Defendants' analysis at the solvent step is very problematic and appears to have lost track of the problem to be solved. This is shown most clearly in Defendants' choice of the '566 patent, which teaches using a dicarboxylic acid ester to *increase* systemic delivery, which appears to be exactly the wrong direction for solving the SCD problem. As to the '295 patent and JP 228, the Court is persuaded by Dr. Lane's testimony that these references teach the use of solvents as penetration enhancers with the effect of increasing drug delivery through the skin. This supports the proposition that a POSA reading the Solvent References before the priority date of the HP Patents would have at least been concerned about the potential for these solvents to increase systemic delivery and thereby

increased systemic absorption, which would have worsened the SCD problem, not remedied it.

¹⁰ In KSR, the Supreme Court held that courts should not restrict the inquiry to the particular problem the patentee was trying to solve. 550 U.S. at 420. Here, however, Padagis has used the same problem as the starting point for its theories.

worsen the SCD problem. Padagis, however, once it has arrived at the step of solvent selection in its obviousness theories, appears to have forgotten about the problem to be solved, and provides no reasoning about why a POSA would have been motivated to use diethyl sebacate, a penetration enhancer, despite the possibility that it might increase penetration all the way into the bloodstream and increase systemic effects. In other words, the Court is not persuaded that a POSA would have been motivated to solve the SCD problem by means of a formulation containing a penetration-enhancing solvent with a superpotent corticosteroid, in the absence of some reason to believe that the penetration enhancer would not increase systemic delivery and HPA suppression.

The Court thus finds serious problems with Defendants' obviousness theories regarding the knowledge and motivation of the prior art POSA. The Court therefore need not reach the issues of the reasonable expectation of success, but, in short, Padagis was not persuasive on that subject either. Bausch, in its opening post-trial brief, cited Dr. Lane's testimony about "the unpredictability of the field." (Tr. 481:9.) Dr. Lane's view was fully supported by Dr. Pillai's testimony about the development process for Duobrii®, summed up in this exchange:

Q. Did you envision what was going to work when you first started the project?

A. No, absolutely not.

(Tr. 66:18-20.) For example, Dr. Pillai testified about one step in the Duobrii® development process, the solubility studies:

So if the drug needs to be in a solution, we need to assess what would be good solvents to keep the drug in solution. And so that's why we ran these solubility studies. And our goal was to keep it in solution.

BY MR. BRUNO:

Q. Did you know what the values on the right-hand column were going to look

like before you actually conducted the studies?

A. No. We had no idea what it would turn out to be.

(Tr. 72:13-21.) As to the tazarotene solubility studies, Dr. Pillai stated: “There's no way we could have predicted these numbers.” (Tr. 73:8-12.) He also characterized the results of the solvent compatibility studies as “extremely surprising.” (Tr. 76:7.) The same was true for the VCA testing. (Tr. 80:9-18.) In response, Padagis argued that Drs. Lane and Pillai are not credible, but the Court disagrees. The evidence of record supports the conclusion that drug development is highly unpredictable for the POSA.

Defendants have offered theories of obviousness of the claims of the HP Patents at issue that all have a number of serious deficiencies. For the reasons stated above, this Court finds that Padagis has misread the prior art references or overlooked their full significance, has failed to demonstrate a motivation to combine those references, and has failed to demonstrate that a POSA combining them to create the patented invention would have had a reasonable expectation of success.

1. Secondary considerations

Padagis contends that lack of commercial success, lack of unexpected results, and lack of a long-felt but unmet need constitute secondary considerations which support a finding that the claims at issue are obvious. Both Bryhali® and Duobrii® are embodiments of the HP Patents. As to lack of commercial success, Padagis asserts that, as to Bryhali®, Bausch does not claim commercial success and, as to Duobrii®, Bausch’s evidence shows no success. In rebuttal, Bausch argues that: 1) Bryhali® satisfied the long-felt but unmet need for a superpotent corticosteroid that could be safely used for longer than two weeks; 2) Bryhali® demonstrated

unexpected results over Ultravate; and 3) Duobrii® is a commercial success. Bausch did not contest Defendants' assertion that it does not claim commercial success for Bryhali®, and so the Court finds no evidence to support a finding that Bryhali® is commercially successful. As to the dispute over the commercial success of Duobrii®, Bausch cites the Federal Circuit's decision in Chemours:

“When a patentee can demonstrate commercial success, usually shown by significant sales in a relevant market, and that the successful product is the invention disclosed and claimed in the patent, it is presumed that the commercial success is due to the patented invention.”

Chemours Co. FC, LLC v. Daikin Indus., 4 F.4th 1370, 1378 (Fed. Cir. 2021) (quoting J.T. Eaton & Co. v. Atl. Paste & Glue Co., 106 F.3d 1563, 1571 (Fed. Cir. 1997)). Both parties presented an expert in economics to testify on the subject, and the experts agreed that Duobrii® had not yet made a profit. (Tr. 747:24-748:4; 765:9-13.) The experts also agreed that the annual sales of Duobrii® have been declining. (Tr. 748:23-749:12; 763:14-16.) The Court finds that Duobrii® has not been a commercial success.

As to unexpected results, Bausch points to the testimony of Dr. Stein Gold, who stated that the safety and efficacy of Bryhali®, at one-fifth the HP dosage of Ultravate, was unexpected and “this wasn’t something we had seen before.” (Tr. 635:14-637:22.) Padagis does not dispute these facts, but argues that the “evidence of unexpected results is not reasonably commensurate in scope with the asserted claims and is entitled to little, if any, weight.” (Defs.’ Br. 22-23.) In support, Padagis quotes Asyst: “objective evidence of non-obviousness must be commensurate in scope with the claims which the evidence is offered to support.” Asyst Techs., Inc. v. Emtrak, Inc., 544 F.3d 1310, 1316 (Fed. Cir. 2008). Padagis, in essence, argues that the results of Bryhali® reflect merely one corticosteroid dosage point within the dosage range stated

in claim 1 of the '307 patent ("0.04% or less"), and so the evidence is not commensurate in scope with the extent of the claims. The Federal Circuit subsequently explained: "While we have held that unexpected results must be commensurate in scope with the claims, we have not required absolute identity of scope; rather, we have rejected unexpected results where the evidence was plainly disproportionate to the scope of the claim." Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc., 655 F.3d 1291, 1308 (Fed. Cir. 2011); see also Rambus Inc. v. Rea, 731 F.3d 1248, 1257 (Fed. Cir. 2013) ("Objective evidence of nonobviousness need only be 'reasonably commensurate with the scope of the claims,' and we do not require a patentee to produce objective evidence of nonobviousness for every potential embodiment of the claim.") The Court finds that the evidence is not plainly disproportionate to the scope of the claim, and that Bausch has demonstrated unexpected results as to the claims at issue in the HP Patents.

As to evidence of a long-felt but unmet need, Bausch points to the evidence that the problem of HP causing HPA axis suppression was known since the 1970s, and that Bryhali® was the first low-concentration HP treatment available; these facts are undisputed. (Tr. 206:25-207:6; 303:6-17.) In opposition, Padagis argues again that the results are not commensurate with the scope of the claims; again, this Court concludes that the evidence is not plainly disproportionate to the scope of the claim, and demonstrates that Bryhali® has met a long-felt but unmet need.

Considering all of the evidence of record, the Court finds that the Padagis has not proven by clear and convincing evidence that the asserted claims of the HP Patents are invalid as obvious.

B. Indefiniteness

Padagis contends that the HP Patents are invalid because the claim term, “liquid oil component,” is indefinite. Padagis acknowledges that the specification of both patents states that the “liquid oil component . . . includes all ingredients of the formulation that are practically insoluble or insoluble in water and which are liquid at room temperature of 22° C.” ’307 patent, col.4 ll.17-20. Padagis also acknowledges that this Court in large part relied on that statement in formulating its construction of the term, “liquid oil component:” “The liquid oil component includes all ingredients of the formulation that are practically insoluble or insoluble in water and which are liquid at room temperature of 22°C.” Bausch Health Ir. Ltd. v. Padagis Isr. Pharm. Ltd., 2021 U.S. Dist. LEXIS 212434 at *35-36 (D.N.J. Nov. 3, 2021).

Padagis contends that Table 2 in the specification is inconsistent with this definition because, in short: 1) sorbitan monooleate (“SMO”) is liquid at room temperature and practically insoluble in water, thus falling within the Court’s construction of “liquid oil component;” 2) Table 1 in Example 1 includes SMO in formulations A through D; and 3) Table 2 states that it contains the concentration of liquid oil component in formulations A through D, but the data values do not include SMO in the liquid oil component. The parties do not dispute any of these propositions.

Although Bausch proposes a way to “harmonize” Table 2 with the Court’s construction, it is not necessary to consider it: even if the Court accepts Defendants’ view that Table 2 is inconsistent with the Court’s construction, Padagis still has not proven indefiniteness by clear and convincing evidence. There are several problems with Defendants’ indefiniteness argument. First and foremost, there is the problem of Dr. Michniak-Kohn’s testimony at trial.

On direct examination, Dr. Michniak-Kohn carefully explained the basis for Defendants' indefiniteness argument. (Tr. 356-361.) She discussed the data in Table 2, and said:

But the POSA says, well, I know that sorbitan monooleate is part of the liquid oil component as well. So these numbers don't quite make sense. It looks as though that was missed out. So there's a little bit of confusion here as to what the '307 patent teaches because the numbers should have been different there in Table 2 if the sorbitan monooleate had been included or any other component that belonged to this class of emulsifiers.

...

Q. Dr. Michniak-Kohn, what conclusions did you reach from your indefiniteness analysis?

A. Sorbitan monooleate falls within the liquid oil component as construed. Table 2 excludes sorbitol monooleate from the liquid oil component section term. Because of this inconsistency, the person of ordinary skill in the art cannot tell you with reasonable certainty what the scope of that term "liquid oil component" would be, making that term indefinite.

(Tr. 360:21-361:4, 24-362:8.) The Court notes that Dr. Michniak-Kohn testified that the problem was that the numbers in Table 2 "don't quite make sense" and that "there's a little bit of confusion here." When asked for her conclusion, Dr. Michniak-Kohn said that the POSA could not say with reasonable certainty what the scope of "liquid oil component" is.

On cross-examination, Dr. Michniak-Kohn was asked whether a POSA would reasonably understand what "ingredients of the formulation that are practically insoluble or insoluble in water" means and what "liquid at room temperature of 22°C" means, and she answered in the affirmative to both questions. (Tr. 421:9-422:2.) The Court therefore inquires: what aspect of the meaning of "liquid oil component" does the POSA not have reasonable certainty about? Dr. Michniak-Kohn said that the numbers in Table 2 did not quite make sense, and there was a "little bit of confusion." She gave no explanation of what questions a POSA would have about the meaning of the term "liquid oil component," nor did she herself express any specific uncertainty

about the scope or meaning of the term, or of the claims in which the term appears.

Padagis contends that the specification contains a statement that sets clear parameters for the term, “liquid oil component,” and then Table 2, which is inconsistent with that statement.

Padagis argues: “the HP Patents provide no guidance on which meaning to apply when determining the components or concentration of the ‘liquid oil component.’” (Defs.’ Br. at 7.)

To a certain extent, Padagis is rearguing an issue resolved at claim construction: the Court decided to construe “liquid oil component” in accordance with the clear statement in the specification, and not in accordance with Table 2. The Court did not then see – nor does it now – two equally viable interpretations of “liquid oil component,” but, rather, one well-supported interpretation and a small conundrum posed by a puzzling table. Dr. Michniak-Kohn may well be correct that Table 2 would produce “a little bit of confusion” in the POSA reading the specification.¹¹ That, however, is not sufficient to say that a POSA would read it to provide an equally viable and alternate interpretation of “liquid oil component.” Padagis does not contend that there is a viable alternate interpretation of “liquid oil component,” nor has Padagis persuaded the Court that Table 2 gives rise to any real uncertainty in the mind of the POSA about the meaning of “liquid oil component” or the claims in which it appears. The meaning of “liquid oil component” is clearly stated in the specification, and Dr. Michniak-Kohn agreed that a POSA would understand it. Dr. Lane agreed. (Tr. 576:5-13.)

Padagis cites the Federal Circuit’s decision¹² in Media Rights: “Notably, a claim is

¹¹ It is essential to distinguish between “a little bit of confusion” about the numbers in Table 2, and indefiniteness in the meaning of the claims containing “liquid oil component.” Dr. Michniak-Kohn expressed minor confusion about Table 2, and clarity about the meaning of “liquid oil component” and the claims in which it appears.

¹² Padagis also cites the Federal Circuit’s nonprecedential affirmance in TVnGO Ltd. (BVI) v.

indefinite if its language ‘might mean several different things and no informed and confident choice is available among the contending definitions.’” Media Rights Techs., Inc. v. Capital One Fin. Corp., 800 F.3d 1366, 1371 (Fed. Cir. 2015) (quoting Nautilus, Inc. v. Biosig Instruments, Inc., 572 U.S. 898, 911 n.8 (2014)). The facts of this case do not support a finding of indefiniteness under Media Rights, for two reasons. First, Padagis has not persuaded the Court that “liquid oil component” might mean several different things. Second, Padagis has not demonstrated that the condition precedent stated in Media Rights has been satisfied: in the present case, this Court made an informed and confident choice at claim construction, and it chose the clear statement in the specification over the “little bit of confusion” about Table 2.

The Federal Circuit has held: “Reasonable certainty does not require absolute or mathematical precision.” BASF Corp. v. Johnson Matthey Inc., 875 F.3d 1360, 1365 (Fed. Cir. 2017). Ultimately, Defendants’ indefiniteness argument rests on Dr. Michniak-Kohn’s conclusory statement that a POSA could not discern the scope of “liquid oil component” with reasonable certainty. But neither Padagis nor Dr. Michniak-Kohn provided an analysis showing the actual difference between the scope of a “liquid oil component” calculated based on Table 2 and the scope of a “liquid oil component” calculated based on the clear specification statement next to Table 2: is there a material difference, or is this a small and immaterial difference, “a little bit?” Is there a meaningful difference, or not? Padagis has not demonstrated a meaningful difference. Padagis has not persuaded the Court that a POSA reading Table 2 would

LG Elecs. Inc., 861 F. App’x 453, 458 (Fed. Cir. 2021), a case in which the patents at issue showed “an inconsistency between the specification and the claims.” In that case, however, the disputed claim phrases *did not appear at all* in the specification. Id. at 459. In the instant case, the disputed phrase not only appears in the specification, but appears with a crisp definition. TVnGO is inapposite.

understand the scope of “liquid oil component” to be materially different from the scope of “liquid oil component” in the absence of Table 2. Padagis has not demonstrated, by clear and convincing evidence, that the “little bit of confusion” over Table 2 renders the claims containing “liquid oil component” indefinite.

Bausch also cites the Federal Circuit’s decision in Cox, which is a thought-provoking, albeit unusual, case on the subject of indefiniteness: “This case presents a peculiar scenario: the sole source of indefiniteness that Cox complains of, ‘processing system,’ plays no discernable role in defining the scope of the claims.” Cox Communs., Inc. v. Sprint Commun. Co. LP, 838 F.3d 1224, 1229 (Fed. Cir. 2016). The Federal Circuit held that, although claim 1 contained the words, “processing system,” those words played no role in defining the scope of that claim. Id. The Court further stated:

As *Nautilus* instructs, the dispositive question in an indefiniteness inquiry is whether the “claims,” not particular claim terms, “read in light of the specification delineating the patent, and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention.” 134 S. Ct. at 2129. To be sure, we have generally acknowledged that an indefiniteness analysis under 35 U.S.C. § 112, ¶ 2 is inextricably intertwined with claim construction. Accordingly, the common practice of training questions of indefiniteness on individual claim terms is a helpful tool. Indeed, if a person of ordinary skill in the art cannot discern the scope of a claim with reasonable certainty, it may be because one or several claim terms cannot be reliably construed. Nevertheless, indefiniteness under § 112, ¶ 2 must ultimately turn on the question set forth by *Nautilus*: whether the “claims, read in light of the specification delineating the patent, and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention.” *Id.* at 2129 (emphasis added). Applied here, “processing system” does not prevent the claims from doing just that.

Id. at 1231-32 (citations omitted.) Applying the reasoning of Cox to this case, Padagis has asked the wrong question, and has failed to demonstrate that the *claims* which contain “liquid oil component” fail to inform the POSA with reasonable certainty about the scope of the invention.

Bausch raised this point in its opening post-trial brief; Padagis, in its responsive brief, did not counter the argument, and the Court construes its silence as a concession that Bausch is correct about Cox.

The Court concludes that Padagis has not proven, by clear and convincing evidence, that the asserted claims of the HP Patents are indefinite.

II. Invalidity of the '895 and '787 patents

Bausch has asserted claims 3 and 6 of the '895 patent and claims 4, 5, and 7 of the '787 patent. The parties agree that the Priority Date for both the '895 and '787 patents is June 18, 2015. The '895 patent has one independent claim:

1. A topical pharmaceutical composition for treating psoriasis the composition comprising: (a) active ingredients consisting of: (i) halobetasol propionate, at a concentration of 0.01 percent by weight of the composition; and (ii) tazarotene at a concentration of 0.045 percent by weight of the composition; and (b) a dermatologically acceptable carrier; wherein the composition is an oil-in-water emulsion; wherein an oil phase in the oil-in-water emulsion comprises a liquid oil component; wherein the liquid oil component is liquid at 22.degree. C. and consists of diethylsebacate and light mineral oil; and wherein the composition comprising the halobetasol propionate and the tazarotene at said concentrations is capable of providing synergistic efficacy and synergistic reduction of at least an adverse event selected from the group consisting of itching, burning, and stinging, for said treating.

Claims 3 and 6 are narrower composition claims. The '787 patent has one independent claim:

1. A method of treating psoriasis, the method comprising topically applying a pharmaceutical composition to an affected area of a body of a subject suffering from psoriasis; wherein the composition comprises: (a) halobetasol propionate at a concentration of 0.01 percent by weight of the composition; (b) tazarotene at a concentration of 0.045 percent by weight of the composition; and (c) an aqueous dermatologically acceptable carrier comprising carbomer copolymer type B, carbomer homopolymer type A, and a liquid oil comprising diethyl sebacate and light mineral oil; wherein said applying is carried out one or more times per day for a period of time sufficient to treat such psoriasis and wherein the composition comprising the halobetasol propionate and the tazarotene at said concentrations is capable of providing synergistic

efficacy and synergistic reduction of at least an adverse event selected from the group consisting of itching, burning, and stinging in said treating.

Claims 4, 5, and 7 are method claims which narrow claim 1.

A. Obviousness

The claims at issue in the Combination Patents all contain the same language about the synergy limitations: “wherein the composition . . . is capable of providing synergistic efficacy and synergistic reduction of at least an adverse event selected from the group consisting of itching, burning, and stinging in said treating.” This language contains two synergy elements: 1) capable of providing synergistic efficacy; and 2) capable of providing synergistic reduction of at least an adverse event.¹³ The parties agreed to this construction of “synergistic efficacy:” “more efficacious than the combined efficacies of compositions, each comprising only one of the active ingredients.” Bausch Health Ir. Ltd. v. Padagis Isr. Pharm. Ltd., 2021 U.S. Dist. LEXIS 212434, at *18 (D.N.J. Nov. 3, 2021). At claim construction, the Court construed the complete “synergistic reduction” phrase to mean: “a frequency of at least an adverse event (selected from the group of itching, burning, and stinging) that is less than the Expected Combination, i.e., the expected frequency of said adverse event derived from combining the performances of the active ingredients as monotherapies.” Id. at *36. The Court Ordered the parties to brief the meaning of “Expected Combination” within this construction. On February 28, 2022, the Court approved the parties’ stipulation that the complete “synergistic reduction” phrase means: “a vehicle-adjusted frequency of at least an adverse event (selected from the group of itching, burning, and stinging) that is less than the vehicle-adjusted frequency of patients reporting said adverse event

¹³ In this Opinion, “at least an adverse event” is used as shorthand for “at least an adverse event selected from the group consisting of itching, burning, and stinging in said treating.”

for halobetasol propionate monotherapy plus the vehicle-adjusted frequency of patients reporting said adverse event for tazarotene monotherapy.” (Docket Entry No. 105 at ¶ 1.)

Padagis first argues that the two synergy limitations should not be given patentable weight because they are inherent to the IDP-118 formulation. The Court begins by noting that the inherency analysis that follows relies on the proposition – which remains to be proven – that the IDP-118 formulation and the claimed method of treating psoriasis with IDP-118 were known in the prior art.

The parties do not dispute the basic principles of inherency in the obviousness inquiry in Federal Circuit law. Padagis cites the Federal Circuit’s decision in Santarus:

The initial blood serum concentration resulting from administering a PPI dosage is an inherent property of the formulation, and an obvious formulation cannot become nonobvious simply by administering it to a patient and claiming the resulting serum concentrations. To hold otherwise would allow any formulation — no matter how obvious — to become patentable merely by testing and claiming an inherent property.

Santarus, Inc. v. Par Pharm., Inc., 694 F.3d 1344, 1354 (Fed. Cir. 2012) (citation omitted).

Bausch does not disagree, but cites the Federal Circuit’s decision in Honeywell as a limiting principle:

We have previously stated that the use of inherency in the context of obviousness must be carefully circumscribed because “[t]hat which may be inherent is not necessarily known” and that which is unknown cannot be obvious. *In re Rijckaert*, 9 F.3d 1531, 1534 (Fed. Cir. 1993) (internal quotation marks omitted) (quoting *In re Spormann*, 363 F.2d 444, 448, 53 C.C.P.A. 1375 (1966)); *see also Par Pharm., Inc. v. TWi Pharms., Inc.*, 773 F.3d 1186, 1195 (Fed. Cir. 2014) (distinguishing a prior case finding obviousness based on inherency because, in that case, “neither party disputed that the [claimed features] were expected in light of the dosages disclosed in the prior art” (emphasis added)).

What is important regarding properties that may be inherent, but unknown, is whether they are unexpected. All properties of a composition are inherent in that composition, but unexpected properties may cause what may appear to be an

obvious composition to be nonobvious.

Honeywell Int'l Inc. v. Mexichem Amanco Holding S.A. De C.V., 865 F.3d 1348, 1354-55 (Fed. Cir. 2017). Padagis, in its responsive brief, agrees that it must “prove that the claimed synergies would have been **reasonably** expected.” (Defs.’ Resp. Br. at 17.) The question, then, is: has Padagis shown that the synergistic reduction of at least an adverse event would have been reasonably expected?

In support, Padagis cites two prior art references, Gollnick and Gandhi, pointing to places where the phrase, “synergistic effects,” appears in the text. Gollnick states:

Combination therapy with tazarotene and a topical corticosteroid appears logical because these agents have some different (as well as some common) mechanisms of action, and thus are likely to have additive or synergistic effects.

(DX-140 at 19.) Gollnick reported adverse events data for the studies performed, but makes no statements involving observed synergy. (DX-140 at 21, 22.) In the discussion section, Gollnick states:

In countries that currently do not favour the use of topical corticosteroids to treat plaque psoriasis. the results of these studies are likely to lead to a revival in the use of corticosteroids and thus a change in the therapeutic armamentarium. It is logical to treat chronic plaque psoriasis with two agents that have additive or synergistic effects and further research is now required to determine the optimal dose regimen for combination therapy utilizing tazarotene and a corticosteroid. In clinical practice, in order to minimize the risk of steroid rebound and other steroid-induced adverse effects, it may be advisable to slowly wean patients off the steroid after the initial 3-4 weeks as the clinical effect from tazarotene starts to become apparent, and then to continue treatment with tazarotene monotherapy (non-atrophogenic mid-potency corticosteroids such as methyprednisone-aceponat or prednicarbet).

(DX-140 at 22.) Of the two studies in Gollnick, one involved daily administration of tazarotene in the evenings and daily administration of a corticosteroid in the mornings, while the other involved alternating evening administration of tazarotene or a corticosteroid. (DX-140 at 19,

20.) In neither study were tazarotene and a corticosteroid administered at the same time.

Gandhi is a published patent application which states:

Accordingly, the present invention discloses an effective combination comprising Halobetasol propionate and Tazarotene useful for treating different types of psoriasis such as Plaque Psoriasis Though these two drugs have entirely different modes of action and when combined in a single formulation, have synergistic effects which lead to more rapid clearing and are notably effective for types of psoriasis which have not responded to either corticosteroids or retinoids alone.

(DX-141 at 6.) The reference contains no other statements about synergy, and does not contain any information about side effects.

In the post-trial brief, Padagis cites a few portions of testimony in support of its synergy position, but the cited testimony generally merely repeats the relevant statements in Gollnick and Gandhi. Dr. Stern's testimony adds a few conclusory statements about synergistic effects, but Dr. Stern did not add anything of substance to the statements in the Gollnick and Gandhi. (Tr. 184:20-185:8.)

Bausch filed an Investigational New Drug Application for Duobrii® with the FDA in October of 2011. (D FOF ¶ 262.) Defendants' post-trial brief contains one paragraph that points to three statements in two documents from the INDA, all expressly referencing synergy or synergistic effects. The first sentence of the paragraph states that Bausch admitted the expectation of synergy in its filings with the FDA. The paragraph and brief contain no additional analysis of the statements in connection with the inherency argument or anything else. At the outset, the Court inquires: what is the relevance of these INDA statements to the inherency issue? Padagis does not contend that the FDA submission is prior art. One of the three statements, Padagis contends, refers to the Menter 2011 reference, but Padagis does not say

anything about what Menter 2011 teaches. Presumably, if Menter 2011 said something helpful to Defendants' case, Padagis would have mentioned it. In short, Padagis has not pointed to any evidence to support the inference that Bausch's statements to the FDA reflect the state of knowledge in the art as of the Priority Date, as opposed to confidential communications of a corporate entity developing a new drug. Padagis has not persuaded the Court that these statements are informative about a prior art POSA's expectations about the synergistic effects of combining HP and tazarotene.

This determination leaves Padagis with only the statements in Gollnick and Gandhi as evidence that the claimed synergies would have been reasonably expected. Although Padagis, in the post-trial brief, argues that these statements show that a POSA would have expected synergistic effects, Defendants' own expert witness, Dr. Stern, agreed on cross-examination that "synergy" had been used incorrectly in the literature, and that he had no way of knowing what Gollnick or Gandhi meant when they used "synergy" words in the references. (Tr. 293:8-294:3.) Plaintiffs' expert Dr. Pillai agreed that the word "synergistic" was used in the literature in multiple ways. (Tr. 126:20-23.) Plaintiffs' expert Dr. Stein Gold testified that "synergy" is used in the literature with two different meanings (Tr. 655:16-656:10), that the Kircik 2011 article discusses these two different meanings in the literature (Tr. 656:15-657:10), that the data in the Gollnick reference does not evidence "synergy" as that term is used in the patents (Tr. 658:1-8), and that Gandhi does not have any information to help with interpretation of "synergy." (Tr. 658:9-14.) The experts thus were in agreement that "synergy" has different meanings and that one could not know with certainty what Gollnick and Gandhi meant when the references used the term.

The Court has read the Gollnick¹⁴ and Gandhi references and agrees with the experts: the references do not provide enough information to ascertain the meaning of the synergy statements with any certainty.¹⁵ Both Gollnick and Gandhi make a synergy statement in close juxtaposition with the observation that HP and tazarotene have “different mechanisms of action” (Gollnick) or “different modes of action” (Gandhi), which weakly points toward a view of synergy as additive. The Court finds that the evidence presented does not demonstrate that, as of the Priority Date, a POSA would have reasonably expected the claimed combination to manifest the properties of synergistic efficacy and synergistic reduction of at least an adverse event, within the meaning of “synergistic” used in the Combination Patents and in the parties’ stipulated construction of the terms. Padagis has not demonstrated that the claimed synergy limitations are properties of the composition or treatment method that would have been reasonably expected by a POSA as of the Priority Date.

The significance of this determination is that Padagis has failed to demonstrate that the synergy limitations of the combination patent claims at issue are inherent and obvious. Because Padagis has no alternative arguments to support finding the synergy limitations to be obvious, Padagis cannot demonstrate that the Combination Patents are invalid due to obviousness.

Nonetheless, the Court will briefly set forth the reasoning in support of some other key determinations that underly the obviousness analysis, even though, at this juncture, those

¹⁴ Furthermore, as Bausch points out, Gollnick does not teach simultaneous application of HP and tazarotene; Padagis has failed to persuade that Gollnick would have taught a POSA anything about simultaneous application of the actives.

¹⁵ Padagis did not even attempt to demonstrate that the statements in Gollnick or Gandhi use “synergistic” in conformity with the meaning of the “synergistic reduction” phrase that it agreed to in the stipulation entered on February 28, 2022.

determinations cannot impact the ultimate conclusion of nonobviousness. Padagis contends that the claims of the Combination Patents are obvious in view of three combinations of prior art. Their first combination is the '824 publication, Gollnick, and the clinicaltrials.gov entry. There is no dispute that U.S. Pub. No. US2012/0129824 (the "'824 Publication") is the published application that matured into the '307 patent.

There is also no dispute that, in January of 2014, Bausch entered information about a study of IDP-118 on the clinicaltrials.gov website, and that certain information was then published on that website (the "Posting"), disclosing the use of the combination of .01% HP and .045% tazarotene in a study of the treatment of psoriasis; the Posting was published in January of 2014, more than one year before the Priority Date of the Combination Patents. Bausch argues that the Posting does not constitute prior art because it falls within the experimental use exception to the statutory bar,¹⁶ incorporating the arguments on this point made in its second motion *in limine*. In that motion, Bausch argued that the Posting was a prerequisite to conducting a clinical trial of a new pharmaceutical and was therefore incidental to the primary purpose of experimentation, within the meaning of Allen Eng'g Corp. v. Bartell Indus., 299 F.3d 1336, 1354 (Fed. Cir. 2002). The Court is not persuaded that the exception in Allen applies here. To start with, Allen involved the on-sale bar:

the question is whether the transaction constituting the sale was 'not incidental to the primary purpose of experimentation,' i.e., whether the primary purpose of the inventor at the time of the sale, as determined from an objective evaluation of the facts surrounding the transaction, was to conduct experimentation.

¹⁶ 35 U.S.C. § 102(a) states: "A person shall be entitled to a patent unless— (1) the claimed invention was patented, described in a printed publication, or in public use, on sale, or otherwise available to the public before the effective filing date of the claimed invention."

Id. The facts of this case do not involve a sale or the on-sale bar and, as Padagis points out, Bausch has cited no authority for the proposition that the experimental use exception can apply to a printed publication. Second, even if this Court nonetheless followed the inquiry stated in Allen, Bausch has not pointed to evidence that the primary purpose of the inventor, in making the Posting, was to conduct experimentation.¹⁷ The 201 Study was indeed an experiment but the Posting, made to satisfy regulatory requirements for a clinical trial,¹⁸ was not an experiment. Bausch has failed to persuade the Court that the Posting does not qualify as prior art because it falls within the experimental use exception.

The determination that the Posting is prior art does not, however, have any material impact on the ultimate issue of obviousness of the Combination Patents. The three obviousness theories proffered by Padagis all suffer from fatal flaws, even beyond, as already discussed, the failure to demonstrate that the synergy limitations were obvious. As Bausch contends, these theories are hindsight-driven, based on finding some (but not all) claimed elements in the prior art and combining them. Padagis argues, in short, that the .01% HP formulation was known in the prior art, as shown in the '824 Publication, the use of tazarotene as a treatment for psoriasis was known, and that it was obvious to use the formulation described in the Posting to produce

¹⁷ In Polara, the Federal Circuit held that “[a] use may be experimental if its purpose is: (1) [to] test claimed features of the invention or (2) to determine whether an invention will work for its intended purpose—itself a requirement of patentability.” Polara Eng'g, Inc. v. Campbell Co., 894 F.3d 1339, 1348 (Fed. Cir. 2018). Bausch has offered no evidence to support the inference that, when it posted the Posting, it was testing claimed features, or determining whether the invention would work for its intended purpose. Certainly, the 201 Study itself is such an experiment, but the evidence does not support the inference that Bausch made the Posting as a test of the invention or its functions.

¹⁸ Because the Court finds that this case does not fall within the scope of the Allen exception, it need not reach the parties’ disputes over which posted elements were required by the regulator and which were unnecessary.

IDP-118.

While Padagis has demonstrated that the elements of the IDP-118 formulation were all known in the prior art, the problem for Defendants concerns the evidence showing that a POSA would have had a motivation to select and combine those elements. Padagis proposes that Gollnick is the starting point for all three combinations – despite the fact that, as already noted, Gollnick does not teach simultaneous application of a corticosteroid and tazarotene. At the outset, the Court asks: how did the POSA get to Gollnick? How did the POSA get from Gollnick to simultaneous application of the actives? Where did the POSA begin? What was the problem to be solved in 2015?¹⁹ Padagis does not explain. Padagis then states:

Gollnick also found, in two double-blind psoriasis clinical studies, that combining tazarotene with a high potency topical corticosteroid significantly improved efficacy and reduced local skin effects compared to tazarotene plus placebo cream. Gollnick's conclusions would have motivated a POSA to combine tazarotene with HP, an even more potent steroid than those used in Gollnick.

(Defs.' Br. 26-27) (citations omitted.) Padagis does not explain what in Gollnick would have motivated a POSA to change the corticosteroid. Nor does Padagis explain what would have motivated a POSA who seeks a superpotent corticosteroid to select HP from the superpotent corticosteroids. In Table 1, the specification of the '895 patent lists five superpotent corticosteroids, of which HP is one. Why would the POSA pick HP?

With Gollnick as the starting point, Padagis proposes three possible combinations of prior art leading to the inventions claimed in the Combination Patents. The three combinations, however, are laid out with little explanation of how the POSA would find and select each

¹⁹ In 2015, the formulation of Bryhali®, disclosed in the '824 Publication, is prior art. If that solved the SCD problem, what now is the problem to be solved?

reference. As discussed above with regard to the HP Patents, the law, as stated by the Federal Circuit in Unigene, requires more explanation than Padagis provides: “obviousness requires the additional showing that a person of ordinary skill at the time of the invention would have selected and combined those prior art elements in the normal course of research and development to yield the claimed invention.” 655 F.3d at 1360. Padagis has not made the necessary showing. As to the Combination Patents, Padagis has not identified the problem to be solved by the POSA, has neither explained nor pointed to evidence that a POSA attempting to solve that problem would have had a motivation to select HP .01%, tazarotene .045%, and the vehicle taught by the ’824 Publication. Padagis begins in the middle, with the POSA already having found and selected all the pieces as well as a prior art reference that does not teach applying them simultaneously. This is pure hindsight, analogous to a meal delivery service that puts all the ingredients for your dinner in a box with a recipe and gives it to you. The motivation for selecting HP as the corticosteroid is absent. As to the selection of tazarotene, Padagis contends: “As described by Bausch, ‘tazarotene was an automatic choice because it was the only retinoid approved at that point.’” (Defs.’ Br. at 26.) But what would have motivated a POSA to look for a retinoid to combine with a corticosteroid? And to select .045% as the concentration of tazarotene? Padagis does not place its prior art references into the context of a theory that accounts for the motivation to select the elements and then combine them, as required by Federal Circuit law.

Furthermore, Padagis makes much of things that Bausch wrote in its INDAs about the reasons supporting the formulation of IDP-118. The inventor’s path, however, is the path of hindsight. The Federal Circuit has stated:

The inventor's own path itself never leads to a conclusion of obviousness; that is hindsight. What matters is the path that the person of ordinary skill in the art would have followed, as evidenced by the pertinent prior art.

Otsuka Pharm. Co. v. Sandoz, Inc., 678 F.3d 1280, 1296 (Fed. Cir. 2012). Padagis has not laid out the path that a POSA would have taken to reach the Combination Patent claims, as evidenced by the prior art.²⁰

A. Secondary considerations

As to secondary considerations, Padagis contends that the evidence shows no unexpected results, no industry skepticism, no commercial success, and no long-felt but unmet need. Bausch, in rebuttal, contends that the evidence demonstrates unexpected results, commercial success, and industry skepticism. The Court has already determined that Duobrii® has not been a commercial success. As to unexpected results, Bausch contends that the synergistic effects were unexpected. As has already been discussed, there is no evidence that the prior art expected a HP/tazarotene combination to show synergistic reduction of at least an adverse event, and the Court concludes that Bausch has demonstrated unexpected results. As to industry skepticism, the Federal Circuit has explained:

Evidence of industry skepticism weighs in favor of non-obviousness. If industry participants or skilled artisans are skeptical about whether or how a problem could be solved or the workability of the claimed solution, it favors non-obviousness. Doubt or disbelief by skilled artisans regarding the likely success of a combination or solution weighs against the notion that one would combine elements in references to achieve the claimed invention.

WBIP, LLC v. Kohler Co., 829 F.3d 1317, 1335 (Fed. Cir. 2016). The Court finds two

²⁰ Bausch characterizes Defendants' obviousness case as follows: "Padagis chooses broad disclosures without providing a roadmap of how a POSA would have used them to arrive at the claimed invention." The Court agrees. Unigene requires a roadmap; Padagis offers a fragment.

problems with Bausch's case for industry skepticism. First, it covers much of the same ground as the unexpected results argument: while Dr. Sugarman did express surprise that such a low dose of HP could significantly reduce the side effects of tazarotene monotherapy, this repeats the basis for the finding of unexpected results. (JTX-006-4 at ¶ 12.) Second, Bausch did not perform the analysis from the perspective of a POSA who had read the '824 Publication and the Posting, which are both prior art. Would a POSA who already knew about the properties of a .01% HP treatment for psoriasis experience disbelief that the same formulation with the addition of tazarotene was also effective? Would a POSA who already had seen the Posting, showing that the formulation was about to enter Stage 2 clinical trials, experience disbelief? Bausch did not address these questions, and the Court is not persuaded that the evidence demonstrates disbelief or skepticism about the Combination Patents which is beyond the disbelief about the achievements of the HP Patents.

Considering all of the evidence of record, the Court finds that the Padagis has not proven by clear and convincing evidence that the asserted claims of the Combination Patents are invalid as obvious.

The Court concludes that Padagis has failed to prove, by clear and convincing evidence, that claims 13, 16, and 20 of the '307 patent, claims 4 and 16 of the '502 patent, claims 3 and 6 of the '895 patent, and claims 4, 5, and 7 of the '787 patent are invalid under their theories based on § 103 obviousness or the definiteness requirement stated in 35 U.S.C. § 112 ¶ 2. This Court determines that all asserted claims are valid and enforceable. The parties have stipulated to infringement, and the Court determines that Padagis has infringed every claim at issue. Judgment will be entered in favor of Plaintiffs on their infringement claims and on Defendants'

affirmative defenses.

Pursuant to FED. R. CIV. P. 52(a), the Court presents its findings of fact and conclusions of law.

FINDINGS OF FACT

- I. This Opinion incorporates by reference all stipulated facts set forth in the Final Pretrial Order.
- II. Based on the evidence presented at trial, this Court now makes the following findings of fact:
 1. As of the Priority Date for the HP Patents, HP was known in the art as a topical treatment for psoriasis and was commercially available as branded product Ultravate at a concentration of .05%. The category of the most potent corticosteroid topical medications was referred to as “superpotent,” and such medications were known to have the potential to cause serious systemic side effects, including HPA axis suppression, if too much steroid penetrated a patient’s skin and entered the bloodstream. As of 1995, the FDA-approved label for Ultravate warned that it should not be used for more than two weeks. Psoriasis is a chronic condition and there are many cases for which two weeks of treatment does not produce sufficient improvement.
 2. As of the Priority Date for the HP Patents, an important problem to the POSA was that many psoriasis patients need topical treatment for longer than two weeks, but, because of the systemic side effect of HPA axis suppression, Ultravate could not be used for longer than two weeks (the superpotent corticosteroid duration problem, or “SCD problem.”)
 3. As of the Priority Date, a POSA would have believed that there is a direct relationship between corticosteroid concentration and potency, and that a reduction in concentration would be associated with a reduction in potency.
 4. As of the Priority Date, a POSA attempting to solve the SCD problem would not have been motivated to reduce the risk of systemic side effects with topical corticosteroids by lowering the concentration of the steroid in the formulation, since the POSA would have expected that such a change would reduce efficacy.
 5. As of the Priority Date, a POSA attempting to solve the SCD problem would have been motivated to formulate a lower concentration of topical corticosteroid, to

minimize this risk of these side effects, while still maintaining efficacy; the POSA would have been motivated to preserve or improve efficacy and would not have been motivated to formulate a less effective treatment.

6. The Temovate E® Label teaches lengthening the duration of treatment by limiting body surface area treated and thus teaches away from the Bryhali® patents by providing a different solution to the two-week limitation problem, rather than lowering corticosteroid concentration in the formulation.
7. The Blum reference teaches that a .02% HP formulation is less effective for the treatment of psoriasis than a .05% HP formulation, that a dermatological preparation needs to contain the appropriate concentration of active ingredient, and that, when conducting research to determine that concentration, the results obtained from patients suffering from severe chronic psoriasis provide the most reliable measurement for comparing efficacy. Blum's data tables show that, for the severe psoriasis group, the significant or cured percentage for the .05% HP treatment was 89.7%, and for the .02% HP treatment was 76.8%. Blum stated a strong preference for the .05% HP treatment as most effective and did not characterize the degree of difference observed with the efficacy of the .02% HP treatment beyond the statement that the .02% HP treatment was less effective. Blum teaches away from using the .02% HP formulation and recommends the .05% HP concentration. A POSA would not have ignored Blum's recommendation based on Blum's finding that no statistically significant differences in effectiveness for treatment groups were observed. Blum would have motivated a POSA to use a .05% HP formulation for maximum efficacy. Blum would have discouraged a POSA from reducing the concentration of a HP treatment below .05%.
8. The '295 patent, the '566 patent, and JP 228 all teach the use of solvents to enhance skin penetration of topical corticosteroids. The '566 patent teaches the use of dibutyl adipate, a dicarboxylic acid ester, to enhance delivery of systemically active therapeutic agents through the skin and into the general circulation. The '566 patent teaches away from using dibutyl adipate in a solution to the SCD problem. JP 228 teaches the use of diisopropyl adipate, diethyl sebacate, and triacetin to improve transdermal absorption. "Transdermal delivery" means "delivery through the skin and into systemic circulation." A POSA considering use in a HP formulation of any of the solvent penetration enhancers disclosed in the '295 patent, the '566 patent, and JP 228 would have been concerned about the potential for these solvents to increase transdermal delivery into the systemic circulation, which would worsen the SCD problem, and would not have been motivated to use them in a formulation intended to solve the SCD problem in the absence of some basis to believe that the solvents would not enhance transdermal delivery. Padagis presented no evidence that a POSA had some basis to believe that the solvents of the '295 patent, the '566 patent, and JP

228 would not enhance transdermal delivery. A POSA would not have been motivated to use a solvent from the '295 patent, the '566 patent, or JP 228 in a formulation intended to solve the SCD problem.

9. Drug development is highly unpredictable for the POSA.
10. No evidence of the commercial success of Bryhali® was presented. Duobrii® had not yet made a profit, and the annual sales of Duobrii® have been declining. The products protected by the HP Patents have not shown commercial success.
11. The safety and efficacy of Bryhali® was an unexpected result.
12. The SCD problem constituted a long-felt but unmet need that Bryhali® met.
13. A POSA reading Table 2 in the HP Patents would have felt “a little bit of confusion” about why the numbers did not include SMO in the liquid oil component, when a specification statement that accompanied Table 2 provided a definition that would have led the POSA to expect the numbers in Table 2 to include SMO. A POSA would understand the specification statement, “liquid oil component . . . includes all ingredients of the formulation that are practically insoluble or insoluble in water and which are liquid at room temperature of 22° C.” ‘307 patent, col.4 ll.17-20. A POSA would not understand Table 2 to present a viable alternative definition of “liquid oil component.” A POSA would have understood with reasonable certainty the scope and meaning of all claims in the HP Patents containing the claim term, “liquid oil component.”
14. The word “synergistic” would have had at least two different meanings to the POSA as of the Priority Date of the Combination Patents. A POSA reading the Gollnick and Gandhi references would not have understood what either author meant when using the word, “synergistic.” Gollnick did not teach simultaneous application of the actives of interest. Bausch’s INDA submissions to the FDA in 2011 contain no assertions about what the POSA expected in terms of synergistic interactions between HP and tazarotene as of the Priority Date of the Combination Patents. As of that Priority Date, a POSA would not have reasonably expected a psoriasis treatment formulation containing HP and tazarotene to demonstrate synergistic efficacy or synergistic reduction of at least an adverse event.
15. The purpose of the Posting was to meet a regulatory requirement for a Stage 2 clinical study of IDP-118. The purpose of the Posting was not to test claimed features of the invention or to determine whether the invention will work for its intended purpose, which were purposes of the clinical study itself.
16. Padagis did not offer a complete roadmap for the obvious development of the inventions of the Combination Patents, beginning with the problem to be solved and leading to the creation of the claimed inventions.

17. The synergistic effects observed in the 201 Study would not have been expected by a POSA and constitute unexpected results. There was no evidence that the prior art had even considered the question of whether a combined HP/tazarotene topical psoriasis treatment would manifest synergistic reduction of at least an adverse event.
18. Bausch did not demonstrate industry skepticism about the inventions of the Combination Patents.
19. The product protected by the Combination Patents has not shown commercial success.

CONCLUSIONS OF LAW

17. This Court has jurisdiction over this case pursuant to 28 U.S.C. § 1331.
18. The parties accept this Court's personal jurisdiction.
19. Venue is proper in this district pursuant to 28 U.S.C. § 1391(b).
20. "A patent shall be presumed valid. Each claim of a patent (whether in independent, dependent, or multiple dependent form) shall be presumed valid independently of the validity of other claims; dependent or multiple dependent claims shall be presumed valid even though dependent upon an invalid claim. The burden of establishing invalidity of a patent or any claim thereof shall rest on the party asserting such invalidity." 35 U.S.C. § 282.
21. "Obviousness requires more than a mere showing that the prior art includes separate references covering each separate limitation in a claim under examination. Rather, obviousness requires the additional showing that a person of ordinary skill at the time of the invention would have selected and combined those prior art elements in the normal course of research and development to yield the claimed invention." Unigene Labs., Inc. v. Apotex, Inc., 655 F.3d 1352, 1360 (Fed. Cir. 2011) (citation omitted).
22. "[A] claim is indefinite if its language might mean several different things and no informed and confident choice is available among the contending definitions." Media Rights Techs., Inc. v. Capital One Fin. Corp., 800 F.3d 1366, 1371 (Fed. Cir. 2015). Padagis did not prove that a POSA would discern at least two definitions of "liquid oil component" in the HP Patents. Padagis did not prove, by clear and convincing evidence, that any claims in the HP Patents containing the term, "liquid oil component," are invalid for indefiniteness. Nor did Padagis prove, by clear and convincing evidence, that the "claims, read in light of the specification delineating the patent, and the prosecution history, fail to inform,

with reasonable certainty, those skilled in the art about the scope of the invention.” Nautilus, Inc. v. Biosig Instruments, Inc., 572 U.S. 898, 901 (2014). The claims of the HP Patents at issue meet the definiteness requirement stated in 35 U. S. C. §112, ¶ 2.

23. A formulation does not “become patentable merely by testing and claiming an inherent property.” Santarus, Inc. v. Par Pharm., Inc., 694 F.3d 1344, 1354 (Fed. Cir. 2012). “What is important regarding properties that may be inherent, but unknown, is whether they are unexpected.” Honeywell Int’l Inc. v. Mexichem Amanco Holding S.A. De C.V., 865 F.3d 1348, 1355 (Fed. Cir. 2017). Padagis did not demonstrate that the synergy properties in the claims at issue in the Combination Patents would have been expected by the POSA as of the Priority Date of those patents; the synergy limitations are entitled to patentable weight.
24. Bausch’s INDA submissions to the FDA in 2011 are not prior art.
25. “A use may be experimental if its purpose is: (1) [to] test claimed features of the invention or (2) to determine whether an invention will work for its intended purpose—itself a requirement of patentability.” Polara Eng’g, Inc. v. Campbell Co., 894 F.3d 1339, 1348 (Fed. Cir. 2018). The Posting is prior art to the Combination Patents and does not fall within the scope of the experimental use exception.
26. None of Defendants’ theories of the obviousness of the claimed inventions of the HP Patents meet the requirements of Unigene. Padagis has failed to prove, by clear and convincing evidence, that the claims of the HP Patents at issue are invalid as obvious. The claims of the HP Patents at issue are nonobvious and sufficiently definite.
27. None of Defendants’ theories of the obviousness of the claimed inventions of the Combination Patents meet the requirements of Unigene. Padagis has failed to prove, by clear and convincing evidence, that the claims of the Combination Patents at issue are invalid as obvious. The claims of the Combination Patents at issue are nonobvious.
28. All claims at issue in this case are valid and enforceable.
29. This Court honors and enforces the stipulation entered into by the parties, in which Padagis agreed to a determination of infringement for the claims at issue. In filing the ANDA applications at issue, Padagis infringed the claims at issue.
30. Padagis has infringed the following valid and enforceable claims: claims 13, 16, and 20 of the ’307 patent, claims 4 and 16 of the ’502 patent, claims 3 and 6 of the ’895 patent, and claims 4, 5, and 7 of the ’787 patent.

An appropriate Order follows.

s/ Stanley R. Chesler
Stanley R. Chesler, U.S.D.J.

Dated: December 1, 2022