65. Taro also testified that Taro's ANDA Product contains [redacted]

66. Accordingly, Taro's ANDA Product meets this element because it contains "about 30% w/w to about 40% w/w diethylene glycol monoethyl ether."

5. Taro's ANDA Product contains "about 2% w/w to about 6% w/w of a polymeric viscosity builder" that is insubstantially different than "about 2% w/w to about 6% w/w of a polymeric viscosity builder comprising acrylamide/sodium acryloyldimethyl taurate copolymer" recited in claim 1.

67. Taro's ANDA Product does not contain A/SA. However, the polymeric viscosity builder used in Taro's ANDA Product is insubstantially different than the claimed "about 2% w/w to about 6% w/w of a polymeric viscosity builder comprising acrylamide/sodium acryloyldimethyl taurate copolymer." Thus, Taro's ANDA Product meets this element under the doctrine of equivalents.

68. Taro's ANDA Product contain [redacted] arbomer Homopolymer Type C, [redacted][34]

69. In my opinion, and as discussed in more detail below, these ingredients, in combination, are the polymeric viscosity builder because in combination they serve substantially the same function, act in substantially the same way, and achieve substantially the same result as the claimed polymeric viscosity builder, as embodied by Sepineo P 600 in ACZONE Gel, 7.5%. Moreover, the polymeric viscosity builder—

[33] Ex. 15, Avramoff Dep. 22:23.

[34] *Id.*

i.e., the combination of Carbomer Homopolymer Type C, [redacted] in Taro's ANDA Product is insubstantially different from the claimed polymeric viscosity builder, as embodied by Sepineo P 600, the polymeric viscosity builder in ACZONE Gel, 7.5% (which is itself an embodiment of the "topical pharmaceutical formulation" recited in claim 1).

70. Based on Taro's ANDA, the combined weight of [redacted] of the polymeric viscosity builder in Taro's ANDA Product also falls within the claimed range of about 2 to about 6 wt. %.

a) Taro's polymeric viscosity builder serves a substantially similar function.

71. As stated above, the Court construed "polymer viscosity builder" to mean "a polymer or polymer-based thickening agent."[35] Sepineo P 600, used in ACZONE Gel, 7.5%, is made up of Acrylamide/Sodium Acryloyldimethyl Taurate Copolymer, Isohexadecane, Sorbitan Oleate, Polysorbate 80, and water; and the '219

[35] Report and Recommendation at 6, June 6, 2018, D.I. 87; Memorandum and Order at 8, Aug. 23, 2018, D.I. 107.

patent explicitly refers to the components of Sepineo P 600 as an embodiment of the claimed polymeric viscosity builder.[36]

72. A polymer is a large molecule composed of many repeated similar subunits.[37] As is evident from its name, the "acrylamide/sodium acryloyldimethyl copolymer" in Sepineo P 600 is the polymer in this polymer-based thickening agent. Similarly, Taro's ANDA Product contains Carbomer Homopolymer Type C (commercially known as Carbopol 980) as the polymer in Taro's polymer-based thickening agent.

73. Taro's ANDA Product also contains the same amounts and percentages of [redacted] that are in Sepineo P 600. In addition, Taro's ANDA Product uses [redacted]

74. The primary role of a polymeric viscosity builder is to thicken the formulation so that it is a suitable topical pharmaceutical composition for application to the skin. In thickening the formulation, the polymeric viscosity builder creates the

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[36] Ex. 1, '219 Patent, col. 5 ll. 47–56, ALG_ACZ0000565, at ALG_ACZ0000572; *see also id.*, tbl. 7, ALG_ACZ0000565, at ALG_ACZ0000577 (listing "Sepineo P 600"); *id.*, tbls. 1–4, 6, ALG_ACZ0000565, at ALG_ACZ0000575–76 (listing "acrylamide/sodium acryloyldimethyl copolymer based thickener" and "acrylamide/sodium acryloyldimethyl copolymer emulsion").

[37] Ex. 18, Alexander T. Florence & David Attwood, *Physicochemical Principles of Pharmacy* 274 (4th ed. 2006), ALG_ACZ0397196, at ALG_ACZ0397490.

[38] Ex. 19, Raymond C. Rowe et al., *Handbook of Pharmaceutical Excipients* 447 (6th ed. 2009), ALG_ACZ0397709, at ALG_ACZ0398184.

Carbomer Homopolymer Type C and A/SA swell to increase the viscosity of the formulation in the same way.[58]

88. Thus, the polymeric viscosity builder used in Taro's ANDA Product and Sepineo P 600, the polymeric viscosity builder in ACZONE Gel, 7.5% (an embodiment of the "topical pharmaceutical composition" recited in claim 1), create the emulgel in the same way.

(2) The combination of Carbomer Homo ol mer Type C, [redacted] in Taro's ANDA Product creates substantially similar rheological profiles in the same way as Sepineo P 600.

89. The polymeric viscosity builders—i.e., the combination of Carbomer Homopolymer Type C, [redacted] in Taro's ANDA Product and Sepineo P 600—act in the same way by providing substantially similar rheological profiles to Taro's ANDA Product and ACZONE Gel,

molecular-weight polymers of acrylic acid that are cross-linked with either ally sucrose or allyl ethers of pentaerythritol.").

[58] Ex. 11, Dapsone Gel, 7.5% Product Development Summary, TARO-DG-00000655, at TARO-DG-00000679.

7.5%. As described above, the rheological profile, including viscosity, of the topical formulation directly affects the qualities of the formulation.

90. Taro determined the spreading properties or "rheological profile" of its ANDA Product and ACZONE Gel, 7.5% by measuring each product's shear stress, shear rate, yield stress, and viscosity.[59]

91. The shear rate versus viscosity and shear rate versus shear stress are reported in Taro's ANDA for an exhibit batch of Taro's ANDA Product (S321-63887) and ACZONE Gel, 7.5%, shown in Figure 5 below:

92. Based on the shear rate versus shear stress data and related viscosity, Taro concluded that its ANDA Product and ACZONE Gel, 7.5% "exhibit similar rheological profiles."[61]

93. Taro also determined the viscosity of ACZONE Gel, 7.5% to be in the range of [redacted][2] with an average viscosity o[redacted][3] Taro's in process bulk testing of four exhibit batches of its ANDA Product showed viscosity ranging from [redacted][64] Thus, the polymeric viscosity builder in Taro's ANDA Product creates a substantially similar viscosity to that observed in ACZONE Gel, 7.5%.[65]

94. Taro also measured the average yield stress of three lots of ACZONE Gel, 7.5% as 114.571 Pa, as shown in Figure 6.[66] The average yield stress of Taro's

[59] Ex. 11, Dapsone Gel, 7.5% Product Development Summary, TARO-DG-00000655, at TARO-DG-00000679 at TARO-DG-00000740.

[60] *Id.*

[61] *Id.*

[62] *Id.* at TARO-DG-00000667.

[63] *Id.* at TARO-DG-00000684.

[64] *Id.* at TARO-DG-00000674.

[65] *Id.* at TARO-DG-00000732.

[66] *Id.* at TARO-DG-00000740.

four exhibit batches was [redacted].[67] Taro concluded that its ANDA Product and ACZONE Gel, 7.5% exhibit similar yield stress values.[68]

95. Accordingly, the polymeric viscosity builder in Taro's ANDA Product and Sepineo P 600, the polymeric viscosity builder in ACZONE Gel, 7.5% (an embodiment of the "topical pharmaceutical composition" recited in claim 1), act in the

[67] Ex. 11, Dapsone Gel, 7.5% Product Development Summary, TARO-DG-00000655, at TARO-DG-00000740.

[68] *Id.*

[69] *Id.* KDEN-2, KEAP, and KDFC-2 are ACZONE Gel, 7.5% lots Taro analyzed. *See id.* at TARO-DG-00000667. S321-63887, S321-63954, S321-63955, and S321-63956I are exhibit batches of Taro's ANDA Product. *See id.* at TARO-DG-00000730.

same way by providing the same or substantially similar shear stress, shear rate, yield stress, and viscosity values.

(3) The combination of Carbomer Homo ol mer Type C, [redacted] in Taro's ANDA Product creates a substantially similar uniform distribution of dapsone in the same way as Sepineo P 600.

96. A uniform distribution of dapsone is critical to the final drug product,[70] because uniform distribution is required to provide the proper dosage of dapsone in each application, thereby maintaining treatment efficacy, minimizing toxicity, and ensuring patient compliance.[71] Indeed, Taro's quality target product profile confirms that uniform distribution of the active ingredient is "[n]eeded for clinical effectiveness and [to] ensure patient safety."[72] Lack of uniform distribution is often a result of precipitation of the active ingredient and/or phase separation.[73]

97. Sepineo P 600 and the polymeric viscosity builder in Taro's ANDA Product each contribute to provide uniform distribution of dapsone in at least two ways. First, the polymeric viscosity builders permanently suspend the dapsone

[70] Ex. 15, Avramoff Dep. 107:13–15.

[71] *Id.* at 106:16–21.

[72] Ex. 11, Dapsone Gel, 7.5% Product Development Summary, TARO-DG-00000655, at TARO-DG-00000673.

[73] *See, e.g.*, Ex. 15, Avramoff Dep. 38:20; Ex. 24, Robert A. Nash, *Pharmaceutical Suspensions, in Pharmaceutical Dosage Forms: Disperse Systems* 151–98 (Lieberman et al. eds., 1988), ALG_ACZ0001177, at ALG_ACZ0001177–1224.

particles in the emulgel vehicle, preventing the particles from settling down.[74] Permanently suspending the dapsone particles maintains a uniform distribution of dapsone particles over time. Second, the polymeric viscosity builders maintain a stable emulgel.[75] Without a stable emulgel, the oil and aqueous phases would separate.[76] With this phase separation, dapsone would no longer be uniformly dispersed.[77]

98. Allergan reported drug content uniformity measurements in its NDA 207154 for ACZONE Gel, 7.5%. Each measurement, after initial manufacture and on stability, was between 100–102% of the ACZONE Gel, 7.5% label claim.[78]

99. Taro set acceptance criteria for dapsone uniformity at [redacted] of the label claim for dapsone gel 7.5%.[79] Across all of its exhibit batches, Taro's

[74] Ex. 11, Dapsone Gel, 7.5% Product Development Summary, TARO-DG-00000655, at TARO-DG-00000678.

[75] *Id.* at TARO-DG-00000679.

[76] Ex. 15, Avramoff Dep. 36:21.

[77] *Id.* at 38:20.

[78] Ex. 25, NDA No. 207154, Section 3.2.P.2.2, ALG_ACZ0016215, at ALG_ACZ0016246–50.

[79] Ex. 11, Dapsone Gel, 7.5% Product Development Summary, TARO-DG-00000655, at TARO-DG-00000738.

measured drug content uniformity between [redacted] the dapsone gel 7.5% label claim:

100. This data demonstrates that the polymeric viscosity builders used in Taro's ANDA Product and ACZONE Gel, 7.5% resulted in a substantially similar distribution of dapsone.

[80] Ex. 11, Dapsone Gel, 7.5% Product Development Summary, TARO-DG-00000655, at TARO-DG-00000738.

(4) The combination of Carbomer Homo ol mer Type C, [redacted] in Taro's ANDA Product creates substantially similar particle size distribution in the same way as Sepineo P 600.

101. The specification of the '219 patent explains that the polymeric viscosity builder influences the crystal size of dapsone in the formulation by reducing aggregation of the crystals.[81] In other words, the polymeric viscosity builder leads to a "reduction in particle size."[82]

102. Particle size is a critical attribute for the drug product.[83] As noted by Taro, particle size is expected to impact the bioequivalence of Taro's ANDA Product.[84] Particle size is also important to the feel of the product, because large dapsone particles can make a product feel rough or "gritty."[85] Particle size distribution measures the full range of crystal sizes in a formulation, and thus is impacted by the individual particle sizes. Particle size distribution is often reported as values known as D10, D50, and D90. [redacted]

103. In order to achieve a similar particle size distribution as ACZONE Gel, 7.5%, Taro set its particle size distribution specification to require [redacted] or

[81] Ex. 1, '219 patent, col. 2 ll. 57–61, ALG_ACZ0000565, at ALG_ACZ0000570.

[82] *Id.*

[83] Ex. 15, Avramoff Dep. 58:19–59:18.

[84] *Id.* at 59:11–18.

[85] Ex. 1, '219 patent, col. 2 ll. 57–61, ALG_ACZ0000565, at ALG_ACZ0000570.

[redacted] As shown by Figure 8 below, each of Taro's exhibit batches has a particle size distribution that is "similar to the RLD," i.e., ACZONE Gel, 7.5%.[87]

[redacted]

104. Taro's particle size distribution data establishes that the polymeric viscosity builder used in Taro's ANDA Product—i.e., the combination of Carbomer Homopolymer Type C, [redacted] and Sepineo P 600, the polymeric viscosity builder in ACZONE Gel, 7.5% (an embodiment the "topical pharmaceutical composition" recited in claim 1), act in the same way by producing a substantially similar particle size distribution.

[86] Ex. 11, Dapsone Gel, 7.5% Product Development Summary, TARO-DG-00000655, at TARO-DG-00000729.

[87] *Id.* at TARO-DG-00000738.

(5) The combination of Carbomer Homo ol mer Type C, [redacted] in Taro's ANDA Product creates substantially similar dapsone solubility in the same way as Sepineo P 600.

105. The combination of Carbomer Homopolymer Type C, [redacted] n Taro's ANDA Product creates substantially similar dapsone solubility in the same way as Sepineo P 600.

106. A portion of the dapsone in ACZONE Gel, 7.5% and Taro's ANDA Product is in solution, while the remaining portion is suspended. Because dapsone must be in solution to penetrate the skin,[88] a similar percent of dapsone must be in solution in Taro's ANDA Product as is in solution in ACZONE Gel, 7.5% to achieve a similar dapsone release rate and, ultimately, bioequivalence. Taro measured the portions of dapsone that were in solution and suspended,[89] and concluded, based on

[88] Ex. 26, Jonathan Hadgraft & Majella E. Lane, *Drug crystallization—Implications for Topical and Transdermal Delivery*, 13(6) Expert Op. on Drug Delivery 817, 819 (2016), ALG_ACZ0399151, at ALG_ACZ0399154 ("For an active to remain in solution, and therefore able to diffuse, it must have some solubility in both water and lipids.").

[89] Ex. 11, Dapsone Gel, 7.5% Product Development Summary, TARO-DG-00000655, at TARO-DG-00000738.

the data reflected in Figure 9, that the solubility of dapsone in Taro's ANDA Product and ACZONE Gel, 7.5% is substantially similar.[90]

107. Thus, the data shows that the polymeric viscosity builder—i.e., the combination of Carbomer Homopolymer Type C [redacted] in Taro's ANDA Product and Sepineo P 600, the polymeric viscosity builder in ACZONE Gel, 7.5% (an embodiment the "topical pharmaceutical composition" recited in claim 1), act in the same way by producing substantially similar percentages of dapsone in solution and in suspension.

(6) The combination of Carbomer Homopolymer Type C, [redacted] Taro's ANDA Product creates substantially similar feel in the same way as Sepineo P 600.

108. The feel of a topical formulation that contains undissolved particles is affected by the particle size and distribution of the active ingredient. As discussed

[90] Ex. 11, Dapsone Gel, 7.5% Product Development Summary, TARO-DG-00000655, at TARO-DG-00000739.

above, Taro's polymeric viscosity builder—i.e., the combination of Carbomer Homopolymer Type C, [redacted] creates a formulation with substantially similar particle size and distribution of dapsone as compared to ACZONE Gel, 7.5%. Specifically, Taro's ANDA Product and ACZONE Gel, 7.5% will have a similar feel because the particle size and distribution of dapsone are substantially the same.

109. Taro's representative testified that Taro changed the formulation of its ANDA Product to simulate the polymeric viscosity builder in ACZONE Gel, 7.5% in part so that it could match the feel of ACZONE Gel, 7.5%.[91] It is well known that emulgels have a different feel than a simple gel because a simple gel only contains a single phase and emulgels have two phases.[92] Specifically, emulgels have good patient acceptability due to their non-greasy nature and "can be conveniently applied to the skin as compared to other topical formulations such as creams [and] ointments which are very much thick, greasy and require excess rubbing."[93]

110. Taro's representative agrees that the [redacted] was added to [redacted][94] Thus, the polymeric viscosity builder in Taro's ANDA Product and Sepineo P 600, the polymeric viscosity builder in ACZONE Gel, 7.5% (an embodiment the "topical pharmaceutical

[91] Ex. 15, Avramoff Dep. 43:3, 124:6–9.

[92] Ex. 22, Ajazuddin et al., *Recent Expansions in an Emergent Novel Drug Delivery Technology: Emulgel*, 171 J. of Controlled Release 122, 123 (2013), ALG_ACZ0399140, at ALG_ACZ00399141.

[93] *Id.*

[94] Ex. 15, Avramoff Dep. 103:3–4.

composition" recited in claim 1), act in the same way by producing a substantially similar feel.

(7) The combination of Carbomer Homo ol mer Type C, [redacted] in Taro's ANDA Product control the dapsone release rate in the same way as Sepineo P 600.

111. The polymeric viscosity builder in Taro's ANDA Product and the Sepineo P 600 both control the dapsone release rate in at least two ways.[95]

112. *First*, both polymeric viscosity builders control the release of the dapsone because the "cross linked network" of polymers "captures small drug particles,"[96] and the emulgel's viscous nature "prolongs the contact period of medication over the skin."[97]

113. *Second*, both polymeric viscosity builders create an [redacted] n the emulgel that [redacted][8] Taro's ANDA Product and ACZONE Gel, 7.5% both have a portion of the dapsone is not in the DGME solution and remains suspended as crystals.[99] The oil phase of the polymeric viscosity builders can impact

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[95] Ex. 22, Ajazuddin et al., *Recent Expansions in an Emergent Novel Drug Delivery Technology: Emulgel*, 171 J. of Controlled Release 122, 123 (2013), ALG_ACZ0399140, at ALG_ACZ00399141.

[96] *Id.*

[97] *Id.*

[98] *Id.*

[99] Ex. 11, Dapsone Gel, 7.5% Product Development Summary, TARO-DG-00000655, at TARO-DG-00000739.

the release rate of the undissolved dapsone crystals. Though the oil phase is only about 1.0% of both products,[100] it has an important effect in the use of the product. Specifically, in both formulations some of the water and DGME evaporate once the formulation is applied to the skin.

114. The oil, by contrast, does not evaporate, leaving a "residual phase" on the skin. The oil in the "residual phase" will dissolve the dapsone.[101] Specifically, dapsone has a favorable "partition coefficient,"[102] (or "LogP" value) of [redacted][103] indicating that it is at least partially soluble in the oil phase. This favorable LogP value indicates that dapsone is soluble to some extent in hydrophobic/lipophilic solvents, like Isohexadecane o [redacted] Once dissolved in the oil, a portion of dapsone remains on the skin thereby allowing a slow release rate of the remaining dapsone into the skin.

115. The data in Taro's documents supports this conclusion. For example, Taro ran *In Vitro* Release Tests (IVRT) to compare the release rates of dapsone from

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[100] Ex. 13, Taro's ANDA, Section 3.2.P.1, TARO-DG-00000609, at TARO-DG-00000611.

[101] Ex. 27, U.S. Patent Application 2006/0204526, ¶ 61, TARO-DG-00064894, at TARO-DG-00064899 ("The oil phase component of the emulsive composition of the invention may include a general class of compounds that will dissolve Dapsone. Although these do not constitute solvation medium for Dapsone, they enable complete or further dissolution of Dapsone in the two phases of the emulsive composition. . . . When such a compound is selected as an oil phase component, it is selected for Dapsone solubility.").

[102] LogP is a measure of whether a compound dissolves in oil or water.

[103] Ex. 28, Dapsone, *Clarke's Analysis of Drugs and Poisons* (Pharm. Press 2005). These values are favorable for the dissolution of dapsone in Light Mineral Oil or Isohexadecane.

varying formulations. The release of the active pharmaceutical ingredient from an emulgel is critical because the active ingredient must be released to diffuse into the skin.[104] In addition, the *rate* of release of an active ingredient is also critical to the emulgel because it influences how effective the emulgel is in treating acne.

116. IVRT is an FDA-recommended method of assessing this release.[105] IVRT uses a synthetic membrane to measure how much drug product is released from a pharmaceutical composition over time. IVRT provides comparisons of drug release between formulations and can detect subtle differences between release rates that may result from formulation changes.[106]

117. With IVRT, the amount of active ingredient released is measured at certain time intervals. This information can be plotted and fitted to a linear equation. The slope of the line provides a useful way to characterize release rate. For example, the slope from two formulations can be compared to determine a "slope ratio." A slope ratio of 100% indicates that the slope for both formulations is the same—i.e., the

[104] Ex. 29, Katrin I. Tiffner et al., *A Comprehensive Approach to Qualify and Validate the Essential Parameters of an* In Vitro *Release Test (IVRT) Method of Acyclovir Cream, 5%*, 535 Int'l J. of Pharms. 217, 217 (2018), ALG-ACZ0399168, at ALG-ACZ0399168.

[105] *Id.*

[106] *Id.*

products had the same release rate. The larger the deviation of the slope ratio from 100%, the greater the variation in the release rates from the two formulations.

118. Using IVRT, Taro compared the dapsone release rates between (1) ACZONE Gel, 7.5% and Taro's 63499 formulation,[107] which does not includ [redacted] and (2) ACZONE Gel, 7.5% and Taro's ANDA Product.[108]

[107] Ex. 11, Dapsone Gel, 7.5% Product Development Summary, TARO-DG-00000655, at TARO-DG-00000713.

[108] Ex. 30, Results for May 25, 2016 *In Vitro* Release Test comparing ACZONE Gel, 7.5% and S321-63499, TARO-DG-00110264, at TARO-DG-00110264.

119. Taro found that its oil-free 63499 formulation had a faster dapsone release rate than ACZONE Gel, 7.5%, resulting in a slope ratio of [redacted] The summary chart from this IVRT is reproduced below:

[redacted]

120. Taro also tested ACZONE Gel, 7.5% as compared to Taro's ANDA Product (exhibit batch 63887),[110] which included [redacted]

[109] Ex. 30, Results for May 25, 2016 *In Vitro* Release Test comparing ACZONE Gel, 7.5% and S321-63499, TARO-DG-00110264, at TARO-DG-00110264.

[redacted] as part of its polymeric viscosity builder.[111] Taro's ANDA Product, the 63887 formulation, had a nearly identical release rate to ACZONE Gel, 7.5%, with a slope ratio o[redacted] Thus, Taro's ANDA Product has a slower release rate than its oil-free formulation, which is beneficial for a once-daily formulation like ACZONE Gel, 7.5%. A summary of those results is reproduced below:

[redacted]

[110] Ex. 31, Results for June 17, 2016 *In Vitro* Release Test comparing ACZONE Gel, 7.5% with S321-63887 and S321-63890, TARO-DG-00110254, at TARO-DG-00110254; Ex. 11, Dapsone Gel, 7.5% Product Development Summary, TARO-DG-00000655, at TARO-DG-00000730.

[111] Ex. 32, Taro Document Comparing S321-63887 and S321-63890, TARO-DG-00113972, at TARO-DG-00113972.

[112] Ex. 31, Results for June 17, 2016 *In Vitro* Release Test comparing ACZONE Gel, 7.5% with S321-63887 and S321-63890, TARO-DG-00110254, at TARO-DG-00110254.

121. The IVRT data for Taro's formulations confirms that the [redacted] helped achieve a substantially similar dapsone release profile to that of ACZONE Gel, 7.5%. Accordingly, the polymeric viscosity builder in Taro's ANDA Product and Sepineo P 600, the polymeric viscosity builder in ACZONE Gel, 7.5% (an embodiment of the "topical pharmaceutical composition" recited in claim 1), act in the same way by providing substantially similar dapsone release rates.

(8) The combination of Carbomer Homopolymer Type C, [redacted] in Taro's ANDA Product creates substantially similar stability in the same way as Sepineo P 600.

122. Instability of an emulgel formulation leads to the separation of the formulation into an oil layer and the gel layer.[113] If such phase separation occurs in

[113] Ex. 15, Avramoff Dep. 37:1–2.

a dapsone formulation like Taro's, different parts of the formulation will have different amounts of dapsone.[114] This non-uniform distribution means the patient will not receive the same dose of dapsone each time the patient applies the product to the skin, or even within the same application. Stability of the formulation is thus critical to maintaining uniformity.[115] Moreover, an unstable, phase-separated product would appear "ugly and not in a physical manner that you can provide . . . to a patient or a customer,"[116] resulting in an "inappropriate product."[117]

123. The specification of the '219 patent repeatedly focuses on storage stability of topical pharmaceutical compositions. For example, Figure 1 of the '219 patent shows the results of storage stability after 4 weeks both at 25° C and at 40° C by comparing formulations A1, which does not contain a polymeric viscosity builder comprising A/SA, and A2, which does contain a polymeric viscosity builder comprising A/SA.[118]

124. The specification also describes a polymeric viscosity builder containing A/SA, Polysorbate 80, Sorbitan Monooleate, and Isohexadecane—the components of Sepineo P 600.[119] The primary role of Polysorbate 80 and Sorbitan Monooleate is to

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[114] Ex. 15, Avramoff Dep. 38:20.

[115] *See supra* Section XI.A.5.b.4.

[116] Ex. 15, Avramoff Dep. 37:7–9.

[117] *Id.* at 37:14.

[118] Ex. 1, '219 patent, col. 3 ll. 15–17, ALG_ACZ0000565, at ALG_ACZ0000571; *see also* Ex. 4, '403 application, specification at 10–11, Fig. 1, ALG_ACZ0000590, at ALG_ACZ0000617–18, ALG_ACZ0000627.

[119] Ex. 1, '219 patent, col. 5 ll. 47–50, ALG_ACZ0000565, at ALG_ACZ0000572.

prevent phase separation of the emulgel, which would occur if those surfactants were removed.

125. As part of its NDA, Allergan provided stability data for ACZONE Gel, 7.5% that showed no significant changes in any stability parameter over time.[120] Specifically, ACZONE Gel, 7.5% maintained a stable appearance, pH, viscosity, dapsone distribution, and particle size, as shown in Figure 12.[121]

[120] Ex. 33, NDA No. 207154, Section 2.3.P.2, ALG_ACZ0004105, at ALG_ACZ0004111; Ex. 25, NDA No. 207154, Section 3.2.P.2.2, ALG_ACZ0016215, at ALG_ACZ00016246.

[121] Ex. 25, NDA No. 207154, Section 3.2.P.2.2, ALG_ACZ0016215, at ALG_ACZ0016230–31.

Figure 12: ACZONE Gel, 7.5% stability data[122]

Table 9 Long-Term (25 °C/60% RH) Development Stability Data: Lot 3811-36

Product Name:	ACZONE (dapsone) Gel, 7.5%			**Lot Number:**	3811-36			
Storage Condition:	25 °C/60% RH			**Batch Size:**	8 kg			
Tests	**0 Month**	**1 Month**	**3 Months**	**6 Months**	**9 Months**	**12 Months**	**18 Months**	**24 Months**
Physical Appearance	Formulation is opaque, white, uniform, and smooth.	Formulation is opaque, white, uniform, and smooth.	Formulation is opaque, white, uniform, and smooth.	Formulation is opaque, white, uniform, and smooth.	Formulation is opaque, white, uniform, and smooth.	Formulation is opaque, white, uniform, and smooth.	Formulation is opaque, white, uniform, and smooth.	Formulation is opaque, white, uniform, and smooth.
Package Integrity	No deformities were noted in the package.	No deformities were noted in the package.	No deformities were noted in the package.	No deformities were noted in the package.	No deformities were noted in the package.	No deformities were noted in the package.	No deformities were noted in the package.	No deformities were noted in the package.
pH (pH units)	6.6	7.1	7.0	6.7	7.1	6.9	6.8	7.3
Viscosity (cP)	396,000	405,000	371,000	421,000	399,000	394,000	415,000	442,000
Dapsone Assay Top of container Sampled Through Cap (% Label Claim, mean of n=2)	103.2	103.3	102.2	103.3	104.0	104.2	104.7	102.9
Dapsone Assay Bottom of Container (% Label Claim, mean of n=2)	102.9	100.3	101.1	104.2	NT	104.3	NT	105.7
MP top of container. (% Label Claim, mean of n=2)	102.0	100.2	100.3	102.0	102.0	101.9	102.4	100.3

Table 9 Long-Term (25 °C/60% RH) Development Stability Data: Lot 3811-36 (Continued)

Product Name:	ACZONE (dapsone) Gel, 7.5%			**Lot Number:**	3811-36			
Tests	**0 Month**	**1 Month**	**3 Months**	**6 Months**	**9 Months**	**12 Months**	**18 Months**	**24 Months**
MP Bottom of Container (% Label Claim, mean of n=2)	102.0	100.1	100.1	102.7	NT	102.1	NT	103.3
Dapsone Related Substances Top of container Sampled Through Cap (% Label Strength)	RRT 1.78[a] 0.07% LS RRT 1.84[a] 0.12% LS	RRT 1.78[a] 0.07% LS RRT 1.85[a] 0.11% LS	RRT 1.78[a] 0.07% LS RRT 1.86[a] 0.12% LS RRT 2.10 0.05% LS	RRT 1.78[a] 0.07% LS RRT 1.83[a] 0.12% LS	RRT 1.77[a] 0.07% LS RRT 1.84[a] 0.12% LS	RRT 1.63[a] 0.07% LS RRT 1.75[a] 0.12% LS	RRT 1.78[a] 0.07% LS RRT 1.83[a] 0.12% LS	RRT 1.76[a] 0.07% LS RRT 1.82[a] 0.11% LS
Dapsone Related Substances Bottom of Container (% Label Strength)	RRT 1.77[a] 0.07% LS RRT 1.85[a] 0.12% LS	RRT 1.78[a] 0.07% LS RRT 1.85[a] 0.11% LS	RRT 1.79[a] 0.07% LS RRT 1.87[a] 0.12% LS	RRT 1.77[a] 0.07% LS RRT 1.83[a] 0.12% LS	NT	RRT 1.63[a] 0.07% LS RRT 1.75[a] 0.12% LS	NT	RRT 1.76[a] 0.07% LS RRT 1.82[a] 0.11% LS
Microbial Enumeration Tests and Tests for Specified Organisms:								
Total Combined Yeasts and Molds (CFU/g)	LT 10	NT	NT	LT 10	NT	NT	NT	NT
Total Aerobic Microbial Count (CFU/g)	LT 100	NT	NT	LT 100	NT	NT	NT	NT
Absence of *S. aureus* and *P. aeruginosa*	Pass	NT	NT	Pass	NT	NT	NT	NT
Antimicrobial Preservative Effectiveness Test	Pass	NT	NT	Pass	NT	NT	NT	NT

NT = Not Tested
RRT = Relative Retention Time
LS = Label Strength
[a] Drug substance process impurities

126. Taro conducted similar stability studies and found that the uniform distribution of dapsone, the pH, and viscosity of the emulgel are maintained over time in its ANDA Product: [123]

127. This data demonstrates that the polymeric viscosity builder—i.e., the combination of Carbomer Homopolymer Type C, [redacted] in Taro's ANDA Product and Sepineo P 600, the polymeric viscosity builder in ACZONE Gel, 7.5% (an embodiment of the "topical

[122] Ex. 25, NDA No. 207154, Section 3.2.P.2.2, ALG_ACZ0016215, at ALG_ACZ0016230–31.

[123] Ex. 11, Dapsone Gel, 7.5% Product Development Summary, TARO-DG-00000655, at TARO-DG-00000716–17.

[124] *Id.*

pharmaceutical composition" recited in claim 1), act in the same way by providing substantially similar stability for their respective products.

(9) The combination of Carbomer Homopolymer Type C, [redacted] in Taro's ANDA Product creates substantially similar visual appearances in the same way as Sepineo P 600.

128. Taro characterized ACZONE Gel, 7.5% as an "off-white to yellow gel,"[125] and selected a polymeric viscosity builder that would provide the same visual appearance as ACZONE Gel, 7.5%.[126] Specifically, both polymeric viscosity builders thicken the products into a gel,[127] and, by including an oil phase and emulsifiers, the polymeric viscosity builders create an emulgel. The emulgel has droplets of oil, mixed throughout the product, that make the product look "more opaque,"[128] and have an "emulsion appearance . . . rather than a transparent gel" appearance.[129] Ultimately, the polymeric viscosity builder in Taro's ANDA Product provides it with the same visual appearance as that of ACZONE Gel, 7.5%: an [redacted][130] Accordingly, the polymeric viscosity builder in Taro's ANDA Product and Sepineo P 600, the polymeric viscosity builder in ACZONE Gel, 7.5% (an embodiment

[125] Ex. 11, Dapsone Gel, 7.5% Product Development Summary, TARO-DG-00000655, at TARO-DG-00000665.

[126] Ex. 15, Avramoff Dep. 43:1–12.

[127] Ex. 11, Dapsone Gel, 7.5% Product Development Summary, TARO-DG-00000655, at TARO-DG-00000679.

[128] Ex. 15, Avramoff Dep. 43:20.

[129] *Id.* at 124:7–8.

[130] Ex. 13, Taro's ANDA, Section 3.2.P.1, TARO-DG-00000609, at TARO-DG-00000609.

of the "topical pharmaceutical composition" recited in claim 1), act in the same way by providing a substantially similar visual appearance.

* * * * *

129. Thus, the combination of the combination of Carbomer Homopolymer Type C, [redacted] in Taro's ANDA Product acts in substantially the same way as the claimed polymeric viscosity builder, as embodied by Sepineo P 600.

c) The combination of Carbomer Homopolymer Type C, [redacted] in Taro's ANDA Product achieves substantially the same result as Sepineo P 600 in the claimed composition.

130. The polymeric viscosity builder in Taro's ANDA Product—Carbomer Homopolymer Type C, [redacted] creates an emulgel with a similar rheological profile, viscosity, yield stress, distribution of the active ingredient, particle size of the active ingredient, solubility of the active ingredient, feel on the skin, release rate of the active ingredient, formulation stability, and visual appearance to ACZONE Gel, 7.5%. These properties contribute to the ability of Taro's formulation to be administered once daily for the treatment of acne vulgaris, just like ACZONE Gel, 7.5%.[131] This conclusion is

[131] Ex. 15, Avramoff Dep. 196:22–198:1; Ex. 7, ACZONE Gel, 7.5% Prescribing Information, ALG_ACZ0397186, at ALG_ACZ0397186.

supported by Taro's ANDA No. 210191, which presents data indicating its product is bioequivalent to ACZONE Gel, 7.5%.[132]

131. All of the data above leads to the conclusion that the combination of Carbomer Homopolymer Type C, [redacted] in Taro's ANDA Product serves substantially the same function, acts in substantially the same way, and achieves substantially the same result as the claimed polymeric viscosity builder, embodied by Sepineo P 600, the polymeric viscosity builder in ACZONE Gel, 7.5% (an embodiment of the "topical pharmaceutical composition" recited in claim 1).

6. Taro's ANDA Product contains water.

132. Taro's ANDA Product contains water.[133]

133. Taro admitted and testified that its ANDA Product contains water.[134]

134. Accordingly, Taro's ANDA Product meets this element because it contains water.

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[132] Ex. 11, Dapsone Gel, 7.5% Product Development Summary, TARO-DG-00000655, at TARO-DG-00000741; Ex. 34, Taro's Clinical Study Report, TARO-DG-00056374, at TARO-DG-00056436–37.

[133] Ex. 12, Taro's ANDA, Section 2.3.P.1, TARO-DG-00000254, at TARO-DG-00000254.

[134] Taro's Response to Request for Admission No. 9; Ex. 15, Avramoff Dep. 186:18–21.

Exhibit B

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

C.A. NO. 17-633 (JFB)(SRF) (Consolidated)

----------x

ALMIRALL, LLC,

Plaintiff,

vs.

TARO PHARMACEUTICAL INDUSTRIES LTD. and TARO PHARMACEUTICALS, INC.,

Defendants.

----------x

December 21, 2018

9:25 a.m.

Videotaped deposition of MAJELLA E. LANE, Ph.D., held at the offices of Fenwick & West, LLP, 902 Broadway, Suite 14, New York, New York 10010, before Suzanne J. Stotz, Certified Realtime Reporter, Registered Professional Reporter, and a Notary Public of the State of New York.

**** Job No. 29325

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ALSO PRESENT:
JOE BARRION, Videographer

I N D E X

EXAMINATION

E X H I B I T S

(Exhibits attached to transcript.)

THE VIDEOGRAPHER: This is the videographer speaking, Joe Barrion, from EcoScribe Chicago. Today's date is December 21st, 2018. The time on the video monitor is 9:25 a.m. We are here at the offices of Fenwick & West located at 902 Broadway, New York, New York, to take the videotaped deposition of Majella Lane in the matter of Almirall, LLC versus Taro Pharmaceutical Industries Limited and Taro Pharmaceuticals, Inc., in the United States District Court for the District of Delaware, Civil Action Number 17-633(JFB)(SRF) (Consolidated).

Will counsel please identify yourselves and state whom you represent.

MR. TRAINOR: James Trainor of Fenwick & West on behalf of the plaintiff Almirall.

MR. BENSON: Stephen Benson from the law firm of Katten Muchin Rosenman on behalf of the Taro defendants. And with me today is also Kimberly Beis, also of Katten and also on behalf of the Taro defendants.

THE VIDEOGRAPHER: And will the court reporter, Suzanne Stotz, please swear in the witness.

MAJELLA E. LANE, Ph. D., having first been duly sworn by a Notary Public, was examined and testified as follows:

EXAMINATION

BY MR. BENSON:

Q. Good morning, Dr. Lane.

A. Good morning.

Q. How are you this morning?

A. Fine. Thank you.

Q. Good. Have you been deposed previously?

A. Yes.

Q. Okay. In a United States court?

A. Yes.

Q. Okay. So I will run through very quickly just some -- something to refresh your mind about the protocol. I will be asking you a series of questions today relating to the opinions you've provided in connection with a lawsuit Almirall has brought against Taro. Okay?

When I ask you a question,

A. -- the dapsone.
Q. Okay. I'm sorry. We are still on A, right? We are still on that it is what I say it is. But I need you to explain to me, why is it what you say it is? Why is the PVB -- why is the PVB carbomer and the three excipients you describe? Why?
A. I have explained in my second report.
Q. Okay.
A. I am just trying to find exactly where I talk about it.
MR. TRAINOR: I could be wrong, but maybe page 12.
THE WITNESS: You could be right.
Yes, it's on page 12 of the second report.
BY MR. BENSON:
Q. Okay.
A. Okay. So here is where I am outlining how Dr. Amiji and I disagree about what the polymeric viscosity builder is. And Dr. Amiji says that the function of the non-polymer excipients is creating an emulsion, and that creating an emulsion has nothing to do

with the claim reciting a polymeric thickening agent.

So a POSA would recognize that the addition of an oil phase to a formulation will alter the viscosity, feel and aesthetic appearance of a topical formulation. And while the Polysorbate 80 and Sorbitan Monooleate are going to stabilize the oil phase, they are also going to contribute to the viscosity of the final formulation.

Q. All right. So that's something that -- you know, not to harp on the claims, but, you know, this is a patent case about whether or not Taro's product falls within the scope of the claims. Where do you see in the claim 1 that the product has to be -- have an oil phase?

A. What I understand is that Sepineo P 600 is an embodiment of the polymeric viscosity builder in claim 1.

Q. But where -- look, if you take 7.5 percent dapsone, 30 percent DGME, AS/A copolymer, water -- does that have an oil phase, that formulation?

A. Could you repeat that again,

please?
Q. Sure. 7.5 percent dapsone --
A. Yes.
Q. -- 30 percent DGME --
A. Uh-huh.
Q. -- AS/A alone, copolymer alone, not Sepineo, but AS/A alone, and water, does that formulation -- those are the main constituent -- does that formulation have an oil phase?
A. Not as you list the components.
Q. Right. That would be a gel, right?
A. It would be formulation containing AS/A as a copolymer.
Q. Okay. All right. And that would be -- fall within the scope of the claims, right? It's an embodiment of the claims.
A. So -- let's go to the patent. It should be close at hand.
Q. Specifically, the claim would be great.
A. Yeah. Okay. So I'm looking at claim 1. And your question is, does a gel -- is that what your question is?
Q. Uh-huh.

Exhibit C

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ALMIRALL, LLC, Plaintiff, v. TARO PHARMACEUTICAL INDUSTRIES LTD. and TARO PHARMACEUTICALS, INC., Defendants.	C.A. No. 17-663 (JFB) (SRF) (Consolidated)

"CONFIDENTIAL" Under the Protective Order

REPLY EXPERT REPORT OF MAJELLA E. LANE, Ph. D.

I declare under penalty of perjury of the laws of the United States of America that the following is, to the best of my knowledge and belief, true and correct.

Dated: November 20, 2018

_____

Majella E. Lane, Ph.D.

Table of Contents

54. In sum, a POSA reading the specification would not understand that the patentee was dedicating Taro's polymeric viscosity builder to the public and the disclosure-dedication rule does not bar Almirall's infringement claim.

C. Ensnarement

55. I have been asked to construct a hypothetical Claim 1 that covers the literal claim scope in addition to Taro's ANDA Product. In my opinion, the proper hypothetical claim reads as follows (additions underlined and bolded):

> **1**. A method for treating a dermatological condition selected from the group consisting of acne vulgaris and rosacea comprising administering to a subject having the dermatological condition selected from the group consisting of acne vulgaris and rosacea a topical pharmaceutical composition comprising:
>
> about 7.5% w/w dapsone;
>
> about 30% w/w to about 40% w/w diethylene glycol monoethyl ether;
>
> about 2% w/w to about 6% w/w of a polymeric viscosity builder comprising acrylamide/sodium acryloyldimethyl taurate copolymer **or Carbomer homopolymer type C**;
>
> and water;
>
> wherein the topical pharmaceutical composition does not comprise adapalene.

56. In his report, Dr. Amiji offers two hypothetical claims: one that expands the polymeric viscosity builder range to "about 1% w/w to about 6% w/w" (as opposed to the claimed range of about 2-6% w/w) and replaces A/SA with Carbomer homopolymer type C; and one that merely replaces A/SA with Carbomer homopolymer type C.[78] In my view, neither of those two hypotheticals is correct. Removing A/SA from the claim changes (and potentially

[78] Amiji Report, paras. 91-92.

Exhibit D

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/885,805	10/16/2015	Kevin S. Warner	19107 DIV (AP)	9004

51957 7590 11/18/2015

ALLERGAN, INC.
2525 DUPONT DRIVE, T2-7H
IRVINE, CA 92612-1599

EXAMINER	
DRAPER, LESLIE A ROYDS	

ART UNIT	PAPER NUMBER
1629	

NOTIFICATION DATE	DELIVERY MODE
11/18/2015	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents_ip@allergan.com
pair_allergan@firsttofile.com

Office Action Summary

Application No.	Applicant(s)		
14/256,805	WARNER ET AL.		
Examiner	**Art Unit**	**AIA (First Inventor to File) Status**	
Leslie A. Royds Draper	1629	Yes	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 October 2015*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *1-10* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-10* is/are rejected.

8)☒ Claim(s) *5,9* is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

4) ☐ Other: _____.

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

DETAILED ACTION

Claims 1-10 are presented for examination.

Acknowledgement is made of the present application as a divisional (DIV) application of U.S. Patent Application No. 14/082,955, filed November 18, 2013, now U.S. Patent No. 9,161,926, which claims benefit under 35 U.S.C. §119(e) to U.S. Provisional Patent Application Nos. 61/728,403, filed November 20, 2012, and 61/770,768, filed February 28, 2013.

Objections to the Claims

Claims 5 and 9 are objected to for reciting "eczema" twice in the claim. Correction is required.

Claims 5 and 9 are objected to for misspelling the term "pilaris" as "piralis". Correction is required.

Claim Rejections - 35 USC § 112(a) (Pre-AIA First Paragraph), Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112(a):

> (a) IN GENERAL.—The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.

The following is a quotation of the first paragraph of pre-AIA 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5 and 7-9 are rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, because the specification, while being enabling for administering the claimed topical dapsone preparation for the treatment of acne vulgaris or rosacea, does not reasonably provide enablement for administering the claimed topical dapsone preparation for the treatment of any other dermatological condition. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In this regard, the application disclosure and claims have been compared per the factors indicated in the decision *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) as to undue experimentation. The factors include:

1) the nature of the invention;
2) the breadth of the claims;
3) the predictability or unpredictability of the art;
4) the amount of direction or guidance presented;
5) the presence or absence of working examples;
6) the quantity of experimentation necessary;
7) the state of the prior art; and,
8) the relative skill of those skilled in the art.

The relevant factors are addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art.

Note that the specification must be enabling as of the filing date. MPEP §2164.05(a).

Applicant's instant claims are directed to a method for the treatment of any dermatological condition by administering a topical pharmaceutical composition comprising about 7.5% w/w dapsone; about 30% w/w to about 40% w/w diethylene glycol monoethyl ether; about 2% w/w to about 6% w/w acrylamide/sodium acryloyldimethyl taurate copolymer; and water, and further wherein the composition does not comprise adapalene (claim 1). Applicant additionally provides for narrower embodiments of the claimed composition, which comprise about 7.5% w/w dapsone; about 30% w/w diethylene glycol monoethyl ether; about 4% w/w acrylamide/sodium acryloyldimethyl taurate copolymer; and water (and does not comprise adapalene) (claims 2, 3, 7). Dependent claims further provide for the composition to contain methyl paraben (claims 4, 8). The claims circumscribe the treatment of any dermatological condition, including those specifically claimed (e.g., acne vulgaris, rosacea, atopic dermatitis, chronic wounds, bed sores, keratosis pilaris, sebaceous cysts, etc.), as well as other numerous and varied dermatological conditions, such as melanoma, squamous cell carcinoma, psoriasis, ichthyosis, Stevens-Johnson syndrome, tinea pedis, keloid formation, etc.

Note, for the purposes of this discussion, that the level of skill in the art is high and is at least that of a medical doctor with several years of experience in the art.

Dapsone was well known in the art at the time of the effective filing date as an effective treatment for acne vulgaris and rosacea. Garrett (WO 2009/108147; 2009) teaches that "[d]apsone was first synthesized in 1908 and has been used medically as an antibiotic and an anti-inflammatory" (p.11, l.4-5). Garrett teaches that both oral and topical formulations of dapsone were known in the art to be effective for the treatment of acne (p.11, l.7-8; p.11, l.31-34), and further discloses the effectiveness of topical dapsone therapy for the treatment of rosacea (abstract; p.1, l.31-35; p.3, l.5-7; p.7, l.30-p.8, l.9; Ex.1, p.23 *et seq.*). Garrett (WO 2009/061298; 2009) further teaches that 5% topical dapsone gel has been proven in clinical studies to be effective for the treatment of acne vulgaris and provides ≤1% of the systemic exposure to dapsone as that seen with typical oral dapsone therapy (p.11, l.1-4). Ahluwalia et al. (WO 2011/014627; 2011) further corroborates the efficacy of dapsone as an anti-acne compound (p.2, l.7-10). Ahluwalia et al. teaches, however, that dapsone's "mechanism of action is not entirely understood" (p.2, l.14-16). Ahluwalia et al. postulates that the anti-acne effect of dapsone is related to its effects in suppressing neutrophil recruitment and local production of toxic products, thereby "inhibiting neutrophil chemotaxis", "reducing generation of oxygen free radicals", inhibiting " release of lysosomal enzymes" and reducing " inflammatory effects of prostaglandins and leukotrienes", thereby providing an anti-inflammatory effect on acne lesions (p.2, l.16-22).

A diligent search of the prior and contemporaneous art at the time of the effective filing date of the claimed invention does not reveal any clear teachings supporting the use of dapsone for the treatment of any possible type of dermatological condition known in the art. McGeer et al. (U.S. Patent No. 5,532,219; 1996) suggests that dapsone is effective for the treatment of certain autoimmune disorders, including rheumatoid arthritis, dermatitis herpetiformis, temporal arteritis, polymyalgia rheumatic, cutaneous lupus erythematosus, Bechet's disease or polyarteritis nodosa (col.1, l.48-52), but fails to teach the usefulness of topical dapsone preparations in the treatment of any dermatological condition, including those specific conditions instantly claimed (e.g., atopic dermatitis, chronic wounds, bed sores, keratosis pilaris, nodular prurigo, sebaceous cysts, etc.), as well as any one or more of such numerous and varied dermatological conditions known in the art, such as, e.g., melanoma, squamous cell carcinoma, psoriasis, ichthyosis, Stevens-Johnson syndrome, tinea pedis, keloid formation, etc.

Applicant's claims, however, assert that the administration of the topical dapsone formulation would be effective to treat any or all such dermatological conditions known in the art (known or unknown) as of the effective filing date of the claimed invention. The concept that the skilled artisan would have been able to reasonably accomplish this objective, however, appears to fly in the face of what was known in the art at the time of the effective filing date of the claimed invention, namely that topical dapsone therapy was only recognized in the art to have clear and established efficacy in the treatment of acne vulgaris or rosacea. Moreover, Applicant's own working examples fail to demonstrate the ability of the claimed topical dapsone preparations to treat any type of dermatological condition (including those specific conditions claimed) in a patient in need thereof. Applicant's working examples are limited to specific topical preparations of dapsone and do not demonstrate the efficacy of such formulations in the treatment of any type of dermatological condition (including any or all of those specific dermatological conditions instantly claimed). There is no clear basis, then, in the proffered working examples to conclude that Applicant's claimed method of administering the recited topical dapsone preparation was capable of treating any or all types of dermatological conditions in a patient suffering from the same. As a result, the as-filed specification fails to clearly enable the full scope of embodiments circumscribed by Applicant's claimed method.

While the lack of adequate working examples cannot be the sole factor in determining enablement, the unpredictable nature of the art and the absence of substantial evidence commensurate in scope with the breadth of the presently claimed subject matter provide additional weight to the present conclusion of insufficient enablement in consideration of the *Wands* factors as a whole.

As the cited art and discussion of the above factors establish, the disclosure and supporting examples provided in the present specification, coupled with the state of the art at the time of the invention, fail to imbue the skilled artisan with a reasonable expectation or ability to use the full scope of the invention as instantly claimed. In order to actually use the claimed invention, it is clear from the discussion above that the skilled artisan could not rely upon Applicant's disclosure as required by 35 U.S.C. §112(a) (pre-AIA first paragraph) in order to practice the full scope of embodiments presently claimed.

Claim Rejections - 35 USC § 112(b) (Pre-AIA Second Paragraph)

The following is a quotation of 35 U.S.C. 112(b):

(b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-10 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

Instant Claims 1 and 7

In claims 1 and 7, the phrase "in need thereof" renders the claim indefinite because it is unclear if the patient is simply in need of the recited step of administering the topical dapsone composition (for any therapeutic purpose) or if the patient is specifically in need of treatment of "a dermatological condition". Clarification is required.

As claims 2-6 and 8-10 fail to remedy this deficiency in the claims, they are also rejected on the same grounds as instant claims 1 and 7.

Instant Claims 5 and 9

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949).

In claims 5 and 9, Applicant recites various examples of broader species of dermatological conditions that contain within their scope other species listed in the Markush group. For example, "dermatitis" is generic to "atopic dermatitis" or "eczema" (Benhamou et al., U.S. Patent Application Publication No. 2012/0064144, March 2012, teaches that eczema is a form of dermatitis; p.1, para.[0003]). Also, claims 5 and 9 recite "inflammatory dermatoses", which is also generic to the species of "atopic dermatitis" or "eczema", as the term "dermatitis" necessarily implies the presence of inflammation (Santa, U.S. Patent No. 5,989,571; col.1, l.50-51). Still further, claims 5 and 9 recite "chronic wounds", which is generic to the species of "bed sores". The use of such conflicting broad and narrow limitations in the same claim renders the claim unclear as to which types of dermatological conditions are permitted within the Markush group and which are not.

For example, contact dermatitis is a type of dermatitis, which suggests that it might be included within the Markush group; however, the Markush group lists other specific types of dermatitis that are not contact dermatitis, indicating that contact dermatitis is not actually within the claimed Markush group. Similarly, seborrheic dermatitis is a type of dermatitis, which suggests that it would be included in the Markush group, but the Markush group lists specific species of dermatitis (i.e., atopic dermatitis) that are not seborrheic dermatitis, which again implies that this species is not actually within the Markush group claimed. Clarification is required.

In claims 5 and 9, the intended distinction between "dermatitis" and "inflammatory dermatoses" is not clearly set forth in the claim. Santa (U.S. Patent No. 5,989,571; col.1, l.50-51) teaches that the term "dermatitis" is necessarily characterized by inflammation (thus, constituting "inflammatory dermatoses"). Either the recitation of both "dermatitis" and "inflammatory dermatoses" is redundant or it defines different conditions that are not clearly distinguished by the claim. Clarification is required.

In claims 5 and 9, the phrase "treatment of chronic wounds" renders the claim indefinite because it is unclear if the "dermatological condition" to be treated is "chronic wounds" *per se* or some other unspecified aspect of "treatment of chronic wounds". Clarification is required.

For these reasons, the claims fail to meet the tenor and express requirements of 35 U.S.C. §112(b) (pre-AIA second paragraph) and are, thus, properly rejected.

Claim Rejections - 35 USC § 103

In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102 of this title, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims the examiner presumes that the subject matter of the various claims was commonly owned as of the effective filing date of the claimed invention(s) absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and effective filing dates of each claim that was not commonly owned as of the effective filing date of the later invention in order for the examiner to consider the applicability of 35 U.S.C. 102(b)(2)(C) for any potential 35 U.S.C. 102(a)(2) prior art against the later invention.

Claims 1-5 and 7-9 are rejected under 35 U.S.C. 103 as being unpatentable over Garrett (WO 2009/108147 A1; 2009) in view of Hani et al. (WO 2010/105052 A1; 2010).

Garrett teaches dapsone compositions with a pharmaceutically acceptable carrier for topical delivery of dapsone (p.12, l.1-2).

Garrett teaches that the topical composition preferably includes a thickening agent or thickener as part of the carrier, such as, e.g., polymeric thickeners, to increase viscosity, stability and improve suspending capability when added to a mixture (p.13, l.22-29). Garrett discloses polymeric thickeners that may be employed in the composition, such as the gelling agent CARBOPOL, a cross-linked acrylic acid polymer (also known as carbomer), and further teaches that the thickener generally comprises between about 0.2-4% w/w of the composition (p.15, l.5-19).

Garrett additionally teaches that the topical composition includes an organic solvent system, preferably diethylene glycol monoethyl ether (DGME, also known as ethoxydiglycol; p.13, l.30-p.14, l.2), which is generally incorporated in an amount of about 25-35% w/w of the composition (p.17, l.4-12).

Garrett teaches that the topical composition also preferably contains a preservative to prevent or diminish microorganism growth, such as methyl paraben (p.17, l.14-21).

Garrett further discloses that the topical composition comprise between 0.5-10% w/w dapsone (p.19, l.24-25).

Garrett teaches a preferred composition comprising about 5% w/w dapsone; about 0.85% w/w carbomer 980; about 25% w/w DGME; about 0.2% w/w methyl paraben; about 0.2% w/w sodium hydroxide; and about 68.75% w/w purified water (p.20, l.6-9).

Garrett teaches that the relative percentages of each of the components of the composition may be varied depending upon the desired strength of the formulation, gel viscosity, and desired ratio of microparticulate to dissolved dapsone (p.20, l.10-13).

Garrett further teaches that the compositions are effective for the treatment of rosacea by applying the dapsone composition once or twice daily (p.3, l.5-6; p.7, l.30-p.8, l.9).

Garrett differs from the instant claims only insofar as it does not explicitly teach (1) acrylamide/sodium acryloyldimethyl taurate copolymer in an amount of "about 2% to about 6% w/w" (claim 1), particularly about 4% w/w (claim 7) or (2) the exact claimed amount of DGME (i.e., "about 30% w/w"; claims 2, 7) or the exact claimed amount of dapsone ("about 7.5% w/w"; claims 1 and 7).

Hani et al. teaches that acrylamide/sodium acryloyldimethyl taurate copolymer is a thickener or viscosity increasing agent suitable for use in topical personal care compositions (p.24-28, para.[0118]; abstract).

A person of ordinary skill in the art before the effective filing date of the claimed invention would have had a reasonable expectation of success in substituting the cross-linked acrylic acid polymer (also known as carbomer or CARBOPOL) thickener of the dapsone formulation described in Garrett as being advantageously incorporated in an amount of 0.2-4% w/w (which clearly suggests amounts of "about 4% w/w" as claimed) with acrylamide/sodium acryloyldimethyl taurate copolymer because each was well

known in the art to be a suitable thickening agent for topical personal care products, as evidenced by Garrett and Hani et al. The substitution, therefore, of one for the other would have been *prima facie* obvious before the effective filing date of the claimed invention because the cross-linked acrylic acid polymer and acrylamide/sodium acryloyldimethyl taurate copolymer were known functional equivalents in the topical pharmaceutical art. "When a patent 'simply arranges old elements with each performing the same function it had been known to perform' and yields no more than one would expect from such an arrangement, the combination is obvious." See *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007) at 1395-1396, quoting *Sakraida v. AG Pro., Inc.*, 425 U.S. 273 (1976) and *In re Fout*, 675 F.2d 297, 301 (CCPA 1982) ("Express suggestion to substitute one equivalent for another need not be present to render such substitution obvious").

In further support of *prima facie* obviousness, note that the teachings in Garrett provide for ranges of dapsone, DGME and polymeric thickener that clearly meet and/or circumscribe the ranges instantly claimed. See, e.g., Garrett at p.15, l.5-19; p.17, l.4-12; and p.19, l.24-25, which disclose the use of 0.5-10% w/w dapsone and about 25-35% w/w DGME, as well as about 0.2-4% w/w polymeric thickener (which clearly suggests the use of the same amount of another thickener, such as that of Hani et al.). Such ranges clearly overlap or encompass Applicant's instantly claimed amounts of:

(i) "about 7.5% w/w" dapsone (claims 1 and 7);

(ii) "about 30% w/w" DGME (claims 2 and 7); and

(iii) "about 2% w/w to about 6% w/w" polymeric thickener (claim 1), particularly "about 4% w/w" (claims 3 and 7).

Note, further, that Garrett clearly suggests the incorporation of a polymeric thickener in an amount of about 0.2-4% w/w of the composition, which clearly suggests the incorporation of another thickener, such as the acrylamide copolymer thickener of Hani et al., within such a desirable range. The disclosure of incorporating the polymeric thickener within the range of 0.2-4% w/w of the composition is a clear suggestion to incorporate the polymeric thickener (such as that of Hani et al.) in an amount that constitutes "about 4% w/w" of the composition as instantly claimed (claims 1, 3 and 7).

Thus, Garrett teaches the use of such components in amounts that clearly meet or encompass the ranges specifically recited in the present claims. As stated by the MPEP at §2144.05, "In the case where the claimed ranges 'overlap or lie inside ranges disclosed by the prior art' a *prima facie* case of obviousness exists. *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990)..."[A] prior art reference that discloses a range encompassing a somewhat narrower range is sufficient to establish a *prima facie* case of obviousness." *In re Peterson*, 315 F.3d 1325, 1330, 65 USPQ2d 1379, 1382-83 (Fed. Cir. 2003). See also *In re Harris*, 409 F.3d 1339, 74 USPQ2d 1951 (Fed. Cir. 2005)."

A person of ordinary skill in the art before the effective filing date of the claimed invention would have had a reasonable expectation of success in varying the amounts of the components of the composition described in Garrett within the disclosed ranges therein. This is because Garrett teaches that the components may be employed in varying amounts within the described parameters, while retaining the therapeutic functionality of the composition. The selection of the optimal amounts of the components of the composition would have been a routine matter of optimization on the part of the artisan of ordinary skill, said artisan recognizing that the individual components may be varied within the broader ranges described in Garrett while still preserving the therapeutic properties of the composition. Moreover, the fact that the claimed ranges overlap and fall within those described in the prior art is clear evidence of *prima facie* obviousness. MPEP §2144.05.

Therefore, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill in the art before the effective filing date of the claimed invention.

Claims 6 and 10 are rejected under 35 U.S.C. 103 as being unpatentable over Garrett (WO 2009/108147 A1; 2009) in view of Hani et al. (WO 2010/105052 A1; 2010), as applied above to claims 1-5 and 7-9, taken in further view of Garrett (WO 2009/061298; 2009).

Garrett '147 in view of Hani et al. as applied above to claims 1-5 and 7-9.

Garrett '147 in view of Hani et al. differ from the instant claims only insofar as they do not explicitly teach administration of the topical dapsone preparation to treat acne vulgaris (claims 6, 10).

Garrett '298 teaches that oral dapsone was known to be effective for the treatment of acne (p.9, l.31-34). Garrett '298 teaches that topical dapsone gel formulations have been shown to be effective in the treatment of acne vulgaris and result in ≤1% of the systemic exposure that is seen with typical oral dapsone treatment (p.11, l.1-4).

A person of ordinary skill in the art before the effective filing date of the claimed invention would have had a reasonable expectation of success in administering the topical dapsone preparation of Garrett '147 in view of Hani et al. for the treatment of acne vulgaris because Garrett '298 teaches that topical dapsone was known in the art to be an effective treatment for acne vulgaris. The skilled artisan would have been motivated to do so because dapsone was well known in the art to be an effective therapy for treating acne vulgaris and topical application of dapsone for this purpose was known to significantly reduce systemic exposure to dapsone as compared to oral therapy, thereby reducing adverse side effects associated with dapsone therapy for acne. It would, therefore, have been *prima facie* obvious to the ordinarily skilled artisan before the effective filing date of the claimed invention to employ the topical dapsone preparation of Garrett '147 in view of Hani et al. for the purpose of treating acne vulgaris.

Therefore, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill in the art before the effective filing date of the claimed invention.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the claims at issue are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the reference application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO internet Web site contains terminal disclaimer forms which may be used. Please visit http://www.uspto.gov/forms/. The filing date of the application will determine what form should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that

meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to http://www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Claims 1-10 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 9,161,926.

'926 claims a topical pharmaceutical composition comprising about 7.5% w/w dapsone, about 30% w/w to about 40% w/w diethylene glycol monoethyl ether, about 2% w/w to about 6% w/w of a polymeric viscosity builder consisting of acrylamide/sodium acryloyldimethyl taurate copolymer, and water, wherein the composition does not comprise adapalene (patent claims 1-3). '926 additionally claims an embodiment of this topical pharmaceutical composition that comprises about 7.5% w/w dapsone, about 30% w/w diethylene glycol monoethyl ether, about 4% w/w of a polymeric viscosity builder consisting of acrylamide/sodium acryloyldimethyl taurate copolymer, and water, also wherein the composition does not comprise adapalene (patent claim 5). '926 additionally provides for the topical composition to further comprise methyl paraben (patent claims 4, 6).

'926 differs from the instant claims only insofar as it does not explicitly claim a method for treating a dermatological condition, e.g., acne vulgaris, by administering the claimed topical composition (claims 1, 5-7, 9-10).

In the '926 disclosure, however, the patentee discloses that the topical dapsone composition is therapeutically effective for the treatment of various dermatological conditions, including acne vulgaris, rosacea, atopic dermatitis, bed sores, keratosis pilaris, etc. (col.3, l.28-45; col.11, l.60-col.12, l.10).

A person of ordinary skill in the art at the time of the invention would have had a reasonable expectation of success in administering the topical dapsone composition as provided for in the '926 claims to a subject in need of treatment of the recited dermatological conditions for the purpose of treating the same because the '926 disclosure specifically teaches that the topical dapsone composition may be formulated for the purposes of treating the same dermatological conditions as instantly claimed. The skilled artisan would have sought to employ the topical dapsone composition of the '926 claims for the additional therapeutic utilities disclosed in the specification of the '926 patent for medicinal purposes. It would, therefore, have been *prima facie* obvious to the ordinarily skilled artisan at the time of the instant invention to utilize the topical dapsone composition of the '926 claims for the treatment of the same

dermatological conditions as instantly claimed in view of the utilities disclosed by the patentee of the '926 claims.

A patent's "disclosure may be used...to answer the question whether claims merely define an obvious variation of what is earlier disclosed and claimed." *AbbVie Inc. v. Mathilda & Terence Kennedy Inst. of Rheumatology Trust*, 112 USPQ2d 1001, 1012 (Fed. Cir. 2014) (quoting *In re Basell Poliolefine Italia S.P.A.*, 89 USPQ2d 1030, 1036 (Fed. Cir. 2008). The '926 patent discloses that the above-cited utilities are within the scope of the invention. These aspects of the instant claims are, therefore, obvious over the '926 patent. The *AbbVie* court explicitly noted that the Federal Circuit has "repeatedly approved examination of the disclosed utility of the invention claimed in an earlier patent to address the question of obviousness" and that "a later expiring patent is not patentably distinct from an earlier expiring patent if it merely claims a disclosed utility of the earlier claimed invention." *Id.* For example, when the claims in a later-expiring patent "merely recite methods of administering" the compositions claimed in the earlier patent, they are not patentably distinct over the claims of the earlier expiring patent." *Id.* (quoting *Pfizer, Inc. v. Teva Pharms. USA, Inc.*, 86 USPQ2d 1001, 1008 (Fed. Cir. 2008)).

This is a non-provisional nonstatutory double patenting rejection.

Claims 1-5 and 7-9 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 8,586,010, or are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1, 4-7 and 13-19 of U.S. Patent Application No. 14/063,841, each alternatively taken in view of Garrett (WO 2009/108147 A1; 2009) and Hani et al. (WO 2010/105052 A1; 2010).

'010 or '841 each individually claim a method of treating rosacea in a patient in need thereof by administering a topical dapsone preparation that comprises about 5 wt% dapsone, about 0.85 wt% carbomer 980, about 25 wt% diethylene glycol monoethyl ether, about 0.2 wt% methyl paraben, about 0.2 wt% sodium hydroxide and about 68.75 wt% purified water.

The amounts of dapsone ("about 5 wt%") or diethylene glycol monoethyl ether ("about 25 wt%") as recited in the '010 or '841 claims are understood to meet Applicant's required amounts of "about 7.5%

w/w" dapsone and "about 30% w/w" diethylene glycol monoethyl ether as provided for in instant claims 1, 2 and 7, absent any explicit definition of the amount of variation tolerated by the term "about" as used in the instant claims.

'010 or '841 differ from the instant claims only insofar as they do not explicitly teach the incorporation of acrylamide/sodium acryloyldimethyl taurate copolymer in an amount of "about 4% w/w" (claims 1, 3, 7).

Garrett teaches dapsone compositions with a pharmaceutically acceptable carrier for topical delivery of dapsone (p.12, l.1-2). Garrett teaches that the topical composition preferably includes a thickening agent or thickener as part of the carrier, such as, e.g., polymeric thickeners, to increase viscosity, stability and improve suspending capability when added to a mixture (p.13, l.22-29). Garrett discloses polymeric thickeners that may be employed in the composition, such as the gelling agent CARBOPOL, a cross-linked acrylic acid polymer (also known as carbomer), and further teaches that the thickener generally comprises between about 0.2-4% w/w of the composition (p.15, l.5-19). Garrett further teaches that the compositions are effective for the treatment of rosacea by applying the dapsone composition once or twice daily (p.3, l.5-6; p.7, l.30-p.8, l.9).

Hani et al. teaches that acrylamide/sodium acryloyldimethyl taurate copolymer is a thickener or viscosity increasing agent suitable for use in topical personal care compositions (p.24-28, para.[0118]; abstract).

A person of ordinary skill in the art before the effective filing date of the claimed invention would have had a reasonable expectation of success in substituting carbomer thickener of the dapsone formulation of the '010 or '841 claims with acrylamide/sodium acryloyldimethyl taurate copolymer because each was well known in the art to be a suitable thickening agent for topical personal care products, as evidenced by Garrett and Hani et al. The substitution, therefore, of one for the other would have been *prima facie* obvious before the effective filing date of the claimed invention because the cross-linked acrylic acid polymer and acrylamide/sodium acryloyldimethyl taurate copolymer were known functional equivalents in the topical pharmaceutical art. "When a patent 'simply arranges old elements with each performing the same function it had been known to perform' and yields no more than one would expect

from such an arrangement, the combination is obvious." See *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007) at 1395-1396, quoting *Sakraida v. AG Pro., Inc.*, 425 U.S. 273 (1976) and *In re Fout*, 675 F.2d 297, 301 (CCPA 1982) ("Express suggestion to substitute one equivalent for another need not be present to render such substitution obvious").

The skilled artisan also would have had a reasonable expectation of success in incorporating the acrylamide copolymer thickening agent into the topical dapsone preparation in an amount of, e.g., "about 4% w/w" as instantly claimed because Garrett teaches topical dapsone formulations for the treatment of rosacea in which the polymeric thickening agent is included in amounts of up to 4% w/w of the composition. The skilled artisan would have recognized that the optimal amount of the polymeric thickening agent would have been a routine matter of optimization on the part of the artisan of ordinary skill, said artisan recognizing that the polymeric thickener may be advantageously included in topical dapsone formulations in an amount of up to 4% w/w of the composition and still constitute a therapeutically effective preparation for the treatment of rosacea, as evidenced by Garrett.

This is a non-provisional rejection over the claims of U.S. Patent No. 8,586,010 and a provisional rejection over the claims of U.S. Patent Application No. 14/063,841.

Claims 6 and 10 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 8,586,010, or are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1, 4-7 and 13-19 of U.S. Patent Application No. 14/063,841, each alternatively taken in view of Garrett (WO 2009/108147 A1; 2009) and Hani et al. (WO 2010/105052 A1; 2010) as applied above to claims 1-5 and 7-9, further in view of Garrett (WO 2009/061298; 2009).

'010 or '841 as applied above to claims 1-5 and 7-9, each alternatively taken in view of Garrett '147 and Hani et al.

'010 or '841, each alternatively taken in view of Garrett '147 and Hani et al., differ from the instant claims only insofar as they do not explicitly teach administration of the topical dapsone preparation to treat acne vulgaris (claims 6, 10).

Garrett '298 teaches that oral dapsone was known to be effective for the treatment of acne (p.9, l.31-34). Garrett '298 teaches that topical dapsone gel formulations have been shown to be effective in the treatment of acne vulgaris and result in ≤1% of the systemic exposure that is seen with typical oral dapsone treatment (p.11, l.1-4).

A person of ordinary skill in the art before the effective filing date of the claimed invention would have had a reasonable expectation of success in administering the topical dapsone preparation of the '010 or the '841 claims, each alternatively taken in view of Garrett '147 and Hani et al., for the treatment of acne vulgaris because Garrett '298 teaches that topical dapsone was known in the art to be an effective treatment for acne vulgaris. The skilled artisan would have been motivated to do so because dapsone was well known in the art to be an effective therapy for the treatment of acne vulgaris and topical application of dapsone for this purpose was known to significantly reduce systemic exposure to dapsone as compared to oral therapy, thereby reducing the adverse side effects associated with dapsone therapy for acne. It would, therefore, have been *prima facie* obvious to the ordinarily skilled artisan before the effective filing date of the claimed invention to employ the topical dapsone preparation of the '010 or '841 as modified by Garrett '147 and Hani et al. for the purpose of treating acne vulgaris.

This is a non-provisional rejection over the claims of U.S. Patent No. 8,586,010 and a provisional rejection over the claims of U.S. Patent Application No. 14/063,841.

Conclusion

Rejection of claims 1-10 is proper.

No claims of the present application are allowed.

Applicant is requested to specifically point out the support for any amendments made to the disclosure in response to this Office action, including the claims (M.P.E.P. §§ 714.02 and 2163.06). In doing so, applicant is requested to refer to pages and line (or paragraph) numbers (if available) in the as-filed specification, not the published application. Due to the procedure outlined in M.P.E.P. § 2163.06 for interpreting claims, other art may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds Draper whose telephone number is (571)272-6096. The examiner can normally be reached on Monday-Friday (8:30 AM-5:00 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey S. Lundgren can be reached on (571)-272-5541. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Leslie A. Royds Draper/
Primary Examiner, Art Unit 1629

November 12, 2015

Exhibit E

Attorney Docket No. 19107 (AP)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Kevin S. Warner *et al.*	Group Art Unit: 1629
Serial No.: 14/082,955	Examiner: Leslie A Royds Draper
Filed: November 18, 2013	Confirmation No.: 1222
For: TOPICAL DAPSONE AND DAPSONE/ADAPALENE COMPOSITIONS AND METHODS FOR USE THEREOF	FILED ELECTRONICALLY

DECLARATION OF KEVIN S. WARNER, PH.D. UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I, Kevin S. Warner, Ph.D., hereby declare:

1. I am a co-inventor in the above-captioned patent application.

2. I am an employee of the Applicant, Allergan, Inc. I have a Bachelor's of Science in chemistry from Brigham Young University and a Ph.D. from the University of Utah in Pharmaceutics and Pharmaceutical Chemistry. I have 12 years of experience conducting research in the areas of dermal and ophthalmic formulation development and leading project teams responsible for all CMC aspects of product development from phase 1 to phase 3 at Allergan, Inc.

3. I have read the above-captioned patent application and its pending claims as of the date of this Declaration. I have read the obviousness rejections made in the

Office Action dated December 1, 2014 and the publications cited by the patent examiner therein (International Patent Publication No. WO 2009/108147 A1, International Patent Publication No. WO 2010/105052 A1,US Patent Publication No. 2006/0204526, and the Lubrizol product description of Carbopol 980).

4. I am part of a team at Allergan responsible for developing a new formulation of Allergan's Aczone (dapsone) Gel, 5% product, wherein dapsone concentration is increased to 7.5% w/w from the 5% w/w level in Aczone 5% Gel. An object of this development project was to facilitate once daily dosing by increasing the concentration of dapsone, as compared to the current twice daily dosing regimen for Aczone 5% Gel.

5. During the course of development of the 7.5% w/w dapsone formulation, we looked to increase DGME concentration above the 25% level in Aczone 5% Gel in order to increase the saturation solubility of dapsone. Dapsone solubility increases with DGME concentration. This increase allows for a dissolved fraction of dapsone (dissolved fraction is calculated as the ratio of dapsone saturated solubility at 25 °C / dapsone concentration) comparable to that of Aczone 5% gel.

6. Under my supervision, a preliminary evaluation of thickeners suitable for use in the dapsone 7.5% gel formulation was performed. Five candidates were screened for their ability to thicken the proposed formulation: Carbopol® 980, Sepineo™ P 600, PPG-12/SMDI Copolymer (4,4'-Diisocyanatodicyclohexylmethane, polypropylene glycol polymer), Povidone/Eicosene (30:70), and Polyvinyl Alcohol. From this screening evaluation, we identified Carbopol 980 and Sepineo P 600 as promising gelling agents.

7. In additional experiments under my supervision, formulations containing Carbopol 980 showed undesired polymer aggregates at 40% diethylene glycol monoethyl ether ("DGME") concentration. This aggregation was not observed

with formulations containing Sepineo P 600 at 40% DGME. These results indicated that Sepineo P 600 is a more robust thickener and therefore more desirable for use in the gel formulation. I did not expect to observe Carbopol 980 incompatibility at a concentration of 40% DGME, especially because Carbopol 980 is compatible at concentrations of 25% DGME.

8. Based on the unexpected observation of Carbopol 980 incompatibility with 40% DGME, the thickener was changed from Carbopol 980 to Sepineo P 600 to mitigate the risk of polymer aggregation in DGME containing formulations.

9. In additional experiments under my supervision, a dapsone particle size assessment revealed that formulations thickened with Sepineo P 600 provided a smaller dapsone particle size as compared to Carbopol 980. The compositions of the formulations evaluated for particle size are outlined in Table 1 of Appendix A of this Declaration. Particle size data are provided in Table 2 (HORIBA data) of Appendix A of this Declaration. The data show that recrystallized dapsone particle size is smaller in the Sepineo P 600 formulation as compared to a Carbopol 980 formulation. I observed this difference even after 6 months storage under accelerated conditions (40 °C/75% RH) thereby showing no significant change in the particle size over time. This stability data suggests that particle size does not change over time irrespective of the stabilizer used (Carbopol or Sepineo). Thus a smaller initial particle size appears to be more relevant parameter that defines improved formulation characterization.

10. Based on the above results, my co-inventors and I selected Sepineo P 600 as the gelling agent for our dapsone 7.5% gel formulation. We made this selection due to Sepineo P 600's compatibility with concentrations of DGME greater than 25% and its improvement in dapsone particle size relative to Carbopol 980.

11. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true;

and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: February 2, 2015

Kevin S. Warner, Ph.D.

APPENDIX A

Table 1 **Composition of Formulations Analyzed for Dapsone Particle Size Comparison in Sepineo P 600 vs. Carbopol 980**

Component	% w/w		
	ACZONE (dapsone) Gel, 7.5%: 7.5% Dapsone, 30% DGME, 4% Sepineo P 600	7.5% Dapsone, 25% DGME, 1% Carbopol	7.5% Dapsone, 30% DGME, 1% Carbopol
Dapsone	7.5	7.5	7.5
DGME	30	25	30
Carbopol 980	N/A	1	1
Sepineo P 600	4	N/A	N/A
Methylparaben	0.2	0.2	0.2
Triethanolamine	N/A	QS pH 5.5 – 6.5	QS pH 5.5 – 6.5
Purified Water	QS 100	QS 100	QS 100

N/A = Not Applicable

Table 2 **Particle Size (HORIBA) Data Comparing Dapsone Particle Size in Sepineo P 600 vs. Carbopol 980 at Time = 0 and 6 Months at 40 °C/75% RH**

Formulation Description	D90 (µm)	
	T=0	T=6 Months 40 °C/75% RH
ACZONE (dapsone) Gel, 7.5%: 7.5% Dapsone, 30% DGME, 4% Sepineo P 600 (Lot ELE)	61	72
7.5% Dapsone 25% DGME 1% Carbopol (Lot ELF)	123	114
7.5% Dapsone 30% DGME 1% Carbopol (Lot ELG)	172	169

Exhibit F

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Kevin S. Warner, et al.	)	Group Art Unit: 1629
Serial No.:	14/885,805	)	Examiner: Draper, Leslie A. Royds
Filed:	October 16, 2015	)	Conf. No.: 9004
For:	TOPICAL DAPSONE AND DAPSONE/ADAPLENE COMPOSITIONS AND METHODS FOR USE THEREOF	)	

RESPONSE TO OFFICE ACTION

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir,

This is filed in response to an Office Action mailed on November 18, 2015. Please amend the above referenced patent application as follows. Authorization is hereby given to charge any fee required for the filing of this paper, to Deposit Account No. 01-0885.

Amendments to the Claims are reflected in the **listing of claims** which begin on page 2 of this paper.

Remarks begin on page 4 of this paper.

Amendments to the Claims:

The following claims replace all claims previously submitted in this application. Only those claims being amended herein show their changes in highlighted form, where insertions appear as underlined text (e.g., insertions) while deletions appear as strikethrough or surrounded by double brackets (e.g. ~~deletions~~ or [[deletions]]).

1. (**Currently Amended**) A method for treating a dermatological condition comprising administering to a subject having the dermatological condition ~~in need thereof~~ a topical pharmaceutical composition comprising:

   about 7.5% w/w dapsone;

   about 30% w/w to about 40% w/w diethylene glycol monoethyl ether;

   about 2% w/w to about 6% w/w of a polymeric viscosity builder consisting of acrylamide/sodium acryloyldimethyl taurate copolymer; and

   water;

   wherein the topical pharmaceutical composition does not comprise adapalene.

2. (Original) The method of claim 1, wherein the diethylene glycol monoethyl ether is present at a concentration of about 30% w/w.

3. (Original) The method of claim 1, wherein the polymeric viscosity builder is present at a concentration of about 4% w/w.

4. (Original) The method of claim 1, wherein the topical pharmaceutical composition further comprises methyl paraben.

5. (**Currently Amended**) The method of claim 1 wherein the dermatological condition is acne vulgaris, rosacea, atopic dermatitis, ~~treatment of chronic wounds,~~ bed sores, keratosis pilarispiralis, sebaceous cysts, ~~inflammatory dermatoses,~~ post inflammatory hyperpigmentation, eczema, xerosis, pruritis, lichen planus, nodular prurigo, ~~dermatitis, eczema,~~ or miliaria.

6. (**Currently Amended**) The method of claim 5 wherein the condition is selected from the group consisting of acne vulgaris and rosacea.

7. (**Currently Amended**) A method for treating a dermatological condition comprising administering to a subject having the dermatological condition ~~in need thereof~~ a topical pharmaceutical composition comprising:

about 7.5% w/w dapsone;

about 30% w/w diethylene glycol monoethyl ether;

about 4% w/w of a polymeric viscosity builder consisting of acrylamide/sodium acryloyldimethyl taurate copolymer; and

water;

wherein the topical pharmaceutical composition does not comprise adapalene.

8. (Original) The method of claim 7, wherein the topical pharmaceutical composition further comprises methyl paraben.

9. (**Currently Amended**) The method of claim 7 wherein the dermatological condition is acne vulgaris, rosacea, atopic dermatitis, ~~treatment of chronic wounds,~~ bed sores, keratosis pilaris ~~piralis~~, sebaceous cysts, ~~inflammatory dermatoses,~~ post inflammatory hyperpigmentation, eczema, xerosis, pruritis, lichen planus, nodular prurigo, ~~dermatitis, eczema,~~ or miliaria.

10. (**Currently Amended**) The method of claim 9 wherein the condition is selected from the group consisting of acne vulgaris and rosacea.

11. (**New**) The method of claim 6 wherein the condition is acne vulgaris.

12. (**New**) The method of claim 10 wherein the condition is acne vulgaris.

REMARKS

This Reply responds to the Office Action sent November 18, 2015, in which the Office Action rejected Claims 1-10. Claims 1, 5-7, and 9-10 have been amended. Claims 11 and 12 are new. Thus Claims 1-12 are currently pending. No new matter has been added by this amendment, and all amendments to the claims are fully supported by the originally filed specification and claims. The Applicants respectfully submit that the claims are in condition for allowance.

Objections to the Claims

Claims 5 and 9 were objected to for reciting "eczema" twice in the claims and for misspelling the term "pilaris" as "piralis". The Applicants submit that the amendments to the claims submitted herewith render the objections to Claims 5 and 9 moot.

Claim Rejections

35 U.S.C. § 112(a)

Claims 1-5 and 7-9 were rejected under 35 U.S.C § 112(a) or 35 U.S.C. § 112 (pre-AIA), first paragraph, because the specification, while being enabling for administering the claimed topical dapsone preparation for the treatment of acne vulgaris or rosacea, does not reasonably provide enablement for administering the claimed topical dapsone preparation for the treatment of any other dermatological condition.

The Applicants submit that all of the pending claims comply with the enablement requirement. According to the MPEP, the test for enablement requires analysis of whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention. *See* MPEP § 2164. The Applicants submit that the disclosure contains sufficient information regarding the subject matter of the claims. The disclosure of the present application clearly states that compositions described in the application are effective in treating dermatological conditions, including, but not limited to those recited in Claims 5 and 9. *See* the present application specification as originally

filed at paragraphs [009], [0018], [0040] and [0024]. Since the disorders being treated by the claimed methods are disclosed in the application as specifically tied to the compositions and formulations described therein, sufficient information regarding the subject matter of the claims exists so as to enable one skilled in the art to make and use the claimed methods. Thus, the Applicants respectfully request that the claim rejections under 35 U.S.C § 112(a) or 35 U.S.C. § 112 (pre-AIA), first paragraph be withdrawn.

35 U.S.C. § 112(b)

Claims 1-10 were rejected under 35 U.S.C. § 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite.

While the Applicants do not agree with the rejections, solely in order to expedite prosecution, the Claims have been amended. The Applicants submit that the amendments to the claims submitted herewith render the indefiniteness rejections raised by the Office Action moot.

Thus, the Applicants respectfully request that the claim rejections under 35 U.S.C. § 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite be withdrawn.

35 U.S.C. § 103

Claims 1-5 and 7-9 were rejected under 35 U.S.C. § 103 as being unpatentable over Garrett (WO 2009/108147 A1; 2009 – "Garrett") in view of Hani, et al. (WO 2010/105052 A1; 2010 – "Hani"). Claims 6 and 10 were rejected under 35 U.S.C. § 103 as being unpatentable over Garrett in view of Hani, et al., as applied above to claims 1-5 and 7-9, taken in further view of Garrett (WO 2009/061298; 2009). The Applicants submit that Claims 1-10 are <u>not</u> obvious in view of the cited references, at least for the reasons stated below. The Applicants note that the arguments presented below and the affidavit submitted herewith are substantially the same or the same as presented in the parent case (US 14/082,955), which claimed the formulation recited in the currently claimed method of use. The arguments and affidavit resulted in the allowance of the parent case.

First, Garrett teaches that a preferred composition comprises about 5% w/w dapsone wherein about 0.85% w/w carbopol 980 is used as a thickening agent.[1] The instant claims recite a new formulation of dapsone wherein the active ingredient is about 7.5% w/w dapsone and an entirely new thickening agent is employed. The new formulation of the instant claims does not include a carbomer such as Carbopol®, but instead utilizes as acrylamide/sodium acryloyldimethyl taurate copolymer, also known as "Sepineo™ P 600," and at a much higher concentration (about 2% to about 6% w/w) as compared to what Garrett teaches for its thickening agent.

Hani teaches a crosslinked PVP polymer for use in low pH topical formulations. While Hani may teach that acrylamide/sodium acryloyldimethyl taurate copolymer may be useful as ***an additional*** thickener with its PVP polymer, it certainly does not teach or suggest the use of Sepineo™ P 600 ***as the sole thickener*** in a topical dermatological formulation prepared with an active pharmaceutical ingredient. Moreover, the only mention of an acrylamide/sodium acryloyldimethyl taurate copolymer is found in paragraph [00118] of Hani, where it is included in a vast laundry list of other potential second thickeners. Finally, there is no guidance as to ***how much*** Sepineo™ P 600 one of ordinary skill in the art would use if it were to be selected from this laundry list in Hani.

Therefore, there are at least three significant distinctions between the present invention and the teachings of the cited art:

(i) The specific amount of dapsone recited in the instant claims; and

(ii) The use of Sepineo™ P 600 as the sole thickening agent in a topical dermatological formulation comprising dapsone; and

(iii) The specific amount of Sepineo™ P 600 recited in the instant claims.

The cited references do not teach or suggest these specific elements – alone or in combination. These facts, considered in view of the current law of obviousness, compels a finding of nonobviousness. The Applicants will now address the law cited by the Patent Office in the present Office Action as it applies to the present case.

---

[1] Garrett teaches other broader formulations of dapsone, but one skilled in the art seeking to improve upon the formulations of Garrett would look to its preferred embodiments.

The Office Action cites *KSR International Co. v. Teleflex Inc.* at page 6 of the Office Action for the proposition that a combination is obvious if it "simply arranges old elements with each performing the same function it had been known to perform and yields no more than one would expect from such an arrangement...." 82 USPQ2d 1385, 1395-96 (U.S. 2007) (internal quotes omitted). This is true, but here we have new elements performing different functions not taught in the cited references, and the combination yields unexpected results. As discussed above, there are at least three new elements: the specific amount of dapsone, the use of Sepineo™ P 600 as the sole thickening agent, and the specific amount of Sepineo™ P 600. None of these elements are taught or suggested in either Garrett or Hani. The combination of these elements is neither taught nor suggested in either Garret or Hani. And as will be demonstrated below, the Applicants present unexpected results from this combination. For these reasons, the Patent Office's reliance on the above selection from *KSR* is inapplicable to the facts of this case.

Furthermore, the Patent Office's reliance on *Wertheim*, *Woodruff*, *Peterson* and *Harris* at page 7 of the Office Action is inapplicable to the presently amended claims as it relates to the specific amount of dapsone, as these cases clearly apply only to questions of the alleged obviousness of ***narrow ranges*** within broad ranges. And again, the specific selection of about 7.5% w/w dapsone is nonobvious based on the teachings of Garrett, which prefers a 5% w/w concentration.

For the above reasons, the instant claims are not *prima facie* obvious over Garrett and Hani. There is simply no teaching or suggestion whatsoever that would leave one of ordinary skill in the art to the precise combination of elements of the claimed dapsone/Sepineo™ P 600 compositions.

Thus, the Applicants respectfully request that the claim rejections under 35 U.S.C. § 103 be withdrawn.

Unexpected Results

As stated above, the Examiner has failed to make a *prima facie* case of obviousness of the instant claims based upon the cited art. But even assuming for sake

of argument that the Examiner had made a proper *prima facie* case, the instant claims would still be patentable over the cited art because the Applicants have demonstrated unexpected results sufficient to overcome the hypothetical *prima facie* case. *See, e.g., In re Chupp*, 816 F.2d 643 (Fed. Cir. 1987) (finding of unexpected results based on superior properties in the context of the pharmaceutical arts).

Filed herewith is the Declaration of co-inventor Kevin S. Warner, Ph.D. ("Warner Declaration"). The present inventors unexpectedly discovered that Carbopol® 980, the thickening agent used in the Applicant's previous 5% dapsone formulation (and taught as preferred in the art cited by the Patent Office), resulted in undesirable polymer aggregates during formulation studies which lead to the present invention. *See* Warner Declaration, paragraphs 7-8. Sepineo™ P 600, on the other hand, performed surprisingly better and proved to be a more robust thickening agent. *Id.* This was an important discovery, as the use of Sepineo™ P 600 allowed for higher concentrations of DGME (*i.e.*, 30-40% w/w) which were found to be incompatible with Carbopol® 980. *Id.*

The inventors also discovered that Sepineo™ P 600 thickened formulations provided a smaller dapsone particle size distribution as compared directly to Carbopol® 980. *Id.* at 9. These particles were found to be stable over the course of 6 months under accelerated conditions. *Id.*

Sepineo™ P 600 was therefore selected as the gelling agent for the 7.5% w/w dapsone formulation of the instant claims. *Id.* at 10. The inventors made this selection based on the combination of the above factors which was entirely unexpected and could not have been predicted based on the previous 5% w/w dapsone formulation (with Carbopol® 980) or the references cited by the Patent Office. These unexpected results, which are commensurate in scope with the instant claims, further support the patentability of the claimed invention and warrant the withdrawal of the Examiner's obviousness rejection. The Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

Obviousness-Type Double Patenting

U.S. Patent No. 9161926

Claims 1-10 have been rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 9161926. The Applicants submit that this rejection is statutorily improper because of the present application's status as a divisional application of U.S. Patent No. 9161926, and thus must be withdrawn.

The Office Action acknowledges the present application's status as a divisional of U.S Patent Application No. 14/082,955, which eventually issued as U.S. Patent No. 9161926. *See* November 18, 2015 Non-Final Office Action at page 2, lines 5-8. 35 U.S.C. § 121 states in part that "[a] patent issuing on an application with respect to which a requirement for restriction under this section has been made, or on an application filed as a result of such a requirement, shall not be used as a reference either in the Patent and Trademark Office or in the courts against a divisional application or against the original application or any patent issued on either of them, if the divisional application is filed before the issuance of the patent on the other application." This is commonly known as the "safe harbor" provision, which prevents, for example, a parent application from being used for a grounds of rejection of a child divisional application. Thus, because the present application is a divisional of U.S. Patent No. 9161926, the double patenting rejection of the present application in view of U.S. Patent No. 9161926 is improper and should be withdrawn.

U.S. Patent No. 8586010

Claims 1-5 and 7-9 have been rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 8586010, or the provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1, 4-7 and 13-19 of U.S. Patent Application No. 14/063,841, each alternatively taken in view of Garrett (WO 2009/108147 A1; 2009) and Hani, et al. (WO 2010/105052 A1; 2010).

Claims 6 and 10 have been rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 8586010, or the provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1, 4-7 and 13-19 of U.S. Patent Application No. 14/063,841, each alternatively taken in view of Garrett (WO 2009/108147 A1; 2009) and Hani, et al.

(WO 2010/105052 A1; 2010) as applied above to claims 1-5 and 7-9, further in view of Garrett (WO 2009/061298; 2009).

The Applicants submit that an obviousness-type double patenting rejection over Claims 1-10 of the '010 patent is improper. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by or would have been obvious over, the reference claims. MPEP § 804. The Applicants submit that the pending Claims of the current application are patentably distinct from Claims 1-10 of the '010 patent, because the Claims of the present application recite several non-obvious elements not recited in Claim 1-10 of the '010 patent, as explained in detail above.

Thus, because the pending Claims in the present application are patentably distinct from Claim 1 of the '010 patent, an obviousness-type double patenting rejection would be improper and thus should not be made.

Applicant requests a Notice of Allowance. The Examiner is invited to call the undersigned attorney if any issues remain unresolved.

Please use Deposit Account 01-0885 for the payment of any extension of time fees, and/or the payment of any other fees due in connection with the present response.

Dated: February 18, 2016

Respectfully submitted,

/Laura L. Wine/

Laura L. Wine
Reg. No. 68681
Attorney for Applicant

Please direct all inquiries and correspondence to:

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2525 Dupont Drive, T2-7H
Irvine, California 92623-9534

19107 DIV (AP)

Tel: 714.246-4758/Fax: 714.246-6996

Exhibit G

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/885,805	10/16/2015	Kevin S. Warner	19107 DIV (AP)	9004

51957 7590 03/07/2016

ALLERGAN, INC.
2525 DUPONT DRIVE, T2-7H
IRVINE, CA 92612-1599

EXAMINER	
DRAPER, LESLIE A ROYDS	

ART UNIT	PAPER NUMBER
1629	

NOTIFICATION DATE	DELIVERY MODE
03/07/2016	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents_ip@allergan.com
pair_allergan@firsttofile.com

Office Action Summary

Application No.	Applicant(s)		
14/333,805	WARNER ET AL.		
Examiner	**Art Unit**	**AIA (First Inventor to File) Status**	
Leslie A. Royds Draper	1629	Yes	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 February 2016*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *1-12* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-5 and 7-9* is/are rejected.

8)☒ Claim(s) *6 and 10-12* is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date *18Feb16*.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

4) ☐ Other: _____.

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

DETAILED ACTION

Claims 1-12 are presented for examination.

Applicant's Amendment and Information Disclosure Statement (IDS) filed February 18, 2016 have each been entered into the present application. As reflected by the attached, completed copy of form PTO/SB/08A (three pages total), the Examiner has considered the cited references.

Claims 1-12 are pending and under examination. Claims 11-12 are newly added. Claims 1, 5-7, 9 and 10 are amended.

Applicant's arguments, filed February 18, 2016, have been fully considered. Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set of rejections and/or objections presently being applied to the instant application.

Applicant's Arguments and Declaration Filed February 18, 2016

In the submission filed February 18, 2016, Applicant provides various remarks directed to the obviousness rejections of record under 35 U.S.C. §103 (Reply, p.5-8), as well as a declaration of inventor Kevin S. Warner (hereinafter "the Warner Declaration") executed under 37 C.F.R. §1.132 in support of nonobviousness.

Applicant's most pertinent argument set forth in the record with regard to the nonobviousness of the claimed invention appears to be the data provided in the Warner Declaration (p.2, para.[4]-p.3, para.[10]). In the Warner Declaration, the Declarant states that he was involved with the development of a topical dapsone formulation with greater dapsone concentration (7.5% w/w) than the conventional 5.0% w/w ACZONE gel formulation (p.2, para.[4]). In order to increase the dapsone concentration from 5.0% w/w to 7.5% w/w as desired, the Warner Declaration states that a corresponding increase in diethylene glycol monoethyl ether (DGME) from its 25% w/w amount typically found in the 5.0% w/w ACZONE gel was necessary to solubilize dapsone in the formulation (p.2, para.[5]). A screening of various thickening

agents for use in the dapsone formulation identified two specific agents selected for their ability to thicken the proposed dapsone formulation: (i) CARBOPOL 980 (the same thickener agent employed in the closest prior art to Garrett) and (ii) SEPINEO P 600 (which is an acrylamide/sodium acryloyldimethyl taurate copolymer as recited for use in the instantly claimed formulation).

Experimental studies described in the Warner Declaration demonstrated that the use of 7.5% w/w dapsone with 40% w/w DGME and CARBOPOL 980 "showed undesired polymer aggregates" at this high concentration of DGME, but that "[t]his aggregation was not observed with [7.5% w/w dapsone] formulations containing SEPINEO P 600 at 40% DGME" (p.2-3, para.[7]). The Warner Declaration further notes that this incompatibility of CARBOPOL 980 with 40% DGME was unexpected as "CARBOPOL 980 is compatible at concentrations of 25% DGME" (p.3, para.[7]). Further comparisons of dapsone particle size of a gel formulation comprising 7.5% w/w dapsone, 30% w/w DGME and 4% w/w SEPINEO P 600 with a 7.5% w/w dapsone gel containing either 25% or 30% w/w DGME and 1% w/w CARBOPOL 980 were made, noting that the 7.5% w/w dapsone gel formulation using SEPINEO P 600 effectively reduced recrystallized dapsone particle size as compared to either CARBOPOL 980 formulation (Warner Declaration, p.5, Tables 1-2). Note that the quantity of CARBOPOL 980 used in the comparative formulations is lower than that of SEPINEO P 600, but it is understand from the Warner Declaration that the use of a greater quantity of CARBOPOL 980 would have further contributed to the polymer aggregation known to occur between higher concentrations of DGME (as used in the comparative formulations) and CARBOPOL 980.

The Warner Declaration, therefore, provides clear evidence that the improved properties of Applicant's claimed 7.5% w/w dapsone formulation (specifically, the reduction in undesirable polymer aggregates, as well as the reduction in dapsone particle size, thereby providing a smoother, less gritty gel formulation with reduced recrystallization of dapsone) yields directly from the selection of the acrylamide/sodium acryloyldimethyl taurate copolymer as the polymeric thickener of the formulation. As the proffered data appears to be reasonably representative of, and commensurate in scope with, the instantly claimed 7.5% w/w dapsone formulation as stipulated by MPEP §716.02(d), and further in view of the fact that the comparative dapsone formulations employed the same thickening agent used by the

closest prior art to Garrett in the same quantity suggested by this prior art reference (thereby constituting a reasonable comparison of the instantly claimed formulation with that of the closest prior art; MPEP §716.02(e)), the Warner Declaration appears to be probative of unexpected properties of the claimed formulation.

Accordingly, the obviousness rejections under 35 U.S.C. §103 (as well as the nonstatutory obviousness-type double patenting rejections over U.S. Patent No. 8,586,010 and U.S. Patent Application No. 14/063,841) are withdrawn in light of the evidence.

Objection to the Claims (New Grounds of Objection)

In view of the evidence and the withdrawal of the above-noted rejections, it is noted that instant claims 6 and 10-12 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim Rejections - 35 USC § 112(a) (Pre-AIA First Paragraph), Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112(a):

> (a) IN GENERAL.—The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.

The following is a quotation of the first paragraph of pre-AIA 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5 and 7-9 remain rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, because the specification, while being enabling for administering the claimed topical dapsone preparation for the treatment of acne vulgaris or rosacea, does not reasonably provide enablement for administering the claimed topical dapsone preparation for the treatment of any dermatological condition, because the specification does not enable any person skilled in the art to which it pertains, or with which it

is most nearly connected, to use the invention commensurate in scope with these claims, for the reasons of record set forth at p.2-5 of the previous Office Action dated November 18, 2015, of which said reasons are herein incorporated by reference.

Response to Applicant's Arguments

In reply, Applicant opines "that all of the pending claims comply with the enablement requirement" in view of the fact that "[t]he disclosure of the present application clearly states that compositions described in the application are effective in treating dermatological conditions, including, but not limited to those recited in [c]laims 5 and 9" (Reply, p.4). Applicant further alleges that "[s]ince the disorders being treated by the claimed methods are disclosed in the application as specifically tied to the compositions and formulations therein, sufficient information regarding the subject matter of the claims exists so as to enable one skilled in the art to make and use the claimed methods" (Reply, p.5).

The arguments have been fully and carefully considered, but are not found persuasive.

Applicant's remarks fail to address the evidence cited in support of the rejection's position that the instant claims, directed to methods for treating any dermatological condition (including, but clearly not limited to, those recited in instant claims 5 and 9), are not adequately enabled for the treatment of any such dermatological condition aside from acne vulgaris or rosacea. Garrett (WO 2009/108147; 2009) and Ahluwahlia et al. (WO 2011/014627; 2011) were cited as evidence of the state of the art with regard to topical dapsone therapy, each documenting the efficacy of topical dapsone preparations in the treatment of acne vulgaris and rosacea only. Neither Garrett nor Ahluwahlia et al., however, provide any evidentiary support to corroborate Applicant's assertions that topical dapsone therapy was known to be useful or effective for the treatment of the various specific dermatological conditions claimed (e.g., atopic dermatitis, bed sores, keratosis pilaris, nodular prurigo, sebaceous cysts, etc.), let alone any or all numerous and varied dermatological conditions known (or unknown) in the art as of the effective filing date of the claimed invention (e.g., melanoma, squamous cell carcinoma, psoriasis, ichthyosis, Stevens-Johnson syndrome, tinea pedis, keloid formation, etc.). Applicant's remarks provide nothing more than speculative and conclusory statements that the instant claims are enabled for the entire breadth of

dermatological conditions known in the art, but points to nothing in Garrett or Ahluwahlia et al. (or even any extraneous evidence in support of his position) that would bolster his allegation that topical dapsone therapy would have been effective for more than just the treatment of acne vulgaris or rosacea.

It was additionally noted that a diligent search of the prior and contemporaneous art at the time of the effective filing date of the claimed invention did not reveal any clear teachings supporting the use of topical dapsone therapy for the treatment of any possible type of dermatological condition known in the art as instantly claimed (aside from acne vulgaris or rosacea). McGeer et al. (U.S. Patent No. 5,532,219; 1996) was previously cited in further support of this position, in which other therapeutic uses of dapsone therapy were suggested, but of which none specifically related to other dermatologic uses of topical dapsone therapy (aside from acne vulgaris or rosacea). The state of the art, therefore, as of the effective filing date of the claimed invention did not clearly and unequivocally recognize the usefulness of topical dapsone therapy for dermatological applications outside of the treatment of acne vulgaris or rosacea as established by Garrett and Ahluwahlia et al. Applicant, therefore, cannot rely upon the state of the art as of the effective filing date of the claimed invention to enable his claimed topical dapsone formulation for the treatment of any or all dermatological conditions known (or unknown) in the art as of the effective filing date of the claimed invention.

The skilled artisan, therefore, has nothing else to rely upon but Applicant's own specification to bridge this clear gap between the knowledge accepted in the art as of the effective filing date of the claimed invention and the asserted applications of Applicant's claimed topical dapsone therapy. This lack of knowledge in the art regarding the effective use of topical dapsone therapy for the treatment of any or all dermatological conditions (including, but not limited to, those recited in instant claims 5 and 9) is not remedied by Applicant's own specification. Applicant's working examples fail to demonstrate the ability of the claimed topical dapsone preparations to treat any type of dermatological condition (including those specific conditions claimed) in a patient in need thereof and, therefore, fail to provide the necessary enabling guidance that is absent from the state of the art. Applicant's proffered working examples are limited to specific topical preparations of dapsone and do not demonstrate the efficacy of such formulations in the treatment of any type of dermatological condition (including any or all of those specific

conditions instantly claimed). The working examples, therefore, fail to provide any evidentiary basis to conclude that Applicant's claimed method of administering the recited topical dapsone therapy was effective to treat any or all types of dermatological conditions. Accordingly, it remains that the disclosure and supporting examples provided in the present specification, coupled with the nascent state of the art at the time of the invention with regard to topical dapsone therapy for the treatment of any or all dermatological conditions, fails to adequately enable the full scope of embodiments presently claimed. The rejection stands.

For these reasons *supra*, rejection of claims 1-5 and 7-9 is proper.

Conclusion

Rejection of claims 1-5 and 7-9 is proper.

Claims 6 and 10-12 are objected to for depending from a rejected base claim.

No claims of the present application are allowed.

Applicant is requested to specifically point out the support for any amendments made to the disclosure in response to this Office action, including the claims (M.P.E.P. §§ 714.02 and 2163.06). In doing so, applicant is requested to refer to pages and line (or paragraph) numbers (if available) in the as-filed specification, not the published application. Due to the procedure outlined in M.P.E.P. § 2163.06 for interpreting claims, other art may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds Draper whose telephone number is (571)272-6096. The examiner can normally be reached on Monday-Friday (8:30 AM-5:00 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey S. Lundgren can be reached on (571)-272-5541. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Leslie A. Royds Draper/
Primary Examiner, Art Unit 1629

March 2, 2016

Exhibit H

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ALMIRALL, LLC, Plaintiff, v. TARO PHARMACEUTICAL INDUSTRIES LTD. and TARO PHARMACEUTICALS, INC., Defendants.	C.A. No. 17-663 (JFB) (SRF) (Consolidated)

RESPONSIVE EXPERT REPORT OF PROFESSOR ALEXANDER M. KLIBANOV

I declare under penalty of perjury of the laws of the United States of America that the following is, to the best of my knowledge and belief, true and correct.

Dated: November 2, 2018

Alexander M. Klibanov, Ph.D.

Table of Contents

aluminum magnesium silicates (Veegum K); acrylic polymers coupled to hydrophobic chains (Aculyn 44®); the family of modified starches; and the family of polyacrylamides. *See* Nadau-Fourcade at [0071].

80. The prior art also taught two distinct thickening agents that comprised an A/SA copolymer, namely Sepineo™ and Simulgel 600 PHA®. *See* Nadau-Fourcade at [0071]. At the time of the invention of the '219 patent, only Simulgel™ had been used in an approved pharmaceutical product, Epiduo®. *See* Epiduo PI at TARO-DG-00147503. According to the FDA's Inactive Ingredient Database of September 2012, Sepineo™ had not yet been used in an FDA-approved drug.[4] *See* ALM-ACZ0000932 (listing Sepineo™ as a "pending" inactive ingredient). The Constantinides Report admits this fact. *See, e.g.*, ¶ 103.

XIII. DEFENDANTS' PRIOR-ART REFERENCES

81. Dr. Constantinides contends that the asserted claims of the '219 patent are obvious based on two combinations of references: Garrett I in view of Bonacucina and Garrett I in view of Nadau-Fourcade. I discuss below these three references—Garrett I, Bonacucina, and Nadau-Fourcade—as well as additional references cited by Dr. Constantinides although not part of the two combinations identified. *See* Constantinides Rpt. at ¶ 18.

A. WO 2009/108147 ("Garrett I") (TARO-DG-00065185–248)

82. Garrett I is a 2009 international patent application entitled "Dapsone to Treat Rosacea," that was already expressly considered and cited by the Patent Office during the

[4] The current Inactive Ingredient Database is available online at http://wayback.archive-it.org/7993/20170112022245/http:/www.fda.gov/Drugs/InformationOnDrugs/ucm113978.htm. To determine what database would have been available to a POSA in 2012, I accessed the Archived Inactive Ingredients Database, which is linked to from the current website, at http://wayback.archive-it.org/7993/20170112022245/http:/www.fda.gov/Drugs/InformationOnDrugs/ucm113978.htm. I then downloaded the September 2012 Inactive Ingredient Database File. *See* ALM-ACZ0000733–996.

prosecution of the '219 patent. *See* '219 prosecution history at ALG_ACZ0000071. While Garrett I purports to discuss methods to "provide treatment of rosacea using topical formulations of dapsone" (Garrett I, Abstract), two important points, explained in detail below but ***wholly ignored by Dr. Constantinides***, should be emphasized at the outset: (i) that the term "dapsone" in the aforementioned title and Abstract of Garrett I is ***broad*** and includes not only the individual chemical compound dapsone itself (*i.e.*, 4,4′-diaminodiphenyl sulfone) but also various other chemical compounds; and (ii) that Garrett I actually taught that dapsone itself in Aczone 5% gel is no more effective than placebo in treating rosacea.

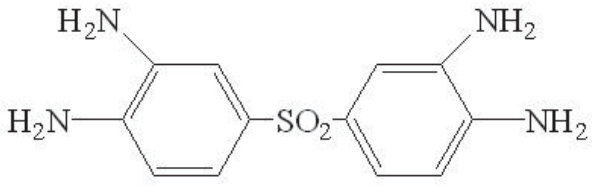
83. Among other things, Garrett I described the results of a clinical trial involving treatment groups given Aczone (dapsone gel) 5% twice a day, Aczone 5% once a day, MetroGel® (metronidazole gel) 1% once a day, Aczone 5% plus MetroGel once a day, and a vehicle control (*i.e.*, a carrier without an API, also called placebo). Garrett I at 35:6–10. The results showed that 5% dapsone once or twice per day fared no better than the vehicle control in reducing inflammatory lesions of rosacea after twelve weeks. *See, e.g.*, *id.* at 35:16–24 (vehicle control group reduced inflammatory lesion counts from baseline by 8.3, while dapsone twice a day reduced lesion counts from baseline by 8.0 and dapsone once a day reduced lesion counts from baseline by 5.7). Dapsone once or twice daily also fared no better than vehicle in IGA success rates[5] than vehicle. *See id.* at 35:24–27 ("Success rates, defined as a score of clear or almost clear with at least 2 points of improvement on a 5-point IGA scale, showed that more subjects treated with dapsone 2x/day had success (27.4%) than subjects treated with dapsone 1x/day (24.1%), but there was no difference from [vehicle control] (27.5%)."). The treatment with MetroGel® alone

[5] The IGA success rate is a measure of the proportion of total patients who achieved an Investigator's Global Assessment score of 0 (clear) or 1 (almost clear) and improved at least 2 points from baseline. *See* Garrett I at 29:22–26.

reduced inflammatory lesions to virtually the same degree as the combination of MetroGel® and dapsone. *See id.* at 35:17–20 (reporting reductions of 11.3 and 11.4, respectively). And the dapsone treatment groups neither substantially improved erythema and telangiectasia nor performed better than other treatment groups, which included vehicle control. *See id.* at 35:30–33.

84. In the Definitions section of its Detailed Description of the Invention, Garrett I expressly defined "dapsone" to mean "the chemical compound dapsone having the chemical formula $C_{12}H_{12}N_2O_2S$ as well as bis(4-aminophenyl)sulfone, 4,4′-diaminodiphenylsulfone and its hydrates, 4,4′-sulfonylbisbenzeneamine, 4,4′-sulfonyldianiline, dia[mino]phenylsulfone, ***dapsone analogs, and dapsone related compounds***." Garrett I at 5:5–9 (emphasis added).

85. "Dapsone analogs" were further defined as "chemical compounds with similar chemical structures and thus similar therapeutic potential to dapsone [itself,] such as the substituted bis(4-aminophenyl)-sulfones." *Id.* at 5:9–11. A POSA would have understood that even the exemplary (due to the phrase "such as") ***substituted*** bis(4-aminophenyl)-sulfones comprise many hundreds of distinct chemical compounds because various substituents can be introduced at least into any of the 8 open positions in the benzene rings.

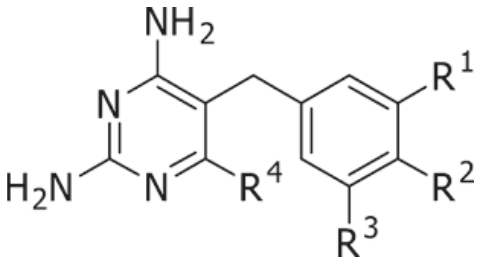


M.W. 278.3
$C_{12}H_{14}N_4O_2S$

As an example, the chemical structure shown above corresponds to bis(3,4-aminophenyl)sulfone, a known compound which is a substituted *bis*(4-aminophenyl)-sulfone where two extra amino

groups are introduced in the benzene rings (one in each ring). However, the two additional amino groups need not be either in the 3,3′-positions or in the different rings. Also, a POSA would have recognized that the number of the extra amino groups introduced is not limited to two and instead can be one, three, four, five, six, seven, or eight. Furthermore, NH_2 groups are just an example here, and Garrett I does not preclude any other substituents (or their numbers), such as hydroxyl, alkyl, alkoxyl, halogen, and numerous others.

86. "Dapsone related compounds" were additionally further defined in Garrett I as "chemical compounds that have similar therapeutic potential, but are not as closely related by chemical structure to dapsone[,] such as substituted 2,4-diamino-5-benzylpyrimidines." *Id.* at 5:12–14. A POSA would have recognized that even substituted 2,4-diamino-5-benzylpyrimidines by themselves, expressly mentioned by Garrett I merely as an ***example*** (due to the preceding "such as"), as a group encompass hundreds, if not thousands, of compounds depending on what the substituent in the benzyl moiety is and its location. A general chemical structure of just one particular substituted 2,4-diamino-5-benzylpyrimidine is depicted here as an example,



where R^1, R^2, R^3, and R^4 represent various chemical substituents.

87. Therefore, in contrast to the '219 patent, where "dapsone" is defined as a ***single individual compound***, 4,4′-diaminodiphenyl sulfone (*see* 2:12), Garrett I expressly defines "dapsone" as a huge family of thousands of distinct chemical compounds.

88. Garrett I expressly disclosed that dapsone analogs and related compounds were described in two earlier prior-art references, U.S. Patent Nos. 4,829,058 ("the '058 patent") and 4,912,112 ("the '112 patent"). Garrett I at 11:9–20. Both the '058 and '112 patents assayed the antimicrobial activity of a subset of such compounds and concluded that certain of the derivative compounds were more effective antimicrobial agents, either alone or in combination with 4,4′-diaminodiphenyl sulfone, than 4,4′-diaminodiphenyl sulfone itself. '058 patent at 9:1–43; '112 patent at 4:27–52, 17:40–50 (Example 21).

89. Garrett I disclosed a "dapsone" concentration range of "between 0.5% and 10%" without identifying any particular chemical compound out of the many discussed above. *See* Garrett I at 19:24–25. A POSA would not have been able to discern whether the entire "dapsone" concentration range would be suitable for all encompassed "dapsone" compounds, including dapsone analogs and related compounds, or whether only certain concentrations within the range were appropriate for a given "dapsone" compound.

90. Garrett I disclosed that its preferred embodiments were in an aqueous gel form, in which there was an "optimal balance" between dissolved and microparticulate (*i.e.*, solid, undissolved) "dapsone." *See id.* at 17:30–18:14. The dissolved "dapsone" would be readily available to enter the skin, while the microparticulate "dapsone" would be retained on the skin surface, where most of it would be slowly dissolved in bodily fluids and delivered through the skin. *See id.* at 17:28–19:2.

91. Garrett I also taught that there were numerous "pharmaceutically acceptable carriers." *See id.* at 6:18–33. A "pharmaceutically acceptable carrier" was, in turn, broadly defined as "a pharmaceutically acceptable solvent, suspending agent or vehicle for delivering an active agent to a patient." *Id.* at 6:18–20. Garrett I listed many categories of carriers, including

"antiadherents, binders, coatings, disintegrants, fillers, diluents, colorants, glidants, lubricants, and preservatives." *Id.* at 6:26–28. For topical preparations, specifically, Garrett I named "glycerides, semi-synthetic and synthetic glycerides, hydrogenated oils, liquid waxes, liquid paraffins, liquid fatty alcohols, sterols, polyethylene glycols and cellulose derivatives;" in a preferred embodiment, the solvent DGME was included in a pharmaceutically acceptable carrier. *Id.* at 6:28–33.

92. In addition, Garrett I taught that there were numerous solvents used in embodiments of the topical compositions. *See id.* at 13:30–14:8, 15:26–17:12 (describing organic solvents, including dozens of specific examples of glycols and their ethers, alcohols, and other substantially non-toxic polar or non-polar solvents). A POSA would have understood that there were at least hundreds of possible organic solvents in the categories disclosed in Garrett I, each with its own chemical structure and unique physical and chemical properties. *See id.* at 15:26–17:3.

93. Garrett I disclosed embodiments where ***a*** glycol ether was present in a concentration range between about 20% to about 40% by weight; it was further stated, however, that "[m]ore specifically, compositions of the present invention have a glycol ether present in about 25.0 wt.% of the composition." *Id.* at 17:4–5, 10–12. DGME was described as a solvent that could be used in preferred embodiments of the invention of Garrett I. *See id.* at 13:34–14:8.

94. Garrett I also disclosed the use of a large variety of thickeners, or gelling agents. *See id.* at 14:28–15:25. Specifically, Garrett I named several particular commercial brands of gelling agents, conspicuously none of which contained A/SA copolymer. *See id.* at 15:5–11. The preferred concentrations of these gelling agents were disclosed to be within the 20-fold range from about 0.2% to about 4%. *See id.* at 15:12–17.

95. Garrett I was ***not*** directed to the treatment of acne. *See id.* at 1:31 ("The invention is directed to the treatment of rosacea.").

B. Giulia Bonacucina *et al.*, "Characterization and stability of emulsion gels based on acrylamide/sodium acryloyldimethyl taurate copolymer." *AAPS PharmSciTech* 10(2): 368–375 (2009) ("Bonacucina") (TARO-DG-00063824–831)

96. Bonacucina is a 2009 article which disclosed the use of Sepineo P 600, a polymeric viscosity builder comprising A/SA copolymer. *See* Bonacucina at 368–369. But Bonacucina also acknowledged that other viscous liquids instead of Sepineo could be suitably used as thickeners or gelling agents for topical administration. *See id.* at 368 and 374 (concluding that Sepineo P 600 was "a prime candidate for use in the formulation of gels and emulsion gels"). Bonacucina did not disclose DGME or related solvents, much less their concentrations.

97. Bonacucina did not relate to the treatment of either acne or rosacea and, in fact, did not address the use of Sepineo with APIs, let alone with dapsone in particular, to treat any medical condition. Instead, Bonacucina focused on characterizing the gel structure of Sepineo and of a Sepineo emulsion in almond oil. *See id.* at 369. Bonacucina notes that "the most important result" observed therein for the emulsion gel "is surely the fact that the addition of an oily phase increased system consistency only minimally." *Id.* at 374.

C. International Publ. No. WO 2010/072958 A2 ("Nadau-Fourcade") (TARO-DG-00148447–459)

98. Nadau-Fourcade is a 2012 United States patent application entitled "Topical Pharmaceutical Composition Containing a Water-Sensitive Active Principle."[6] The patent

[6] The United States patent application is an English translation of the international patent application of Nadau-Fourcade.

O. WO 2011/014627 ("Ahluwalia") (TARO-DG-00065298–331)

135. Ahluwalia is a 2011 international patent application entitled "Combination of Dapsone with Adapalene." It was expressly considered and cited by the Patent Office during the prosecution of the '219 patent. *See* '219 prosecution history at ALG_ACZ0000071. Ahluwalia described topical compositions for the treatment of acne and other dermatological conditions containing at least dapsone and another API selected from adapalene, tazarotene, and treinion. *See* Ahluwalia at Abstract.

136. Ahluwalia generally teaches a concentration range of 0.5–10% w/w for dapsone and 1–50% w/w for DGME. Ahluwalia at Table 1. But each of the figures of Ahluwalia disclosed compositions containing 5.0% w/w of dapsone and 25.0% w/w of DGME (referenced by one of its trade names, Transcutol® P). *See id.* at Figures 1–5; *see also id.* at 6:19–33, Tables 2A and 2B (providing examples of potential combinations that all include 5% w/w of dapsone).

137. Ahluwalia also taught the use of other solvents besides DGME. The figures in Ahluwalia demonstrated the use of DGME and, for example, dimethyl isosorbide (Figures 1, 3A–D, 4A–D, and 5) and/or propylene glycol (Figures 1, 4A–D, and 5). Dimethyl isosorbide and propylene glycol were known solvents for "dapsone." *See, e.g.*, Garrett I at 15:34–16:3.

XIV. THE CLAIMED ACZONE 7.5% INVENTION WOULD NOT HAVE BEEN OBVIOUS

A. The Asserted Claims of the '219 Patent Would Not Have Been Obvious over the Combination of Garrett I and Bonacucina

138. Dr. Constantinides first opines that the asserted claims of the '219 patent would have been obvious over the combination of Garrett I and Bonacucina. *See* Constantinides Rpt. at ¶ 81. I disagree, at least because:

- a POSA would ***not*** have been motivated to use the claimed dapsone or its claimed concentration;

- a POSA would ***not*** have been motivated to choose a DGME concentration of "about 30% w/w to about 40% w/w," or "about 30% w/w," as required by the claims; and

- a POSA would ***not*** have been motivated to use a polymeric viscosity builder concentration comprising A/SA copolymer of "about 2% w/w to about 6% w/w," as required by the claims.

139. I understand from counsel that Dr. Julie Harper, MD, will be offering additional opinions as to why the asserted claims would not have been obvious from a medical perspective. My report, therefore, should not be understood as an indication that there are no other reasons why the claims were non-obvious.

1. *A POSA Would Not Have Been Motivated to Select the Dapsone of the Claimed Invention or Its Claimed Concentration of About 7.5%*

140. The dapsone of the asserted claims of the '219 patent is expressly a particular compound known as 4,4′-diaminodiphenyl sulfone. *See* '219 patent at 2:13–14 ("Dapsone, (4,4′-diaminodiphenyl sulfone) is a medicament possessing several beneficial medicinal activities."). An initial reason the asserted claims would not have been obvious is that a POSA would have been motivated to select neither specifically 4,4′-diaminodiphenyl sulfone nor its claimed concentration of about 7.5%, in view of the combination of Garrett I and Bonacucina.

141. Nothing in Bonacucina would have motivated a POSA seeking to make an improved acne or rosacea treatment to select either any "dapsone" compound, or the particular dapsone compound of the asserted claims, or its concentration of about 7.5%. Bonacucina nowhere mentions dapsone or any concentration of dapsone (or of any API), nor does it discuss acne or rosacea treatments. See above at ¶¶ 96–97.

142. Nor would Garrett I have motivated a POSA seeking to select the particular dapsone of the asserted claims of the '219 patent (*i.e.*, 4,4′-diaminodiphenyl sulfone), let alone in a concentration of about 7.5%. A POSA seeking to make an improved acne or rosacea treatment

would not have even looked to Garrett I. With regard to acne treatment, a POSA would not have seen Garrett I, which is only directed to ***rosacea***, as relevant. *See, e.g.* Garrett I at 1:31 ("The invention is directed to the treatment of rosacea.").[8] Nor would a POSA have looked to Garrett I even if seeking to make a rosacea treatment, because Garrett I makes clear that its dapsone-alone formulation was not successful, *i.e.*, no more effective in treating rosacea than control vehicle alone (*i.e.*, a carrier with no API). See above at ¶ 83. And because a POSA would not have looked to Garrett I, (s)he would not have motivated by Garrett I to select the particular dapsone compound in the asserted claims.

143. Additionally, even if a POSA had looked to Garrett I, that reference would not have directed him/her to the particular 4,4′-diaminodiphenyl sulfone in the asserted claims. As noted above, Garrett I expressly defined "dapsone" very broadly to encompass a vast array of distinct compounds (a fact that Dr. Constantinides failed to even mention in his report), meaning that it would not have been obvious to choose any particular compound, including the 4,4′-diaminodiphenyl sulfone of the claimed invention. See above at ¶¶ 84–87. Moreover, a POSA would have understood from the prior art cited by Garrett I that several dapsone derivatives are actually ***more effective*** antimicrobial agents, either alone or in combination with 4,4′-

[8] Dr. Constantinides opines that Garrett I also disclosed use of dapsone as an acne treatment, *see* Constantinides Rpt. at ¶ 82 fn. 17 (citing Garrett I at 11:29–34), but the passage he cites merely incorporated patents from the late 1990s and early 2000s, including Osborne I. As explained below, Osborne I, viewed in conjunction with subsequent prior art, shows that a concentration of 7.5% dapsone would not have been obvious because it reflects an understanding that a 5% dapsone concentration was optimized and that there was accordingly no reason to further increase dapsone concentration to 7.5%. See below at ¶¶ 149–152. I am further informed by counsel that Dr. Harper, a medical doctor, will explain that, from a clinical perspective, there would not have been motivation to select dapsone as an anti-acne agent because the prior art viewed dapsone as less effective than cheaper alternatives. *See, e.g.*, Coutinho at 2.

diaminodiphenyl sulfone, than the 4,4′-diaminodiphenyl sulfone of the claimed invention. See above at ¶ 88.

144. Nor would it have been obvious to choose a concentration of about 7.5% of the claimed compound. Dr. Constantinides notes that in one preferred embodiment, Garrett I discloses a composition that includes "about 0.5% to 10% of dapsone that exists in both a dissolved state and a microparticulate state." Constantinides Rpt. at ¶ 89. In view of such range, he opines that a POSA "would have understood that each point in the range of 0.5% to 10% w/w, including 7.5%, could have been used to make a topical dapsone composition" and, therefore, that a topical composition "having ***any*** amount of dapsone 0.5% [*sic*] to 10% w/w, including 7.5%, would have been obvious." *Id.* (emphasis added). I disagree.

145. For the reasons stated above at ¶ 142, there would have been no reason for a POSA to look to Garrett I ***at all***, and hence no reason to look to its "dapsone" concentration range—meaning that it would not have obvious to select ***any*** concentration of "dapsone" within Garrett I's range. And even if a POSA had consulted the concentration range in Garrett I, (s)he would not have been led to a specific concentration of "about 7.5% w/w" of the particular dapsone compound (*i.e.*, 4,4′-diaminodiphenyl sulfone) in the asserted claims of the '219 patent.

146. Because the definition of "dapsone" in Garrett I is so broad, the 20-fold concentration range for "dapsone" in Garrett I yields an immense number of possible "dapsone"/concentration combinations—ranging in the many thousands of options. Therefore, there would have been way too many possibilities to be obvious for a POSA to select, as Dr. Constantinides contends.[9] *See* Constantinides Rpt. at ¶ 89.

[9] Furthermore, a POSA would have understood that the concentration range in Garrett I applied collectively to "dapsone" ***as a broad group***, not that every one of the thousands of potential "dapsone" species would work at each concentration in the range of 0.5% to 10%. Garrett I sheds

147. Nor would anything in Garrett I have led a POSA to the particular concentration of about 7.5% w/w of the claimed compound, as opposed to any other concentration. Garrett I discloses no embodiment containing a 7.5% concentration and does not otherwise recommend using this particular concentration. Accordingly, Garrett I would have neither motivated a POSA to select the claimed compound in a concentration of about 7.5% nor provided a reasonable expectation of success in doing so.

148. Dr. Constantinides also arbitrarily looks outside of his proposed combination and observes that a "topical dapsone 5% gel had been marketed since at least 2008 under the name Aczone Gel, 5%, with a topical twice-daily administration." Constantinides Rpt. at ¶ 90. But nothing about the original Aczone 5% gel would have provided a POSA with a reason to select the claimed dapsone compound in a concentration of about 7.5%, either. To the contrary, (s)he would have surmised from the Aczone 5% gel and other prior art that a concentration of 5% was optimal.

149. A POSA would have understood that the Aczone 5% gel was developed under the Osborne I patent, which issued in 1999. See above at ¶ 115. As Dr. Constantinides himself observes, Osborne I contained a range of possible concentrations for dapsone of 0.5 to 10%. *See* Constantinides Rpt. at ¶ 108 (citing Osborne I at 4:66–5:4). A POSA, therefore, would have recognized that the developers of the Aczone 5% gel chose a dapsone concentration of 5% even though Osborne I indicated that a dapsone concentration of up to 10% was possible. A POSA

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no light on which compounds the disclosed range of "dapsone" concentrations pertains to; given the sheer multitude of "dapsone" compounds encompassed by Garrett I, it would have been impossible for a POSA to determine which values within the 20-fold concentration range would have been suitable for a given dapsone compound, such as the 4,4′-diaminodiphenyl sulfone of the claimed invention of the '219 patent. Thus, a POSA would have had no rational reason to understand Garrett I as teaching that each and every concentration in its range would work for 4,4′-diaminodiphenyl sulfone of the claimed invention.

hence would have concluded that the selection of 5% dapsone in the original Aczone product signaled that the 5% concentration was ***optimal***: otherwise, the developers of dapsone would have selected a higher concentration if they had believed it would yield a better product, such as one requiring application of the treatment only once-daily rather than twice-daily.

150. The Osborne 2011 reference would have further reinforced the conclusion that as of 2012 5% was an optimal dapsone concentration. As discussed above, Osborne 2011 teaches that the 5% concentration allowed not only an optimal ratio of dissolved to undissolved dapsone, but also an optimal "amount" of dapsone that would penetrate the stratum corneum, which according to Osborne 2011 was important for control of inflammation associated with acne. See above at ¶¶ 104–106.

151. Because a POSA would have understood that the dapsone concentration had already been optimized at 5%, (s)he would have seen no reason to raise it. That is especially true because the Aczone 5% gel product information warned of side effects, and sharply increasing the dapsone concentration by 50% (from 5% w/w to 7.5% w/w) would have been expected to exacerbate those adverse effects, including severe hemolysis in patients with G6PD deficiency. *See, e.g.*, Aczone 5% label at TARO-DG-00063818 (describing symptoms "suggestive of hemolytic anemia" observed in some patients treated with Aczone 5% gel and listing serious adverse reactions reported by patients in a clinical trial, including a suicide attempt, abdominal pain, severe vomiting, and pancreatitis).

152. Dr. Constantinides also cites to dapsone concentration ranges in other patents, including Osborne I, Lathrop, and Garrett II (again disregarding that in the last two references, the term "dapsone" expressly includes both dapsone itself (*i.e.*, 4,4′-diaminodiphenyl sulfone) and at least its various analogs and derivatives; *see* Lathrop at [0043] and Garrett II at

7:18–27), for the proposition that "dapsone amounts ranging up to 10% w/w in topical formulations were known in the art as well." Constantinides Rpt. at ¶¶ 90, 108, 89 (fn. 20). But a POSA would have viewed these ranges in light of subsequent prior art, including the Aczone 5% formulation and Osborne 2011, which taught that the 5% concentration had been ***optimized*** and hence there would have been no reason to increase it further despite these ranges. Likewise, a POSA would have viewed the statement from the 2006 Lathrop reference that especially preferred "dapsone" embodiments "may be [at] such percentages as 1, 2, 5 and 7.5" (Lathrop at [0047]) in view of subsequent prior art, which reflected an understanding that the 5% concentration for dapsone itself (*i.e.*, 4,4′-diaminodiphenyl sulfone) had been optimized and that there consequently was no reason to raise it. And Dr. Constantinides continues to ignore the undeniable fact that the term "dapsone" of Garrett I, Garrett II, and Lathrop is expressly far broader than that of the '219 patent.

2. *A POSA Would Not Have Increased the Concentration of DGME Above 25%*

153. Claims 1, 4, and 5 of the '219 patent cover a topical pharmaceutical formulation with a DGME concentration ranging from "about 30% w/w to about 40% w/w." Claim 2 further narrows the DGME concentration to "about 30% w/w." A POSA would have seen no reason to select those particular concentrations of DGME based on the combination of Garrett I and Bonacucina. This is an additional reason why the asserted claims would not have been obvious.

154. As of 2011, it was known that the Aczone gel 5% product used the solvent DGME in a concentration of 25% by weight.[10] For example, Osborne 2011 discussed the Aczone 5% gel product and disclosed that the product contained 25% DGME. *See* Osborne 2011 at 327

[10] The 5% dapsone topical gel as described in Osborne 2011 is the first pharmaceutical product to use DGME.

("The vehicle for topical dapsone is <1% carbomer, water, 25% DEGEE [also known as DGME], and a standard amount of methyl paraben.").

155. Dr. Constantinides opines that because a POSA would have wanted to increase the concentration of dapsone from 5% w/w in the original Aczone product to 7.5% w/w, (s)he would also have wanted to increase the DGME concentration from 25% w/w to 30–40% w/w. *See* Constantinides Rpt. at ¶ 92. According to Dr. Constantinides, "a POSA would know, generally speaking, [that] increasing the amount of solute would require an increased amount of solvent, and thus a 7.5% w/w dapsone gel formulation would require a corresponding increase in DGME." *Id.* He further opines that "[o]ptimization would lead [a] POSA to determine at least that the claimed range of 30-40% DGME is appropriate for a 7.5% w/w dapsone formulation." *Id.* I disagree.

156. The predicate for Dr. Constantinides's increased DGME concentration argument is the contention that a POSA would have wanted to increase the dapsone concentration to 7.5%. But, as discussed above at ¶¶ 144–152, a POSA would not have been so motivated. With no compelling reason to raise the dapsone concentration, there would also have been no rational reason to raise the DGME concentration under Dr. Constantinides's logic.

157. Additionally, there are other reasons why a POSA would not have increased the DGME concentration above 25%. (S)he would have understood that increasing the concentration of DGME would alter the optimized ratio between dissolved and undissolved dapsone achieved by the Aczone 5% gel. As explained in Osborne 2011, Aczone 5% gel not only optimized the ***amount*** of dapsone that penetrated the stratum corneum, but also maintained an optimal ratio of dissolved dapsone (which would pass through the stratum corneum to treat inflammation) and undissolved dapsone (which would stay on the skin to target pathogenic

bacteria). See above at ¶¶ 105–106. A POSA would not have wanted to increase the DGME level because this would change that ratio of dissolved and undissolved dapsone, which had been achieved with a formulation containing 5% dapsone and 25% DGME. Moreover, it was known that the relationship between dapsone solubility and DGME concentration was non-linear and hence not readily predictive. See above at ¶¶ 58–59.

158. Safety concerns would have further dissuaded a POSA from selecting DGME in a concentration over 25%. As late as in 2011, it was reported that DGME had only recently begun to be used in topical products. *See* Osborne 2011 at 325. The highest concentration that had been used in an approved product was 25%, as reflected in the Inactive Ingredients Database,[11] and other prior art suggested that further increasing DGME could give rise to safety concerns. *See* September 2012 Inactive Ingredient Database File at ALM-ACZ0000788; European Commission's Scientific Committee on Consumer Safety, Opinion on Diethylene Glycol Monoethyl Ether (DEGEE) (2010) (ALM-ACZ0000414–466) at 5, 43. Such potential safety concerns are a further reason why a POSA would have been reluctant to increase DGME beyond the 25% concentration previously used in approved pharmaceutical products.

159. Dr. Constantinides observes (and I agree) that the "IIG [FDA's Inactive Ingredient Guide] is a useful tool for selecting excipients, as it will tell the formulator what excipients have been previously used in topical products and the concentration[s] of such use." Constantinides Rpt. at ¶ 44. He further notes that "[u]sing the same excipients and concentrations for new topical compositions simplifies FDA review as FDA considers those IIG

[11] Although Osborne 2011 states that dermatologists were treating patients who applied topical products containing 5–40% of DGME, *see* Osborne 2011 at 325, DGME concentrations above 25% had not been used in FDA-approved drug products. *See* September 2012 Inactive Ingredient Database File at ALM-ACZ0000788.

listed excipients to be generally safe at the listed concentrations" and that "use of the excipient will simplify the requirements as it relates to demonstrating excipient safety." *Id.* These prudent observations further support my opinion that a POSA would not have wanted to increase DGME concentration above 25%: such higher concentrations of DGME had not been listed in the IIG and thus had not been accepted as safe by FDA—at a minimum substantially complicating FDA approval and possibly even undermining it.

160. Furthermore, such concerns about DGME would have been exacerbated because of safety concerns with dapsone itself. DGME was known to increase the skin permeability of drugs such as dapsone. *See* Osborne 2011 at 327 ("Many studies evaluating DEGEE [DGME] as a skin penetration modifier have shown that DEGEE [DGME] enhances a permeant's solubility in the skin without significantly influencing the diffusivity of the permeant in the skin, that is, stratum corneum."). Increasing the dapsone permeability would increase the systemic exposure to dapsone, thereby increasing the risk of side effects. Dapsone at 5% was already known to cause symptoms suggestive of hemolysis in some patients; a POSA would not have wanted to increase the dapsone concentration even further and hence expose patients to still greater risk of hemolysis or other adverse systemic effects observed in Aczone 5% patients. *See* 2008 Aczone 5% PI at TARO-DG-00063818. Given the known dangers of 5% dapsone, a POSA would not have been motivated to increase the concentration of DGME beyond 25% because it would have increased the permeability of dapsone and consequently the risk of adverse effects.

161. Moreover, even if a POSA had wanted to increase a concentration of dapsone above 5%—and believed on that basis that more solvent was necessary—(s)he instead could have added solvents other than DGME, rather than increasing the concentration of DGME above 25%. The prior art, including Garrett I, taught the use of dozens of possible solvents that

would have been compatible with dapsone for topical pharmaceutical use, and specifically pointed to using ***combinations*** of different solvents. See above at ¶¶ 91–92, 122. Adding a second solvent (*i.e.*, a co-solvent) with an established favorable safety record would have avoided the need to increase the concentration of DGME above 25% and consequently bypassed the related safety concerns and complications with FDA approval.

162. For the same reasons, if a POSA had sought to add another API in addition to dapsone and believed that more solvent was necessary on that basis, (s)he would have used solvents other than DGME, rather than increasing DGME concentration above about 25%. For example, Ahluwalia described compositions of dapsone plus adapalene and held the concentration of DGME at 25% while adding co-solvents such as dimethyl isosorbide and/or propylene glycol. *See* Ahluwalia at Figs. 1, 3A–D, 4A–D, 5.

163. Nothing in Dr. Constantinides's combination of Garrett I and Bonacucina would have altered this analysis. Bonacucina does not even mention DGME, much less recommend any particular concentration thereof, and thus would have neither motivated a POSA to use DGME in a concentration of 30%, let alone 30% to 40%, nor provided a reasonable expectation of success in doing so.

164. Nor would a POSA have selected a concentration of 30%, let alone a range of 30% to 40% DGME, in view of Garrett I. Contrary to what Dr. Constantinides states in his report, Garrett I does ***not*** teach that a concentration of up to 40% DGME could successfully be used (even aside from the undeniable fact that the term "dapsone" in Garrett I is expressly far broader than in the '219 patent, with the solubility of the other Garrett I's "dapsones" being compound-specific and often unknown).

165. Dr. Constantinides states that Garrett I "discloses an embodiment containing about 25% and other embodiments where DGME is present in about 20% w/w to about 40% w/w" and, therefore, that a POSA "would have understood that Garrett I teaches using up to 40% DGME in up to 10% w/w dapsone topical compositions." Constantinides Rpt. at ¶ 91. Dr. Constantinides misstates the teachings of Garrett I.

166. Garrett I does ***not*** disclose, as Dr. Constantinides falsely contends, "embodiments where DGME is present in about 20% to about 40% w/w." Constantinides Rpt. at ¶ 91. Therefore, it is not true that Garrett I teaches using DGME concentrations "up to 40% DGME." Garrett I states that:

> In ***some*** embodiments, compositions of the invention have ***a glycol ether*** present in about 20 wt.% to about 40.0 wt.%. In some embodiments, compositions of the invention have ***a glycol ether*** present in about 20.0 wt.% to about 35.0 wt.%. In some embodiments, compositions of the invention have ***a glycol ether*** present in about 25.0 wt.% to about 40.0 wt.%. In yet another embodiment, compositions of the present invention have ***a glycol ether*** present in about 25.0 wt.% to about 35.0 wt.% of the composition. More specifically, compositions of the present invention have ***a glycol ether*** present in about 25.0 wt.% of the composition.

Garrett I at 17:4–12 (emphases added).

167. This passage simply states that in "some"—but not all—embodiments, "a glycol ether" (notably ***not*** DGME specifically) is present in a concentration of up to 40%. But this is not a statement that each and every possible glycol ether—of which Garrett I provides a vast list whose even ***preferred*** members expressly run into many hundreds[12] (Garrett I at 16:13–17:3)—

[12] Garrett I states: "A glycol ether is an ether formed from at least one glycol and at least one lower alkyl alcohol. Preferably, the glycol is selected from an alkylene glycol such as ethylene glycol, propylene glycol, and butylene glycol. The ether portion of the glycol ether is a radical of a lower alkyl alcohol such as a C_1 to C_6 alcohol. Preferably, the ether portion alcohol is selected from methyl alcohol, ethyl alcohol, propyl alcohol, isopropyl alcohol, butyl alcohol, and isobutyl alcohol." Garrett I at 16:15–21. Garrett I then provides a list of over a dozen exemplary specific glycol ethers, including "ethylene glycol monopropyl ether (propoxyethanol), ethylene glycol monobutyl ether (butoxyethanol), diethylene glycol monoethyl ether (ethoxydiglycol, DGME),

could be used in a concentration of about up to about 40%, or 30% to 40%. To the contrary, the passage makes clear that in ***other*** embodiments, a glycol ether is present in lesser concentrations, including only "about 25.0 wt.%." Garrett I at 17:10–12.

168. Furthermore, nothing in this passage indicates that that DGME, as opposed to numerous preferred and other expressly allowed, let alone all possible, glycol ethers, is one of the glycol ethers that could be used in a concentration of up to 40%, as compared to lesser concentration, such as 25%. Indeed, where DGME is called out in a specific example, it is present in a concentration of about 25%, which Garrett I states is preferred. *See id.* at 20:6–9.

169. Therefore, Garrett I does not teach that DGME can, let alone should, be used in a concentration of up to about 40%; hence nothing in Garrett I would have motivated a POSA to choose a DGME concentration of up to 40%, much less provided a reasonable expectation of success in doing so. There are at least hundreds of solvents encompassed by the category of glycol ethers in Garrett I that would have been understood by a POSA to exhibit different chemical properties, including different solubilities and compatibilities; thus a statement that ***some*** glycol ethers could be used in a concentration of up to about 40% would ***not*** have been equated by a POSA to a statement that ***all*** glycol ethers could be used in such concentrations successfully.

170. Nor did Garrett I teach how to maintain the optimized ratio between dissolved and undissolved dapsone, discussed in Osborne 2011, if the concentration of DGME

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diethylene glycol monobutyl ether (butoxydiglycol), diethylene glycol monoisopropyl ether (isopropyldiglycol), and diethylene glycol monoisobutyl ether (isobutyl diglycol)," as well as also "propylene glycol monomethyl ether, dipropylene glycol monomethyl ether (PPG-2 methyl ether), tripropylene glycol monomethyl ether (PPG-3 methyl ether), propylene glycol n-propyl ether, dipropylene glycol n-propyl ether (PPG-2 propyl ether), propylene glycol monobutyl ether, dipropylene glycol monobutyl ether (PPG-2 butyl ether), propylene glycol monoisobutyl ether, and dipropylene glycol dimethyl ether." *Id.* at 16:22–34.

were to be increased above 25%—either with or without a corresponding increase in dapsone concentration over 5%. And maintaining that delicate ratio would ***not*** have been a simple matter because it would not have been predictable how the dissolved and undissolved dapsone relative amounts would change with an increase in DGME. Furthermore, this would have involved difficult choices for a POSA about which other components to ***decrease*** if one were to increase the percentages of dapsone and DGME. While Dr. Constantinides opines that it would have been a matter of routine optimization to arrive at 30%, or 30% to 40% DGME if one were to increase dapsone concentration to 7.5% (*see* Constantinides Rpt. at ¶ 92), he provides neither support nor analysis for such a contention.

171. Dr. Constantinides also states in a footnote that Garrett II discloses a preferred embodiment that includes "about 10% to 30% [DGME]." Constantinides Rpt. at ¶ 91, fn. 22 (citing Garrett II at 3:2–5). But the Garrett II passage as a whole indicated that when 5% "dapsone" is used, a DGME concentration of 25% is preferred. *See* Garrett II at 3:9–12 (describing preferred embodiment with 25% DGME and 5% "dapsone"). Furthermore, nothing in the passage taught that it would have been appropriate to use a DGME concentration of 30% (or higher) with a "dapsone" concentration of 7.5%. The passage Dr. Constantinides points to simply states that in a preferred embodiment the composition includes, among other things, about 10% to 30% DGME and 5% to 10% "dapsone" in a microparticulate and dissolved state. *See* Garrett II at 3:2–5. Furthermore, in no event would the range of 10% to 30% DGME in Garrett II have motivated a POSA to use a DGME range of 30% to 40% with a reasonable expectation of success given the substantial difference in the ranges. And Dr. Constantinides continues to ignore that the term "dapsone" in Garrett II is expressly far broader than just 4,4′-diaminodiphenyl sulfone itself in the '219 patent.

3. *The Claimed Concentration Range of the Polymeric Viscosity Builder Comprising A/SA Copolymer Was Not Obvious*

172. The polymeric viscosity builder comprising A/SA copolymer of the asserted claims of the '219 patent is at "about 2% w/w to about 6% w/w." But a POSA would not have been motivated to use a polymeric viscosity builder comprising A/SA copolymer at this concentration range in view of Dr. Constantinides's proposed first combination.

173. Since Garrett I is silent as to thickening or gelling agents that comprise A/SA copolymers, it would not have motivated a POSA to use a polymeric viscosity builder comprising A/SA in the range of about 2% to about 6%.

174. Dr. Constantinides nonetheless asserts that a POSA would have been generally motivated to replace the thickener Carbopol 980 in Aczone 5% because that formulation was gritty and Garrett I taught that "crystalline microparticles" of "dapsone" form when Carbopol 980 is added during manufacture. *See* Constantinides Rpt. at ¶¶ 96–97 (citing Garrett I at 25). But Garrett I discloses that these microparticles contribute to an optimal formulation because they are "retained above the stratum corneum to serve as a reservoir to provide dapsone to the supracorneum zone." Garrett I at 17:30–18:9. Osborne 2011 similarly taught that the dapsone microparticles are beneficial because they accumulate in follicles and reduce bacterial levels. Osborne 2011 at 326–327. Thus, a POSA would not have sought to prevent their formation by replacing Carbopol 980 as the thickener.

175. Dr. Constantinides further opines at ¶¶ 96–103 that a POSA would have been motivated to use a concentration of 2% to 6% of a polymeric viscosity builder based on Bonacucina, which discussed Sepineo (comprising A/SA copolymer) and concentrations of Sepineo from 0.5% to 5.0% by weight. *See* Bonacucina at 374. But Bonacucina did not disclose Sepineo's use in treatment of ***any*** disorder, much less specifically of acne or rosacea. Nor did

Bonacucina disclose use of Sepineo in conjunction with any API. A POSA interested in making a treatment for rosacea or acne would, therefore, have had no reason to look to Bonacucina or any discussion of concentration ranges of Sepineo within it.

176. Moreover, Dr. Constantinides acknowledges that at the time of the claimed invention, Sepineo was not yet used in FDA-approved drugs.[13] *See* Constantinides Rpt. at ¶ 103; *see also* IIG December 2012 Database at ALM-ACZ0000668 (showing that Sepineo was still listed as "pending" in the FDA Inactive Ingredients Database even after the date of the claimed invention).[14] I also agree with Dr. Constantinides that a POSA would generally have been discouraged from using ingredients whose safety had not been established by the FDA. *See* Constantinides Rpt. at ¶¶ 8, 44 ("Using the same excipients and concentrations [as those in the IIG] for new topical compositions simplifies FDA review as FDA considers those IIG listed excipients to be generally safe at the listed concentrations."). A POSA would have been especially disinclined to use a relatively new thickener that had not yet been used in an FDA-approved product when numerous well-established IIG-listed thickener alternatives, including xanthan gum and carbomers, existed in the art. *See* IIG December 2012 Database at ALM-ACZ0000731 (xantham gum); *id.* at ALM-ACZ0000493–494 (carbomers).

177. Dr. Constantinides suggests that a POSA would have known to use Sepineo P 600 based on the use of Simulgel PHA 600, "an equivalent product," in a different acne

[13] Later, in his discussion of the combination of Garrett I and Nadau-Fourcade, Dr. Constantinides obscures this fact and claims that "FDA allowed the use of a PVB comprising up to 4% A/SA" because Sepineo was listed in the IIG in 2011 (Constantinides Rpt. at ¶ 128), thus contradicting his earlier admission that Sepineo was only listed as "pending" in the IIG.

[14] The current Inactive Ingredient Database is available online at http://wayback.archive-it.org/7993/20170112022245/http:/www.fda.gov/Drugs/InformationOnDrugs/ucm113978.htm. I downloaded the December 2012 Inactive Ingredient Database File using the same method described in ¶ 80 fn. 4. *See* ALM-ACZ0000467–732.

medication, Epiduo®. *See* Constantinides Rpt. at ¶ 103. Assuming that a POSA would have been motivated to use Sepineo at all, which in my opinion is unsupported by the combination of Garrett I and Bonacucina, the use of Simulgel in Epiduo® would ***not*** have led to the concentrations of A/SA copolymer in the claimed invention of the '219 patent. The Epiduo® label does not disclose the concentrations of any ingredients besides its two APIs. *See* Epiduo PI at TARO-DG-00147500, -503. Thus, a POSA would not have known what concentration of a polymeric viscosity builder was used in Epiduo® and would have had no motivation to select the "about 2% w/w to about 6% w/w" range for the polymeric viscosity builder in the claimed invention of the '219 patent.

B. The Asserted Claims Would Not Have Been Obvious over the Combination of Garrett I and Nadau-Fourcade

178. Dr. Constantinides also opines that the asserted claims of the '219 patent would have been obvious over the combination of Garrett I and Nadau-Fourcade (*i.e.*, keeping Garrett I and replacing Bonacucina with Nadau-Fourcade). I disagree.

179. As an initial matter, Dr. Constantinides's proposed combination fails because a POSA would have seen no reason to combine these two references. Nadau-Fourcade relates to a topical pharmaceutical composition comprising a water-sensitive API "in a dissolved form," where "dissolved form of the active agent" means "a dispersion of the active agent in molecular form in a liquid, no crystallization of the active agent being visible to the naked eye or even under a cross-polarized optical microscope." Nadau-Fourcade at [0001], [0021]. In other words, a fundamental aspect of Nadau-Fourcade is that (i) the API is susceptible to hydrolysis or some other water-induced chemical degradation (which dapsone is ***not*** to the best of my knowledge, and Dr. Constantinides has not presented any evidence to the contrary), and (ii) all of the API is completely dissolved (which is ***not*** the case for dapsone, as discussed above). *See, e.g.*, *id.* at [0008]–[0009].

Exhibit I

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ALMIRALL, LLC, Plaintiff, v. TARO PHARMACEUTICAL INDUSTRIES LTD. and TARO PHARMACEUTICALS, INC., Defendants.	C.A. No. 17-663 (JFB) (SRF) (Consolidated)

RESPONSIVE EXPERT REPORT OF JULIE HARPER, MD

I declare under penalty of perjury of the laws of the United States of America that the following is, to the best of my knowledge and belief, true and correct.

Dated: November 2, 2018

Julie Harper, M.D.

TABLE OF CONTENTS

T. Seppic Sepineo™ P 600 Brochure (2008)

140. This description of Sepineo does not discuss acne, acne treatment, rosacea, rosacea treatment, or dapsone. *See* Ex. 52, Seppic Sepineo P 600 Brochure at ALG_ACZ0375156–57.

XV. THE ASSERTED CLAIMS OF THE '219 PATENT WOULD NOT HAVE BEEN OBVIOUS

141. In his report, Dr. Constantinides opines that the asserted claims of the '219 patent would have been obvious as of the time of the invention. Constantinides Rpt. ¶¶ 64–148. I disagree. In my opinion, the asserted claims would not have been obvious for at least the following reasons:

- a person of ordinary skill in the art at the time of the invention would not have been motivated to select dapsone as an acne or rosacea treatment;
- even if a person of ordinary skill had opted to pursue a dapsone formulation, that person would not have selected a concentration of about 7.5% by weight;
- if a person of ordinary skill in the art at the time of the invention had opted to pursue a dapsone formulation, that person would have combined it with adapalene, which the asserted claims prohibit; and
- unexpected results and industry praise for the Aczone 7.5% product further support the non-obviousness of the invention.

142. I understand that Dr. Alexander Klibanov will also be responding to Dr. Constantinides's report, and offering additional opinions as to why the asserted claims would not have been obvious. My report is not intended to suggest that there are no other reasons that the claims would not have been obvious.

143. I further understand that Dr. Klibanov will be responding to Dr. Constantinides's opinions concerning alleged indefiniteness and lack of written description.

144. Below, I set forth general reasons that I do not believe the asserted claims would have been obvious, and then address the particular combinations that Dr. Constantinides proposes.

A. A Person of Ordinary Skill in the Art at the Time of the '219 Patent Would Not Have Selected Dapsone.

145. *For acne.* At the time of the '219 patent, there were numerous approaches to treating acne, including a variety of topical and systemic (oral) treatments, as well as other therapies such as photodynamic therapy, chemical peels, and a possible vaccine for *Propionibacterium acnes*—and numerous directions in which a person seeking to make an improved acne treatment could potentially have gone. *See supra* ¶¶ 59–79.

146. Against this backdrop of options, a person of ordinary skill in the art in 2012 seeking to make an improved acne treatment would not have seen a reason to select dapsone in a topical treatment. Topical dapsone had only recently been introduced as an acne medication in the form of the Aczone 5% product, and as of 2012, had been viewed with skepticism by the prior art. For example, a 2010 prior art review of the Dapsone (Aczone) 5% product denigrated dapsone as an inferior agent whose role as an acne treatment was uncertain:

> Although not directly compared, dapsone gel has lower response rates than currently available topical treatments that are less expensive. It may have a role in those few patients who are allergic to or cannot tolerate other treatments, but should not be used as first-line therapy.

Ex. 15, Coutinho at 2.

147. Other prior art expressed similar sentiments. For example, another review of topical dapsone provided guidelines and therapeutic options for the management of acne, but noted that "[t]opical dapsone was not included in the recommendations for therapy at this time." Ex. 54, MaryAnn Steiner, *Dapsone Topical Gel for Acne*, 12 J Pharm Soc. Wisc. 67, 67 (2009); *see also* Ex. 54, Steiner at 70 (observing that "[g]uidelines for acne management emphasize

multimodal therapy," but none of the guidelines "specifically mention a role for dapsone" even though "it fits into the anti-inflammatory and antimicrobial category").

148. Likewise, a 2011 review concerning "Management of Acne" did not specify dapsone as either a first- or a second-line treatment option in its table of therapeutic options for treating acne, even though that reference elsewhere recognized that topical dapsone 5% gel was an option for treating acne. *See* Ex. 29, Kraft at Table 2, E434. Similarly, a reference by Williams observed that "[d]espite recent interest in topical dapsone . . . , [it is not] licensed in the UK, and current comparative evidence does not support a change in practice." Ex. 62, Williams at 366. These references collectively reflect that topical dapsone, though approved by FDA for treatment of acne, was nonetheless viewed with skepticism.

149. One reason for such skepticism was the perception that dapsone had lower response rates than other topical treatments (even though it had not been directly compared to other agents). Ex. 15, Coutinho at 2. Another reason for such skepticism was the understanding that topical dapsone was "minimally more effective than placebo in reducing inflammatory and noninflammatory lesions." Ex. 60, Titus at 737.

150. Topical dapsone was understood to have anti-inflammatory properties. *See* Ex. 15, Coutinho at 1. But a person of ordinary skill seeking to improve upon existing topical products would have selected a first-line agent for addressing inflammation, not one that had been marginalized as a second-line treatment at best. And if a person of ordinary skill had not been satisfied with other first-line options for reducing inflammation, that person would have been free to develop a new anti-inflammatory agent.

151. Moreover, when Aczone, 5% was first approved for the treatment of acne in 2005, it was understood by the dermatological community, including myself, to be effective

because of its anti-inflammatory properties, not because of its antimicrobial activity. For example, one commentator noted:

> The drug has been recognized as conferring anti-inflammatory effects—beneficial in the management of leprosy—but current evidence questions the degree to which dapsone provides antimicrobial effects. One trial found that even at very high concentrations, dapsone demonstrated no antibacterial effects against *Streptococcus pyogenes*, *Staphylococcus aureus*, or *Escherichia coli*. No published data report antibacterial effects of dapsone against *P acnes*. Though, as the maxim holds, absence of evidence is not evidence of absence, these facts present interesting questions. Publications describe topical dapsone gel as an antibacterial agent; marketing materials for the new formulation do not mention antibacterial effects.

Ex. 63, Dina Anderson, *Finding a Place for Topical Anti-inflammatory Acne Therapy*, Practical Dermatology 17, 17 (July 2009); *see also* Ex. 24, James I at 653 ("It is thought that dapsone possesses anti-inflammatory properties that are especially beneficial in treating inflammatory acne."). Because of this understanding, the dermatological community was excited to have an additional option for acne treatment whose use would not be limited by antibiotic resistance. *See supra* ¶ 79 & n.1; *see also* Ex. 54, Steiner at 70 ("Because of concerns about long-term oral antibiotic use and bacterial resistance, dapsone offers an alternative for those who have had suboptimal response with currently available therapies.").

152. Over time, however, dermatologists came to appreciate that both the anti-inflammatory and antimicrobial properties of dapsone contribute to treatment of acne when applied topically. *See, e.g.*, Ex. 45, Osborne 2011 at 327 ("By adjusting the ratio of dissolved dapsone to particulate dapsone, the amount of active crossing the epithelium (dissolved dapsone) to treat the inflammation was optimized with regard to the amount of active agent targeted to remain within the follicle (particulate dapsone) to reduce the levels of *Propionibacterium acnes*."); Ex. 64, Michael Ghods et al., *The Role of Dapsone Gel in the Acne Armamentarium*, The Dermatologist (June 10, 2010), available at https://www.the-dermatologist.com/content/role-

dapsone-gel-acne-armamentarium, at ALM-ACZ0000349 ("Dapsone's dual anti-inflammatory and anti-microbial effects may offer physicians a novel multimodal monotherapy for targeting acne."). As a result, a person of ordinary skill seeking to make an improved acne treatment would be discouraged from using dapsone for the additional reason that they would be concerned by possible development of *P. acnes* resistance to dapsone.

153. *For rosacea.* Nor would a person of ordinary skill seeking to make an improved rosacea treatment have selected dapsone, as the prior art revealed that dapsone was no more effective than vehicle in treating rosacea.

154. For example, in an article entitled "Aczone Fails to Impress for Rosacea" by David Pascoe ("Pascoe") dated July 23, 2012,[6] the Rosacea Support Group reported on the results of a clinical trial that had been conducted on the dapsone formulation Aczone 5%. *See* Ex. 47, David Pascoe, *Aczone Fails to Impress for Rosacea*, Rosacea Support Group (July 23, 2012), *available at* https://rosacea-support.org/aczone-fails-to-impress-for-rosacea.html.

155. The article noted that it was learned in 2006 that Aczone 5% would be studied as a treatment for rosacea in a clinical trial that compared Aczone 5% to an inactive gel vehicle—as well as to Metrogel 1%, and a combination of Aczone and Metrogel. *See* Ex. 47, Pascoe at 1. Pascoe observed that if all things had gone well, the clinical trial "would [have been]

[6] Using the Wayback Machine, I confirmed that this article was available online as of August 2012, and therefore available as of the time of the invention. The Wayback Machine archives the content of webpages as of certain dates. I entered the URL of the Pascoe article (https://rosacea-support.org/aczone-fails-to-impress-for-rosacea.html) into the Wayback Machine's search function and determined that it was published online at least as of August 1, 2012. *See* Ex. 61, Wayback Machine Results for Pascoe Article, *available at* https://web.archive.org/web/20120801225046/http:/rosacea-support.org:80/aczone-fails-to-impress-for-rosacea.html (showing Pascoe article captured on August 1, 2012).

able to position Aczone as a viable adjunct to, or indeed a more effect[ive] alternative to the market leading MetroGel." Ex. 47, Pascoe at 1.

156. The article observed, however, that the "trial of Aczone as a rosacea treatment [could] only be described as disappointing," as the results of the trial showed that Aczone 5% was "not significantly better than the vehicle gel twice a day," and that combining Aczone and Metrogel 1% was not significantly better than Metrogel 1% on its own. Ex. 47, Pascoe at 1. The article further reported that dapsone was not able to make a "significant dent" in erythema or telangiectasia, even in combination with other treatments.[7] Ex. 47, Pascoe at 1.

157. The article further observed that "[r]osacea treatments are hard," that "[f]ailures are going to be more common than successes," and that "[e]ven established acne treatments" would be "no shoe-in to treat the papules and pustules of rosacea." Ex. 47, Pascoe at 2.

158. Pascoe added that a promising option for rosacea sufferers would be an oxymetazoline-based topical treatment, and suggested that Allergan, the sponsor of the rosacea trial on dapsone, would pursue that agent as an alternative for rosacea treatment instead of dapsone. *See* Ex. 47, Pascoe at 2 ("Despite this set back, Allergan continues the research and development of new treatments for several conditions. For rosacea sufferers . . . the most promising would be

[7] Results of this clinical trial are also reported in the Clinical Study Report as well as a results summary. *See* Ex. 14, A Phase II, Randomized, Partial-Blind, Parallel-Group, Active- and Vehicle-Controlled, Multicenter Study of the Safety and Efficacy of Aczone™ (Dapsone) Gel, 5% in Subjects With Papulopustular Rosacea (QLT Inc. publ., Feb. 5, 2007); Ex. 6, AZC ROS 01 Web Results Summary, A Phase II, Randomized, Partial-Blind, Parallel-Group, Active- and Vehicle-Controlled, Multicenter Study of the Safety and Efficacy of Aczone™ (dapsone) Gel, 5% in Subjects with Papulopustular Rosacea, *available at* http://www.allerganclinicaltrials.com/pdfs/medical_aesthetics/Results_Web_PostingACZ-ROS-01.pdf.

the Oxymetazoline based topical that they call AGN-199201" and noting in the link below that Allergan was "Developing "Oxymetazoline (AGN-199201/V-101) Cream Formulations.").

159. Aczone 5% did not have an indication to treat rosacea, *see* Ex. 7, Aczone 5% PI § 1 at TARO-DG-00063818, even though the makers of Aczone had originally been interested in obtaining one. The absence of such an indication as of 2012 would have struck the person of ordinary skill as meaningful: as an indication of the limited efficacy of dapsone as rosacea treatment, and as further confirmation that Allergan had abandoned dapsone in search of another agent for treating rosacea.

160. A person of ordinary skill in the art would not have been motivated to select, or reasonably expected success in selecting, a compound that could "only be described as disappointing," that had been abandoned in search of a different option, and that was no more effective than vehicle alone in treating rosacea. Ex. 47, Pascoe at 1. Selection of such agent would pose a risk of side effects without providing a treatment benefit.

161. Dr. Constantinides relies on the Garrett I reference in contending that a person of ordinary skill would have wanted to select, and reasonably expected success in selecting, dapsone as a treatment for rosacea. As I discuss further below, however, Garrett I would have provided no motivation or expectation of success, and would in fact have taught away from dapsone. An examination of Garrett I reveals that it discusses the very same clinical trial discussed in the Pascoe article,[8] and that it discloses that dapsone was no more effective in treating rosacea than vehicle alone.

[8] That Pascoe describes the same clinical trial as Garrett I would have been clear from, for example, the description of the trial design in each reference. *Cf.* Ex. 47, Pascoe at 1 ("The trial, NCT000249782[,] a multiple arm Phase II trial, would compare Aczone once and twice a day, to the inactive gel vehicle, Metrogel 1% on its own and Aczone in the morning in combination with Metrogel in the evening.") *with* Ex. 2, Garrett I at 23:25–36:30 (describing the clinical trial design

B. A Person of Ordinary Skill Would Not Have Selected a Dapsone Concentration of About 7.5%.

162. As discussed above, a person of ordinary skill in the art seeking to make an improved acne or rosacea product would not have selected dapsone at all. But even if such a person had pursued dapsone, that person would not have selected a concentration of about 7.5%, as required by the asserted claims.

163. According to Dr. Constantinides, a person of ordinary skill would have wanted to increase the dapsone concentration from the 5% used in the original Aczone 5% product, because the Aczone 5% product required twice-daily application to treat acne, and a person would have wanted to make a once-daily product. *See, e.g.*, Constantinides Rpt. ¶ 118 ("Indeed, a POSA would have known that a topical dapsone 5% gel had been marketed since at least 2008 under the name Aczone Gel, 5%, with a topical twice-daily administration . . . A POSA would have also known that less frequent dosing correlates with increased treatment adherence."). Dr. Constantinides further opines that a person of ordinary skill would have understood that the way to achieve a once-daily acne treatment would have been to increase the concentration of dapsone to 7.5%. *See* Constantinides Rpt. ¶ 118 ("Using this typical knowledge in the field and his common sense, a POSA seeking to maximize efficacy and adherence of topical dapsone formulations would be motivated to set the dapsone weight percentage at 7.5% w/w.").

164. I disagree that a person of ordinary skill would have been motivated to select a dapsone concentration of 7.5%, even if that person pursued a dapsone treatment. A person of ordinary skill in 2012 would have believed that the makers of Aczone *had already* optimized the

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and same comparisons). This would also have been clear from the results, including the fact that "Aczone twice a day was not significantly better than the vehicle gel twice a day," and that "[n]one of any combination of the treatments was able to make a significant dent in erythema or telangiectasia." *Cf.* Ex. 47, Pascoe at 1; Ex. 2, Garrett I at 35:6–33.

dapsone concentration in the original 5% formulation, and therefore would have seen no benefit in increasing the dapsone concentration to 7.5%.

165. Dr. Constantinides explains that a person of ordinary skill would have thought it would be desirable to make a once-daily topical treatment, because less frequent application would enhance convenience and compliance, and thus likely improve treatment outcomes. *See* Constantinides Rpt. ¶¶ 67, 118. While I agree that a once-daily topical acne treatment would have been viewed as desirable, I do not agree that this would have led a person of ordinary skill to select a dapsone concentration of 7.5%.

166. Well before 2012, it was appreciated that once-daily, as compared to twice-daily, topical acne treatments were desirable. Indeed, it had long been appreciated that decreasing the frequency of administration could minimize compliance burdens, and therefore improve treatment outcomes. *See, e.g*, Ex. 36, Marazzi at 116 (reporting that a once-daily acne treatment achieved better compliance than a twice-daily product).

167. Given that understanding, a person of ordinary skill would have believed that the makers of the original dapsone Aczone 5% acne treatment had every incentive to make a once-daily product when they developed the original Aczone product the first time around. That the original Aczone product required twice-daily application therefore would have been understood to be meaningful—as an indication that dapsone was not well suited to be a once-daily product, as the makers of the original Aczone product would otherwise have made a once-daily product the first time around. A person of ordinary skill would not have believed that using a dapsone concentration of about 7.5% would allow one to make a successful once-daily product, as otherwise they would have used that concentration when formulating the original Aczone product.

168. The prior art, including Osborne I, confirms this understanding. The Osborne I patent, which issued in 1999 before the development of the original Aczone product, disclosed preferred concentrations of dapsone for acne treatment in a range from 0.5% to 10%. *See* Ex. 46, Osborne I at 4:62–5:4. Given the existence of that range, a person of ordinary skill in the art would have believed that the developers of the original dapsone product explored all values in that range, and arrived at 5% as the optimal concentration of dapsone.

169. It would not have made sense for the developers of the original dapsone product to have selected the 5% concentration instead of higher concentrations in the range, if higher concentrations yielded better products, such as a product that could successfully be applied once-daily. Thus, the fact that the makers of the original dapsone product used a concentration of 5%, and not the higher values in the range of Osborne I, would have been an indication that a concentration of 7.5% would not yield a better result, such as a successful once-daily product.

170. Subsequent prior art reinforces the conclusion that a person of ordinary skill in the art would have understood the 5% dapsone concentration to be optimal. *See* Ex. 45, Osborne 2011 at 327. For example, as noted above, a 2011 publication by David Osborne (the inventor of the Osborne I patent) noted that the 5% concentration allowed for an "optimized" "amount" of drug to cross the epithelium to combat inflammation, and in a ratio that was in balance with the with the amount of drug that was not dissolved and therefore available to remain in the upper part of the sebaceous unit to combat *P. acnes* bacteria. *See supra* ¶ 133.

171. Given that the dapsone formulation would have been understood to be optimized at the 5% value, a person of ordinary skill would have seen no reason to select a dapsone concentration of 7.5%.

172. Dr. Constantinides suggests that increasing concentrations of active agents would have been desirable, but a person of ordinary skill in the art in 2012 would have understood that increasing drug concentration would not necessarily yield a more effective product. For example, it had long been known that benzoyl peroxide treatments with concentrations *above 2.5%* were not more effective than a benzoyl peroxide product with a 2.5% concentration. *See, e.g.*, Ex. 38, Otto H. Mills et al., *Comparing 2.5%, 5%, and 10% Benzoyl Peroxide on Inflammatory Acne Vulgaris*, 25 Int'l J. Dermatology 664, 664 (1986) ("The 2.5% benzoyl peroxide formulation was more effective than its vehicle and equivalent to the 5% and 10% concentrations in reducing the number of inflammatory lesions (papules and pustules)."). A person of ordinary skill in the art would have understood that, as with other pharmaceuticals, topical products reach a threshold at which further increasing drug concentration will yield no additional therapeutic benefit.

173. A person of ordinary skill would have also understood that increasing drug concentration could also increase undesirable side effects, further dissuading a person of ordinary skill from seeking to increase dapsone concentration above 5%. Given that in 2012, the 5% concentration would have been understood to have been optimized, a person of ordinary skill would have concluded that further increasing dapsone concentration would pose risks of increased side effects without a corresponding therapeutic benefit.

174. For example, the Prescribing Information for the Aczone 5% product explained that oral dapsone treatment was associated with dose-related hemolysis and hemolytic anemia,[9] especially in individuals with G6PD deficiency. Ex. 7, Aczone 5% PI § 5.1 at TARO-DG-00063818. While the Prescribing Information reported that there was no evidence of clinically

[9] Symptoms of hemolytic anemia are similar to other forms of anemia (fatigue and shortness of breath), but the breakdown of red cells associated with this form of anemia can lead to jaundice and increase the risk of long-term complications such as gallstones and pulmonary hypertension.

relevant hemolysis or anemia in patients treated with Aczone 5%, "[s]ome subjects with G6PD deficiency using ACZONE Gel developed laboratory changes suggestive of mild hemolysis." Ex. 7, Aczone 5% PI § 5.1 at TARO-DG-00063818.

175. Given that there was some evidence of mild hemolysis with the 5% concentration, a person of ordinary skill would have had concern that increasing the concentration of dapsone from 5% to 7.5% could increase systemic absorption, thereby potentially increasing the risk that some G6PD-deficient individuals could experience clinically relevant hemolysis or anemia. Especially given that a person of ordinary skill would have believed that the 5% concentration had already been optimized, there would have been no reason to create a risk of causing hemolytic anemia in some users by increasing the dapsone concentration.

176. Oral dapsone had also been associated with methemoglobinemia (a potentially life-threatening condition in which the oxygen-carrying capacity of blood in body tissues is reduced), and dapsone hypersensitivity syndrome (characterized by fever, skin rash, hepatitis and lymphadenopathy). *See* Ex. 12, John V. Ashurst et al., *Pathophysiological Mechanisms, Diagnosis, and Management of Dapsone-Induced Methemoglobinemia,* 110 J. Am. Osteopathic Assoc. 16, 16, 20 (2010); Ex. 13, J.S. Chun et al., *Dapsone hypersensitivity syndrome with circulating 190-kDA and 230-kDA autoantibodies*, 34 Clinical and Experimental Dermatology e798, e798 (2009). The possibility that increasing concentration above 5% would increase the risks of causing these conditions also would have been further reason that a person of ordinary skill in the art would not have been motivated to select a concentration of 7.5% if trying to make a product with dapsone.

177. A person of ordinary skill would also have seen no reason to use a 7.5% dapsone concentration for rosacea, especially in light of the poor performance of dapsone on rosacea and the side effect concerns with dapsone noted above.

C. If a Person of Ordinary Skill Had Sought to Use Dapsone as Part of an Improved Acne Product, that Person Would Have Done So in Combination with Adapalene.

178. The asserted claims require that the composition used to treat acne or rosacea exclude adapalene, a retinoid that was commonly used in 2012. *See* Ex. 1, '219 patent at 15:40–16:22. In my opinion, this is further reason that the asserted claims would not have been obvious. If a person of ordinary skill had sought to make a treatment that included dapsone, that person would also have included adapalene.

179. As discussed above, as of 2012, there was an interest in developing combination products for acne, *i.e.*, products containing multiple active agents. *See supra* ¶¶ 70–77. The reason for this interest was straightforward. As of 2012, no single topical agent addressed all four causes of acne. *See supra* ¶¶ 70–71. Because combination products contained multiple active agents in a single formulation, they were able to address more causes of acne in a single formulation than formulations containing a single agent alone. *See, e.g.*, Ex. 42, Nguyen at 123 ("[I]n multiple trials, topical combination therapies are more effective than monotherapy as they target *multiple* pathogenic mechanisms." (emphasis added)).

180. The prior art noted the advantages of combination products. *See, e.g.*, Ex. 24, James I at 655 ("Due to their convenience and efficacy, combination therapies that address multiple mechanisms in acne pathogenesis will become standard first-line agents."); Ex. 44, Orsoni at 1:39–46 ("The combination of several local treatments (antibiotics, retinoids, peroxides and zinc) is also used in dermatology to increase the efficacy of the active principles and to reduce their toxicity . . . The multiple application of various dermatological products may be relatively

burdensome and restricting for the patient."); Ex. 10, Ahluwalia at 3:14–16 ("A combination acne product would provide the benefit of enhanced efficacy compared to the products containing single active agent by taking advantage of the synergistic mechanism of action of the active agents for treatment of acne."). Thus, if a person of ordinary skill in 2012 had sought to develop an improved acne treatment that used dapsone, that person would have done so as part of a combination product containing at least one other active agent.

181. Furthermore, in my opinion, that agent would have been adapalene. Adapalene is a retinoid, and retinoids were the "foundation of topical acne therapy and [we]re considered a first-line treatment of mild to moderate acne." Ex. 24, James I at 650. Retinoids addressed a cause of acne that dapsone did not: the excessive buildup of dead skin, called hyperkeratinization, that was known to contribute to the clogged pores that give rise to acne. *See* Ex. 24, James I at 650 (noting that retinoids inhibit hyperkeratinization); Ex. 29, Kraft at E431; Ex. 10, Ahluwalia at 2:25–31. Thus, if a person of ordinary skill had wanted to make a formulation containing dapsone, that person would have coupled it with a retinoid.

182. Within the class of retinoids, adapalene was understood to be the best tolerated topical retinoid. *See, e.g.*, Ex. 42, Nguyen at 123 ("Adapalene 0.1% is associated with less erythema, dryness and burning than tazarotene 0.1% gel, tretinoin 0.25-0.1% gel, tretinoin 0.05% cream and isotretinoin 0.05% gel.") And a number of prior art references, including references identified by Dr. Constantinides, specifically preferred adapalene over other retinoids. *See, e.g.*, Ex. 35, Mallard at [0058] ("Advantageously, the naphthoic acid compound in the compositions according to the invention is . . . adapalene."); Ex. 32, Louis at [0084] ("In particular, preference will be given to adapalene and its salts."); Ex. 10, Ahluwalia Figures 1–5 (using adapalene in all exemplary figures); Ex. 18, Epiduo PI § 3 at TARO-DG-00147500 (combination

product in which adapalene was chosen as the retinoid to be used with benzoyl peroxide); Ex. 44, Orsoni at 4:48–49 ("In particular, adapalene and also precursors and/or derivatives thereof will be preferred."). Thus, if a person of ordinary skill in the art had sought to pursue a product with dapsone, it is my opinion that person would have combined it with adapalene.

183. Prior art further suggested that if one were to use dapsone, there would be advantages in combining it with adapalene. For example, Ahluwalia discussed a method of dermatologic treatment in which another agent would be combined with dapsone, and emphasized adapalene as that agent. *See* Ex. 10, Ahluwalia at 3:14–23 ("A combination acne product would provide the benefit of enhanced efficacy compared to the products containing single active agent by taking advantage of the synergistic mechanism of action of the active agent for treatment of acne. The present invention is directed to acne products with at least two active compounds and in particular are directed to dapsone and adapalene combination formulations for use in the treatment of dermatological conditions such as *acne vulgaris* [and] rosacea . . . .").

184. With regard to the negative limitation expressly excluding the anti-acne active agent adapalene from the claimed composition, Dr. Constantinides opines that it would have been obvious not to use adapalene because "[d]apsone was known in 2012 to be an effective treatment for skin conditions such as monotherapy," and that the prior art taught that "topical dapsone compositions did not require the presence of adapalene." Constantinides Rpt. ¶ 94. But a person of ordinary skill would have wanted to make an improved dermatologic treatment, and the prior art suggested that if one were to make a composition with dapsone, its performance would be enhanced with adapalene. *See* Ex. 10, Ahluwalia at 3:14–23.

185. Ahluwalia further underscores another point that I made earlier: that a person of ordinary skill would have understood a 5% concentration of dapsone to be optimal.

Ahluwalia heavily emphasizes a 5% concentration, listing 5% as the dapsone concentration for each and every formulation in Figures 1, 2, 3A, 3B, 3C, 3D, 4A, 4B, 4C, 4D, and 5. *See* Ex. 10, Ahluwalia at Figures 1–5. In none of the specific formulations in any of the figures is a concentration greater than 5% used, and at no point in the discussion of any of these examples is there a suggestion that going above 5% would be beneficial. Other examples also include 5% dapsone. *See* Ex. 10, Ahluwalia at 6:19–34, Tables 2A–2B. This emphasis on a 5% dapsone concentration would have been in keeping with the understanding of a person of ordinary skill in the art that 5% was the optimal concentration for a topical dapsone formulation.

186. With its focus on a concentration of 5% dapsone, Ahluwalia further clarifies that a person of ordinary skill would have understood that the way to improve a formulation containing dapsone would be to add another pharmaceutical agent, not to increase the dapsone concentration above 5%.

D. The Combinations Asserted by Dr. Constantinides Would Not Have Rendered the Asserted Claims Obvious.

187. Dr. Constantinides opines that the asserted claims would have been obvious over two combinations of references: (1) Garrett I in view of Bonacucina, and (2) Garrett I in view of Nadau-Fourcade. I disagree. The asserted claims would not have been obvious for at least the general reasons discussed above, and nothing in either of Dr. Constantinides's proposed combinations alters these conclusions. I discuss these combinations below.

i. Garrett I in view of Bonacucina

a) A person of ordinary skill would have had no reason to select dapsone.

188. *For acne.* Nothing in the combination of Garrett I and Bonacucina would have motivated a person of ordinary skill to select dapsone if seeking to make an improved acne treatment, or altered the general thinking about dapsone discussed above. *See supra* ¶¶ 145–152.

Garrett I does not even address acne; it is instead directed to treatment for rosacea. But rosacea is a very different condition than acne, and thus a reference about treatment of rosacea would not have led a person of ordinary skill in 2012 to select any particular treatment for acne.

189. As of 2012, the pathogenesis of acne was better understood than rosacea. Whereas acne was understood to be caused by multiple factors associated with clogged follicles, *see supra* ¶¶ 50–54, there was a "poor understanding" of the pathogenesis of rosacea. Ex. 28, Korting at 877. Moreover, to the extent that rosacea's causes were understood, it was believed to be associated with issues in the capillaries and blood vessels below the skin, not in the pores, as with acne. Given the differences between acne and rosacea, it was understood that treatments that worked for one condition would not necessarily work for the other. *See, e.g.*, Ex. 47, Pascoe at 2 (noting that "[e]ven established acne treatments are no shoe-in to treat the papules and pustules of rosacea").

190. Dr. Constantinides observes that Garrett I "discloses the known use of topical dapsone formulations for acne treatment," but the passage he cites (11:29-34) merely incorporates by reference patents from the late 1990s and early 2000s concerning acne treatment, including Osborne I. Constantinides Rpt. ¶ 82 n.17. As discussed above, however, dapsone had been marginalized as an acne treatment as of 2012, and thus Garrett I's mention of the Osborne patents would not have motivated a person of ordinary skill to use dapsone or provided a reasonable expectation of success in doing so.

191. Nor would Bonacucina have led a person to select dapsone, as it does not mention dapsone or acne.

192. *For rosacea.* Nothing in Dr. Constantinides's proposed combination of Garrett I and Bonacucina would have motivated a person of ordinary skill in the art seeking to

make an improved rosacea treatment to select dapsone, either. Garrett I actually taught away from selecting dapsone.

193. As noted above, Garrett I reports on a clinical trial that examined the efficacy of dapsone in treating rosacea. *See supra* ¶¶ 94–97. Far from motivating a person of ordinary skill to select dapsone, these results would have discouraged a person of ordinary skill from doing so, as dapsone fared no better in the trial than vehicle in treating papulopustular rosacea, erythema, and telangiectasia—meaning that it would only pose a risk of side effects, without providing any corresponding treatment benefit.[10]

194. Nothing in Garrett I, moreover, would have provided any expectation that dapsone would be effective in treating the less common phymatous rosacea (thickened, nodular skin and prominent pores most commonly expressed as rhinophyma, or an enlargement of the sebaceous glands in the nose)[11] or ocular rosacea (itching, tearing, dryness, gritty sensations, crusting of eyelids and an inability to wear contact lenses, as well as frequent styes). Garrett I provided no evidence that topical dapsone is effective in addressing these conditions, and the fact that dapsone was not successful in treating even papulopustular rosacea—the rosacea subtype that

[10] Pascoe also noted that "[c]ombining Aczone and Metrogel 1% was not significantly better than Metrogel 1% on its own." Ex. 47, Pascoe at 1; *see also* Ex. 2, Garrett I at 35:16–20 (reporting that MetroGel alone reduced lesions by a mean of 11.3 after 12 weeks, while the combination reduced lesions by a mean of 11.4 after 12 weeks); Ex. 6, AZC ROS 01 Web Results Summary at ALM-ACZ0000003 ("The success rate for the combination treatment of Aczone + MetroGel was higher than MetroGel alone (39.5% success rate compared with 32.5%), but since there was no difference in the reduction in lesion counts between these regimens, this result probably does not reflect a real additive effect of using these 2 treatments in combination.").

[11] A person of ordinary skill in the art would have believed that a laser or device would be needed to remove the thickened, hardened skin associated with phymatous rosacea. *See* Ex. 50, Powell at 794. Certainly there would have been no reason that a topical treatment with anti-inflammatory properties would remove such thick, hard skin.

most plausibly could have been addressed by a medication with anti-inflammatory properties such as dapsone—would have been further reason that a person of ordinary skill would have doubted dapsone's ability to treat other subtypes of rosacea effectively.

195. Garrett I therefore would have reinforced the understanding that topical dapsone would not provide a successful treatment for rosacea—an understanding already apparent from other prior art that noted dapsone's effects on rosacea could "only be described as disappointing," and that the makers of Aczone 5% had not been able to obtain an indication for rosacea treatment using dapsone. *See supra* ¶¶ 153–160.

196. Nor would Bonacucina have motivated a person of ordinary skill to select dapsone to treat rosacea with a reasonable expectation of success. Bonacucina does not even mention rosacea or dapsone.

b) A person of ordinary skill would have had no reason to use dapsone at a concentration of about 7.5%.

197. As explained above, a person of ordinary skill would not have selected a dapsone concentration of about 7.5%, even if that person had sought to make an improved acne or rosacea treatment using dapsone. *See supra* ¶¶ 162–177. Nothing in Garrett I or Bonacucina alters these conclusions.

198. *For acne*. As noted above, Garrett I addressed rosacea, not acne, and would not have led a person of ordinary skill seeking to make an improved acne treatment to select dapsone in any concentration.

199. Moreover, because the potential dapsone concentration range of 0.5% to 10% in Garrett I to which Dr. Constantinides relies was for *rosacea*—and rosacea and acne are very different conditions with different causes and treatments—a person of ordinary skill in the art seeking to make an improved *acne* treatment would not have seen the range in Garrett I as relevant.

I therefore disagree that a person of ordinary skill would have understood Garrett I—which was directed to a rosacea treatment—as providing that each point in Garrett I's potential range of 0.5 to 10% could be used to make a successful topical *acne* treatment.

200. Perhaps aware of this shortcoming in Garrett I, Dr. Constantinides also references Osborne I for the proposition that dapsone amounts "ranging up to 10%" in topical acne formulations were also known. *See, e.g.*, Constantinides Rpt. ¶ 108. But Osborne I is not part of his combination, and Osborne I only confirms my point that a concentration of about 7.5% dapsone would not have been obvious. *See supra* ¶¶ 129, 168–169. As discussed above, the Osborne I patent, which issued in 1999 before the development of the original Aczone product, disclosed preferred weight percentages (concentrations) of dapsone in a range from 0.5% to 10% for treatment of acne, and from that range, the makers of the Aczone product chose 5%. *See* Ex. 46, Osborne I at 4:62–5:4. It would have made no sense for the developers of the original dapsone product to have selected the 5% concentration instead of higher potential concentrations in the range, if it were obvious that higher concentrations yielded better products, such as a product that could successfully be applied once-daily. *See supra* ¶¶ 168–169. And subsequent prior art by Osborne in 2011 would have further confirmed the understanding that a 5% concentration was optimal. *See* Ex. 45, Osborne 2011 at 327.

201. Dr. Constantinides also cites to Lathrop—which again is outside of his proposed combination—noting that "Lathrop teaches topical dapsone concentrations in which 5% w/w and 7.5% w/w dapsone were 'especially preferred.'" Constantinides Rpt. ¶ 90. But Lathrop was published in 2006, and a person of ordinary skill in the art at the time of the invention would have understood Lathrop in the context of the prior art as a whole, which made clear that the 5%

concentration had already been optimized.[12] *See supra* ¶¶ 120, 164–170. Furthermore, the fact that Lathrop also "especially preferred" a 5% concentration would have meant that a person of ordinary skill would have seen no reason to select a 7.5% concentration, as the lower concentration would have been expected to provide lower side effects, and the 5% concentration did not raise the same questions about safety as a preparation with a 7.5% concentration. *See* Ex. 30, Lathrop at [0014].

202. Bonacucina also would have provided no reason for a person of ordinary skill to select a dapsone concentration of about 7.5%, as it does not mention dapsone in any concentration.

203. *For rosacea*. As discussed above, Garrett I taught away from selecting dapsone, because Garrett I taught that dapsone was no more effective in treating rosacea than vehicle alone. *See* Ex. 2, Garrett I at 35:6–33. A person of ordinary skill in the art therefore would not have been motivated to use any concentration of dapsone.

204. Pointing to the dapsone concentration range of 0.5 to 10% in Garrett I, Dr. Constantinides opines that a person of ordinary skill in the art "would have understood that each point in the range of 0.5% to 10%, including 7.5%, could have been used to make a topical dapsone composition, and therefore a topical composition having any amount of dapsone 0.5% to 10% w/w, including 7.5%, would have been obvious." Constantinides Rpt. ¶ 89. But a person of ordinary skill in the art would have understood Garrett I's range in conjunction with other disclosures, including that values within the range were no more effective than vehicle, and that dapsone's effects in treating rosacea could "only be described as disappointing." *See supra* ¶¶ 95–

[12] The same analysis applies to Dr. Constantinides's attempt to rely on a range of 5 to 10% dapsone in Garrett II, *see* Constantinides Rpt. ¶ 89 n.20, as well as his attempt to rely on other prior art ranges of dapsone. *See, e.g.*, Constantinides Rpt. ¶ 108.

97, 153–161. A person of ordinary skill therefore would not have given credence to the values in Garrett I's range, or even looked to the range in Garrett I if seeking to make a rosacea treatment.

205. Bonacucina also would not have motivated a person to select a dapsone concentration of about 7.5%, nor provided any reasonable expectation of success with such endeavor, as Bonacucina does not even mention dapsone.

c) A person of ordinary skill formulating with dapsone would have also used adapalene.

206. As discussed above, the asserted claims also would not have been obvious because, if a person of ordinary skill had opted to pursue a topical dapsone formulation, that person would have also used adapalene. *See supra* ¶¶ 178–186. Nothing in Garrett I or Bonacucina would have dissuaded a person of ordinary skill from making a combination product that included adapalene.

207. Garrett I provides no reason to believe that using dapsone as a monotherapy would be advantageous, or otherwise suggests that use of adapalene would be problematic if one were to pursue a dapsone formulation.

208. Nor would Bonacucina have prevented a person of ordinary skill from making a combination product that included adapalene. Bonacucina does not address acne, acne treatments, rosacea, or rosacea treatments, and therefore would not have altered the understanding that including adapalene could offer advantages as part of a topical treatment.

ii. Garrett I in view of Nadau-Fourcade

209. Nothing in the combination of Garrett I and Nadau-Fourcade would have rendered the asserted claims obvious either.

a) A person of ordinary skill in the art would have had no reason to select dapsone.

210. *For acne.* Nothing in the combination of Garrett I and Nadau-Fourcade would have motivated a person of ordinary skill to select dapsone if seeking to make an improved acne treatment, or altered the general thinking about dapsone discussed above. *See supra* ¶¶ 145–152. Garrett I does not even address acne; it is instead directed to treatment for rosacea. But rosacea is a very different condition than acne, and thus a reference about treatment of rosacea would not have led a person of ordinary skill in 2012 to select any particular treatment for acne.

211. As of 2012, the pathogenesis of acne was better understood than rosacea. Whereas acne was understood to be caused by multiple factors associated with clogged follicles, there was a "poor understanding" of the pathogenesis of rosacea. Ex. 28, Korting at 877. Moreover, to the extent that rosacea's causes were understood, it was believed to be associated with issues in the capillaries and blood vessels below the skin, not in the pores, as with acne. Given the differences between acne and rosacea, it was understood that treatments that worked for one condition would not necessarily work for the other. *See, e.g.*, Ex. 47, Pascoe at 2 (noting that "[e]ven established acne treatments are no shoe-in to treat the papules and pustules of rosacea").

212. Dr. Constantinides observes that Garrett I "discloses the known use of topical dapsone formulations for acne treatment," but the passage he cites in Garrett I (11:29-34) merely incorporates by reference patents from the late 1990s and early 2000s concerning acne treatment, including Osborne I. Constantinides Rpt. ¶ 82 n.17. As discussed above, however, dapsone had been marginalized as an acne treatment as of 2012, and thus Garrett I's mention of the Osborne patents would not have motivated a person of ordinary skill to use dapsone or provided a reasonable expectation of success in doing so.

213. Nor would Nadau-Fourcade have led a person to select dapsone if seeking to make an improved acne treatment. Nadau-Fourcade does not mention dapsone, and therefore would not have motivated a person of ordinary skill in the art to use, or have provided a reasonable expectation of success in using, dapsone.

214. *For rosacea.* Nothing in Dr. Constantinides's proposed combination of Garrett I and Nadau-Fourcade would have prompted a person of ordinary skill in the art seeking to make an improved rosacea treatment to select dapsone, either. Garrett I actually taught away from selecting dapsone.

215. As noted above, Garrett I reports on a clinical trial that examined the efficacy of dapsone in treating rosacea. *See supra* ¶¶ 94–97. Far from motivating a person of ordinary skill to select dapsone, these results would have discouraged a person of ordinary skill from doing so, as dapsone fared no better in the trial than vehicle in treating papulopustular rosacea, erythema, and telangiectasia—meaning that it would only pose a risk of side effects, without providing any corresponding treatment benefit.[13]

216. Nothing in Garrett I, moreover, would have provided any expectation that dapsone would be effective in treating the less common phymatous rosacea (thickened, nodular skin and prominent pores most commonly expressed as rhinophyma, or an enlargement of the

[13] Pascoe also noted that "[c]ombining Aczone and Metrogel 1% was not significantly better than Metrogel 1% on its own." Ex. 47, Pascoe at 1; *see also* Ex. 2, Garrett I at 35:16–20 (reporting that Metrogel alone reduced lesions by a mean of 11.3 after 12 weeks, while the combination reduced lesions by a mean of 11.4 after 12 weeks); Ex. 6, AZC ROS 01 Web Results Summary at ALM-ACZ0000003 ("The success rate for the combination treatment of Aczone + MetroGel was higher than MetroGel alone (39.5% success rate compared with 32.5%), but since there was no difference in the reduction in lesion counts between these regimens, this result probably does not reflect a real additive effect of using these 2 treatments in combination.").

sebaceous glands in the nose)[14] or ocular rosacea (itching, tearing, dryness, gritty sensations, crusting of eyelids and an inability to wear contact lenses, as well as frequent styes). Garrett I provided no evidence that topical dapsone is effective in addressing these conditions, and the fact that dapsone was not successful in treating even papulopustular rosacea—the rosacea subtype that most plausibly could have been addressed by a medication with anti-inflammatory properties such as dapsone—would have been further reason that a person of ordinary skill would have doubted dapsone's ability to treat other subtypes of rosacea effectively.

217. Garrett I therefore would have reinforced the understanding that topical dapsone would not provide a successful treatment for rosacea—an understanding already apparent from other prior art that noted dapsone's effects on rosacea could "only be described as disappointing," and the fact that the makers of Aczone 5% had not been able to obtain an indication for rosacea treatment. *See supra* ¶¶ 153–160.

218. Nor would Nadau-Fourcade have led a person of ordinary skill in the art to select dapsone if seeking to make an improved rosacea treatment. To the contrary, Nadau-Fourcade points away from dapsone by specifically identifying and preferring an agent other than dapsone for rosacea treatment. *See* Ex. 4, Nadau-Fourcade at [0149] ("Preferentially, the composition according to the invention containing ivermectin will be used for treating rosacea . . . .").

b) A person of ordinary skill would have had no reason to use dapsone at a concentration of about 7.5%.

219. As explained above, a person of ordinary skill would not have been motivated to select a dapsone concentration of about 7.5%, even if that person had sought to make

[14] A person of ordinary skill in the art would have believed that a laser or device would be needed to remove the thickened, hardened skin associated with phymatous rosacea. *See* Ex. 50, Powell at 794.

an improved acne or rosacea treatment using dapsone. *See supra* ¶¶ 162–177. Nothing in Garrett I or Nadau-Fourcade alters these conclusions.

220. *For acne*. As noted above, Garrett I addressed rosacea, not acne, and would not have led a person of ordinary skill seeking to make an improved acne treatment to select dapsone in any concentration.

221. Moreover, because the potential dapsone concentration range of 0.5% to 10% in Garrett I to which Dr. Constantinides relies was for *rosacea*—and rosacea and acne are very different conditions with different causes and treatments—a person of ordinary skill in the art seeking to make an improved *acne* treatment would not have seen the range in Garrett I as relevant. I therefore disagree that a person of ordinary skill would have understood Garrett I—which was directed to a rosacea treatment—as providing that each point in Garrett I's potential range of 0.5 to 10% could be used to make a successful topical *acne* treatment.

222. Perhaps aware of this shortcoming in Garrett I, Dr. Constantinides also references Osborne I for the proposition that dapsone amounts "ranging up to 10%" in topical acne formulations were also known. *See, e.g.*, Constantinides Rpt. ¶ 133. But Osborne I is not part of his combination, and Osborne I only confirms my point that a concentration of about 7.5% dapsone would not have been obvious. *See supra* ¶¶ 129, 168–169. As discussed above, the Osborne I patent, which issued in 1999 before the development of the original Aczone product, disclosed preferred weight percentages (concentrations) of dapsone in a range from 0.5% to 10% for treatment of acne, and from that range, the makers of the Aczone product chose 5%. *See* Ex. 46, Osborne I at 4:62–5:4. It would have made no sense for the developers of the original dapsone product to have selected the 5% concentration instead of higher potential concentrations in the range, if it were obvious that higher concentrations yielded better products, such as a product that

could successfully be applied once-daily. *See supra* ¶¶ 168–169. And subsequent prior art by Osborne in 2011 would have further confirmed the understanding that a 5% concentration was optimal. Ex. 45, Osborne 2011 at 327.

223. Dr. Constantinides also cites Lathrop—which again is outside of his proposed combination—noting that "Lathrop teaches topical dapsone concentrations in which 5% w/w and 7.5% w/w dapsone were 'especially preferred'" and taught dapsone amounts ranging up to 10%. Constantinides Rpt. ¶¶ 118 n.28, 133. But Lathrop was published in 2006, and a person of ordinary skill in the art at the time of the invention would have understood Lathrop in the context of the prior art as a whole, which made clear that the 5% concentration had already been optimized.[15] *See supra* ¶¶ 120, 164–170. Furthermore, the fact that Lathrop also "especially preferred" a 5% concentration would have meant that a person of ordinary skill would have seen no reason to select a 7.5% concentration, as the lower concentration would have been expected to provide lower side effects, and the 5% concentration did not raise the same questions about safety as preparation with a 7.5% concentration. *See* Ex. 30, Lathrop at [0014].

224. Nadau-Fourcade would not have motivated a person of ordinary skill to make an improved acne formulation with a dapsone concentration of about 7.5%. Nadau-Fourcade does not mention dapsone or suggest a dapsone concentration of 7.5% for any purpose.

225. *For rosacea*. As discussed above, Garrett I taught away from selecting dapsone, because Garrett I taught that dapsone was no more effective in treating rosacea than vehicle alone. *See* Ex. 2, Garrett I at 35:6–33. A person of ordinary skill in the art therefore would not have been motivated to use any concentration of dapsone.

[15] The same analysis applies to Dr. Constantinides's attempt to rely on a range of 5 to 10% dapsone in Garrett II, *See* Constantinides Rpt. ¶ 89 n.20, and other prior art ranges up to 10% dapsone on which he seeks to rely. *See, e.g.*, Constantinides Rpt. ¶ 133.

226. Pointing to the dapsone concentration range of 0.5 to 10% in Garrett I, Dr. Constantinides opines that a person of ordinary skill in the art "would have understood that each point in the range of 0.5% to 10%, including 7.5%, could have been used to make a topical dapsone composition, and therefore a topical composition having any amount of dapsone 0.5% to 10% w/w, including 7.5%, would have been obvious." Constantinides Rpt. ¶ 89. But a person of ordinary skill in the art would have understood Garrett I's range in conjunction with other disclosures, including that values within the range were no more effective than vehicle, and that dapsone's effects in treating rosacea could "only be described as disappointing." *See supra* ¶¶ 95–97, 153–161. A person of ordinary skill therefore would not have given credence to the values in Garrett I's range, or even looked to the range in Garrett I if seeking to make a rosacea treatment.

227. Nadau-Fourcade would not have provided a reason for a person of ordinary skill seeking to make a rosacea treatment to select a dapsone concentration of about 7.5%, nor provided any reasonable expectation of success with such endeavor. Nadau-Fourcade does not mention dapsone, and does not suggest any concentration of dapsone for any purpose. Nadau-Fourcade instead prefers a different pharmaceutical agent for treatment of rosacea. *See supra* ¶¶ 101, 218.

c) A person of ordinary skill formulating with dapsone would have also used adapalene.

228. As discussed above, the asserted claims also would not have been obvious because, if a person of ordinary skill in the art had opted to pursue a dapsone formulation, that person would have also used adapalene. *See supra* ¶¶ 178–186. Nothing in Garrett I and Nadau-Fourcade would have dissuaded a person of ordinary skill in the art from making a combination product with adapalene if that person had chosen to pursue a dapsone product.

229. Garrett I provides no reason to believe that using a dapsone as a monotherapy would be advantageous, or otherwise suggests that use of adapalene would be problematic if one were to pursue a dapsone formulation.

230. Nor would Nadau-Fourcade have prevented a person of ordinary skill from making a combination product that included adapalene. Nadau-Fourcade does not suggest that use of adapalene would pose difficulties, and in fact mentions that the retinoid dispersed in the aqueous phase may be adapalene. *See* Ex. 4, Nadau-Fourcade at [0035].

E. Objective Evidence Further Supports the Non-Obviousness of the Asserted Claims

231. In addition to the considerations above, unexpected results and industry praise support the non-obviousness of the asserted claims and the Aczone 7.5% formulation. Further, it is my opinion that there is a nexus, or relationship, between the unexpected results and industry praise, and the patented attributes of the claimed invention.

i. Unexpected Results

232. I am informed that a showing that an invention produced an unexpected result tends to suggest that the invention was not obvious, because that which is surprising tends not to be obvious. In my opinion, it is surprising that the Aczone 7.5% product, an embodiment of the asserted claims, is successful as a once-daily product.

233. As discussed above, a person of ordinary skill in the art at the time of the invention would have understood that the Aczone 5% treatment had already been optimized. *See supra* ¶¶ 166–170. That person would have further understood, however, that although the product was optimized, it was a product that required twice-daily application. *See, e.g.*, Ex. 7, Aczone 5% PI at TARO-DG-00063817 ("DOSAGE AND ADMINISTRATION . . . Apply twice daily (2)"). A person of ordinary skill therefore would have expected that increasing the concentration of

dapsone would not improve the efficacy of the product, and therefore would not have expected that increasing the dapsone concentration to 7.5% would yield a successful once-daily product.

234. Surprisingly, however, the Aczone 7.5% formulation has been just that. *See, e.g.*, Ex. 8, Aczone 7.5% PI at ALM-ACZ0000005 ("DOSAGE AND ADMINISTRATION—Apply once daily."); Ex. 11, Zaina T. Al-Salama & Emma D. Deeks, *Dapsone 7.5% Gel: A Review in Acne Vulgaris*, 22 Am. J. Clinical Dermatology 1, 1 (2016) ("[D]apsone 7.5% gel is an effective and well tolerated option for the topical treatment of acne vulgaris in patients aged ≥ 12 years, with the convenience of once-daily application."). In addition, despite the higher concentration of the dapsone 7.5% gel, there were no clinically significant differences in the mean cumulative irritancy index (MCII) score for dryness, scaling, and erythema between dapsone 7.5% and 5% gel formulations. *See, e.g.*, Ex. 11, Al-Salama at 4.

ii. Praise

235. That Aczone is an effective once-daily application with very high tolerability has made Aczone 7.5% a valuable addition to the dermatologist's armamentarium, and many in the industry have recognized it as such. *See, e.g.*, Ex. 39, Shelley Moench-Kelly, *Banishing Blemishes*, 13 MedEsthetics 22, 26 (November/December 2017) ("[Aczone 7.5%] does a great job treating milder acne cases and helping adult women with acne—which is a huge market."); Ex. 53, Linda Stein Gold et al., *Efficacy and Safety of Once-Daily Dapsone Gel, 7.5% for Treatment of Adolescents and Adults with Acne Vulgaris: First of Two Identically Designed, Large, Multicenter, Randomized, Vehicle-controlled Trials*, 15 J. Drugs in Dermatology 55, 560-61 (2016) ("Dapsone gel, 7.5% applied topically once daily is an effective, safe, and well-tolerated treatment for acne. . . . Reducing the frequency of acne treatment applications is an important strategy to improve treatment adherence."); Ex. 25, Michael T. Jarratt et al., *Safety and Pharmacokinetics of Once-Daily Dapsone Gel, 7.5% in Patients with Moderate Acne Vulgaris*,

15 J. Drugs in Dermatology 1250, 1259 (2016) ("Once-daily dapsone gel, 7.5% offers a convenient alternative to twice-daily dapsone gel, 5% in the treatment of acne vulgaris, and may improve treatment adherence."); Ex. 59, Diane M. Thiboutot et al., *Efficacy, Safety, and Dermal Tolerability of Dapsone Gel, 7.5% in Patients with Moderate Acne Vulgaris: A Pooled Analysis of Two Phase 3 Trials*, 9 J. Clinical and Aesthetic Dermatology 18, 25 (2016) ("Dapsone gel, 7.5% applied topically once daily is an effective, safe, and well-tolerated treatment for acne over 12 weeks."); Ex. 11, Al-Salama at 1 ("Thus, dapsone 7.5% gel is an effective and well tolerated option for the topical treatment of acne vulgaris in patients aged ≥12 years, with the convenience of once-daily application."); Ex. 27, Devon Kelley, *Kate Bosworth on Adult Acne: It Sucks,* Yahoo Beauty (June 3, 2016), *available at* https://www.yahoo.com/lifestyle/kate-bosworth-on-adult-acne-1443085524475958.html, at ALM-ACZ0000170–171 ("'I have been working about 16, 17 hour days for the last three to four weeks, and that kind of stress and exhaustion compounded with a lot of travel definitely brings up issues in the skin.' . . . Bosworth has been struggling with hormonal acne around her chin since she was a teenager. . . . So how did she rebuild her confidence? By getting into skincare, so that she could start to prevent, rather than constantly treat acne (that's why her skin is so flawless now). . . . 'In the evening I cleanse, and that's when I apply Aczone – right after cleansing, right before moisture, then I use moisturizer. I use something a little bit richer to feel like I'm really getting the hydration in, and night cream, and that's essentially it.'"); Ex. 40, Victoria Moorhouse, *I've Only Had One Pimple Since Starting This Acne Treatment,* InStyle, (Apr. 23, 2018), *available at* https://www.instyle.com/beauty/common-acne-treatment, at ALM-ACZ0000211–212 ("Until I turned 26, I never struggled with regular breakouts. Understandably, I freaked out . . . That was enough for me to bring it up during an appointment with my dermatologist in January. She got

the gist and prescribed me an acne treatment called Aczone. It's basically changed my life . . . ."), ALM-ACZ0000212 ("The reason why it's such a popular medication is that, unlike other topical acne formulations, it does not cause dryness or irritation of the skin, and the lightweight gel can easily be used within a skincare routine as a standalone active ingredient or in combination with other acne medications."); Ex. 58, Susan C. Taylor et al., *Efficacy, Safety, and Tolerability of Topical Dapsone Gel, 7.5% for Treatment of Acne Vulgaris by Fitzpatrick Skin Phototype*, 17 J. Drugs in Dermatology 160, 160 (2018) ("CONCLUSION: Once-daily dapsone gel, 7.5% was effective, safe, and well tolerated in patients with all skin phototypes who were treated for moderate acne."); Ex. 55, Toni C. Stockton et al., *Clinical Experience With Once-Daily Dapsone Gel, 7.5% Monotherapy in Patients With Acne Vulgaris*, 17 J. Drugs in Dermatology 602, 602 (2018) ("CONCLUSION: "Photographs, dermatologist reports, and patient commentary in an office-based practice demonstrated that 12 weeks of treatment with only topical dapsone gel, 7.5%, applied once daily, was effective and well tolerated as a stand-alone treatment in 8 patients with facial acne vulgaris, with results that are consistent with the phase 3 pivotal trials.").

236. Recognized benefits of Aczone 7.5% include its once-daily application and excellent tolerability. As one leading dermatologist explained in praising Aczone 7.5%, "[e]ase-of-use is crucial to patient compliance," and the "easiest protocols are the once-a-day products that are used in the morning and go on well with makeup." Ex. 39, Moench-Kelly at 26. As explained in the article, the combination of excellent tolerability and once-daily application makes Aczone 7.5% a topical product of choice for patients with milder acne. *See* Ex. 39, Moench-Kelly at 26 (Aczone 7.5% "does a great job treating milder acne cases" and "helping adult women with acne").

237. Others have also recognized the compliance benefit and excellent tolerability of Aczone 7.5%. *See,* e.g., Ex. 53, Stein Gold at 560–61 ("Dapsone gel, 7.5% applied topically one daily is an effective, safe, and well-tolerated treatment for acne. . . . Reducing the frequency of acne treatment applications is an important strategy to improve treatment adherence."); Ex. 25, Jarratt at 1259 ("Once-daily dapsone gel, 7.5% offers a convenient alternative to twice-daily dapsone gel, 5% in the treatment of acne vulgaris, and may improve treatment adherence."); Ex. 40, Moorhouse at ALM-ACZ0000212 ("The reason why [Aczone 7.5%] is such a popular medication is that, unlike other topical acne formulations, it does not cause dryness or irritation of the skin . . . .").

238. Dapsone 7.5% has been recognized as being especially useful for meeting the needs of women. *See, e.g.*, Ex. 39, Moench-Kelly at 26 (Aczone 7.5% "does a great job . . . helping adult women with acne—which is a huge market"). This is in part due to the fact that it is a "lightweight gel [that] can easily be used within a skincare routine as a standalone active ingredient or in combination with other acne medications," and also works well with makeup—which is a crucial requirement for many women. Ex. 40, Moorhouse at ALM-ACZ0000212; *see also* Ex. 27, Kelley at ALM-ACZ0000171.

239. The praise for Aczone 7.5% is consistent with my clinical experience. I have found that Aczone 7.5% works extremely well in my adult female patients particularly, including in patients whom have not fared well with other products. I also have found that Aczone 7.5% works well with other acne products, as well as makeup, without contributing to dryness or irritation, or causing bleaching—key attributes for a product to work well for adult women. In addition, unlike teenage girls, whose acne tends to be comedonal and concentrate in the "T-zone" of the forehead and nose, adult women tend to have more visible inflammatory acne, typically in

the "U-zone" of the chin and jowls. The oilier skin of teenage girls, who have higher sebum production, also allows them to tolerate more medications, whereas adult women are more likely to need gentler products.

240. The once-daily indication of Aczone 7.5% is also very important, because it enhances convenience and reduces compliance burdens in patients. With acne medications, this is critical, because the treatment cannot work unless patients use it. I have found that compliance among my patients using Aczone 7.5% has been excellent, and that Aczone 7.5% has been a valuable addition to my treatment options for acne, with patients asking for refills of Aczone 7.5% more than for other medications.

241. In my opinion, the praise that the Aczone 7.5% product has received is linked to its patented features. Aczone's 7.5% dapsone concentration allows the product to be applied once-daily and be effective yet still extremely well-tolerated. And its formulation features provide a lightweight gel that does not feel gritty and that can work well with other skincare products, including makeup. The combination of these features has made this product a valuable addition to acne treatments for doctors and patients alike.

XVI. RIGHT TO SUPPLEMENT

242. I reserve the right to amend or supplement my opinions in light of evidence presented by Taro and Dr. Constantinides, or additional information that may be made available to me in the future. I also reserve the right to convey my opinions through the use of demonstrative exhibits at trial. I have not yet created the exhibits I expect to use to illustrate, summarize, or support my opinions, but they will likely include diagrams, presentations, or blowups showing aspects of the science and opinions described in this report.

Exhibit J

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

C.A. No. 17-663 (JFB)(SRF)
CONSOLIDATED

ALMIRALL, INC.,
Plaintiff,
V.
TARO PHARMACEUTICAL INDUSTRIES, LTD., and
TARO PHARMACEUTICALS, INC.,
Defendants.

VIDEO DEPOSITION TRANSCRIPT OF JULIE HARPER, M.D.

DECEMBER 10, 2018
9:11 A.M.

WELLS FARGO TOWER
420 20TH STREET NORTH
SUITE 2200
BIRMINGHAM, ALABAMA 35203

Job No. 29324
BEFORE CARRIE M. ROBINSON, RPR, CRR, CRI

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

C.A. No. 17-663 (JFB)(SRF)

CONSOLIDATED

ALMIRALL, INC.,

Plaintiff,

V.

TARO PHARMACEUTICAL INDUSTRIES, LTD., and TARO PHARMACEUTICALS, INC.,

Defendants.

VIDEO DEPOSITION TRANSCRIPT OF

JULIE HARPER, M.D.

DECEMBER 10, 2018

9:11 A.M.

WELLS FARGO TOWER

420 20TH STREET NORTH

SUITE 2200

BIRMINGHAM, ALABAMA 35203

Job No. 29324

BEFORE CARRIE M. ROBINSON, RPR, CRR, CRI

I N D E X

E X H I B I T S

A P P E A R A N C E S

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ALSO APPEARING:

PAIGE ALI, VIDEOGRAPHER

I, Carrie M. Robinson, RPR, CRR, CRI, Certified Court Reporter of the State of Alabama, and a Notary Public for the State of Alabama at Large, acting as Commissioner, certify that on this date, pursuant to the Federal Rules of Civil Procedure and the foregoing stipulation of counsel, there came before me at the Wells Fargo Tower, 420 20th Street North, Suite 2200, Birmingham, Alabama, 35203, commencing at approximately 9:11 a.m. on December 10, 2018, Julie Harper, M.D., witness in the above cause, for oral examination, whereupon the following proceedings were had:

(Defendants' Exhibit Numbers 1 - 4 were marked for identification.)

VIDEOGRAPHER: This marks the beginning of Videotape Number 1 of the deposition of Dr. Julie Harper in the matter of Almirall, Incorporated, versus Taro Pharmaceutical Industry, LTD, and Taro Pharmaceuticals, Incorporated; Civil Action Number 17-663(JFB)(SRF), Consolidated -- all consolidated cases filed in the United States District Court for the District of

Delaware.

The date is December 10th, 2018. The time is 9:11 a.m.

All attorneys present, will you please state your name and whom you represent.

MR. BENSON: Stephen Benson on behalf of Defendants -- the Taro defendants, from the law firm of Katten, Muchin, Rosenman. And with me is Kimberly Beis, also of Katten Muchin and on behalf of the Taro defendants.

MS. HAGAN: Elizabeth Hagan of Fenwick & West on behalf of Almirall, Incorporated. And with me I have Rebecca Fewkes also with Fenwick & West.

VIDEOGRAPHER: Court reporter, will you please swear in the witness.

JULIE HARPER, M.D.,

being first duly sworn, was examined and testified as follows:

EXAMINATION

BY MR. BENSON:

Q Good morning, Dr. Harper.

A Good morning.

Q -- to help us get on the same page.
A That's fine.
Q So I am looking at Tab 2 of Exhibit 2, and this is the -- what we have referred to as the Garrett I reference. And I'd like to direct you to the Bates ending in 65186.
A Okay.
Q And this is the section Background of the Invention, and I would like you to go to the last sentence of the third paragraph.
A Yes.
Q And take a moment to review that and let me know when you're ready.
A I'm ready.
Q Okay. Now, Garrett is indicating here that there is a study -- it's Nase, 2005 -- indicating dapsone antibiotic is effective for treating rosacea when administered orally.
Did you review that reference?
A I did not review Nase.
Q Okay. Do you have any knowledge

of dapsone -- oral dapsone having been used to -- or effective in treating rosacea?
A I do not.
Q Okay. Are you aware of any use -- of any prescription of dapsone for the purposes -- orally for the purposes of treating rosacea?
A No.
Q Okay. Have you ever used oral dapsone to treat patients with acne?
A No.
Q Okay. Is oral dapsone available --
A Yes.
Q -- for that purpose?
A It is available, and we as physicians can prescribe it for whatever we want to.
Q Sure. But you yourself have never prescribed oral dapsone to treat acne?
A I prescribe oral dapsone, but I have never prescribed it for acne.
Q Okay. For what reason would you prescribe oral dapsone?
A Most of the time for dermatitis

herpetiformis.
Q And what -- can you explain for me what that condition is?
A Dermatitis herpetiformis is a skin eruption that oftentimes will go with gluten-sensitive enteropathy. Under the microscope it is characterized by an influx of neutrophils, and dapsone has a reputation of being able to have activity against neutrophils. So we will also use it for other neutrophilic dermatoses.
Q Okay. Are you -- is there a -- are you aware in the dermatology community at large of any use of oral dapsone to treat acne?
A I've not. It is -- it would not be a mainstream thing. It would not be in any recommendation that I have seen for the treatment of acne or rosacea.
Q Okay. All right. Now, you have reviewed the opinion of Dr. Klibanov as to what constitutes a person of ordinary skill in the art as it relates to the '219 Patent, correct?
A Yes, sir.

Q Okay. Do you regard yourself as being a person of ordinary skill in the art?
A No.
Q And in particular, you also looked at Dr. Constantinides' opinion about the person of ordinary skill in the art and his opinion that such a person may have consulted with persons having expertise in treating acne or rosacea, right?
A Correct.
Q Now, you'll agree with me that a person having expertise in treating acne or rosacea could be a person working for a pharmaceutical company, right?
MS. HAGAN: Objection. You may answer.
A I would think that a person who is an expert on acne and rosacea is a clinician. They may not be serving at that role at that time, but they have got experience treating patients with acne and rosacea.
Q Could a person who's not a clinician have expertise in the treatment of acne or rosacea?

MS. HAGAN: Objection. You may answer.
A I think they could have expertise in the conditions of acne and rosacea, but I would say they couldn't have expertise in treating them.
Q So even if such a person was fully apprised of all clinical trials relating to the treatment of acne, talks to other physicians, and was active in that regard, you feel they wouldn't have expertise in treating acne?
MS. HAGAN: Objection.
A Well, as someone who is a practicing clinician myself, no. I think that would be very difficult because it is one thing to understand these products. It's one thing to talk about how they might work. But it's very different sitting and talking to a patient and dealing with them as they use it and after they've used it. So, no, I think it needs to be a person who's at least had clinical experience.
Q Okay. Do you feel you have a full understanding of the formulation

sciences?
A No, sir. I do not. I'm a clinician.
Q Okay. Do you have any understanding as -- what the role of the DGME plays in the -- with respect to the formulations claimed in the patent?
A Could you repeat that?
Q How does DGME -- let me rephrase it.

What, if any, impact do you understand DGME to have on the formulations claimed in the patent at suit?
A So I -- my understanding is that dapsone is not easily solubilized in water. It doesn't play well with water. And so another solvent was needed that we could put in with dapsone, and DGME was the solvent that was able to do that. It keeps the product both dissolved and as a particulate and keeps that in a certain ratio in the follicle. And then also the -- it dissolved can then penetrate through the stratum corneum or through the wall of the upper part of the follicle.

Q So if you increase the amount of DGME, would you expect the ratio of dissolved to particulate dapsone to change?
MS. HAGAN: Objection.
A I would have to look at the Osborne 2011 article. There's a nice chart in there that does show us DGME concentration goes up. I think you can get more dissolved dapsone into the product. But, again, I am a clinician, and I would have to leave most of that to the formulation scientists.
Q Okay. How about the polymeric viscosity builder, do you have any understanding as to how that component operates within the formulations claimed in the patent and suit?
A As a clinician, I do not think about viscosity builders.
Q Okay. And do you have any understanding as to how the ratio of DGME to the polymeric viscosity builder might impact the bioavailability of dapsone in a formulation?
A I have reviewed this material

with counsel, and particularly with the Warner declaration, I have some understanding of that. But really I would leave most of that to the formulation scientists.

Q As a clinician, would you expect every formulation manufactured according to the claims would have the exact same benefits as the Aczone Gel 7.5 percent product?

MS. HAGAN: Objection.

A Can you repeat that again?

Q Sure.

So do you understand that the claims are not limited to the Aczone Gel 7.5 percent product?

A From my clinical standpoint, that's the only 7.5 percent product that I have any access to.

MR. BENSON: Okay. All right. I'll tell you what. I think we're getting to the point where we're going to have to break for a court hearing, so I don't -- we can revisit this when we get back.

So we'll take a short break.

Hopefully it's not too long and -- okay.
VIDEOGRAPHER: This ends Videotape Number 1 of the deposition of Dr. Julie Harper. The time is now 9:57 a.m.
(Recess was taken.)
VIDEOGRAPHER: This marks the beginning of Videotape Number 2 of the deposition of Dr. Julie Harper. The time is now 10:23 a.m.
Q (By Mr. Benson) Welcome back, Dr. Harper.
A Thank you.
Q So one of the -- I think right before the break, you had indicated that the Aczone Gel 7.5 percent product was the only product you had available as a clinician and so the only embodiment of the claims you could speak to in that regard, correct?
A I've had the 7.5 and the 5 percent.
Q Okay. And we can agree that 5 percent is not claimed in the '219 Patent, correct?
A That is correct.
Q Okay. So the 7.5 percent product

effects on the skin. So I could not make a guess based on what I know about the 30 percent. I would have to see data on the 40 percent.

Q Okay. All right. Now, Claim 4 -- going back to the patent, Claim 4 is also being asserted against Taro. Is that your understanding?

A Yes, sir.

Q Okay. Now, combining Claim 1 with Claim 4, you'll agree with me that that also does not disclose to anyone the specific composition of Aczone Gel 7.5 percent, right?

MS. HAGAN: Objection.

A That is correct.

Q And the same with respect to Claim 5 which is also being asserted against Taro, right?

MS. HAGAN: Objection.

A That is correct.

Q Okay. Now, you've given an opinion about unexpected results, correct?

A I have.

Q And one of -- and one of the

unexpected results you believe as a benefit of the claim is the fact that the Aczone Gel product can be administered once a day, right?
A That is correct.
Q But as you sit here today, you have no knowledge as to whether any other formulation of these claims would be effective treatment for acne at once a day, correct?
A I've had no opportunity to use any other product, so I couldn't be surprised by their results.
Q Okay. The question I asked is: As you sit here today, you have no knowledge as to whether or not any other formulation in the claims could be marketed as an effective treatment for acne once a day, right?
A I have no knowledge of any other formulation.
Q Okay. So the unexpected result may be an unexpected result with respect to Aczone Gel 7.5 percent but not necessarily every formulation in the claim. Isn't that

fair?

MS. HAGAN: Objection.

A Again, I can only speak from my own experience, and the only product that I've used is the 7.5.

Q Right. Okay. And so -- and, again, we established earlier that were the 7.5 percent product not available to you, you would not be able to provide the obviousness opinion you're providing today, correct?

MS. HAGAN: Objection.

A If the 7.5 was not -- that is true from a clinical standpoint. There may be more that could be said from a formulation science standpoint.

From a clinician's standpoint, there has to be a product that I've used for me to have an opinion about that.

Q Okay. That's fair.

Okay. Now, you testified earlier that you, you know -- in your practice, you know, around the time of the invention, you were prescribing the 5 percent product, correct?

A That is correct.
Q And when I say "5 percent product," I mean the Aczone Gel 5 percent product. Is that -- so is that your understanding?
A That is correct.
Q Okay. All right. So I'll just keep with that -- with that simplification. It will just move things along.
Now, at that time, did you ever prescribe the 5 percent product once a day for patients?
A Yes, I did.
Q Okay. So describe for me a scenario where you would prescribe the 5 percent product once a day for a patient in, for example, 2012.
A So the Aczone product itself -- you know, we talk about the four pathogenetic targets for acne. And so to be a good treater of acne, you need to understand what your targets are. And they are: Follicular hyperkeratinization, excess sebum, inflammation, and propionibacterium acnes, which is the bacteria. And so we

want to hit as many of the four targets as we can.

And Aczone, for the most part, we had relegated to just being anti-inflammatory. Yes, we talk a little bit at some point about is it antimicrobial, but there's no evidence out there that I know of that it's effective against P. acnes in particular. So because it's only hitting one of the four targets, when we used the product, we would most of the time -- I would most of the time be using it in combination with another product.

Now, you can stack medicines on top of each other, and sometimes we do that, again, for ease of use. But in this case we would try the Aczone 5 percent once a day and then add, for example, a product like Epiduo the other times a day, because Epiduo now adds a retinoid which is going to help with follicular hyperkeratinization, plus clindamycin, which is an antimicrobial. So now by doing those in combination, I've hit three of the four.

And so that's why we would move

C E R T I F I C A T E

I hereby certify that the above and foregoing deposition of Julie Harper, M.D., was taken down by me in stenotype and the questions and answers thereto were transcribed by means of computer-aided transcription, and that the foregoing represents a true and correct transcript of the testimony given by said witness upon said hearing.

I further certify that I am neither of counsel, nor of kin to the parties to the action, nor am I in anywise interested in the result of said cause.

I further certify that I am duly licensed by the Alabama Board of Court Reporting as a Certified Court Reporter as evidenced by the ACCR number following my name found below.

Certified on December 21, 2018.

Carrie M. Robinson

/s/ Carrie M. Robinson
Carrie M. Robinson, RPR, CRR, CRI
Court Reporter and Commissioner
ACCR#: 71, Expires: 9-30-2019
Commission Expires: 1-20-2022

Plaintiff's Opposition to Defendant's Motion *in Limine* No. 1

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ALMIRALL, LLC, Plaintiff, v. TARO PHARMACEUTICAL INDUSTRIES LTD. and TARO PHARMACEUTICALS, INC., Defendants.	C.A. No. 17-663 (JFB) (SRF) CONSOLIDATED

PLAINTIFF'S OPPOSITION TO DEFENDANTS' MOTION *IN LIMINE* TO EXCLUDE ARGUMENT, EVIDENCE OR TESTIMONY RELYING ON PLAINTIFF'S COMMERCIAL PRODUCT TO PROVE INFRINGEMENT

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Taro moves *in limine* to preclude Plaintiff from comparing Taro's ANDA Product to Plaintiff's ACZONE® Gel, 7.5% in support of Plaintiff's infringement case. The Federal Circuit has repeatedly rejected the blanket prohibition Taro requests. Instead, where a commercial product meets all the claim elements—as the parties agree that ACZONE® Gel, 7.5% does—such comparison ***is*** appropriate and is relevant and admissible evidence of infringement. Thus, Plaintiff is entitled to present arguments and evidence comparing Taro's ANDA Product and ACZONE® Gel, 7.5%. Taro's motion should be denied.

The Federal Circuit has explicitly rejected Taro's argument "that the patent infringement inquiry requires a comparison of the accused product to the claims at issue, not the patent holder's commercial product." *See* Taro's Motion *in Limine* ("MIL") at 1. Federal Circuit case law "does not contain [such] a blanket prohibition." *Adams Respiratory Therapeutics, Inc. v. Perrigo Co.*, 616 F.3d 1283, 1288 (Fed. Cir. 2010). Although infringement is typically determined with reference to the claims (as the cases Taro cites hold), "when a commercial product meets all of the claim limitations, then a comparison to that product may support a finding of infringement." *Id.* at 1289; *see also Glaxo Group Ltd. v. Torpharm*, 153 F.3d 1366, 1373 (Fed. Cir. 1998). As recently as last year, the Federal Circuit reaffirmed this principle from *Adams* and upheld a finding of infringement under the doctrine of equivalents—the very theory to be tried in this case—based on a comparison between the patentee's products and the allegedly infringing products. Ex. 1, *WCM Indus., Inc. v. IPS Corp.*, 721 F. App'x. 959, 968–69 (Fed. Cir. 2018) (nonprecedential).

Taro cites only one case dating after the Federal Circuit's decision in *Adams* where a court allegedly excluded evidence comparing an accused product to a commercial embodiment. *See ICU Med., Inc. v. Rymed Techs, Inc.*, 752 F. Supp. 2d 486 (D. Del. 2010). *ICU Medical* is not controlling Federal Circuit precedent, and in any event, it does not support Taro's position. In *ICU Medical*, the parties agreed that comparisons between the accused product and an alleged commercial embodiment would not be offered for purposes of infringement, but that such comparisons could be used to respond to allegations of willful copying and nonobviousness. *Id.*

at 491. Those are not the facts here. In *ICU Medical*, whether the commercial embodiment met the claim limitations was never argued; in fact, the *Adams* holding was never addressed or even cited by either the parties or the court. The Court's decision in that case therefore did not—and cannot here—abrogate the principle that comparison to a commercial product meeting every claim limitation can support a finding of infringement. *Adams*, 616 F.3d at 1288.

In her reports, Plaintiff's expert, Dr. Majella Lane, supports her infringement opinion with comparisons between Taro's ANDA Product and ACZONE® Gel, 7.5%, which Dr. Lane concludes, and Taro does not dispute, meets all claim limitations of the asserted claims. *See, e.g.*, Ex. A to Taro's MIL, Lane Opening Rpt. ¶¶ 42, 49–142. Specifically, Dr. Lane opines that the polymeric viscosity builder ("PVB") in ACZONE® Gel, 7.5%, Sepineo P 600, is an embodiment of the only disputed claim element: "about 2% w/w to about 6% w/w of a polymeric viscosity builder comprising acrylamide/sodium acryloyldimethyl taurate copolymer." *Id.* at ¶¶ 69, 71. The specification of the '219 Patent-in-suit explicitly identifies Sepineo P 600 (either by its name or its ingredients) as a PVB of the invention—in fact, it is the only PVB embodiment specifically described in the patent. *See, e.g.*, Ex. 2, '219 patent at 5:47–50, table 7. Taro's own infringement expert, Dr. Mansoor Amiji, agrees that Sepineo P 600 satisfies the disputed claim element. Ex. 3, Amiji Rpt. ¶ 108; *see also* Ex. 4, Amiji Dep. Tr. at 81:2–82:9, 121:13–122:14. Thus, under controlling Federal Circuit authority, comparisons between Taro's ANDA Product and ACZONE® Gel, 7.5% are relevant evidence of infringement.

Despite its own expert's admissions, Taro disputes whether certain ***excipients*** can form part of the claimed PVB, when they are not separately and explicitly recited in the claims. *See* Taro's MIL at 2. A POSA's understanding of which excipients can form the claimed PVB, and whether the PVB in ACZONE® Gel, 7.5% is an embodiment of the claimed PVB (if that is disputed), are both questions for the trier of fact to decide based on the record developed at trial. *Adams*, 616 F.3d at 1288–89. Taro's dissatisfaction with Plaintiff's position is not grounds for excluding admissible and relevant evidence of infringement.

Relatedly, Taro disputes whether certain unclaimed ***properties*** are attributable to the PVB.[1] *See* Taro's MIL at 2-3. Again, this issue goes to the weight but not admissibility of Almirall's infringement evidence. The Federal Circuit "ha[s] never held that a patent must spell out a claim element's function, way, and result in order for the doctrine of equivalents to apply as to that element. To the contrary, [it] ha[s] held that '[w]hen the claims and specification of a patent are silent as to the result of a claim limitation, . . . we should turn to the ordinary skilled artisan.'" *Intendis GmbH v. Glenmark Pharms., Inc.*, 822 F.3d 1355, 1362 (Fed. Cir. 2016) (quoting *Stumbo v. Eastman Outdoors, Inc*., 508 F.3d 1358, 1365 (Fed. Cir. 2007)). Dr. Lane is prepared to identify various properties of the claimed PVB and explain how they would be relevant to a POSA determining whether Taro's ANDA Product is insubstantially different. *See, e.g.*, Ex. A to Taro's MIL, Lane Opening Rpt. ¶¶ 67–131. Bioequivalence of these properties, contrary to Taro's assertions, ***can be*** relevant to the doctrine of equivalents. *See Allergan, Inc. v. Teva Pharms. USA, Inc*., No. 2:15-cv-1455-WCB, 2017 U.S. Dist. LEXIS 4535, at *7–8 (E.D. Tex., Jan. 12, 2017); *Adams*, 616 F.3d at 1288-89; *Abbott Labs. v. Sandoz, Inc*., 566 F.3d 1282, 1298 (Fed. Cir. 2009). Whether these properties would ultimately be relevant to a POSA is inarguably a question of fact for the Court to decide. *Abraxis Bioscience, Inc. v. Mayne Pharma Inc*., 467 F.3d 1370, 1379 (Fed. Cir. 2006); *see also Intendis*, 822 F.3d at 1361 ("Each prong of the function-way-result test is a factual determination.").

Taro's motion is a transparent attempt to obtain a summary judgment ruling on key issues in this case—namely, a POSA's understanding of what the PVBs are in the commercial embodiment of the claims and in Taro's equivalent ANDA Product—before the record has been fully developed at trial. Taro's motion has no basis in law, and accordingly should be denied.

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[1] Taro states that "Dr. Lane[] testified she did not conduct her function-way-result analysis with reference to the missing claim element, [A/SA]." As explained in Almirall's Opposition to Defendants' *Daubert* Motion Re: Dr. Lane, the missing claim element is not A/SA, but "about 2% w/w to about 6% w/w of a polymeric viscosity builder comprising [A/SA]," and Dr. Lane confirmed in her deposition and her reports that she appropriately conducted her analysis with reference to that missing element. *See* Almirall's Opposition to Defendants' *Daubert* Motion Re: Dr. Lane, p. 2.

MORRIS, NICHOLS, ARSHT & TUNNELL LLP

/s/ Anthony D. Raucci

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January 7, 2019

EXHIBIT 1

WCM Indus., Inc. v. IPS Corp.

United States Court of Appeals for the Federal Circuit

February 5, 2018, Decided

2016-2211, 2016-2268

Reporter
721 Fed. Appx. 959 *; 2018 U.S. App. LEXIS 2949 **; 2018 WL 707803

WCM INDUSTRIES, INC., A COLORADO CORPORATION, Plaintiff-Cross-Appellant v. IPS CORPORATION, A DELAWARE CORPORATION, Defendant-Appellant, AMERICAN BRASS & ALUMINUM FOUNDRY COMPANY, A CALIFORNIA CORPORATION, JOHN DOE, AN INDIVIDUAL, Defendants

Notice: THIS DECISION WAS ISSUED AS UNPUBLISHED OR NONPRECEDENTIAL AND MAY NOT BE CITED AS PRECEDENT. PLEASE REFER TO *FEDERAL RULES OF APPELLATE PROCEDURE RULE 32.1* GOVERNING THE CITATION TO UNPUBLISHED OPINIONS.

Prior History: [**1] Appeals from the United States District Court for the Western District of Tennessee in No. 2:13-cv-02019-JPMtmp, Chief Judge Jon P. McCalla.

WCM Indus. v. IPS Corp., 2016 U.S. Dist. LEXIS 134079 (W.D. Tenn., Sept. 29, 2016)

Disposition: REVERSED-IN-PART, AFFIRMED-IN-PART, VACATED-IN-PART, AND REMANDED.

Case Summary

Overview

HOLDINGS: [1]-The court concluded that plaintiff provided sufficient evidence for a reasonable jury to have found infringement under the doctrine of equivalents and to have found that defendant's infringement was willful. It therefore reversed the district court's grant of defendant's motion for judgment as a matter of law as to no infringement under the doctrine of equivalents and affirmed the district court's denial of defendant's motion for judgment as a matter of law as to no willfulness; [2]-The court also affirmed the district court's denial of defendant's motion for judgment as a matter of law as to no indirect infringement; [3]-Finally, the court vacated the district court's award of maximum enhanced damages under *35 U.S.C.S. § 284* and remanded for the district court to reconsider the amount by which the damages should be enhanced, if at all.

Outcome

Reversed-in-part, affirmed-in-part, vacated-in-part, and remanded.

Counsel: J. MICHAEL JAKES, Finnegan, Henderson, Farabow, Garrett & Dunner, LLP, Washington, DC, argued for plaintiff-cross-appellant. Also represented by KATHLEEN DALEY, JASON LEE ROMRELL; IAN WALSWORTH, Lewis Brisbois Bisgaard & Smith, Denver, CO.

DAVID JOHN SILVIA, Locke Lord LLP, Stamford, CT, argued for defendant-appellant. Also represented by HUGH S. BALSAM, Chicago, IL; JOSEPH ANTHONY FARCO, New York, NY; BRUCE JOSEPH ROSE, Alston & Bird LLP, Charlotte, NC.

Judges: Before PROST, Chief Judge, WALLACH and TARANTO, Circuit Judges.

Opinion by: PROST

Opinion

[*961] PROST, *Chief Judge*.

WCM Industries, Inc., filed this patent infringement action in the United States District Court for the Western District of Tennessee, No. 2:13-cv-02019, alleging that certain IPS Corporation bathtub waste and overflow drain assemblies infringed its patents, U.S. Patent Nos. 8,302,220 ("'220 patent"); 8,321,970 ("'970 patent"); and 8,584,272 ("'272 patent"). The case was tried to a jury,

which found that IPS willfully infringed WCM's patents. The jury awarded WCM over $1 million in damages, and the district court awarded WCM maximum enhanced [**2] damages because of IPS's willfulness. After trial, the district court granted IPS's motion for judgment as a matter of law as to no infringement under the doctrine of equivalents as to one of its product lines, but it let stand the jury's verdict of indirect infringement and willfulness.

IPS appeals the district court's denial of its motions for judgment as a matter of law as to no indirect infringement and as to no willfulness. IPS also appeals the district court's award of maximum enhanced damages. WCM cross-appeals the district court's grant of IPS's motion for judgment as a matter of law as to no infringement under the doctrine of equivalents.

Reviewing the record in the light most favorable to WCM, we conclude that WCM provided sufficient evidence for a reasonable jury to have found infringement under the doctrine of equivalents and to have found that IPS's infringement was willful. We therefore reverse the district court's grant of IPS's motion for judgment as a matter of law as to no infringement under the doctrine of equivalents and affirm the district court's denial of IPS's motion for judgment as a matter of law as to no willfulness. We also affirm the district court's denial [**3] of IPS's motion for judgment as a matter of law as to no indirect infringement. Finally, we vacate the district court's award of maximum enhanced damages and remand for the district court to reconsider the amount by which the damages should be enhanced, if at all.

BACKGROUND

WCM's patents generally describe improvements in bathtub overflow assemblies. The assemblies include an overflow portion that prevents an accidental overflow of water from a bathtub and a drain portion that allows the drainage of water from the bathtub. Traditional bathtub overflows were difficult to install. Tightening screws during installation often left sharp burrs that could cut through skin. Traditional overflows were also prone to leaks, which could result in significant, yet hidden, damage to both property and health (i.e., exposure to mold and mildew). Disassembling traditional overflows for testing was also difficult.

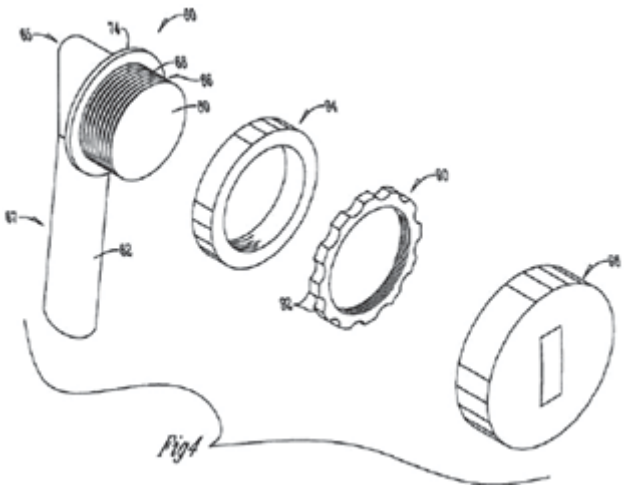
One of WCM's employees, William Ball, developed a solution to these problems. WCM's new technology (referred to as the "Innovator Product") eliminated leaks, and it could be installed more easily without the need for screws. Mr. Ball filed his original patent application on June 13, 2000, which—by [**4] way of WCM filing numerous continuing applications off of the original patent—later resulted in the three patents-at-issue in this case. WCM began selling its Innovator Product in August 2001.

On appeal, the parties focus on Claim 12 of the '220 patent, which is representative of the other claims-at-issue and reads as follows:

> 12. An overflow assembly adapted for interconnection to a bathtub, which has a bottom, side walls, end walls, and an [*962] overflow port in one end wall, comprising:
>
> an overflow pipe with an elbow portion defining an upper end portion and a lower end portion, said upper end portion having an outer end defining an inlet, said upper end having threads on an outer surface thereof;
>
> a lip extending radially outwardly from said outer surface of the overflow pipe between said elbow portion and said upper end portion and being spaced from said inlet;
>
> a nut element with a threaded portion that is compatible with said threads of said overflow pipe, *said nut element having an outer periphery with a series of radially extending lugs that detachably engage an inner surface of a cap that fits over said nut*.

'220 patent col. 7 l. 8—col. 8 l. 3 (emphasis added); J.A. 226.

Figure 4 of the '220 patent depicts an exemplary [**5] overflow assembly embodiment of the asserted claims.



J.A. 218.

The overflow assembly has an overflow pipe 62 that has an elbow portion 65, a washer 94, a nut element 90, and a cap 96. The nut element 90 has threads compatible with the threads 68 on the overflow pipe 62. The nut element 90 secures the overflow pipe 62 to the bathtub by compressing the bathtub wall between the nut element 90 and the lip 74 of the overflow pipe 62.

The nut element 90 has a series of radially extending lugs 92 along its outer periphery. These lugs 92 detachably engage the inner surface of a cap 96. The cap 96 serves to cover the overflow assembly 60 hardware once installed.

Between 2002 and 2003, American Brass and Aluminum Foundry Company ("AB&A") began offering for sale a bathtub draining product that the parties to this lawsuit call the "Classic Product." [*963] The Classic Product Full Kit provided all of the necessary components of a complete bath waste and overflow assembly and includes the overflow portion (as shown in the image below, including the overflow elbow, overflow washer, a locknut, and an overflow plate); the drain portion; and the pipes and tee that connect the two portions together and to the [**6] sewer or septic system.

J.A. 6800.

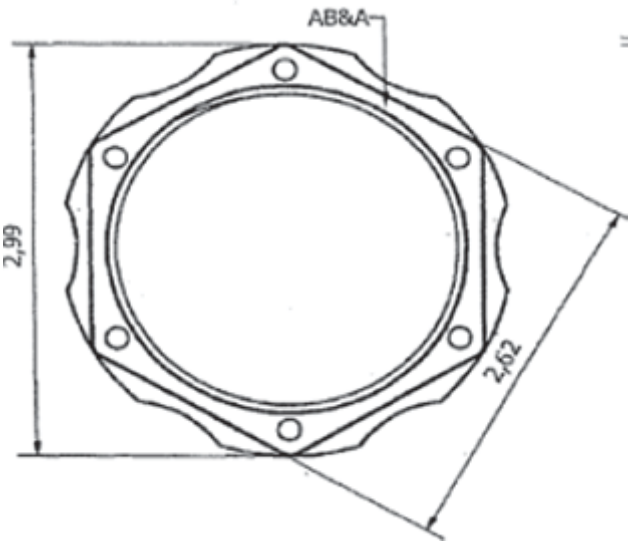
In 2010, IPS bought the assets of AB&A. Following the asset acquisition, AB&A ceased operations and IPS continued to source and sell the Classic Product under the AB&A brand name.

On December 11, 2012, WCM filed suit against IPS in the United States District Court for the District of Colorado for patent infringement of two of its patents. Those patents had only recently been granted: the '220 patent issued November 6, 2012, and the '970 patent issued December 4, 2012. The next month, WCM voluntarily dismissed the Colorado suit and refiled the same complaint in the Western District of Tennessee, initiating this action. WCM's '272 patent issued on November 19, 2013, and was later added to the suit.

In 2014, after the filing of the Tennessee suit, IPS revised its Classic Product and ceased manufacturing and importing that product line. The parties refer to the redesigned product as the "Revised Classic Product" ("Revised Product"). Like its predecessor, the Revised Product Full Kit represented the entire assembly.

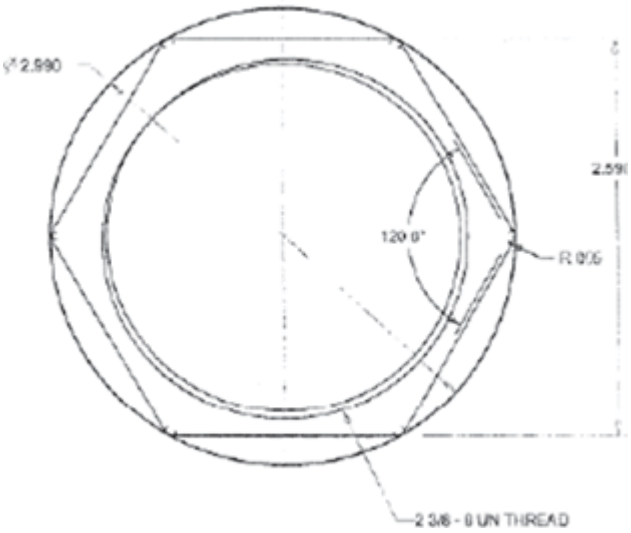
To create the Revised Product, IPS's modified the design of the locknut used in the overflow assembly. The drawing below shows the original locknut of the Classic Product having [**7] "high points" (the six angular points around the circumference of the locknut) and "finger indentations" (the curved indentations around the circumference of the locknut). *See* J.A. 2026-28.

[*964]



J.A. 6531.

The only difference between the original locknut (above) and the modified locknut (below) is that there are no finger indentations on the modified locknut. J.A. 2026-28.



J.A. 6533.

Granting a pre-trial motion, the district court excluded the report and testimony of WCM's technical expert who was to opine on various issues, including infringement under the doctrine of equivalents.

At the end of the trial, the jury found that as to the Classic Product, IPS infringed literally, contributorily infringed, and induced infringement. As to the Revised Product, while the jury found that IPS had not literally infringed, it did find that IPS infringed under the doctrine of equivalents, contributorily infringed, and induced infringement. The jury also found that IPS's infringement was willful, that the reasonable royalty rate per infringing unit was $1.00, and that IPS sold 1,241,524 infringing units. The jury was not asked to decide willfulness or damages on a product-by-product basis. Based on sales [**8] of additional infringing units, the total number of infringing units was 1,383,978, and the total damages amount was $1,383,978. The district court awarded WCM maximum [*965] enhanced damages pursuant to *35 U.S.C. § 284* because of IPS's willfulness and ultimately awarded WCM a total of $4,151,934 in damages.

After trial, the district court ruled on various motions for judgment as a matter of law. In particular, it granted IPS's motion that IPS's Revised Product did not infringe under the doctrine of equivalents. The court upheld IPS's liability for indirect infringement with respect to the Revised Product. Because the '272 patent had not issued until after the complaint was filed, the court granted IPS's motion of no willful infringement with respect to that patent. The district court denied, however, IPS's motion for judgment as a matter of law of no willfulness in all other respects.

IPS appeals the district court's denial of its motions for judgment as a matter of law as to no indirect infringement with respect to the Revised Product and as to no willfulness. IPS also appeals the district court's award of maximum enhanced damages. WCM cross-appeals the district court's grant of IPS's motion for judgment as a matter [**9] of law that IPS's Revised Product did not infringe under the doctrine of equivalents.

We have jurisdiction under *28 U.S.C. § 1295(a)(1)*.

DISCUSSION

I

We begin with WCM's cross appeal because the issue raised is a predicate for the matters raised in IPS's appeal. On cross-appeal, WCM asks this court to reverse the district court's judgment as a matter of law of no infringement under the doctrine of equivalents and to reinstate the jury's verdict.[1] We review, under Sixth Circuit law, the grant or denial of judgment as a matter of law de novo. *Barnes v. City of Cincinnati, 401 F.3d 729, 736 (6th Cir. 2005)*; *see ClearValue, Inc. v. Pearl River Polymers, Inc., 668 F.3d 1340, 1343 (Fed. Cir. 2012)* ("We review the grant or denial of a motion for judgment as a matter of law under the law of the regional circuit."). For IPS's motions for judgment as a matter of law, we view the evidence in the light most favorable to WCM, and WCM receives the benefit of all reasonable inferences. *Barnes, 401 F.3d at 736*. The Sixth Circuit instructs that we must "indulge all presumptions in favor of the validity of the jury's verdict, and should refrain from interfering with a jury's verdict unless it is clear that the jury reached a seriously erroneous result." *Williams v. Nashville Network, 132 F.3d 1123, 1131 (6th Cir. 1997)* (internal quotation marks omitted). Thus, the jury's verdict must stand, and

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[1] A properly filed cross-appeal requires that, upon acceptance of appellee's argument, our determination would result in a reversal or modification of the judgment rather than an affirmance. *Symantec Corp. v. Computer Assocs. Int'l, Inc., 522 F.3d 1279, 1294 (Fed. Cir. 2008)*. Because WCM's cross-appeal does not seek to enlarge the district court's judgment of infringement in its favor, we dismiss its cross-appeal as improper. *See Howmedica Osteonics Corp. v. Wright Med. Tech., Inc., 540 F.3d 1337, 1343 n.2 (Fed. Cir. 2008)*. We may nonetheless consider the arguments raised, as we do here, as alternative grounds for sustaining the judgment. *Symantec, 522 F.3d at 1294*.

IPS's motion for judgment as a matter of law of no infringement [**10] under the doctrine of equivalents must be denied unless reasonable minds could come to but one conclusion in favor of IPS. Barnes, 401 F.3d at 736.

Under the doctrine of equivalents, "a product or process that does not literally infringe upon the express terms of a patent claim may nonetheless be found to infringe if there is 'equivalence' between the elements of the accused product or process and the claimed elements of the [*966] patented invention." Warner-Jenkinson Co. v. Hilton Davis Chem. Co., 520 U.S. 17, 21, 117 S. Ct. 1040, 137 L. Ed. 2d 146 (1997). The "essential inquiry" is whether "the accused product or process contain[s] elements identical or equivalent to each claimed element of the patented invention." Id. at 40. Thus, "[i]n order to arrive at its verdict of infringement under the doctrine of equivalents, the jury must have found that one or more claim elements were met by equivalents, and could have found the remainder of the claim elements were met literally." Comark Commc'ns, Inc. v. Harris Corp., 156 F.3d 1182, 1188 (Fed. Cir. 1998).

"[T]o ensure that a jury is provided with the proper evidentiary foundation from which it may permissibly conclude that a claim limitation has been met by an equivalent," *id.*, a patentee must establish equivalency by "particularized testimony and linking argument as to the 'insubstantiality of the differences' between the claimed invention and the [**11] accused device . . . ," Tex. Instruments Inc. v. Cypress Semiconductor Corp., 90 F.3d 1558, 1567 (Fed. Cir. 1996).[2] Generalized testimony as to the overall similarity between the claims and the accused infringer's product or process will not suffice. *Id.* "These evidentiary requirements assure that the fact-finder does not, under the guise of applying the doctrine of equivalents, erase a plethora of meaningful structural and functional limitations of the claim on which the public is entitled to rely in avoiding infringement." *Id.* (internal quotation marks omitted).

WCM first contends that the district court's decision to disregard the jury's verdict of infringement under the doctrine of equivalents rested on a misapprehension of the law. Specifically, WCM points to the district court's holding that because it had excluded WCM's expert opinion on the doctrine of equivalents and "WCM did not present *opinion* testimony on infringement, *none* of the evidence introduced at trial is sufficient to prove infringement under the doctrine of equivalents." J.A. 5653-54 (emphases added) (footnote omitted). WCM further highlights that in setting aside the jury's verdict, the court simply rejected the evidence introduced at trial for not being opinion testimony and never reviewed the record [**12] for substantial evidence. Thus, WCM maintains, the court adopted an improper per se rule that opinion testimony—and in particular, expert testimony—is required to establish equivalency.

We agree with WCM that our precedent does not require opinion testimony, and certainly does not require expert opinion testimony, for a finding of equivalence. Rather, "[p]roof can be made in any form: through testimony of experts or others versed in the technology; by documents, including texts and treatises; and, of course, by the disclosures of the prior art." Graver Tank & Mfg. Co. v. Linde Air Prod. Co., 339 U.S. 605, 609, 70 S. Ct. 854, 94 L. Ed. 1097, 1950 Dec. Comm'r Pat. 597 (1950). Such evidence, however, given "the difficulties and complexities of the doctrine," must "be presented to the jury or other fact-finder through the particularized testimony of a person of ordinary skill in the art." AquaTex Indus., Inc. v. Techniche Sols., 479 F.3d 1320, 1329 (Fed. Cir. 2007). While this person is "*typically* a qualified expert," he need not be in every case. *Id.* (emphasis added). As is the case here, where the technology is [*967] "easily understandable without the need for expert explanatory testimony," expert testimony is not required. *See* Union Carbide Corp. v. Am. Can Co., 724 F.2d 1567, 1573 (Fed. Cir. 1984).

Although the grounds for the district court's judgment were erroneous, we review a grant or denial of judgment as a matter of law, as noted above, de novo. IPS argues, [**13] as it did before the district court, that the evidence of record is legally insufficient proof of infringement under the doctrine of equivalents to support the jury's finding. In response, and in support of the jury verdict, WCM relies on the testimony of a number of witnesses, including: Mr. Humber (IPS's Director of Engineering), Mr. Fink (a WCM employee), and Mr. Ball (the inventor of the infringed WCM patents).

The infringement dispute at trial focused on only a

[2] Such evidence must also be presented on a limitation-by-limitation basis. Tex. Instruments, 90 F.3d at 1567. Here, the infringement dispute at trial involved only a single claim limitation. Accordingly, this "limitation-by-limitation" requirement is not at issue here because the only evidence at issue on appeal was presented at trial for the single disputed limitation.

single claim limitation: the "lugs" on the nut element that "detachably frictionally engage[]" a cap.[3] IPS does not dispute that all of the claim elements were met literally by the Classic Product. Nor does IPS dispute that the only difference between the Classic Product and the Revised Product is the modified locknut design. Accordingly, our inquiry on appeal is whether there is sufficient evidence such that a reasonable jury could have found that the claimed "lugs" limitation was met by equivalents. *See* Comark, 156 F.3d at 1188. In particular, we must determine whether there is sufficient particularized testimony as to the insubstantiality of the differences between the "lugs" limitation of the claimed nut element and the "high points" of the [**14] accused modified locknut of IPS's Revised Product such that a reasonable jury could have made an equivalency finding. If so, then we must reinstate the jury verdict. *See id.*

First, with respect to the "lugs" limitation of the claimed nut element, WCM points to Mr. Ball's testimony regarding the purpose of the lugs in his invention and how the lugs engage the inner surface of a cap. J.A. 1483, 1522-23. As Mr. Ball explained, frictional engagement holds the cap in place once the lugs contact the inner surface of the cap. J.A. 1522. The term "frictional engagement" refers to "the resistance" felt "when . . . passing one object over another object" and, more particularly, "the resistance between the cap and the nut." *Id.*

Next, with respect to the "high points" of the accused modified locknut of the Revised Product, WCM identifies the testimony of Mr. Fink and Mr. Humber.

Mr. Fink demonstrated the installation of the Revised Product's modified locknut and cap while referring to the instructions accompanying that product. J.A. 1255-57. The instructions read: "Place the Overflow plate onto the locknut . . . . Turn the Overflow plate clockwise until it reaches a *high point* on the locknut. The [**15] Overflow plate will then stay in position." J.A. 6687 (emphasis added). Mr. Fink testified while turning the Overflow plate to a high point that "[y]ou can feel that there's greater resistance at certain points than there are at other points, and then it clicks a little bit." J.A. 1257. Mr. Fink also testified that IPS's modified locknut and cap were interchangeable with WCM's Innovator locknut and cap. J.A. 1257. Mr. Humber, an IPS employee, also testified that the modified locknut has six features, "one on every corner point along the locknut," that "are all along the outer periphery of the modified locknut," "on the outer circumference [*968] of the nut," "in places where the cap fits over the nut." J.A. 2054, 2082.

Immediately preceding this testimony, Mr. Fink first demonstrated the installation of the Classic Product's original locknut and cap while referring to the instructions accompanying that product. J.A. 1251-52. The instructions for the installation of the original locknut are identical to those for the modified locknut. J.A. 6686. Mr. Fink testified while performing this step that "[a]s you turn it, you can feel points where the cap hits high points; and you can hear those as [**16] you turn it." J.A. 1252. As with the modified locknut, Mr. Fink also demonstrated and testified that IPS's original locknut and cap were compatible with WCM's overflow elbow and thus interchangeable with WCM's Innovator locknut and cap. J.A. 1252-53.

This testimony demonstrating that the modified locknut functioned in the same way as IPS's original locknut, and that both locknuts were interchangeable with WCM's Innovator products, was also corroborated by Mr. Humber's testimony. Mr. Humber testified that the only change between the original locknut of the Classic Product and the modified locknut of the Revised Product was the removal of the finger indentations. J.A. 2028. He also testified that this removal of the finger indentations did not change the way IPS's cap snapped onto the modified locknut and that it still covered the modified locknut once it was installed. J.A. 2058-59.

IPS maintains that this evidence is legally insufficient. According to IPS, Mr. Humber did not discuss the patent claims and only compared IPS's modified locknut to IPS's original locknut. IPS submits that Mr. Fink's testimony also only involves irrelevant product-to-product comparisons. Citing to a footnote [**17] in *Read Corp. v. Portec, Inc.*, IPS submits "the comparison must be between the accused product and the patent claims, and not between the accused product and the patentee's commercial embodiment." IPS Reply Br. 6 (citing 970 F.2d 816, 822 n.2 (Fed. Cir. 1992), *superseded on other grounds as recognized by* Markman v. Westview Instruments, Inc., 52 F.3d 967 (Fed. Cir. 1995) ("Equivalency to limitations of the claim must be the focus of the inquiry, particularly in jury trials. . . . Otherwise, laymen may be led to comparison of devices, rather than between the accused device and the claim, and to rely on generalities in the overall purpose of the devices")).

[3] The district court construed the term "detachably engage" as "detachably frictionally engaged." J.A. 4457.

But this court's "case law does not contain a blanket prohibition against comparing the accused product to a commercial embodiment" in an infringement analysis. *Adams Respiratory Therapeutics, Inc. v. Perrigo Co., 616 F.3d 1283, 1288 (Fed. Cir. 2010)*. "[W]hen a commercial product meets all of the claim limitations, then a comparison to that product may support a finding of infringement." *Id. at 1289* (emphasis added). Here, not only does WCM's Innovator Product meet all of the claim limitations, but IPS does not dispute that its Classic Product also literally meets all of the claim limitations. This, of course, includes meeting the single claim limitation at issue on appeal: the lugs on the nut element that detachably frictionally engage [**18] a cap. In addition to there being just one claim limitation in dispute, the understandable claim language and the straightforward mechanical technology of the invention also help mitigate any risks that might typically arise when devices are compared. Here, for example, the jury did not "rely on generalities in the overall purpose of the devices," *Read Corp., 970 F.2d at 822 n.2*, nor did the jury "erase a plethora of meaningful structural and functional limitations of the claim," *Tex. Instruments, 90 F.3d at 1567*. Accordingly, in the specific circumstances presented here, [*969] the comparisons between WCM's Innovator Product and IPS's Classic and Revised Products and the comparisons between IPS's Classic and Revised Products are sufficient to establish infringement under the doctrine of equivalents.

Reviewing the record in the light most favorable to WCM, we conclude that WCM provided sufficient evidence for a reasonable jury to have found that the lugs limitation of the claimed nut element was met by equivalents. Accordingly, it is not clear that the jury reached a "seriously erroneous result" and, therefore, the district court erred in granting IPS's motion for judgment as a matter of law. *Williams, 132 F.3d at 1131*.

II

A

IPS appeals the district court's denial of judgment as a [**19] matter of law that IPS does not indirectly infringe as to its Revised Product. IPS's sole argument on appeal is that it cannot indirectly infringe as to this product line because the district court granted judgment as a matter of law of no infringement under the doctrine of equivalents and WCM failed to prove any other underlying direct infringement. Because we reverse the district court's grant of judgment as a matter of law of no infringement under the doctrine of equivalents, we affirm the district court's denial of judgment as a matter of law of no indirect infringement with respect to the Revised Product.

B

IPS also appeals the district court's denial of judgment as a matter of law of no willfulness. As discussed above, we review, under Sixth Circuit law, the grant or denial of judgment as a matter of law de novo. *Barnes, 401 F.3d at 736*. Again, we view the evidence in the light most favorable to WCM, and WCM must be given the benefit of all reasonable inferences. *Id.*

The jury here was instructed on the old *Seagate* standard for subjective willfulness, and found that WCM proved, by clear and convincing evidence, that IPS's infringement was willful. Before the Supreme Court's decision in *Halo*, this court's [**20] two-part *Seagate* test required a patentee to prove both an objective and a subjective prong to establish willfulness. *Halo Elecs., Inc. v. Pulse Elecs., Inc., 136 S. Ct. 1923, 1930, 195 L. Ed. 2d 278 (2016)*. The subjective prong required a showing "that the risk of infringement 'was either known or so obvious that it should have been known to the accused infringer.'" *Id.* (quoting *In re Seagate Tech., LLC, 497 F.3d 1360, 1371 (Fed. Cir. 2007)* (en banc)).

While the Court rejected *Seagate's* requirement that a patentee prove objective recklessness in every case, *Halo* did not disturb the substantive standard for the second prong of *Seagate*, subjective willfulness. *WesternGeco L.L.C. v. ION Geophysical Corp., 837 F.3d 1358, 1362 (Fed. Cir. 2016)*, *cert. granted on other grounds No. 16-1011, 138 S. Ct. 734, 199 L. Ed. 2d 601, 2018 U.S. LEXIS 619, 2018 WL 386561 (Jan. 12, 2018)*. "Rather, *Halo* emphasized that subjective willfulness alone . . . can support an award of enhanced damages." *Id.*; *see also Halo, 136 S. Ct. at 1933* ("The subjective willfulness of a patent infringer, intentional or knowing, may warrant enhanced damages, without regard to whether his infringement was objectively reckless."). *Halo* also rejected the *Seagate* test's clear-and-convincing standard of proof and held that this inquiry should be governed by the less demanding preponderance of the evidence standard. *136 S. Ct. at 1934*.

The district court, in denying IPS's motion for judgment as a matter of law of no [*970] willfulness, concluded that sufficient evidence supported the jury's verdict that [**21] WCM proved the subjective *Seagate* prong by clear-and-convincing evidence. On appeal under the new *Halo* standard, we must determine whether the

evidence, when viewed in the light most favorable to WCM, was sufficient to prove by a preponderance of the evidence that IPS acted despite a risk of infringement that was either known or so obvious that it should have been known to IPS. *See* Arctic Cat Inc. v. Bombardier Recreational Prods. Inc., 876 F.3d 1350, 1371 (Fed. Cir. 2017).

IPS's principal argument on appeal is that the district court erred in refusing to grant judgment as a matter of law of no willfulness because there is no evidence that IPS had knowledge of the patents before the lawsuit began. In support, IPS largely relies on State Industries, Inc. v. A.O. Smith Corp., 751 F.2d 1226 (Fed. Cir. 1985), and Gustafson, Inc. v. Intersystems Industrial Products, Inc., 897 F.2d 508 (Fed. Cir. 1990). In *State Industries*, the court concluded that "[t]o willfully infringe a patent, the patent must exist and one must have knowledge of it." 751 F.2d at 1236. Accordingly, the court held that the defendant's infringement in that case was not willful because, among other reasons, its first notice of the existence of the issued patent came with the filing of the infringement suit against it. *Id.* Similarly, *Gustafson* held that "a party cannot be found to have 'willfully' infringed a patent of which the party had no knowledge." 897 F.2d at 511.

We find IPS's arguments unpersuasive. [**22] First, this court has already held that *State Industries* does not establish a per se rule, as IPS contends, but rather, "is in harmony with our prior and subsequent case law, which looks to the 'totality of the circumstances presented in the case.'" Shiley, Inc. v. Bentley Labs., Inc., 794 F.2d 1561, 1568 (Fed. Cir. 1986) (quoting Cent. Soya Co. v. Geo. A. Hormel & Co., 723 F.2d 1573, 1577 (Fed. Cir. 1983)). The *Gustafson* opinion itself also recognizes that "[w]hether an act is 'willful' is by definition a question of the actor's intent, the answer to which must be inferred *from all the circumstances*." 897 F.2d at 510-11 (emphasis added). Second, unlike in State Industries and Gustafson, here WCM provided sufficient evidence for a reasonable jury to conclude that IPS *did* know of WCM's patents as they issued, if not earlier.[4] Not to mention, it is undisputed that IPS had knowledge of the '220 patent and the '970 patent at least as of the date the first Colorado suit was filed, about a month before this action was initiated.

In support of the jury's verdict, WCM points to the evidence of record. First, although Mr. Casella, President of IPS's [*971] Plumbing Division, knew that AB&A did not employ engineers or full-time product developers to create the Classic Product, he did not conduct an investigation into how AB&A developed the Classic Product during the [**23] due-diligence period of the acquisition. Additionally, IPS was aware of a 2010 patent lawsuit between WCM and AB&A at the time of the acquisition. Mr. Humber, IPS's employee, testified that he had monitored WCM's products for decades and possessed catalogs and other literature indicating that WCM's products were marked with "patent pending."[5]

WCM also introduced evidence of what it refers to as "a culture of copying at IPS," including testimony from Mr. Kirk, former IPS Product Manager, regarding an email copying Gary Clarke, IPS's Vice-President of Marketing and Engineering, in which Mr. Kirk asked Mr. Humber about one of WCM's Watco drains. WCM provided evidence at trial that Mr. Ball had meticulously devised WCM's Innovator Product and that a rational explanation for the Classic Products' identical measurements and compatibility with WCM's Innovator Product was that AB&A had copied the Innovator.

In sum, WCM argues that the jury had more than enough evidence to conclude that IPS knew of WCM's patents as they issued (if not earlier) and that the risk of infringement was known to IPS or so obvious that it should have been known. IPS continues to dispute several of these facts and what [**24] inferences might be drawn from them. For example, IPS points to Mr.

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[4] IPS argues that knowledge of a pending patent application cannot support a finding of willfulness. The cases that IPS points to, however, were all decided prior to the enactment of 35 U.S.C. § 122(b)(1)(A) in 1999, which provides for the publication of patent applications filed on or after November 29, 2000, eighteen months after the effective filing date of the application. *See* Hyatt v. U.S. Patent & Trademark Office, 797 F.3d 1374, 1378 n.2 (Fed. Cir. 2015). For example, *State Industries* stressed that the defendant was in "the dark about State's patent application prosecution activity" and that "[w]hat the scope of claims in patents that do issue will be is something totally unforeseeable." 751 F.2d at 1236. Of course, these concerns are no longer valid when patent applications and real-time prosecution activity are published. It is no longer the case that all "[p]atent applications are secret." Gustafson, 897 F.2d at 511. Because we conclude that WCM provided sufficient evidence for a reasonable jury to conclude that IPS did know of WCM's patents at least when they issued, which was before the lawsuit was initiated as to the '220 patent and the '970 patent, we need not decide whether the cases cited by IPS still support its argument.

[5] WCM also refers to other evidence of record that has been deemed confidential information by a protective order.

Casella's testimony that IPS did not have any notice of WCM's asserted bath waste and overflow patents. The jury was free to decide, however, whose evidence it found more compelling on the question of willfulness and it found in WCM's favor. Georgetown Rail Equip. Co. v. Holland L.P., 867 F.3d 1229, 1245 (Fed. Cir. 2017). "We will not disturb that finding here, where substantial evidence supports the jury's conclusions." *Id.*

Reviewing the record in the light most favorable to WCM, we conclude that WCM provided sufficient evidence for a reasonable jury to have found that IPS's infringement was willful. Accordingly, it is not clear that the jury reached a "seriously erroneous result" and, therefore, we affirm the district court's denial of IPS's motion for judgment as a matter of law. Williams, 132 F.3d at 1131.

C

Finally, IPS appeals the district court's grant of WCM's motion for enhanced damages and the district court's decision to treble damages pursuant to § 284. We review a district court's decision to enhance damages on appeal for abuse of discretion. Halo, 136 S. Ct. at 1934. Such a decision cannot stand if "the determination was based on an erroneous conclusion of law, clearly erroneous factual findings, or a clear error of judgment amounting to [**25] an abuse of discretion." Rite-Hite Corp. v. Kelley Co., 56 F.3d 1538, 1543 (Fed. Cir. 1995) (en banc).

Although district courts enjoy discretion in deciding whether to award enhanced damages, and in what amount, "the channel of discretion [is] narrow[]" and damages are generally reserved for egregious cases of culpable behavior. Halo, 136 S. Ct. at 1932.

> Awards of enhanced damages . . . are not to be meted out in a typical infringement case, but are instead designed as a [*972] "punitive" or "vindictive" sanction for egregious infringement behavior. The sort of conduct warranting enhanced damages has been variously described in our cases as willful, wanton, malicious, bad-faith, deliberate, consciously wrongful, flagrant, or—indeed—characteristic of a pirate.

Id.

Moreover, there is no requirement that enhanced damages *must* follow a finding of egregious misconduct. Id. at 1933. "As with any exercise of discretion, courts should continue to take into account the particular circumstances of each case in deciding whether to award damages, and in what amount." Id. at 1933-34.

Because a finding of willful infringement does not command the enhancement of damages, the *Read* factors, although not mandatory, do assist the trial court in evaluating the degree of the infringer's culpability and in determining whether to [**26] exercise its discretion to award enhanced damages at all, and if so, by how much the damages should be increased. Read Corp., 970 F.2d at 828; *see* Presidio Components, Inc. v. Am. Tech. Ceramics Corp., 875 F.3d 1369, 1382-83 (Fed. Cir. 2017) (explaining that an explicit discussion of the *Read* factors is not mandatory).

The district court here analyzed the *Read* factors, but for many of the factors, the court's analysis was either non-existent or incorrect. We address each factor in turn.

The first factor is "whether the infringer deliberately copied the ideas of another." Read Corp., 970 F.2d at 827. The district court concluded that this factor weighed in favor of enhancing damages because there was evidence of copying on IPS's part. In particular, the district court cited to testimony from Mr. Kirk, former IPS Product Manager, regarding an email copying Gary Clarke, IPS's Vice-President of Marketing and Engineering, in which Mr. Kirk asked Mr. Humber about one of WCM's Watco drains. That product, however, was not WCM's Innovator product in this suit. Therefore, while there is evidence of a possible "culture of copying" at IPS that weighs in favor of enhancement, given that the email does not refer to a product involved in the litigation, this factor should not be weighed very strongly in favor of enhancing damages.

The second factor [**27] is "whether the infringer, when he knew of the other's patent protection, investigated the scope of the patent and formed a good-faith belief that it was invalid or that it was not infringed." Id. The district court found that this factor was "perhaps most important[]" and that IPS's failure to investigate the asserted patents weighed strongly in favor of enhancing damages. J.A. 38. The evidence that the court cited in support of its conclusion, however, involves patents or products not at issue in this case. For example, the court cited to evidence that IPS knew that WCM's products in general were patent protected and that IPS did not investigate certain patents involved in a different lawsuit. Thus, based on the record before the district court, this factor only slightly favors enhancing damages. The evidence certainly cannot support the district court's conclusion that this factor was the most

important and that it weighed strongly in favor of enhancing damages.

The third factor is "the infringer's behavior as a party to the litigation." *Read Corp., 970 F.2d at 827*. The court found that IPS did not engage in litigation misconduct and properly determined that this factor counseled against enhancement. The fourth [**28] and fifth factors are the "[d]efendant's size and financial condition" and the "[c]loseness of the case." *Id.* Despite IPS's arguments to the contrary on appeal, the [*973] district court's analysis of these factors is also reasonable. The district court determined that IPS's size and financial condition weigh in favor of enhanced damages and that the closeness of the case was also in WCM's favor because the jury verdict was not a close call and the evidence strongly supported WCM's case.

The court did not analyze the sixth factor, which is the "[d]uration of the defendant's misconduct." *Id.* This factor would likely weigh against enhancement. For example, the patents issued only a short time before the filing of the lawsuit. Nor did the court analyze the seventh factor, "[r]emedial action by the defendant," which may also weigh slightly against enhancement because IPS attempted to take remedial action (albeit ineffectively) when it modified its Classic Product and began selling its Revised Product during the pendency of this litigation. *See id.* (citing *Intra Corp. v. Hamar Laser Instruments, Inc., 662 F. Supp. 1420, 1439 (E.D. Mich. 1987)*, *aff'd*, *862 F.2d 320 (Fed. Cir. 1988)* (damages only doubled because defendant "voluntarily ceased manufacture and sale of infringing systems during the pendency of this [**29] litigation")).

In sum, the district court clearly erred when it concluded that the second factor weighed strongly in favor of enhancement. Compounding this error, the district court did not appropriately weigh the third factor and other potentially mitigating factors, such as the sixth and the seventh factors, against the enhancement of damages. As WCM itself stated to the district court, when only a subset of factors weigh in favor of enhanced damages a court should award less than treble damages. Accordingly, we conclude that the district court made a clear error of judgment amounting to an abuse of discretion in deciding to award the maximum amount of damages.

Although the district court "*may* increase the damages *up to* three times the amount found or assessed," *35 U.S.C. § 284* (emphases added), where the maximum amount is imposed, "the court's assessment of the level of culpability must be high," *Read Corp., 970 F.2d at 828*. The district court is also particularly obligated to explain the basis for the award where it awards treble damages. *Id.* Here, the district court provided only a single conclu-sory sentence as to why it was awarding the maximum amount. J.A. 41 ("The Court further finds, based on the egregious nature of [**30] IPS's conduct, that treble damages are appropriate."). We therefore vacate the district court's decision to award treble damages and remand for the district court to reconsider, consistent with this opinion, the amount by which the damages should be enhanced, if at all.[6]

CONCLUSION

Reviewing the record in the light most favorable to WCM, we conclude that WCM provided sufficient evidence for a reasonable jury to have found infringement under the doctrine of equivalents as to IPS's Revised Product and to have found that IPS's infringement was willful. We therefore reverse the district court's grant of IPS's motion for judgment as a matter of law as to no infringement under the doctrine of equivalents and affirm the district court's denial of IPS's motion for judgment as a matter of law as to no willfulness. [*974] Because we reverse the district court's grant of judgment as a matter of law of no infringement under the doctrine of equivalents, we affirm the district court's denial of judgment as a matter of law of no indirect infringement with respect to the Revised Product. Finally, we vacate the district court's award of maximum enhanced damages and remand.

REVERSED-IN-PART, AFFIRMED-IN-PART, [**31] **VACATED-IN-PART, AND REMANDED**

COSTS

The parties shall bear their own costs.

End of Document

[6] Although the jury was not asked to decide the total number of infringing units sold by IPS on a product-by-product basis, on remand, in determining how much the damages should be increased, if at all, the district court may also consider whether the degree of the IPS's culpability might be different for sales of the Classic Product as compared to sales of the Revised Product.

EXHIBIT 2

U 7697471

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

June 06, 2017

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF:

U.S. PATENT: *9,517,219*
ISSUE DATE: *December 13, 2016*

By Authority of the
Under Secretary of Commerce for Intellectual Property
and Director of the United States Patent and Trademark Office

P. SWAIN
Certifying Officer

(12) **United States Patent**
Warner et al.

(10) **Patent No.: US 9,517,219 B2**
(45) **Date of Patent: Dec. 13, 2016**

(54) **TOPICAL DAPSONE AND DAPSONE/ADAPALENE COMPOSITIONS AND METHODS FOR USE THEREOF**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

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(60) Provisional application No. 61/728,403, filed on Nov. 20, 2012, provisional application No. 61/770,768, filed on Feb. 28, 2013.

(51) **Int. Cl.**

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CPC ***A61K 31/192*** (2013.01); ***A61K 9/0014*** (2013.01); ***A61K 31/136*** (2013.01); ***A61K 31/145*** (2013.01); ***A61K 47/10*** (2013.01); ***A61K 47/14*** (2013.01); ***A61K 47/183*** (2013.01); ***A61K 47/32*** (2013.01); ***A61K 47/34*** (2013.01)

(58) **Field of Classification Search**

None

See application file for complete search history.

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Notification of Transmittal of the International Search Report and the Written Opinion of the International Searching Authority, or the Declaration, International Application No. PCT/US2013/070613, International Filing Date, Nov. 18, 2013, Date of Mailing Feb. 12, 2014.

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(57) **ABSTRACT**

Dapsone and dapsone/adapalene compositions can be useful for treating a variety of dermatological conditions. The compositions of this disclosure include dapsone and/or adapalene in a polymeric viscosity builder. Subject compositions can be adjusted to optimize the dermal delivery profile of dapsone to effectively treat dermatological conditions and improve the efficiency of pharmaceutical products applied to the skin. Use of the polymeric viscosity builder provides compositions with increased concentrations of diethylene glycol monoethyl ether relative to compositions without the polymeric viscosity builder.

8 Claims, 3 Drawing Sheets

Figure 1. Appearance of formulations following 4 weeks of storage

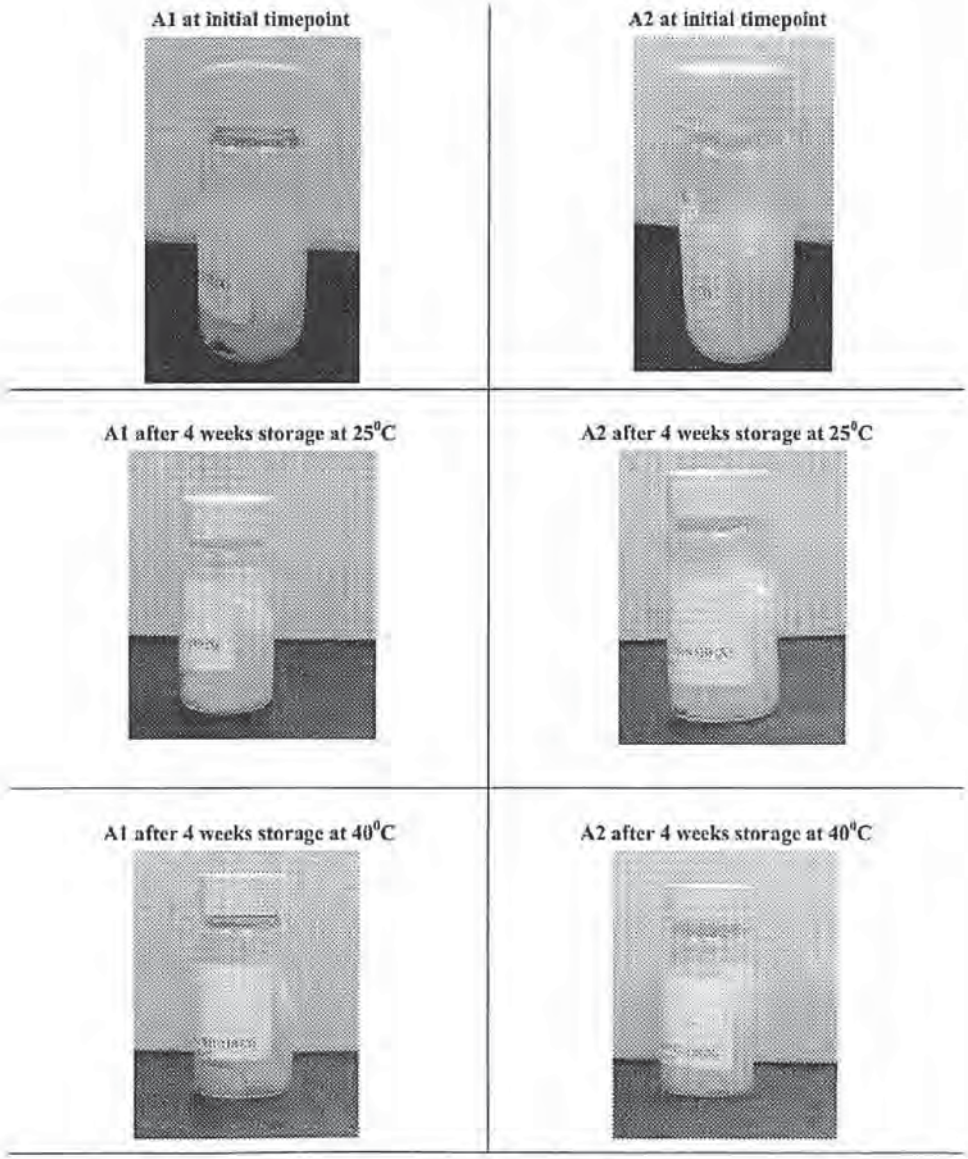


Figure 2. Polarized light images of dapsone in suspension formulations

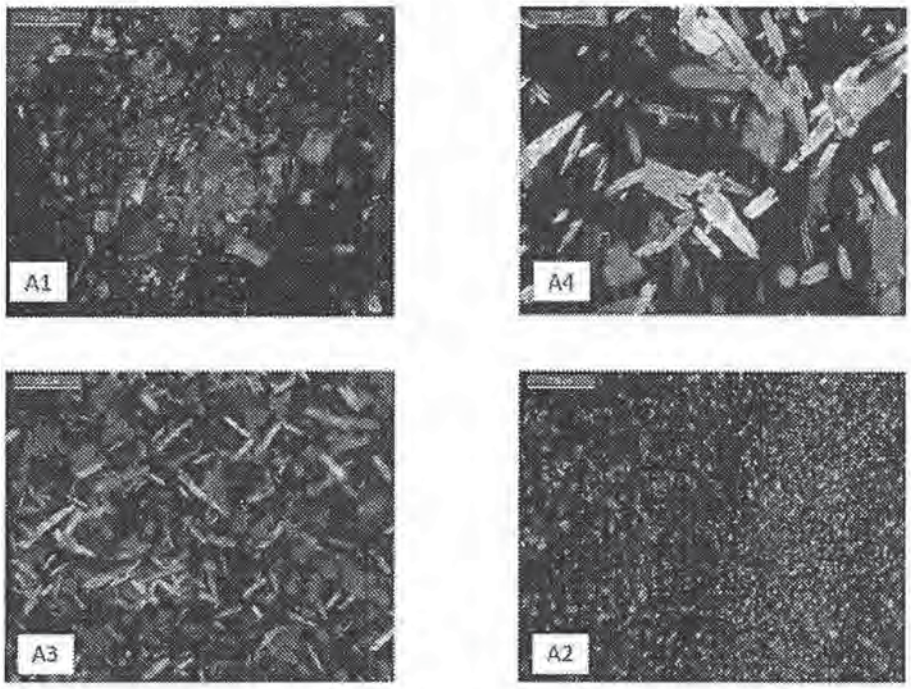
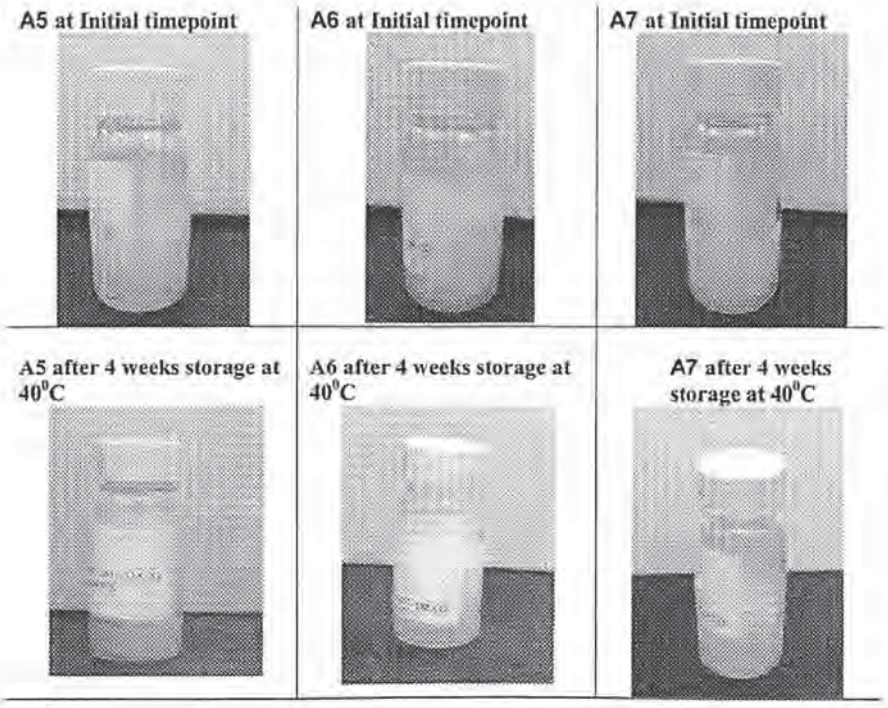


Figure 3. Appearance of formulations with antioxidants or chelating agents over 4 weeks



TOPICAL DAPSONE AND DAPSONE/ADAPALENE COMPOSITIONS AND METHODS FOR USE THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a divisional of copending U.S. patent application Ser. No. 14/082,955, filed on Nov. 18, 2013, which claims the benefit of U.S. Provisional Application Ser. No. 61/728,403 filed on Nov. 20, 2012 and U.S. Provisional Application Ser. No. 61/770,768 filed on Feb. 28, 2013, all of which are incorporated by reference herein in their entirety.

FIELD

The present embodiments relate generally to compositions useful for treating a variety of dermatological conditions. In particular, some embodiments relate to dapsone and dapsone/adapalene compositions and methods for use thereof.

BACKGROUND

Acne is a group of common skin conditions characterized by the so-called "acneiform" or acne-like skin eruptions, which can be contaminated with bacteria, such as *Propionibacterium acnes*, and can also be marked by inflammation. Acne tends to occur in the areas of skin where the sebaceous glands are most active, such as the face. Acne is associated with psychological trauma, and, if left untreated, can lead to scar formation and disfigurement.

Classification and the diagnosis of various acne conditions can be complex, and even contradictory. Given this complexity and unpredictability, medication and other therapies, are often developed on a trial-and-error basis in order to determine the most effective course of treatment for a particular patient. The outcome of any particular acne treatment regimen greatly varies from patient to patient, as well as throughout treatment of a particular patient. In addition to the complexity and variability of acne conditions, treatment efficacy can be greatly affected by a patient's compliance with the treatment regimen. Patient compliance during acne treatment may be influenced by side effects, which, for topical medications, commonly include redness, itching, and skin peeling. The complexity of the drug regimen can also negatively affect patient compliance, particularly where two or more different topical medications are prescribed simultaneously. Another factor that negatively affects patient compliance is the cost of a drug regiment, which is considerably higher when multiple medications are prescribed. In some countries, acne is considered a cosmetic problem, and acne treatments are not covered by insurance plans, thus further increasing patient's treatment costs. Certain compositions for treatment of acne are available. Many of the available compositions include one active agent known to have anti-acne activity. Stability of compositions with multiple anti-acne agents can be problematic. Also, these compositions can be difficult to manufacture.

The problems described above are not confined to the treatment or acne, but are also applicable to a variety of other skin conditions, including, but not limited, to conditions or classes of conditions with complex or unknown etiology and that are difficult to classify or diagnose, in which, nevertheless, topical application of agents are known to be effective at least in some cases. Examples of such conditions or classes of conditions include psoriasis, rosacea and ichthyosis.

Accordingly, there is a continuing need for compositions and methods used in a treatment of a variety of skin conditions, such as acne, in which topical application is potentially effective. The compositions and methods provided herein address these and other needs in the art.

SUMMARY

Dapsone, (4,4'-diaminodiphenyl sulfone) is a medicament possessing several beneficial medicinal activities. Dapsone is typically administered as one of the medicinal agents used in the treatment of leprosy. Dapsone and its derivatives are also effective for treatment of bacterial infections, protozoal infections such as malaria, *pneumocystis carinii*, and plasmonic infections such as toxoplasmosis.

Dapsone is also useful as an anti-inflammatory agent. It has been used to treat skin diseases characterized by the abnormal infiltration of neutrophils, such as Dermatitis herpetiformis, linear IgA dermatosis, pustular psoriasis, pyoderma gangrenosum, acne vulgaris, and Sweet's Syndrome.

Use of topical compositions of dapsone can be problematic. Topical compositions may act as drying agents for the skin. They remove essential oils and natural skin softeners from the skin thus causing it to be dry, itch and crack. Inclusion of exogenous skin emollients, oils and the like, however, causes phase separation and precipitation of dapsone. Use of typical emulsifiers does not solve the dapsone precipitation owing to the lowered dapsone solubility and conflicting physical characteristics of the phases of the resulting composition. In particular, topical compositions including dapsone and methods are needed that would, for example, exhibit improved effectiveness, reduced side effects, or both, when used in a particular patient with a skin condition. Such improved topical compositions including dapsone and methods of their uses are also needed to improve treatment of patients with acne or suspected acne. The present dapsone and dapsone/adapalene compositions can be useful for treating a variety of dermatological conditions. Some useful compositions include dapsone and/or adapalene in a polymeric viscosity builder. Some compositions can be adjusted to optimize the dermal delivery profile of dapsone to effectively treat dermatological conditions and improve the efficiency of pharmaceutical products applied to the skin. Diethylene glycol monoethyl ether is a solubilizer for dapsone, thereby allowing compositions to be prepared with increased solubilized concentrations of dapsone. As a result, the compositions described herein are effective in treating dermatological conditions in a subject in need thereof.

Moreover, it has been found that use of a polymeric viscosity builder minimizes the intensity of yellowing of the composition caused by the increased solubility of dapsone in diethylene glycol monoethyl ether. In addition, the polymeric viscosity builder influences dapsone crystallization. This, in turn, results in compositions with improved aesthetics (i.e., reduction in particle size which minimizes "gritty" feeling upon application).

In one embodiment, there are provided compositions including dapsone, a first solubilizing agent which is diethylene glycol monoethyl ether, optionally at least one second solubilizing agent, a polymeric viscosity builder, and water, wherein the dapsone is present at a concentration of about 5% w/w to about 10% w/w.

In one embodiment, there are provided compositions including dapsone, a first solubilizing agent which is diethylene glycol monoethyl ether, optionally at least one second solubilizing agent, a polymeric viscosity builder, and water, wherein the dapsone is present at a concentration of about 3% w/w to 8% w/w.

In another embodiment, there are provided methods for treating a dermatological condition. Such methods can be performed, for example, by administering to a subject in need thereof a therapeutically effective amount of a pharmaceutical composition described herein.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 presents the impact of an acrylamide/sodium acryloyldimethyltaurate copolymer emulsion viscosity builder on color change.

FIG. 2 presents the impact of an acrylamide/sodium acryloyldimethyltaurate copolymer emulsion viscosity builder on dapsone crystal growth.

FIG. 3 presents the impact of anti-oxidants and chelating agents on color change.

DETAILED DESCRIPTION

It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and do not restrict the claims. As used herein, the use of the singular includes the plural unless specifically stated otherwise. As used herein, "or" means "and/or" unless stated otherwise. Furthermore, use of the term "including" as well as other forms, such as "includes," and "included," is not limiting. The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

Some embodiments include compositions and products for treatment of skin conditions and methods of treating skin conditions. The term "skin condition" as used herein encompasses human and animal conditions, disorders, or diseases affecting skin. Such skin conditions include, but are not limited to, conditions involving skin inflammation, conditions involving sebaceous glands and hair follicles, conditions characterized by acneiform symptoms, and conditions involving skin dryness, skin thickening, skin scaling or skin flaking. Skin conditions that can be treated using some compositions, products and methods described herein include, but are not limited to, acne, rosacea, folliculitis, perioral dermatitis, photodamage, skin aging, psoriasis, ichthyosis, atopic dermatitis, treatment of chronic wounds, bed sores, keratosis pilaris scars, including surgical and acne scars, sebaceous cysts, inflammatory dermatoses, post inflammatory hyperpigmentation, eczema, xerosis, pruritus, lichen planus, nodular prurigo, eczema, and miliaria.

The term "acne," as used herein, encompasses skin conditions involving acneiform or acne-like symptoms. For example, a skin condition characterized by follicular eruptions, such as papules and pustules resembling acne, can be categorized as acne. It is to be understood that the term "acne" is not to be limited to diseases and conditions characterized by papules and pustules, but can be characterized by a variety of symptoms. It is also to be understood that a particular patient having acne can be in remission, or the patient's acne can be controlled by continuing treatments, and therefore the patient can exhibit reduced symptoms or be asymptomatic. Nevertheless, continuing treatment of acne can be recommended in such a patient in order to reduce the probability of the return of the acne symptoms.

Symptoms of acne or acne-like conditions include, but are not limited to, the appearance of various skin lesions. The term "lesion" is generally used to denote an infected or diseased patch of skin. A lesion can involve an infected sebaceous gland. Some lesions are more severe than others. Examples of skin lesions are comedones, macules, papules, pustules, nodules and cysts. The term "comedo" (plural "comedones") is used to describe a sebaceous follicle plugged with dirt, other cells, tiny hairs, or bacteria. Comedones include the so-called "blackheads," which can also refer to as "open comedones," which have a spot or a surface that appears black. Comedones also include slightly inflamed, skin colored bumps, as well as "whiteheads," which have a spot or a surface that appears white. The term "macule" generally refers to a flat spot or area of the skin with a changed color, such as a red spot. The term "pustule" is generally used to refer to an inflamed, pus-filled lesion, or a small inflamed elevation of the skin that is filled with pus. The term "papule" is generally used to refer to a small, solid, usually inflammatory elevation of the skin that does not contain pus. The term "nodule" is generally used to refer to an elevation of a skin that is similar to a papule but is white and dome-shaped. Colloquially, a papule, a pustule or a nodule can be referred to as "a pimple" or "a zit." The term "cyst" generally refers to an abnormal membranous sac containing a liquid or semi-liquid substance containing white blood cells, dead cells, and bacteria. Cysts can be painful and extend to deeper layers of skin.

In dermatological science and dermatological and cosmetology practice, acne can be classified or categorized into one or more types or categories, according to one or more lines of categorization, such as a predominantly observed type of symptoms, severity of condition or predominant localization. It is to be understood that classification of acne into one of the subtypes does not mean that the characteristics of the classified condition are limited to the symptoms associated with the specific type.

Comedonal acne is characterized by the appearance of non-inflammatory lesions, such as blackheads and whiteheads. Localized cystic acne is characterized by appearance of a few cysts on face, chest and back. Diffuse cystic acne is characterized by the appearance of cysts on wide areas of face, chest and back. Nodular acne is characterized by the appearance of nodules. Nodulocystic acne is characterized by appearance of nodules and cysts. Acne vulgaris is a common form of acne characterized by the appearance of several types of lesions, which may appear together or separately. Individual acne lesions usually last less than two weeks but the deeper papules and nodules may persist for months. Acne vulgaris commonly affects adolescents, but it may also appear, persist or become more severe in adulthood. Acne vulgaris may occur on the face, chest, back and sometimes even more extensively.

Depending on severity, acne can be mild, moderate or severe. Mild acne is generally categorized by the appearance of with blackheads and whiteheads, but can also include papules and pustules. Moderate acne is generally characterized by appearance of more painful, deep-rooted, inflamed lesions, which can result in scarring. Severe acne is characterized by the appearance of deep-rooted inflammatory lesions, including cysts and nodules which can be painful and can produce scarring. Acne conglobata is a category of acne characterized by highly inflammatory cysts that communicate under the skin with abscesses and burrowing sinus tracts.

Some other skin conditions exhibiting acne-like symptoms which can be treated by the compositions and methods

described herein are discussed below. Pyoderma faciale, also known as rosacea fulminans, is a condition that appears in females and is characterized by abrupt appearance of inflamed cysts and nodules localized on the face. Rosacea, which can be referred to as acne rosacea, is a condition that can affects both the skin and the eyes and is characterized by redness, bumps, pimples, and, in advanced stages, thickened skin on the nose. In some classification systems, rosacea and acne are considered as separate conditions. Rosacea usually occurs on the face, although the neck and upper chest are also sometimes involved. A mild degree of eye (ocular) involvement occurs in more than fifty percent of people with rosacea. Perioral dermatitis is characterized by the appearance of small tiny papules, pustules, red bumps and scaling with intense itching. It is usually localized to the surrounding area of the mouth and on the chin, or extends to involve the eyelids and the forehead. Gram-negative folliculitis is a bacterial infection characterized by the appearance of pustules and cysts, possibly occurring as a complication resulting from a long term antibiotic treatment of acne vulgaris.

As used herein, the terms "treatment" or "treating" in reference to a skin condition generally mean "having positive effect on a skin condition" and encompass alleviation of at least one symptom of a skin condition, a reduction in the severity of the skin conditions, or delay, prevention, or inhibition of the progression of the skin condition. Treatment need not mean that the condition is totally cured. A composition or a product useful for treatment of a skin condition, or a method of treating a skin condition, needs only to reduce the severity of a skin condition, reduce the severity of symptoms associated therewith, provide improvement to a patient's quality of life, or delay, prevent, or inhibit the onset of symptoms of a skin condition.

In one embodiment, there are provided compositions including dapsone, a first solubilizing agent which is diethylene glycol monoethyl ether, optionally at least one second solubilizing agent, a polymeric viscosity builder, and water, wherein the dapsone is present at a concentration of about 5% w/w to about 10% w/w, about 1% w/w to about 10% w/w, about 3% w/w to about 10% w/w, about 3% w/w to about 8% w/w, about 4% w/w to about 6% w/w, or about 5%. In certain embodiments, dapsone is present in the composition at 5.0%, 5.5%, 6.0%, 6.5%, 7.0%, 7.5%, 8.0%, 8.5%, 9.0%, 9.5%, or 10.0% w/w.

In some embodiments, the polymeric viscosity builder is an acrylamide/sodium acryloyldimethyltaurate copolymer, and further includes isohexadecane, sorbitan oleate, water, and Polysorbate 80. In some embodiments, the polymeric viscosity builder is present at a concentration of about 2% w/w to about 6% w/w. In some embodiments, the polymeric viscosity builder is present at a concentration of about 3% w/w to about 5% w/w. In some embodiments, the polymeric viscosity builder is present in the composition at about 4% w/w.

In some embodiments, diethylene glycol monoethyl ether is present at a concentration of about 25% w/w to about 40% w/w. In some embodiments, diethylene glycol monoethyl ether is present at a concentration of about 30% w/w to about 40% w/w. In some embodiments, diethylene glycol monoethyl ether is present at a concentration of about 35% w/w to about 40% w/w.

In some embodiments, diethylene glycol monoethyl ether is present at a concentration of about 10% w/w to about 40% w/w, about 20% w/w to about 30% w/w, or about 25%.

In another embodiment, there are provided compositions further including adapalene. In some embodiments, adapalene is present at a concentration of about 0.1% w/w to about 0.3% w/w.

In some embodiments, the second solubilizing agent is selected from alcohols, glycols, esters, ethers, or silicones. Such second solubilizing agents include, but are not limited to, PEG 400, lactic acid, dimethyl isosorbide, propylene glycol, propylene carbonate, hexylene glycol, isostearyl alcohol, benzyl alcohol, diethyl sebacate, and ethanol.

In certain embodiments, the second solubilizing agent is propylene glycol. In some embodiments, propylene glycol is present at a concentration of about 2% w/w to 8% w/w. In some embodiments, propylene glycol is present at a concentration of about 3% w/w to 7% w/w. In some embodiments, propylene glycol is present in the composition at about 5% w/w.

In certain embodiments, the second solubilizing agent is propylene carbonate. In some embodiments, propylene carbonate is present at a concentration of about 2% w/w to 8% w/w. In some embodiments, propylene carbonate is present at a concentration of about 3% w/w to 7% w/w. In some embodiments, propylene carbonate is present in the composition at about 5% w/w.

In certain embodiments, the second solubilizing agent is ethanol. In some embodiments, ethanol is present at a concentration of about 1% w/w to about 5% w/w. In some embodiments, ethanol is present at a concentration of about 2% w/w to about 4% w/w. In some embodiments, ethanol is present in the composition at about 3% w/w.

In some embodiments, the compositions further include methyl paraben.

In other embodiments, the compositions further include carbomer homopolymer type C. In some embodiments, carbomer homopolymer type C is present at a concentration of about 0.7% w/w to about 1.5% w/w. In other embodiments, carbomer homopolymer type C is present at a concentration of about 0.85% w/w to about 1.0% w/w.

In some embodiments, the compositions further include a neutralizing agent. In certain embodiments, the neutralizing agent is an ionic or amine buffer. In certain embodiments, the neutralizing agent is sodium hydroxide or triethanolamine. Use of a neutralizing agent results in compositions typically having a pH from 5.5 to 6.5.

In some embodiments, the compositions further include a chelating agent. In some embodiments, the chelating agent is ethylene diamine tetraacetic acid (EDTA). EDTA is typically present in the compositions from about 0.02% w/w to about 0.04% w/w. In certain embodiments, EDTA is present in the compositions at about 0.03% w/w.

Compositions described herein are typically in the form of a gel, an emulsion, a cream, a liquid, a paste, a lotion, a nanoemulsion, a microemulsion, a reverse emulsion, or a liposomal cream.

EMBODIMENTS

The following embodiments are specifically contemplated herein.

Embodiment 1

A composition comprising dapsone, a first solubilizing agent which is diethylene glycol monoethyl ether, optionally at least one second solubilizing agent, a polymeric viscosity

builder, and water, wherein the dapsone is present in the composition at a concentration of about 3% w/w to about 10% w/w.

Embodiment 2

The composition of embodiment 1, wherein the diethylene glycol monoethyl ether is present at a concentration of about 10% w/w to about 40% w/w.

Embodiment 3

The composition of embodiment 1, wherein the diethylene glycol monoethyl ether is present at a concentration of about 20% w/w to about 30% w/w.

Embodiment 4

The composition of embodiment 1, wherein the diethylene glycol monoethyl ether is present in the composition at a concentration of about 25% w/w.

Embodiment 5

The composition of embodiment 1, further comprising adapalene.

Embodiment 6

The composition of embodiment 5, wherein the adapalene is present at a concentration of about 0.1% w/w to about 0.3% w/w.

Embodiment 7

The composition of embodiment 1 wherein the second solubilizing agent is selected an alcohol, a glycol, an ester, or an ether.

Embodiment 8

The composition of embodiment 1, wherein the second solubilizing agent is PEG 400, lactic acid, dimethyl isosorbide, propylene glycol, propylene carbonate, hexylene glycol, isostearyl alcohol, diethyl sebacate, or ethanol.

Embodiment 9

The composition of embodiment 8, wherein the second solubilizing agent is propylene glycol.

Embodiment 10

The composition of embodiment 9, wherein the propylene glycol is present in the composition at a concentration of about 5% w/w.

Embodiment 11

The composition of embodiment 8, wherein the second solubilizing agent is propylene carbonate.

Embodiment 12

The composition of embodiment 11, wherein the propylene carbonate is present in the composition at a concentration of about 5% w/w.

Embodiment 13

The composition of embodiment 8, wherein the second solubilizing agent is ethanol.

Embodiment 14

The composition of embodiment 13, wherein the ethanol is present in the composition at a concentration of about 3% w/w.

Embodiment 15

The composition of embodiment 1, wherein the polymeric viscosity builder comprises an acrylamide/sodium acryloyldimethyltaurate copolymer.

Embodiment 16

The composition of embodiment 1, wherein the polymeric viscosity builder is present at a concentration of about 2% w/w to about 6% w/w.

Embodiment 17

The composition of embodiment 1, wherein the polymeric viscosity builder is present at a concentration of about 4% w/w.

Embodiment 18

The composition of embodiment 1, further comprising methyl paraben.

Embodiment 19

The composition of embodiment 1, further comprising Carbomer interpolymer type A, Carbomer interpolymer type B, or Carbomer Homopolymer Type C.

Embodiment 20

The composition of embodiment 19, wherein the Carbomer Homopolymer Type C is present at a concentration of about 0.7% w/w to about 1.5% w/w.

Embodiment 21

The composition of embodiment 19, wherein the Carbomer Homopolymer Type C is present at a concentration of about 0.85% w/w to about 1.5% w/w.

Embodiment 22

The composition of embodiment 19, wherein the Carbomer interpolymer Type A is present at a concentration of about 1% w/w to 2% w/w.

Embodiment 23

The composition of embodiment 19, wherein the Carbomer interpolymer Type B is present at a concentration of about 0.1% w/w to about 0.5% w/w.

Embodiment 24

The composition of embodiment 1, further comprising a neutralizing agent.

Embodiment 25

The composition of embodiment 24 wherein the neutralizing agent is NaOH or triethanolamine.

Embodiment 26

The composition of embodiment 1 further comprising a chelating agent.

Embodiment 27

The composition of embodiment 26, wherein the chelating agent is ethylene diamine tetraacetic acid.

Embodiment 28

The composition of embodiment 27, wherein the ethylene diamine tetraacetic acid is present at a concentration of about 0.02% w/w to about 0.04% w/w.

Embodiment 29

The composition of embodiment 27, wherein the ethylene diamine tetraacetic acid is present in the composition at about 0.03% w/w.

Embodiment 30

The composition of embodiment 1 wherein the composition is in the form of a gel, a suspension, an emulsion, a cream, a liquid, a paste, a lotion, a nanoemulsion, a microemulsion, a reverse emulsion, or a liposomal cream.

Embodiment 31

A method for treating a dermatological condition comprising administering to a subject in need thereof a therapeutically effective amount of a composition of embodiment 1.

Embodiment 32

The method of embodiment 31 wherein the condition is acne vulgaris, rosacea, atopic dermatitis, treatment of chronic wounds, bed sores, keratosis pilaris, sebaceous cysts, inflammatory dermatoses, post inflammatory hyperpigmentation, eczema, xerosis, pruritus, lichen planus, nodular prurigo, dermatitis, eczema, or miliaria.

Embodiment 33

The method of embodiment 32 wherein the condition is acne vulgaris.

Embodiment 34

The composition of embodiment 1, 2, 3, or 4, further comprising adapalene.

Embodiment 35

The composition of embodiment 34, wherein the adapalene is present at a concentration of about 0.1% w/w to about 0.3% w/w.

Embodiment 36

The composition of embodiment 1, 2, 3, 4, 34, or 35, wherein the second solubilizing agent is selected an alcohol, a glycol, an ester, or an ether.

Embodiment 37

The composition of embodiment 1, 2, 3, 4, 34, 35, or 36, wherein the second solubilizing agent is PEG 400, lactic acid, dimethyl isosorbide, propylene glycol, propylene carbonate, hexylene glycol, isostearyl alcohol, diethyl sebacate, or ethanol.

Embodiment 38

The composition of embodiment 37, wherein the second solubilizing agent is propylene glycol.

Embodiment 39

The composition of embodiment 38, wherein the propylene glycol is present in the composition at a concentration of about 5% w/w.

Embodiment 40

The composition of embodiment 37, wherein the second solubilizing agent is propylene carbonate.

Embodiment 41

The composition of embodiment 40, wherein the propylene carbonate is present in the composition at a concentration of about 5% w/w.

Embodiment 42

The composition of embodiment 37, wherein the second solubilizing agent is ethanol.

Embodiment 43

The composition of embodiment 42, wherein the ethanol is present in the composition at a concentration of about 3% w/w.

Embodiment 44

The composition of embodiment 1, 2, 3, 4, 34, 35, 36, 37, 38, 39, 40, 41, 42, or 43, wherein the polymeric viscosity builder comprises an acrylamide/sodium acryloyldimethyltaurate copolymer.

Embodiment 45

The composition of embodiment 1, 2, 3, 4, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, or 44, wherein the polymeric viscosity builder is present at a concentration of about 2% w/w to about 6% w/w.

Embodiment 46

The composition of embodiment 45, wherein the polymeric viscosity builder is present at a concentration of about 4% w/w.

Embodiment 47

The composition of embodiment 1, 2, 3, 4, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, or 46, further comprising methyl paraben.

Embodiment 48

The composition of embodiment 1, 2, 3, 4, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, or 47, further comprising Carbomer interpolymer type A, Carbomer interpolymer type B, or Carbomer Homopolymer Type C.

Embodiment 49

The composition of embodiment 48, wherein the Carbomer Homopolymer Type C is present at a concentration of about 0.7% w/w to about 1.5% w/w.

Embodiment 50

The composition of embodiment 48, wherein the Carbomer Homopolymer Type C is present at a concentration of about 0.85% w/w to about 1.5% w/w.

Embodiment 51

The composition of embodiment 48, wherein the Carbomer interpolymer Type A is present at a concentration of about 1% w/w to 2% w/w.

Embodiment 52

The composition of embodiment 48, wherein the Carbomer interpolymer Type B is present at a concentration of about 0.1% w/w to about 0.5% w/w.

Embodiment 53

The composition of embodiment 1, 2, 3, 4, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, or 52, further comprising a neutralizing agent.

Embodiment 54

The composition of embodiment 53 wherein the neutralizing agent is NaOH or triethanolamine.

Embodiment 55

The composition of embodiment 1, 2, 3, 4, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, or 54, further comprising a chelating agent.

Embodiment 56

The composition of embodiment 55, wherein the chelating agent is ethylene diamine tetraacetic acid.

Embodiment 57

The composition of embodiment 56, wherein the ethylene diamine tetraacetic acid is present at a concentration of about 0.02% w/w to about 0.04% w/w.

Embodiment 58

The composition of embodiment 56, wherein the ethylene diamine tetraacetic acid is present in the composition at about 0.03% w/w.

Embodiment 59

The composition of embodiment 1, 2, 3, 4, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, or 58, wherein the composition is in the form of a gel, a suspension, an emulsion, a cream, a liquid, a paste, a lotion, a nanoemulsion, a microemulsion, a reverse emulsion, or a liposomal cream.

Embodiment 60

A method for treating a dermatological condition comprising administering to a subject in need thereof a therapeutically effective amount of a composition of embodiment 1, 2, 3, 4, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, or 59.

Embodiment 61

The method of embodiment 60 wherein the condition is acne vulgaris, rosacea, atopic dermatitis, treatment of chronic wounds, bed sores, keratosis pilaris, sebaceous cysts, inflammatory dermatoses, post inflammatory hyperpigmentation, eczema, xerosis, pruritus, lichen planus, nodular prurigo, dermatitis, eczema, or miliaria.

Embodiment 62

The method of embodiment 60 wherein the condition is acne vulgaris.

The following examples are intended only to illustrate the some embodiments and should in no way be construed as limiting the claims.

EXAMPLES

Example 1

Table 1 lists two formulations (containing equivalent levels of diethylene glycol monoethyl ether) that show the impact of acrylamide/sodium acryloyldimethyltaurate copolymer based thickener on dapsone particle size. FIG. 2 presents impact of acrylamide/sodium acryloyldimethyltaurate copolymer based thickener on dapsone crystal growth. The microscopic image of ENA (30% diethylene glycol monoethyl ether, 4% acrylamide/sodium acryloyldimethyltaurate copolymer based thickener) in comparison to ENC (30% diethylene glycol monoethyl ether, 1% Carbopol 980) shows a clear difference in particle size of the dapsone. Larger crystals were observed in the sample with carbomer homopolymer type C (ENC vs. ENA).

TABLE 1

Formulations Tested For Dapsone Crystal Size

Formulation #	ENA	ENC
Dapsone	7.5	7.5
Diethylene glycol monoethyl ether	30	30
Carbomer homopolymer type C	—	1

TABLE 1-continued

Formulations Tested For Dapsone Crystal Size

Formulation #	ENA	ENC
acrylamide/sodium acryloyldimethyltaurate copolymer based thickener	4	—
Methyl paraben	0.2	0.2
pH adjusting solution	pH 5.5-7	pH 5.5-7
Purified Water	Q.S 100	Q.S 100

Example 2

Example compositions contemplated for use as described herein are set forth in Table 2 below:

TABLE 2

Composition #	1	2	3	4	5	6	7	8	9	10
Dapsone	5-10									
Adapalene	—						0.1-0.3			
Diethylene glycol monoethyl ether	30	35	40	30	35	30	35	40	30	35
Carbomer homopolymer type C	—			0.85-1.5		—	—	—	0.85-1.5	
Acrylamide/sodium acryloyldimethyltaurate copolymer emulsion	4			—		4			—	
Methyl paraben	0.2									
NaOH/pH adjusting solution	pH 5.5-6.5									
Purified Water	Q.S 100									

Example 3

Anti-oxidants and chelating agents such as sodium metabisulfite, citric acid and EDTA were added to formulations to help slow down or completely stop any impurity formation. Table 3 presents the composition of formulations tested. Formulation A7 with sodium metabisulfite minimized the intensity of yellow color caused by the increased solubility of dapsone in diethylene glycol monoethyl ether and maintained the low color intensity over time at accelerated condition (40° C.). See FIG. 3 for appearance of the formulations over 4 weeks. Table 4 presents the formulation panel summarizing other formulation options with chelating agents and antioxidants.

TABLE 3

Compositions Tested containing Antioxidants or Chelating Agents

Composition #	A5	A6	A7
Dapsone	7.5		
Diethylene glycol monoethyl ether	35	40	35
carbomer homopolymer type C	1.25	—	1.25
Acrylamide/sodium acryloyldimethyltaurate copolymer emulsion	—	4	—
EDTA	0.05		—
Anhydrous Citric Acid	0.1		—
Sodium Metabisulfite	—		0.2
Methyl paraben	0.17		0.2
Propyl paraben	0.03		—
NaOH/pH adjusting solution	pH 5.5-6.5		
Purified Water	Q.S 100		

TABLE 4

Formulation panel summarizing other formulation options

Composition #	1	2	3	4	5	6	7	8	9	10
Dapsone	5-10									
Adapalene	—						0.1-0.3			
Diethylene glycol monoethyl ether	30	35	40	30	35	30	35	40	30	35
carbomer homopolymer type C	—			0.85-1.5			—		0.85-1.5	
Acrylamide/sodium Acryloyl - dimethyltaurate copolymer emulsion	4			—			4		—	
EDTA	0-0.1									
Citric Acid	0-0.1									
Sodium Metabisulfite	0-0.5									
Methyl paraben	0.2									
NaOH/pH adjusting solution	pH 5.5-6.5									
Purified Water	Q.S 100									

Example 4

Additional example compositions contemplated for use as described herein are set forth in Table 5 below.

TABLE 5

Additional examples containing alternate neutralizer

Materials	% w/w 5-1	5-2	5-3	5-4	5-5	5-6
Dapsone	7.5					
Adapalene	—			0.3		—
Diethylene glycol monoethyl ether	30	35	40	30	40	25
carbomer homopolymer type C	1					
Methylparaben	0.2					
Triethanolamine (TEA) Q.S.	pH 5.5-6.5					
Hydrochloric Acid Q.S	pH 5.5-6.5					
Purified Water	q.s.a.d. 100					

Example 4

Additional example compositions contemplated for use as described herein are set forth in Table 6 below.

TABLE 6

Additional examples (containing co-solvents, stabilizer and alternate thickener)

Materials	% w/w 6-1	6-2	6-3	6-4	6-5	6-6
Dapsone	7.5		10		7.5	
Adapalene	—			0.3		
Diethylene glycol monoethyl ether	25	35	35	25	30	40
Propylene glycol	5					
Propylene Carbonate	5					
Ethanol (absolute)	3			—	3	
EDTA	0.03					
Carbomer Interpolymer Type A	—			1.5		
Carbomer Interpolymer Type B	—			0.3		
Acrylamide/sodium acryloyldimethyltaurate copolymer emulsion	4			—		4
Methyl Paraben	0.2					
Triethanolamine	—			Q.S. pH 5.5-6.5		
Purified Water	q.s.a.d. 100					

Example 5

Another useful composition is depicted in Table 7.

TABLE 7

Ingredient	Amount (% w/w)
Dapsone	5-8
Adapalene	0.1-0.3
Diethylene glycol monoethyl ether	40.00
Propylene glycol	5.00
Ethanol (absolute)	3.00
Ethylene Diamine Tetraacetic acid (EDTA)	0.03
Methyl Paraben	0.20
Sepineo P 600	4.00
Purified Water	Q.S.

Example 6

Another useful composition is depicted in Table 8.

TABLE 8

Ingredient	Amount (% w/w)
Dapsone	5.0
Diethylene glycol monoethyl ether	25
Methyl Paraben	0.2
Carbopol 980	0.85
Sodium Hydroxide	0.2
Purified Water	Q.S.

While this some embodiments have been described with respect to these specific examples, it is understood that other modifications and variations are possible without departing from the spirit of the invention. Each and every reference identified herein is incorporated by reference in its entirety.

What is claimed is:

1. A method for treating a dermatological condition selected from the group consisting of acne vulgaris and rosacea comprising administering to a subject having the dermatological condition selected from the group consisting of acne vulgaris and rosacea a topical pharmaceutical composition comprising:

about 7.5% w/w dapsone;

about 30% w/w to about 40% w/w diethylene glycol monoethyl ether;

about 2% w/w to about 6% w/w of a polymeric viscosity builder comprising acrylamide/sodium acryloyldimethyl taurate copolymer; and

water;

wherein the topical pharmaceutical composition does not comprise adapalene.

2. The method of claim 1, wherein the diethylene glycol monoethyl ether is present at a concentration of about 30% w/w.

3. The method of claim 1, wherein the polymeric viscosity builder is present at a concentration of about 4% w/w.

4. The method of claim 1, wherein the topical pharmaceutical composition further comprises methyl paraben.

5. The method of claim 1 wherein the dermatological condition is acne vulgaris.

6. A method for treating a dermatological condition selected from the group consisting of acne vulgaris and rosacea comprising administering to a subject having the dermatological condition selected from the group consisting of acne vulgaris and rosacea a topical pharmaceutical composition comprising:

about 7.5% w/w dapsone;

about 30% w/w diethylene glycol monoethyl ether;

about 4% w/w of a polymeric viscosity builder comprising acrylamide/sodium acryloyldimethyl taurate copolymer; and

water;

wherein the topical pharmaceutical composition does not comprise adapalene.

7. The method of claim 6, wherein the topical pharmaceutical composition further comprises methyl paraben.

8. The method of claim 6 wherein the dermatological condition is acne vulgaris.

* * * * *

EXHIBIT 3

CONFIDENTIAL

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ALMIRALL, LLC, Plaintiff, v. TARO PHARMACEUTICAL INDUSTRIES LTD. and TARO PHARMACEUTICALS, INC., Defendants.	)	C.A. No. 17-663 (JFB) (SRF) CONSOLIDATED

[CONFIDENTIAL]

REBUTTAL EXPERT REPORT OF MANSOOR M. AMIJI, PH.D, R.PH.

I. INTRODUCTION

1. I, Mansoor M. Amiji, Ph.D., R.Ph. submit my expert report in the above-captioned case on behalf of Defendants Taro Pharmaceutical Industries Ltd. and Taro Pharmaceuticals Inc. (collectively, "Taro").

2. I have been asked to respond to the report submitted on behalf of Plaintiff[1] by Majella E. Lane, Ph.D. alleging that the product described in Taro's ANDA No. 21-0191, if sold and used according to its label, would induce infringement of certain claims of U.S. Patent No. 9,517,219 ("the '219 patent"). In particular, I have been asked for my opinions regarding alleged infringement of claims 1, 2, 4 and 5 of the '219 patent (collectively the "asserted claims") pursuant to the Doctrine of Equivalents ("DOE").

II. QUALIFICATIONS

3. In 1988, I graduated with honors from Northeastern University and received a Bachelor of Science degree in Pharmacy and became a Registered Pharmacist in Massachusetts. In 1992, I received a Ph.D. in Pharmaceutical Science/Pharmaceutics from the School of Pharmacy and Pharmacal Sciences at Purdue University, under the supervision of Professor Kinam Park. My dissertation focused on biomaterials and water-soluble polymers. During my graduate studies at Purdue University, I took several industrial pharmaceutics courses and had hands-on training pharmaceutical formulations.

4. I am currently a University Distinguished Professor and Professor of Pharmaceutical Sciences in the School of Pharmacy, Bouve College of Health Sciences at Northeastern University in Boston, Massachusetts. I am also jointly appointed as a Professor of Chemical Engineering in the College of Engineering at Northeastern University. I am also

[1] I understand Almirall has been substituted for Allergan as the Plaintiff in this action. I also understand I am to respond to Dr. Lane's report and refer to any prior submissions, opinions, statements, etc. as if they were provided by Almirall as opposed to Allergan.

currently an Affiliate Faculty Member in the Department of Biomedical Engineering at Northeastern University. I have taught and carried out research in pharmaceutical sciences at Northeastern University since 1993, and from 2010 to 2016, I served as the Chairman of the Department of Pharmaceutical Sciences. In 2000, I was a Visiting Research Scholar in the Department of Chemical Engineering at the Massachusetts Institute of Technology (MIT) in Cambridge, Massachusetts in the laboratory of Professor Robert Langer.

5. As a tenured faculty member at Northeastern University, I have over 25 years of experience in teaching drug formulations to both graduate and undergraduate students. In theory and laboratory courses that I have taught and continue to teach, I extensively cover the manufacturing and composition of pharmaceutical formulations. I also serve as a consultant to several pharmaceutical, biotechnology, and medical device companies regarding product development and drug delivery.

6. Over the course of my career I have published extensively and am ranked as a Thompson-Reuters Highly Cited (top 1%) author in Pharmacology and Toxicology. I have coauthored over 60 book chapters and more than 300 peer reviewed scientific articles. I am also an inventor on several issued United States patents covering pharmaceutical devices, materials and methods. I have taught courses in pharmaceutics; drug design, evaluation, and development; dosage forms; and pharmacokinetics.

7. I have served as a grant reviewer for the National Institutes of Health, the Department of Defense, the United States Department of Agriculture, and the American Chemical Society. I am a member of several professional and industrial societies, including the American Association of Pharmaceutical Scientists (AAPS) and the Controlled Release Society (CRS), and have participated as a reviewer for more than 50 scientific journals. I have also

received a number of professional awards and honors, including the Nano Science and Technology Institute (NSTI) Fellowship Award for Outstanding Contributions towards the Advancement in Nanotechnology, Microtechnology, and Biotechnology in 2006; a Fellowship and Meritorious Manuscript Award from the AAPS in 2007; the Tsuneji Nagai Award from the CRS in 2012; and the Northeastern University School of Pharmacy Distinguished Alumni Award in 2016. Over the course of my career, I have advised numerous post-doctoral associates, doctoral students, master's students, visiting scientists, and research fellows.

8. A true and correct copy of my curriculum vitae, which includes a list of the published papers that I have written, professional honors and memberships, and presentations that I have given, is attached to this report as Exhibit A. The matters in which I have testified in the past four years are included in Exhibit B.

9. I am being compensated at a rate of $850 per hour for testimony.

III. OVERVIEW OF OPINION

10. In formulating and providing my opinions herein, I reviewed relevant portions of Taro's ANDA, the expert reports of Dr. Lane and Dr. Panayiotis P. Constantinides, the '219 patent and prosecution history, the patent and prosecution history of U.S. Patent No. 9,161,926, as well as background literature and other documents cited throughout this report, including the documents set forth in Exhibit C. The bases for my opinions include the references and observations cited in this report, my education, and my many years of experience in industry and academia, including the development of formulations of pharmaceutical products.

11. The product described in Taro's ANDA will not infringe any of the asserted claims of the '219 patent. Taro's ANDA describes a product that does not include "about 2% w/w to 6% w/w of a polymeric viscosity agent comprising A/SA". Because each asserted claim

of the ’219 patent requires treatment with a formulation containing A/SA, Taro’s Product if sold doctrine of equivalents.

IV. LEGAL STANDARDS

12. I am not a patent attorney, nor have I independently researched the law of patent validity. I have been informed of certain legal standards below that I have relied on in forming my opinions in my report.

13. I understand that for a claim to be found to be infringed, Plaintiff bears the burden of establishing by a preponderance of the evidence that each and every claim limitation is present in the accused product or method. I understand that each claim is to be evaluated individually.

14. I understand that patent claims can be independent or dependent. Dependent claims incorporate all the limitations of an identified independent claim, and then further narrow the claim through additional limitations. I understand that if an independent claim is not infringed by an accused product, then all claims that depend from that claim are also not infringed because each would be missing a shared limitation.

15. I understand that the process for determining infringement requires two steps. First, I have been instructed to apply the Court’s claim construction to those identified terms, then, for the remaining terms, use the plain and ordinary meaning to a person of ordinary skill in the art (“POSA”) at the time of the invention. Second, I have been informed that I should compare the construed claims to the identified accused product or method to determine if all elements are present. I understand that if any claim element is not present in the accused product or method, then the overall product or method does not infringe the claim.

16. I understand that a claim element that is not literally present in the accused product or method may still infringe under the legal doctrine of equivalents. I understand the doctrine of equivalents exists so that an accused infringer may not avoid infringement because of

minor or insubstantial changes that take a product or method outside the literal scope of the claims. I understand that the doctrine of equivalents applies when there are insubstantial differences between the claim element that is not literally present and the accused equivalent structure or method step in the accused device or process.

17. I understand that one test to determine whether an accused equivalent element is insubstantially different from a claim limitation is the "function-way-result" test. I understand that under that test, an accused equivalent infringes if it performs substantially the same function in substantially the same way to achieve substantially the same result as the claim element in question. I also understand that this is only one way of determining equivalence, and that it may not be appropriate in all situations.

18. I understand that the doctrine of equivalents is applied on a claim element-by-element basis. In other words, I understand that I am not to consider the claim as a whole when analyzing whether a claim element is present under the doctrine of equivalents.

19. I also understand that there are situations where the doctrine of equivalents is not allowed to be applied at all.

20. I have been informed and understand there is a doctrine referred to as prosecution history estoppel. It is my understanding prosecution history estoppel prevents a patentee from recapturing subject matter is surrendered during the prosecution of the patent. I understand the surrender of the subject matter does not need to be explicit, but that it must be clear and unequivocal.

21. I have also been informed and understand there is a doctrine referred to as the "dedication to the public" or the "dedication-disclosure" rule, which generally means if a patent

drafter discloses but declines to or does not claim certain subject matter, that unclaimed subject matter is dedicated to the public and its use will not infringe the patent.

22. I also understand under the doctrine of ensnarement a patentee is barred from asserting a scope of equivalents that would encompass or "ensnare" the prior art to find an accused product infringes.

V. TECHNOLOGY BACKGROUND

23. The '219 patent generally claims methods of treating acne with a formulation containing 7.5% dapsone, a solubilizing agent and a polymeric viscosity builder ("PVB" or "thickening agent"). The '219 patent was distinguishing from the prior art during prosecution because the formulation used a polymeric thickening agent called acrylamide/sodium acryloyldimethyl taurate copolymer ("A/SA") instead of the prior used carbomer homopolymer type C ("Carbomer"). Carbomer is commercially available as Carbopol 980.

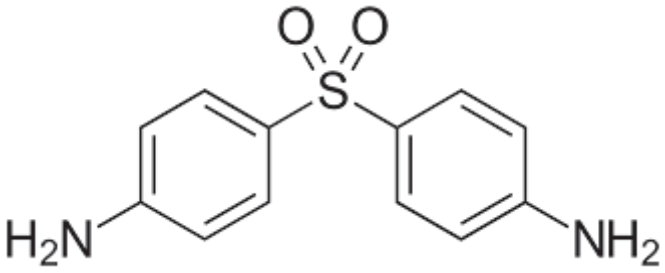
24. The '219 patent, along with the prosecution history of the patent inclusive of the references cited in those documents, include descriptions and evidence of background relevant to the technology claimed in the patents-in-issue. The background information relates, for example, to dapsone, formulations of dapsone at varying concentrations, including formulations containing Carbomer as the thickening agent. If asked, I am prepared to discuss the background of the invention claimed in the '219 patent, in particular with reference to the patent-in-suit, prosecution histories of the patent, and art cited within that document. I will also reference the parent application to the '219 patent, including its prosecution history. Finally, I will also rely on my own personal knowledge and experience.

25. Basic topical drug formulation relevant to the '219 patent can be found in established references such as Remington's Pharmaceutical Sciences. Basic information on pharmaceutical excipients can be found in the references such as the Handbook for

Pharmaceutical Excipients. In describing the basic background of the patent-in-suit, I may additionally rely on these texts along with my own knowledge gained from a career designing pharmaceutical dosage forms, including topical formulations utilizing thickening agents.

A. Dapsone as a Topical Anti-inflammatory Agent

26. Dapsone, whose chemical name is diaminodiphenyl sulfone (chemical structure shown below) was first synthesized in 1908 and was available as an antibacterial and antiprotozoal antibiotic in 1937 and was commonly used in combination with other drugs, such as rifampicin and clofazimine, for the treatment of leprosy. Additionally, it is a second-line medication for the treatment and prevention of Pneumocystis carinii pneumonia and for the prevention of toxoplasmosis in HIV positive patients and those who have poor immune function.



27. Dapsone has intrinsic anti-inflammatory properties and has been indicated topically for treatment of many different types of skin conditions such as for acne, dermatitis herpetiformis and others. The anti-inflammatory effects of dapsone resemble those seen with non-steroidal anti-inflammatory agents such as ibuprofen or meloxicam. Dapsone is poorly soluble in water (solubility = 0.2 mg/mL), but can dissolve readily in organic solvents such as methanol (solubility = 50 mg/mL).

28. The first animal tests for the anti-inflammatory effects of dapsone were carried out in 1970's using various rodent models of inflammatory diseases. Although the exact mechanisms of anti-inflammatory effects of dapsone has not been well understood, the drug

tends to inhibit inflammatory conditions through multiple biological processes including decrease in reactive oxygen species generation, inhibition of specific enzymes, as well as lowering pro-inflammatory cytokine levels.

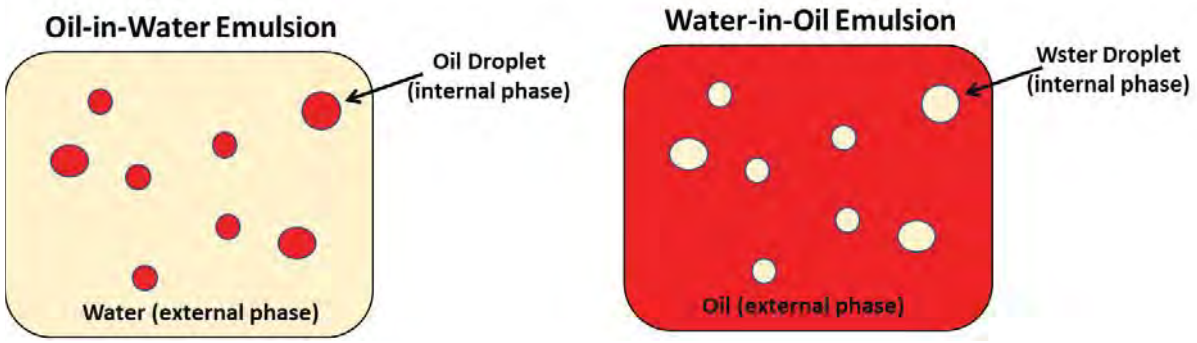
29. When ingested for antimicrobial effects, dapsone has significant issues with toxicity in the liver and other organs in the body. As such, dapsone use as an anti-inflammatory agent is generally restricted to topical administration, such as on the skin, in order to decrease systemic availability and side effects.

B. Topical Drug Products

30. As opposed to systemic administration where the drug products are given by oral or injectable route of administration, a drug product is administered topically for local treatment of diseases of the skin and mucosal surfaces that are accessible. The main advantage of topical drug administration is achievement of maximum benefits of treating the disease condition locally without systemic side effects. Many different diseases of the skin, such as dry skin, eczema, hives, acne, etc., benefit from topical products that confine the medication to the affected area.

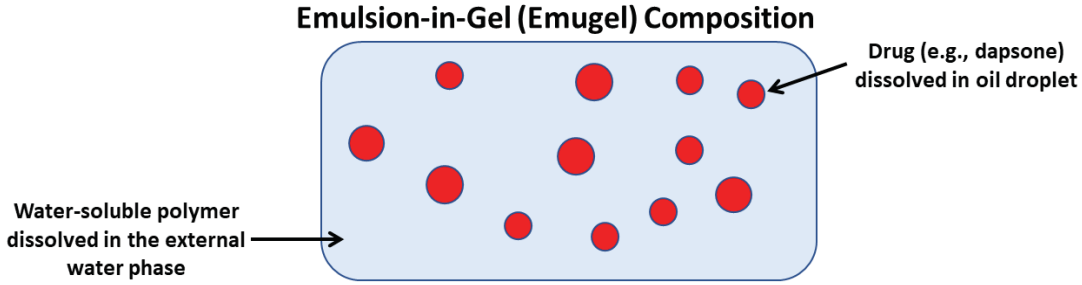
31. Skin is the largest organ in the body and provides the greatest surface area for topical drug administration. In order to achieve maximum benefit for local treatment of skin diseases, a topical drug product needs to have desired attributes that can provide therapeutic benefits in a safe and effective manner. For example, the drug product should be formulated to give the required dose of the active agent in an amount sufficient to cover the affected area and remain at the site for a reasonable period of time. Additionally, the product consistency should be such that it is easy to spread on the skin surface, but not too thin to have poor residence. The formulation should also maintain drug stability over the course of the shelf-life of the product.

32. For these formulation attributes to be met, a person of skill in the art ("POSA") would develop a topical drug product in an ointment, cream, lotions, foams or gel composition. An ointment is a lipid product intended for application on the skin that is usually prepared with petrolatum base. Creams and lotions are prepared by mixing oil and water to form emulsions. These simple emulsions can be either oil-in-water (O/W) or water-in-oil (W/O) depending on the relative percentage by weight of the oil and water phases and the choice of the emulsifier or surfactant used (see figure below). Common household examples of O/W and W/O emulsions are salad dressings and margarine, respectively. Foams are prepared by incorporation of a propellant that aerosolizes upon release, such as in shaving cream. Lastly, gels are made using water-soluble polymers that at a specific concentration will create a product with gel-like consistency that is required to have a product spread easily on the skin. In contrast to ointment, which generally do not absorb or dissolve in water, emulsions and gel products would be able to either imbibe water or completely dissolve in water.



33. Emulsion-gel hybrid or "emugels" are topical drug products that combine the properties of O/W emulsion with a water-soluble polymer gel incorporated to increase the viscosity of the final product (Vivek Sharma, et al, Polymeric Gels, Characterization, Properties and Biomedical Applications, Chapter 9, Emulgels,, pp. 251 – 264 (2018)). The water-soluble polymers used to prepare emugels are also referred to as "polymeric viscosity builders" (PVB).

As shown in the figure below, an emugel will consist of oil droplets (internal phase) surrounded by water (external phase) of an emulsion. A water-soluble polymer is dissolved in the external water phase to create a hydrogel, such that the final product is useful for topical drug administration. Based on the properties of the active drug, it could be dissolved either in the internal oil phase or the external water phase. Dapsone, for example, is water-insoluble and would preferentially dissolve in the oil phase of the emulsion. Additionally, water-soluble and oil-soluble excipients can be incorporated in the respective phases of the emulsion.



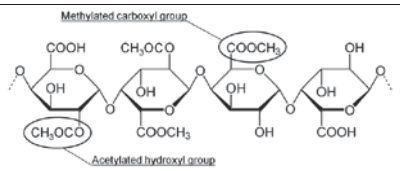
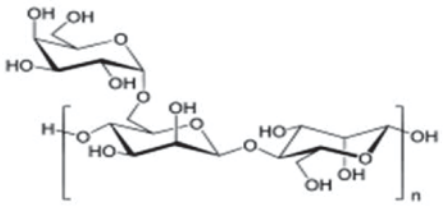
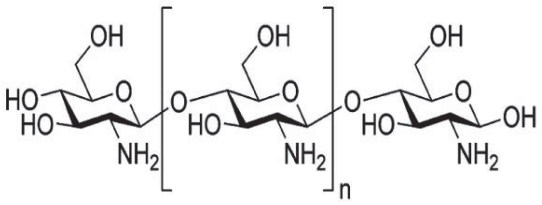
C. Viscosity Enhancement in Topical Emugels

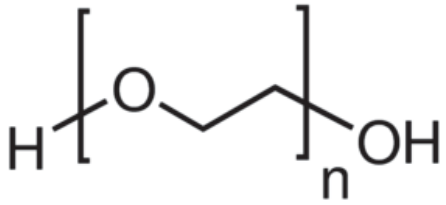
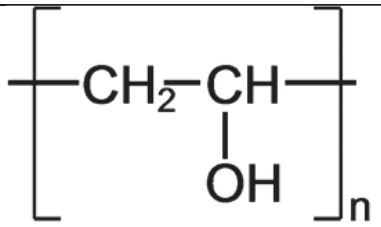
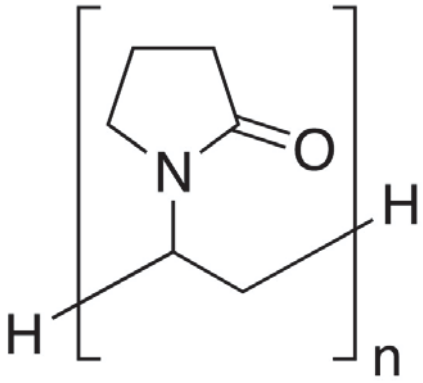
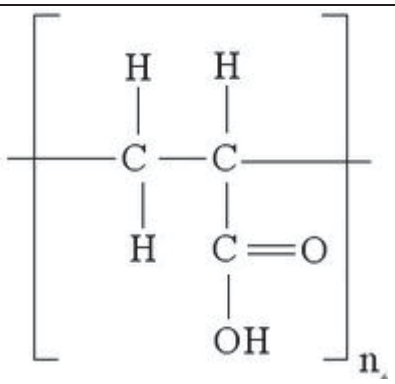
34. There are many benefits of emulsions, gels, and emugels as a topical drug product, including aesthetic appeal, ease of incorporation of diverse types of water-soluble and oil-soluble drugs and excipients, as well as the possibility of washing the product off of the skin when needed. However, since emulsions are heterogenous formulations with oil and water, they are also susceptible to stability issues such as phase separation and creaming as well as stability and homogeneity of drug dispersion within the formulation. Increasing the viscosity of the water phase in an O/W emulsion ensures that the final product will be dispensed as a semi-solid composition that will be easier to spread, will remain on the skin, and will have other desired properties as opposed to liquid emulsions.

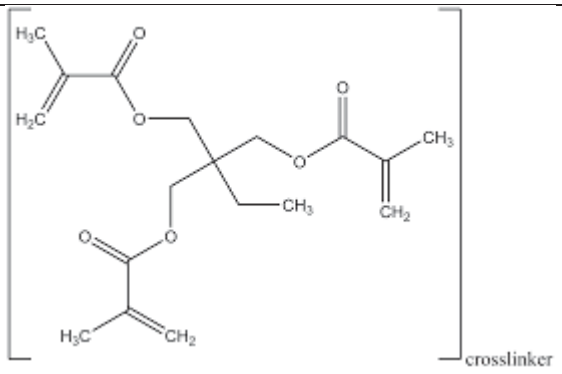
D. Polymeric Viscosity Builders

35. To increase the viscosity of the external water phase in an O/W emulsion of an emugel, water-soluble polymers can be added to induce gelation. In the context of pharmaceutical products, these polymeric viscosity builders (PVB) or gelators are pharmaceutical excipients that can create interconnecting networks in solution to imbibe water and increase viscosity of the final product. Both natural and synthetic water-soluble polymers are used to increase viscosity of the emugels.

36. The Table below shows some illustrative examples and structures of natural and synthetic water-soluble polymers used in pharmaceutical products to increase viscosity. The final viscosity of the formulation is determined by the type of polymer, the molecular weight, and the concentration in the final composition.

Polymer Type	**Name**	**Chemical Structure**
Natural	Pectin	
	Guar gum	
	Chitosan	

Synthetic		
	Poly(ethylene glycol) (PEG) or poly(ethylene oxide) (PEO	
	Poly(vinyl alcohol) (PVA)	
	Poly(N-vinylpyrrolidone) (PVP)	
	Crosslinked polyacrylic acid resins (Carbopol, Carbomer)	

	Acrylamide/sodium acryloyldimethyl taurate copolymer (e.g., Sepineo P600)	

37. Neutral polymers such as PEG or PVA dissolve in water by hydrogen bonding. However, charged polymers, such as Carbopol will dissolve through ion-dipole interactions especially when the pH is increased to above 5.0 when the carboxylic acid group is ionized. Since the ion-dipole interaction is stronger than hydrogen bonding, Carbopol tends to provide greater increase in viscosity when the pH is raised to between 5.0 to 7.0.

VI. TARO'S ANDA PRODUCT AND MANUFACTURING METHOD

38. Taro has submitted ANDA No. 210191 for Dapsone Gel 7.5% ("Taro's ANDA"). I have reviewed relevant portions of Taro's ANDA to analyze whether the product described therein ("Taro's Product") if used according to its labeling would cause infringement of any of the Asserted Claims.

39. Taro's ANDA describes the composition and manufacturing process to create Taro's Product. In the "Description and Composition of the Drug Product" of Taro's ANDA (Section 3.2.P.1), the Quantitative Formulation and Functions of Ingredients tables for Taro's Product are included. TARO-DG-00000610. These tables describing the composition of Taro's Product are reproduced below:

Table 2: Quantitative Formula

Strength (Label claim):	7.5% Dapsone	
Component and Quality Standard	**Quantity per unit** (mg/g)	**%** (w/w)
Dapsone, USP	75.00	7.50
Purified Water, USP	596.5	Calculated 59.65[1]
[redacted]		

Table 3: Functions of Ingredients

Component	**Intended Functions**
Dapsone, USP	Active Pharmaceutical Ingredient (API)
Purified Water, USP	Vehicle/anti-solvent
[redacted]	

40. Dapsone is the sole active ingredient in Taro's Product.[2] The product additionally includes water, [redacted]

[2] The excipients of Taro's Product, including commonly known uses of the same are indicated at TARO-DG-00000679-80.

[redacted] These excipients in combination constitute an aqueous phase of Taro's Product.[3]

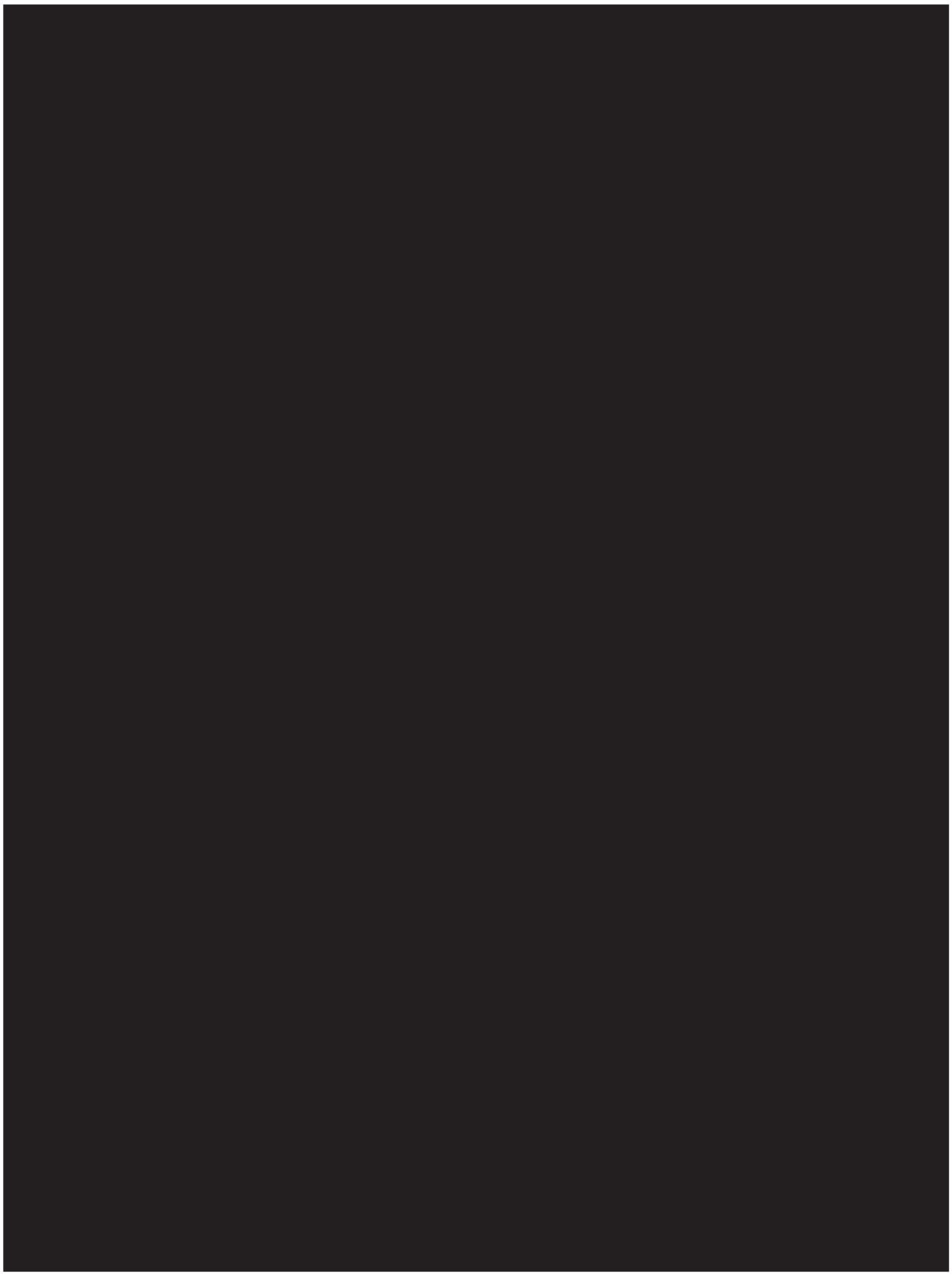
41. Taro's Product additionally includes [redacted]

42. Lastly, Taro's Product includes Carbomer Homopolymer Type C, also commonly referred to as Carbopol 980 or simply "Carbomer." *See* Lubrizol, Viscosity of Carbopol Polymers in Aqueous Systems (2010). Carbomer is a polymeric thickening (or "gelling") agent consisting of a single synthetic high-molecular-weight polymer of acrylic acid. Carbomer is used in Taro's Product to increase the viscosity of the gel and it is the sole thickening agent in Taro's formulation. As described below with reference to the manufacturing protocol for Taro's Product, Carbomer must be carefully mixed with water followed by activation using some form of neutralizing agent, in this case sodium hydroxide. Addition of Carbomer to topical pharmaceutical products must be carefully controlled to prevent clumping of the polymer.

43. Taro's ANDA describes Taro's Manufacturing Process in detail. The Manufacture section of Taro's ANDA (3.2.P.3) contains a subsection entitled, "Description of manufacturing process and process control" (3.2.P.3.3) which provides narrative and graphical information about the manufacturing process. This section also describes what controls are implemented by Taro to ensure adherence to the product and manufacturing specifications.

[3] As described below, Taro's Product additionally includes an oil phase. Topical formulations having an aqueous and oil phase are common.

Section 3.2.P.3.3 contains a "Flow Diagram" that shows a graphical representation of the full manufacturing process for Taro's ANDA Product. TARO-DG-00000769. The Flow Diagram identifies [redacted] *Id.* The Flow Diagram is reproduced in full below:



44. In addition to the graphical description, Section 3.2.P.3.3 contains a Narrative Summary of the manufacturing process. TARO-DG-00000770-71. This narrative provides more detail about each step of the manufacturing process shown in the Flow Diagram.[4]

45. The Narrative Summary describes [redacted]

46. At this point, [redacted] Thereafter, water is added to the mixture to arrive at the target weight and the product is packaged in airless pump containers of 30, 60 and 90 gram sizes. *Id.*

47. As clearly stated in Flow Diagram and the Narrative Summary, Taro does not [redacted] and Carbomer to create a polymeric thickening agent. Instead, Carbomer is added separate from all other ingredients in a

[4] Batch Records for Taro's Product are also a good source for learning the manufacturing protocol. *See* TARO-DG-00000798-821.

time consuming and carefully managed process as is typical with topical pharmaceutical formulations containing Carbomer.

VII. PATENTS-IN-SUIT

A. Disclosures of the '219 and '926 Patents

a. The '219 Patent

48. For the purposes of my report, I separately refer to the Abstract, Specification and Claims of the '219 patent as issued.

49. The Abstract is presented on the face of the '219 patent. It is my understanding the purpose of an abstract is to enable the public to determine quickly from a cursory inspection the nature and gist of the technical disclosure in the specification. *See* 37 CFR § 1.72(b). The abstract reads:

> Dapsone and dapsone/adapalene compositions can be useful for treating a variety of dermatological conditions. The compositions of this disclosure include dapsone and/or adapalene in a polymeric viscosity builder. Subject compositions can be adjusted to optimize the dermal delivery profile of dapsone to effectively treat dermatological conditions and improve the efficiency of pharmaceutical products applied to the skin. Use of the polymeric viscosity builder provides compositions with increased concentrations of diethylene glycol monoethyl ether relative to compositions without the polymeric viscosity builder.

50. In my opinion, the Abstract of the '219 patent provides very little to apprise the public the nature of the invention. At most, the abstract describes dapsone and/or adapalene compositions with a PVB and that the use of the PVB somehow allows for higher concentrations of DGME. It is important to note the abstract does not specifically identify A/SA and also describes adapalene compositions that are explicitly excluded from the claims. See Claims 1 and 6. In my opinion, a person reading the abstract in combination with the claims (described in more detail below) would understand the patent disclosed subject matter that was not claimed and

therefore could be practiced without infringing the issued claims. This understanding would be reinforced by further examination of the Specification and Claims, as described below.

51. It is my understanding the specification of a patent is a written description of the invention and of the manner and process of making and using the invention. *See* 37 CFR § 1.71. It is my further understanding the specification must be in such full, clear, concise, and exact terms as to enable any person skilled in the relevant art to make and use the same. *Id.* It is also my understanding the specification must set out the precise invention in a manner to distinguish it from other inventions and from what is old. *Id.* In my report I refer to the "Field and Background of the Invention", the "Summary of the Invention" and the "Description of the Preferred Embodiments" as the specification of the '219 patent.[5]

52. The Field and Background of the Invention (the "Background") begin with general reference to compositions useful for treating dermatological conditions, with a focus on acne, using dapsone and dapsone/adapalene compositions. Col. 1, ln. 19- Col. 2, ln. 8. The Background generally discusses challenges associated with the treatment of acne, including the need for trial-and-error in determining the most effective treatment, efficacy being affected by patient compliance with treatment, side effects associated with available treatment and cost. The Background also notes the availability of compositions with multiple-anti-acne agents having stability concerns as well as difficult with manufacture.

53. The inventors conclude the Background by stating there is a "continuing need for compositions and methods used in treatment of a variety of skin conditions, such as acne, in which topical application is potentially effective" and that the compositions and methods of the '219 patent address those needs. Col. 2, ln. 4-8. In my opinion, the concluding statement makes

[5] It is my understanding original claims as filed with the patent application are part of the invention disclosure.

clear the inventors were not purporting to solve the foregoing problems, but were offering compositions that were "potentially effective." *Id.* This conclusion would be confirmed by further reading of the Specification, as discussed below. In example, "treating" or "treatment" is defined in the patent as simply having some positive effect on a skin condition. *See* Col. 5:22-34. That is an extremely low bar for compositions comprising active ingredients well-known to provide benefits to patients having acne.

54. The Summary of the Invention begins with a somewhat generic discussion of dermatological issues, including acne and the prior treatments thereof. It is my understanding the Summary of the Invention should be "commensurate with the invention as claimed and any object recited should be that of the invention as claimed." *See* 37 CFR 1.73. The summary states a problem with prior dapsone compositions is they cause drying of skin, itching and cracking. Col 2:25-28. It is stated inclusion of skin emollients and oils in the composition causes "phase separation and precipitation of dapsone." Col 2:29-31. It is further stated improved compositions would improve treatment options and minimize problems with prior formulations and the compositions of the invention include dapsone solubilized with DGME and optionally include a PVB. It is further stated the compositions can be "adjusted to optimize the dermal delivery profile of dapsone[.]" Col 2:44-48. In view of the fact the prior art described dapsone formulations with DGME and a PVB, a person of skill in the art reading this conclusion would not understand the nature of the invention. More specifically, such a person would have noted the complete absence of clinical information of any kind in the patent suggesting improved treatment or reduction in side effects associated with the methods of the invention. (Clinical information or data also was not included during prosecution of the application resulting in the '219 patent.)

55. At the conclusion of the Summary the patent stated that use of a PVB reduces yellowing and the particle size of dapsone in formulations, thereby reducing the feeling of grittiness. Col 2:54-61. The specification does provide information about yellowing and grittiness, specifically at Figures 1 and 3 (yellowing) and 2 (particle size). The Figures are of very little help, however, as there is no way of discerning the "yellowing" in the images of Figures 1 and 3 and Figure 2 does not include information about the formulations at issue. As such, it is impossible to know what formulations are being compared. In conclusion, a POSA would understand the inventors were alleging some benefit of compositions with respect to yellowing and particle size, but the support for those benefits is of almost no value.

56. The Detailed Description and Embodiments (the "Detailed Description") begins with two columns focused on general information relating to dermatological conditions, none of which have any obvious pertinence to the invention disclosed. Cols. 3-4. The conclusion of the clinical information defines the term "treating" or "treat" in the context of the invention as previously described, namely by setting a very low bar of efficacy. Col 5:22-34.

57. The Detailed Description next generally disclose compositions of the invention, such compositions containing dapsone in the ranges of 5 to 10% w/w, DGME in the range of 10 to 40% w/w and the use of different PVBs, including A/SA and Carbomer. Cols. 5-6. There is no representation that the compositions solve any of the foregoing treatment challenges or have any particular clinical benefit beyond being dapsone formulations. Instead, a list of embodiments of the invention follows. The first embodiment is extremely broad, covering a composition with dapsone between 3 and 10% w/w, a first solubilizing agent, a second optional solubilizing agent, a PVB and water. Col 6:65-Col 7:3. Many of the subsequent embodiments refer to this first embodiment, including Embodiment 20 wherein Embodiment 1 is further defined as including

Carbomer between 0.7 and 1.5% w/w. A specific formulation falling under Embodiment 20 appears in Table 5 wherein compositions contemplated for use according to the invention are disclosed. The composition includes 7.5% w/w dapsone, DGME and 1% w/w Carbomer. In view of this, and other information in the patent, a person of skill in the art would have understood the Detailed Description was disclosing dapsone compositions having Carbomer as the PVB in 1% w/w concentration. The claims of the patent, however, do not encompass such compositions.

58. The patent disclosed many other formulations wherein Carbomer was used in combination with dapsone and/or adapalene. A further example is found, for instance, at Example 1 comparing A/SA with 1% w/w Carbomer and noting a larger crystal size with Carbomer formulations than with A/SA (Col. 12, l. 55). Tables 1, 2, 5, 6, and 8 also disclose Carbomer containing formulations. As such, a person reading the specification and examining the claims would have understood Carbomer formulations were disclosed as being part of the invention, but not subsequently claimed. As described below, the reason those formulations were not claimed is due to the applicant specifically disavowing formulations wherein the thickening agent was Carbomer in response to a rejection by the patent office.[6] Similarly, adapalene formulations are described as being part of the invention, but those formulations are expressly precluded by the claims. The only polymeric viscosity builder or thickener referenced in the claims themselves is A/SA.[7]

[6] I have reviewed the deposition of inventor Kevin Warner and understand Carbomer formulations were proposed for Phase I clinical studies along with the formulation that eventually became Aczone® 7.5% gel. Warner Dep. 245:15-248:19. The eventual formulation was selected, but Dr. Warner does not know if the Carbomer formulations would have succeeded if pursued. 266:13-270:3.

[7] It is interesting the applicant claimed A/SA as opposed to Sepineo P 600, as that is what they claim to be the PVB in its Aczone 7.5% Gel product and the only form of A/SA that was ever considered.

59. If asked, I am prepared to talk about the '219 patent, including the Background, Summary and Detailed Description. I am also prepared to discuss how a person of ordinary skill in the art would have understood the disclosure of the '219 patent alone and in view of the prosecution history (described in detail below). Finally, I am prepared to talk about the claims and claim scope.

B. The Parent Application No. 14/082,955

60. It is my understanding the application that resulted in the '219 patent was a division of Application No. 14/082,955. I refer to Application No. 14/082,955 as the "Parent Application" as I understand that to be the proper designation to indicate its relation to the application that resulted in the '219 patent (the "Divisional Application"). The Parent Application issued as U.S. Patent No. 9,161,926 ("the '926 Patent"). It is my understanding the '926 Patent has not been asserted against Taro. Nevertheless, I have been informed the prosecution of the Parent Application can be relevant to an understanding of the subject matter of a divisional application and the claims of a patent issuing from such a divisional application. For this reason, I have reviewed the prosecution history of the '926 patent and, if asked, am prepared to describe the prosecution history for the Court.

61. The Parent Application was submitted with an original twenty (20) proposed claims. The original proposed claim 1 stated the following:

> A composition comprising dapsone, a first solubilizing agent which is diethylene glycol monoethyl ether, optionally at least one second solubilizing agent, a polymeric viscosity building, and water, wherein the dapsone is preset in the composition at a concentration of about 3% w/w to about 10% w/w. TARO-DG-00063859

The original proposed dependent claim 10 claimed:

> The composition of claim 1, wherein the polymeric viscosity building comprising an acrylamide/sodium acryloyldimethyl taurate copolymer. *Id*.

And dependent claim 11 and 12 claim the PVB present at a concentration of about 2% w/w to about 6% w/w and a concentration of about 4% w/w respectively. *Id.* These claims are consistent with embodiments in the specification of the '219 patent, as previously discussed.

62. The original proposed dependent claim 14 claims:

> The composition of claim 1, further comprising Carbomer interpolymer type A, carbomer interpolymer type B or Carbomer Homopolymer Type C. TARO-DG-00063860.

Claim 14 is a claim covering a composition with 7.5% dapsone, 30% DGME, 1% Carbomer and water. It would also cover the same composition additionally including Polysorbate 80, sorbitan monooleate, light mineral oil and a neutralizing agent. That claim was withdrawn based on an examiner's patentability rejection.

63. In a January 14, 2014 Office Action, the patent examiner noted the applicants claimed two separate inventions (composition and method) and required the applicant to choose which invention the applicant wished to have examined. TARO-DG-00063901-63902. Further, the applicant was required to make an election of a single disclosed species for, among other things, claim 14. TARO-DG-00063902-63904. In a February 20, 2014, Response to the Restriction Requirement and Election of Species, the applicant elected invention 1 (the composition). Further, the applicant elected carbomer homopolymer type C as the carbomer polymer listed in Claim 14. TARO-DG-00063911.

64. In the next Office Action dated March 18, 2014, the Examiner issued claim rejections as, among other references, being anticipated by both Lathrop and Ahluwalia. TARO-DG-00063918-63923. I understand Lathrop teaches topical emulsive compositions of dapsone, and claims a composition containing both dapsone and Carbomer. TARO-DG-00063918-919. Ahluwalia teaches topical compositions with dapsone and adapalene for the treatment of acne.

Ahluwalia teaches exemplary compositions such as 5% w/w dapsone; .1% w/w or .3% w/w adapalene; 25% w/w DGME; 15% w/w propylene glycol; .01% w/w EDTA; .75% w/w Carbopol 980; sodium hydroxide and purified water. TARO-DG-00063919. The Examiner cited Lubrizol advertising literature for the fact Carbopol 980 is a polymeric thickener synonymous with carbomer homopolymer type C. TARO-DG-00063919. The Examiner noted Ahluwalia taught ranges of dapsone, DGME and a polymeric viscosity builder and concluded the ranges clearly encompass the ranges being claimed by the applicant. TARO-DG-00063921-922.

65. In response to the March Office Action, on May 20, 2014, the applicant submitted amended claims limiting, among other things, the polymeric viscosity builder in claim 1 to A/SA and cancelling multiple claims, including claim 14. TARO-DG-00064079.

66. The applicant went on to argue against the prior rejections and specifically noted the "unexpected advantages" of the claimed composition in providing improved aesthetics and noted the particle size improvement using A/SA in comparison to Carbomer. TARO-DG-00064088-64089. The applicant specifically stated and included in bold "the composition comprising [A/SA] thickener has unexpected advantages over a composition where the thickener/viscosity builder in Carbomer homopolymer type C." TARO-DG-00064089.

67. On June 5, 2014, the Examiner again rejected multiple claims as being obvious and unpatentable over the prior art. TARO-DG-00064097-64102. The Examiner further discussed the applicant's claim of "unexpected advantages." The Examiner noted the tested formulations cited by the applicant were not commensurate in scope with the claims presented, and further found "a showing of unexpected results must necessarily be accompanied by a clear indication of what the skilled artisan would have expected, as well as a clear showing of how the claimed invention exceed such expectation so as to provide properties or results that were

unexpected, unobvious and of statistical and practical significance" which the applicant had not done. TARO-DG-00064105-64108.

68. In response to another rejection, on February 2, 2015, the applicant submitted a declaration from Kevin S. Warner, one of the co-inventors of the patent application stating: "Based on the unexpected observation of Carbopol 980 incompatibility with 40% DGME, the thickener was changed from Carbopol 980 to Sepineo P 600 [i.e., A/SA] to mitigate the risk of polymer aggregation in DGME containing formulations." ALG-ACZ0000292. He further stated: [We] selected Sepineo P 600 as the gelling agent for our dapsone 7.5% gel formulation. We made this selection due to Sepineo P 600's compatibility with concentrations of DGME greater than 25% and its improvement in dapsone particle size relative to Carbopol 980." *Id*. This same declaration was submitted again in support of the '219 patent application.

69. After the submission of the declaration the applicant further amended and canceled certain claims and responded to the latest rejection. TARO-DG-00064182-64184. In focusing on unexpected results, the applicant reiterated the "unexpected results" discussed by the co-inventor in his declaration. TARO-DG-00064188. They noted undesirable polymer aggregates during formulations studies (using Carbomer) which lead to the utilization of A/SA. TARO-DG-00064188-64189. The applicant went on to state Sepineo P 600 allowed for higher concentrations of DGME, which were found to be incompatible with Carbomer and that Sepineo P 600 formulations provided smaller particle size as compared to Carbomer formulations, which is why Sepineo P 600 was selected as the gelling agent. TARO-DG-00064189. It was emphasized this result was "entirely unexpected and could not have been predicted" based on the 5% dapsone formulation, which used Carbomer or the prior art formulation. *Id*.

70. After these repeated references to the unexpected superiority of A/SA over the well-known and previously utilized Carbopol 980, the Examiner issued a notice of allowability. TARO-DG-00064344.

C. Prosecution of the '219 Patent

71. I have reviewed the prosecution history of the '219 patent and, if asked, I am prepared to describe the prosecution history for the Court. As explained below, and throughout my report, the applicants' responses and representations made to the patent examiner, both about the basic and novel characteristics of the invention being claimed in the application that led to the '219 patent and the nature of the prior art, are relevant to my non-infringement analysis. As explained in detail below, a full review of the prosecution history makes clear the applicants were focused on the novelty of using A/SA as the thickening agent and expressly disclaimed Carbomer formulations.

72. Originally, all of the claims were rejected as unpatentable over Garrett in view of Hani, a rejection nearly identical to those made during prosecution of the Parent Application. (The claims were also rejected on the ground on nonstatutory double patenting, as being unpatentable over claims 1-6 of the '926 patent.). ALG_ACZ0000052-72. By way of amendment and response to the office action dated February 18, 2016, the applicants argued the amount of dapsone, the use of Sepineo P 600 as the sole thickening agent in a topical dermatological formulation comprising dapsone and the specific amount of Sepineo P 600 recited in the claims made the claims distinct from the prior art.[8] ALG_ACZ0000284. Applicants claimed the combination of Sepineo P 600 with dapsone was not suggested in either Garrett or Hani:

[8] This argument is interesting in that the applicant did not claim Sepineo P 600, but a PVB comprising A/SA. As previously mentioned, the claim is broad enough to cover the use of A/SA *alone* as the PVB.

> First, Garrett teaches that a preferred composition comprises about 5% w/w dapsone wherein about 0.85% w/w carbopol 980 is used as a thickening agent. The instant claims recite new formulations of dapsone wherein the active ingredient is about 7.5% dapsone and an entirely new thickening agent is employed. The new formulation of the instant claims does not include a carbomer such as Carbopol®, but instead utilizes as [A/SA], also known as Sepineo™ P 600, and at a much higher concentration (about 2% to about 6% w/w) as compared to what Garrett teaches for its thickening agent.

ALG_ACZ00000284. In this response, applicants were absolutely clear: "the formulation of the instant claims does not include a carbomer such as Carbopol® …" ALG_ACZ0000283-284. As discussed below, the examiner withdrew its rejection based on Garrett and Hani.

73. In this response the applicant also included the declaration of Kevin Warner previously submitted in connection with prosecution of the Parent Application. Warner Declaration, ALG_ACZ0000290-294. In arguing the unexpected nature of the invention, the applicants argued, for example, Sepineo P 600 was found to be a more robust thickener than Carbomer, which was used in the prior 5% dapsone gel formulations. ALG_ACZ0000292. Applicant further argued Sepineo P 600 allowed for higher concentrations of DGME than with Carbomer and resulted in reduced particle size as compared to Carbomer. *Id*. Applicants concluded: "Sepineo P 600 was therefore selected as the gelling agent for the 7.5% w/w dapsone formulation of the instant claims." Response to Office Action, ALG_ACZ000286.

74. The Examiner determined the Warner Application provided enough support for the unexpected results of A/SA over Carbomer and the rejections for obviousness were withdrawn. ALG_ACZ0000503-505. It was noted by the Examiner in the prosecution of both the '926 and the '219 patents that the testing done with Sepineo and Carbopol did not use the same concentrations, but in this instance, the Examiner noted the inventor's explanation that higher concentrations of Carbopol 980 would have results in even greater aggregation. ALG_ACZ0000504. The Examiner went on to note "The Warner Declaration … provides clear

evidence that the improved properties of the Applicant's claimed 7.5% w/w dapsone formulation … yields directly from the selection of the [A/SA] copolymer as the polymeric thickener of the formulation. ALG-ACZ0000504.

75. I note throughout the prosecution of both the '926 and '219 patents, the applicants noted the superiority of A/SA to Carbomer and the incompatibility of Carbomer with their invention. Such consistent efforts to distinguish the alleged invention from the prior art utilizing, claiming and describing the use of Carbomer put the public and a person of skill in the art on notice that only products containing A/SA could be covered by the claims of the '926 and '219 patents and more specifically the thickening agent Carbomer was not covered by the claims.

VIII. CLAIM CONSTRUCTION

76. I understand the Court has construed the term "polymeric viscosity builder" ("PVB") and that the construction is applicable to my analysis of the '219 patent (Markman Order dated June 6, 2018, C.A. No. 17-663, Docket No. 87). The Parties' proposed constructions and the Court's construction are reproduced below:

Allergan	Taro	Court
"polymer-based system with one or more components that contributes to creating or maintaining the viscosity of the topical pharmaceutical composition"	"a polymer or polymer-based thickening agent"	"a polymer or polymer-based thickening agent"

77. My opinions set forth below apply the Court's claim construction. For all terms that have not been construed by the Court, I apply the plain and ordinary meaning to a POSA as of November 20, 2012.[9]

IX. DR. LANE'S INFRINGEMENT THEORIES ARE BARRED

78. Dr. Lane's infringement analysis requires a finding the 1% Carbomer used as a thickening agent in Taro's Product is equivalent to "about 2% w/w to about 6% w/w of a polymeric viscosity builder comprising [A/SA]". *See* Lane Report at ¶ 67. As explained in more detail below, I disagree with Dr. Lane's opinion regarding the identity of the thickening agent in Taro's Product or that the thickening agent in Taro's Product is equivalent to the missing claim elements. (Furthermore, I disagree with Dr. Lane's attempt to show equivalence between excipients in Taro's Product and unclaimed elements.) Nevertheless, *even if* one were to accept Dr. Lane's construction of the PVB in Taro's Product, numerous limitations on the DOE preclude a finding of infringement. Specifically, Dr. Lane's DOE opinions are precluded under the doctrines of 1) prosecution history estoppel; 2) commitment to the public; and 3) ensnarement. Additionally, it appears Dr. Lane is utilizing a "whole claim" analysis instead of analyzing the specific element at issue. For these reasons alone, it is my opinion Dr. Lane has not demonstrated Taro infringes the '219 patent.

A. Prosecution History Estoppel

79. I have been informed there is a doctrine called prosecution history estoppel which essentially bars a patentee from making narrowing amendments and/or narrowing the scope of the claims during the prosecution of the patent and then broadening the scope of the claims to invoke the doctrine of equivalents.

[9] I understand from Counsel Almirall is asserting a priority date of November 20, 2012. By using this date I am giving no opinion as to whether to this an appropriate priority date for the '219 patent.

80. During prosecution of the Parent Application, the applicant attempted to claim Carbomer and then chose to cancel that claim in direct response to a rejection by the Examiner. Specifically, as noted above in Section VII. B. the original proposed claims in the Parent Application included a claim for multiples types of carbomer, which in response to an Office Action the applicant limited to carbomer homopolymer type C (referred to herein as, Carbomer). The applicant then in response to yet another rejection, canceled the claim in its entirety, thus no longer claiming Carbomer. Based on the applicant's original attempt to claim carbomer homopolymer type C and its subsequent cancelation of that claim a POSA would understand that Carbomer was not claimed in the invention and could not be claimed by the applicant.

81. The claim to Carbomer did not reappear in the Divisional Application that resulted in the '219 patent. However, the patent examiner found the claims obvious in view of Garrett and Hani. As described above, the applicants specifically overcame the objections by arguing the claims did not include Carbomer.

> First, Garrett teaches that a preferred composition comprises about 5% w/w dapsone wherein about 0.85% w/w carbopol 980 is used as a thickening agent. The instant claims recite new formulations of dapsone wherein the active ingredient is about 7.5% dapsone and an entirely new thickening agent is employed. The new formulation of the instant claims does not include a carbomer such as Carbopol®, but instead utilizes as [A/SA], also known as Sepineo™ P 600, and at a much higher concentration (about 2% to about 6% w/w) as compared to what Garrett teaches for its thickening agent.

ALG_ACZ00000284. It bears repeating, applicants were absolutely clear: "the formulation of the instant claims does not include a carbomer such as Carbopol® …" ALG_ACZ0000283-284.

82. In further response to obviousness objections, one of the co-inventors submitted a declaration explaining that Carbomer was unexpectedly not compatible with higher percentages of DGME. The Warner Declaration went on to state the inventors chose A/SA over Carbomer because A/SA was a more robust thickener. These arguments were successful in convincing the

patent examiner to withdraw its objections and allow the patent claims drawn to formulations having thickening agents comprised of A/SA.

83. It is clear to me, as it would be to any skilled person in the pharmaceutical arts, the patentee narrowed the scope of the claims, removing any reference to and claiming superiority over Carbomer during the prosecution of the patent. A person of skill in the art would understand formulations comprising 7.5% dapsone, DGME and Carbomer would not be covered by the claims. It is my opinion Almirall is estopped from bringing its doctrine of equivalents argument to encapsulate Taro's Product.

B. Dedication To The Public

84. I understand there is a rule referred to as the "dedication-disclosure rule" or "dedication to the public." I understand this rule applies when an applicant discloses subject matter but does not then claim the subject matter, thus dedicating it to the public. As discussed above, there are multiple Carbomer formulations disclosed as being consistent with the invention. None of these formulations are claimed, as evidenced by Dr. Lane's opinion Taro's Product does not fall within the literal scope of the patent.

85. For example, the compositions in multiple embodiments listed in the '219 patent include Carbomer. In some embodiments, Carbomer is present at a concentration of about 0.7% w/w to about 1.5% w/w. In other embodiments, Carbomer is present at a concentration of about 0.85% w/w to about 1.0% w/w. This disclosure alone, when read in connection with the claims, would lead a POSA to believe Carbomer, in concentrations from .7 w/w to 1.5% w/w or .85% w/w to about 1.0% w/w had been explicitly disclosed by the patentee and not claimed, and therefore the use thereof would not be considered practicing the patent.

86. Specific examples of Carbomer containing embodiments include 19, 20, 21, 48, 49, 50. Further, Example 2/Table 2, Example 4/Table 5, Example 4/Table 6 and Example 6

/Table 8 all explicitly disclose Carbomer in combination with dapsone and are stated to be consistent with the scope of the invention.

87. The '219 patent also makes clear the inventors believed Carbomer formulations to be inferior to those containing A/SA. In Example 1, the patentee specifically differentiates its invention utilizing A/SA to a composition containing Carbopol, claiming a clear difference in the particle size of the dapsone. The Specification notes larger crystals were observed with Carbomer formulations. So, while the examples include Carbomer as an option, it is not claimed and the examples specifically tout the superiority of A/SA over Carbomer in the invention. This comparison, extolling a purported benefit of A/SA over the well-known and previously utilized Carbomer would lead a POSA to understand Carbomer was disclosed by the patentee, not the preferred thickening agent described by the patentees and, not claimed.

88. A POSA reviewing the specification would understand Carbopol 980 was dedicated to the public through the applicant's decision to repeatedly disclose but not claim Carbopol 980. A POSA would have therefore concluded the use of Carbopol 980 (among other PVBs) would be appropriate to use in a topical pharmaceutical formulation and would not be covered by the claims or inventions of the '926 or '219 patents.

89. Additionally, the applicant repeatedly used A/SA and Sepineo interchangeably in the prosecution of the patent, but in the actual claims the patentee claimed A/SA, not Sepineo. While it appears the, based on the label of ACZONE 7.5%, excipients like polysorbate 80, sorbitan monolete and isohexadecane are utilized in Sepineo P 600, the applicant did not claim Sepineo P 600 – it claimed A/SA. Applicants disclosed some of the additional excipients utilized in Taro's ANDA product [redacted] in the Detailed Description and the Examples but neither those excipients nor Sepineo P 600 not appear

anywhere in the claims. [redacted]

C. The Ensnarement Doctrine Bars Almirall's DOE Theory

90. I have been informed that determining whether an equivalent would impermissibly ensnare the prior art is typically resolved through a hypothetical claim analysis. I understand there are two steps to this analysis. The first step is to construct a hypothetical claim that literally covers the accused product. I understand that while the scope of the hypothetical claim may be broader, it may not add any narrowing limitation.

91. In this case, a hypothetical claim for purposes of an ensnarement analysis would expand the claimed PVB amount to cover [redacted] of a PVB and replace A/SA with Carbomer. That claim would read as follows[10]:

> A method for treating a dermatological condition selected from the group consisting of acne vulgaris and rosacea comprising administering to a subject having the dermatological condition selected from the group consisting of acne vulgaris and rosacea a topical pharmaceutical composition comprising:
>
> about 7.5% w/w dapsone;
>
> about 30% w/w to about 40% w/w diethylene glycol monoethyl ether;
>
> about [[2]][redacted] w/w to about 6% w/w of a polymeric viscosity builder comprising ~~acrylamide/sodium acryloyldimethyl taurate copolymer~~ Carbomer homopolymer type C; and
>
> water;

[10] Insertions appear as underlined text (e.g., insertions) while deletions appear as strikethrough or surrounded by double brackets (e.g., ~~deletions~~ or [[deletions]]).

wherein the topical pharmaceutical composition does not comprise adapalene.

92. Almirall disputes Taro's ANDA Product contains [redacted]

Thus, under Almirall's infringement theory, a hypothetical claim for purposes of an ensnarement analysis would simply replace A/SA with Carbomer. That claim would read as follows:

> A method for treating a dermatological condition selected from the group consisting of acne vulgaris and rosacea comprising administering to a subject having the dermatological condition selected from the group consisting of acne vulgaris and rosacea a topical pharmaceutical composition comprising:
>
> about 7.5% w/w dapsone;
>
> about 30% w/w to about 40% w/w diethylene glycol monoethyl ether;
>
> about 2% w/w to about 6% w/w of a polymeric viscosity builder comprising ~~acrylamide/sodium acryloyldimethyl taurate copolymer~~ Carbomer homopolymer type C; and
>
> water;
>
> wherein the topical pharmaceutical composition does not comprise adapalene.

93. The second step to an ensnarement analysis is to determine whether the PTO would have found the hypothetical claim patentable over the prior art. If such a hypothetical claim would not have been patentable under either 35 U.S.C. §§ 102 (i.e., anticipation) or 103 (i.e., obviousness), then the patentee has overreached and the accused product does not infringe.

94. I have reviewed the Expert Report of Dr. Panayiotis P. Constantinides, Ph.D. in Support of Defendants' Ensnarement Defense served concurrently herewith ("Constantinides Ensnarement Report"), in which he opines that the hypothetical claims I constructed above (including the dependent claims) would have been obvious to a POSA at the time of the alleged

invention. (Constantinides Ensnarement Report ¶¶ 5-22). I agree with Dr. Constantinides' obviousness analysis and ultimate conclusion.

95. Because the hypothetical claim analysis confirms Almirall's equivalents theory impermissibly ensnares the prior art, Almirall should be barred from asserting Taro's ANDA Product infringes under the doctrine of equivalents.

X. THE USE OF TARO'S PRODUCT WILL NOT INDUCE INFRINGEMENT OF ANY ASSERTED CLAIM OF THE '219 PATENT

96. Dr. Lane offers the opinion use of Taro's Product will induce infringement of independent claim 1 and dependent claims 2, 4 and 5 of the '219 patent. Claim 1 of the '219 patent is the sole independent claim being asserted against Taro. As described below, Claim 1 describes a method of treating a dermatological condition with a described topical pharmaceutical formulation. In the event Taro's Product does not meet each element of the topical pharmaceutical formulation set out in Claim 1, either directly or through the doctrine of equivalents, it is my understanding Taro cannot induce infringement of the '219 patent, irrespective of the labeling described in Taro's ANDA. *See* Lane Report at ¶¶ 50-53. Furthermore, it is my understanding if Taro does not infringe, either directly or indirectly, the only asserted independent claim it also cannot infringe any other claim depending on the independent claim.

97. Claim 1 of the '219 patent is reproduced below:

> 1. A method for treating a dermatological condition selected from the group consisting of acne vulgaris and rosacea comprising administering to a subject having the dermatological condition selected from the group consisting of acne vulgaris and rosacea a topical pharmaceutical composition comprising:
>
> about 7.5% w/v dapsone;
>
> about 30% w/w to about 40% w/w diethylene glycol monoethyl ether;

about 2% w/w to about 6% w/w of a polymeric viscosity builder comprising acrylamide sodium acryloyldimethyl taurate copolymer; and

water

wherein the topical pharmaceutical composition does not comprise adapalene.

98. Dr. Lane separates claim 1 into seven different limitations, the fifth being "about 2% w/w to about 6% w/w of a polymeric viscosity builder comprising [A/SA]." Lane Report at ¶ 67.[11] Taro's Product neither includes "about 2% w/w to about 6% w/w of a polymeric viscosity builder" nor a PVB "comprising [A/SA]."[12] Therefore, Taro's Product when used according to its label does not literally infringe independent claim 1 of the '219 patent. Further, as described in detail below, Taro's Product does not infringe independent claim 1 under the doctrine of equivalents, because the [redacted] Carbomer used in Taro's Product is not equivalent to "about 2% w/w to about 6% w/w of a [PVB] comprising [A/SA]."[13] (As described above, Dr. Lane's DOE arguments are also barred.)

A. Dr. Lane Improperly Interprets the Claims

99. Dr. Lane's entire analysis treats the missing claim element as being Sepineo P 600, instead of A/SA. The '219 patent claims a thickening agent "comprising A/SA." It does not claim a thickening agent consisting of Sepineo P 600. The fact Almirall chose to formulate the Aczone® 7.5% gel product by using a purchased product (one that was created by someone other than Almirall) containing Polysorbate 80, sodium monooleate and isohexadecane in addition to

[11] Throughout my report, when responding to Dr. Lane's infringement claims, unless otherwise noted I respond to the limitation conventions she has chosen. By doing so I am in no way conceding she has properly separated the various elements of the claims in the patent-in-suit.
[12] My opinion focuses on the fact Taro's Product is not a topical pharmaceutical composition described in the Asserted Claims. It is not necessary for me to offer an opinion on whether Taro's proposed labeling would induce others to practice the methods of the Asserted Claims *if* Taro's Product was a topical composition described by the claims. *See* Lane Report at ¶¶ 50-53.
[13] For the same reason, Taro's Product, if sold and used according to its label, does not infringe the Asserted Claims depending, either directly or indirectly, on claim 1, namely claims 2, 4 and 5 of the '219 patent.

A/SA does not convert the claim to one reciting those excipients. Dr. Lane repeatedly states Taro's Product is equivalent to "the claimed polymeric viscosity builder, as embodied by Sepineo P 600", but never once shows the polymeric thickening agent in Taro's product, Carbomer, is equivalent to A/SA.[14]

100. At Section 5(a) of Dr. Lane's report, it is clear her understanding of the claims is incorrect. Dr. Lane begins by listing the ingredients of Sepineo P 600 and arguing the Sepineo P 600 product is "an embodiment" of the claims. The remaining portion of her analysis set out in Section 5 is to show equivalency between Sepineo P 600 and Taro's Product. [redacted] *See* Lane Report at ¶¶ 44, 73 and 86. It is my understanding comparing unclaimed features of an embodiment of a claim to an accused product for the purpose of establishing equivalency is improper as it is not comparing a missing claim feature to a corresponding feature in the accused product.

101. Dr. Lane also appears to be taking the position that all thickening agents pursuant to the claims must result in emulgels. *See* Lane Report at ¶¶ 74, 81-88. As an initial matter, I agree the role of a PVB is to thicken a formulation. Lane Report at ¶ 74. I disagree "the polymeric viscosity builder … determines the type of semisolid that is formed – e.g., an emulsion gel (emulgel)." *Id.* As Dr. Lane herself admits in her report, [redacted] *See* Lane Report ¶ 47.[15] The thickening agent

[14] The closest Dr. Lane comes to comparing the two polymers are the basic observations that both Carbomer and A/SA are polymers that serve to thicken formulations. *See* Lane Report at ¶ 87.

[15] The Aczone® 5% gel also was not an emulgel. That formulation is set out at Table 8 in the '219 patent as a "useful composition." It is not an emulgel and uses Carbomer as the thickening agent at 0.85% w/w.

used in that formulation (as in its final formulation) was Carbomer.[16] As Dr. Lane further concedes, [redacted]

102. Nothing in the claims mandates the topical pharmaceutical formulation need be an emulgel. As exemplified by the Garrett reference that was a basis of the patent examiner's obviousness rejections discussed above, it was well understood in the art in 2012 that a topical formulation could be formulated with dapsone, DGME and Carbomer (as the thickening agent) and that such formulations could optionally be formulated as an emulsion by addition of oil and surfactants. TARO-DG-00065190. This is similarly set out in the '219 patent wherein the inventors state: "Compositions described herein are typically in the form of a gel, an emulsion, a cream, a liquid, a paste, a lotion, a nanoemulsion, a reverse emulsion, or a liposomal cream." '219 patent at Col. 6:53-56. I also disagree with Dr. Lane's surprising statement that the Aczone® 7.5% gel and Taro's Product formulations not included an oil-phase those products would be "simple liquid formulations not suitable for treatment of acne because they would not stay on the skin." Lane Report at ¶ 84. Dr. Lane seems to forget the Aczone® 5% Gel product

[16] It is telling that Dr. Lane's theory appears to be Taro's thickening agent was Carbomer in the first formulation and then Carbomer and the added excipients in the second formulation, all the while conceding the other formulation excipients were not added to thicken Taro's Product, but to create an oil-phase in the product. *See e.g.* Lane Report at Section 5(b)(1). It is worth noting the persons responsible for developing Aczone® 7.5% gel knew Carbomer was the thickening agent in Carbomer formulations. *See e.g.* ALG_ACZ0264306.

[17] I have reviewed the expert declaration of Dr. Klibanov. Dr. Klibanov also appears to concede A/SA in the Aczone® formulation and Carbomer in Taro's Product are the thickening agents in the products. March 1, 2018, Declaration of A. Klibanov, Docket No. 59, at ¶¶ 38 and 43. I agree.

only had an aqueous phase, was deemed suitable for treatment of acne and is currently marketed and sold by Almirall. The formulation is *not* a "simple liquid", but a gel.

103. The problem, inevitably, with Dr. Lane's analysis is she attributes advantages of unclaimed excipients to the missing term "A/SA." Dr. Lane knows the function of Polysorbate 80, sodium monooleate and isohexadecane is creating an emulsion, or emulgel in the formulation. That has nothing to do with the claim element reciting a polymeric thickening agent. Imagine a car company has a patent on a car seat comprising leather and a competitor sells a car seat with vinyl. Now imagine a doctrine of equivalents arguments wherein the patentee seeks to claim equivalence based on the fact its cars have heated seats and the accused product also has heated seats and both are warm in the winter. The fact they both have seat heaters and are warm in the winter would be irrelevant to the claims of the patent. Dr. Lane's argument is no different.

104. In summary, the fact that Almirall purchased a product containing both a polymeric thickening agent and common excipients used to create an emulsion and used that product in its formulation does not transform the missing claim element reciting a thickening agent comprising A/SA into one reciting a thickening agent comprising a polymer and excipients capable of creating an oil-phase in the topical pharmaceutical formulation.[18] The inventors, for whatever reason, chose to claim the polymer A/SA alone and my understanding is they cannot now transform that broad claim into a narrower claim so as to capture Taro's Product.[19] The

[18] It is clear Taro understood A/SA in the Aczone® 7.5% gel was the gelling agent in the product and the other excipients served to create the oil phase. TARO-DG-00000682. Dr. Lane does not disagree.

[19] 3. My understanding is the inventors never tested a formulation with A/SA alone and I have not seen any testing done with Sepineo P 600 at a concentration other than 4% w/w. It appears 4% Sepineo P 600 was chosen because that percentage had previously been approved in the IIG. Warner Dep. 294:22-297:5. The claims are much broader.

claims allow for formulations that are gels and do not contain an oil-phase, as such Dr. Lane is incorrect to attempt to show equivalency of the oil-phase of Taro's Product to the oil-phase of Aczone® 7.5% Gel.

B. Dr. Lane Incorrectly Identifies the Thickening Agent Used in Taro's Product

105. The Court has construed "polymeric viscosity builder" to mean "a polymer or polymer-based thickening agent." *See* Section VIII, *supra*. As explained previously, thickening agents are commonly used in topical pharmaceutical applications. Although not all thickening agents are polymeric, the most common types of polymeric thickeners are acrylamide thickeners. A well-known example of this type thickener is Carbomer Homopolymer Type C, commercially available as Carbopol® 980 from Lubrizol. In this report, for ease of reference I have referred to Carbomer Homopolymer Type C as "Carbomer."

106. Taro's product contains [redacted] Carbomer. *See* Section VI, *supra*. It is the only thickening agent in Taro's Product, which also includes a solubilizer, a preservative, emulsifiers and oil. The fact Carbomer is a thickening agent cannot be argued. *See* Lubrizol, Viscosity of Carbopol Polymers in Aqueous Systems, 2010. Plaintiff's NDA clearly states its own development work included looking at both Carbomer and Sepineo P 600 as thickening agents in developing Aczone® 7.5% Gel. [redacted]

107. Dr. Lane incorrectly identifies other pharmaceutical excipients as being part of Taro's thickening agent so as to arrive at her opinion that Taro's thickening agent is not just Carbomer, but Carbomer in combination [redacted] By combining these other excipients [redacted]

[redacted] Dr. Lane arrives at a "thickening agent" that falls within the concentration range of Claim 1. However, Dr. Lane seems to concede Taro added the Oil-Phase Excipients *not* to act as a "thickening agent", but to create an emulgel that more closely mimicked the reference listed drug.[20] Lane Report at ¶¶ 17-18. Dr. Lane is correct, Taro's addition of the Oil-Phase Excipients function to create an emulsion (it is also correct Taro's product prior to addition of the Oil-Phase Excipients appeared to be an acceptable topical pharmaceutical composition.) Avramoff Dep. 143:17-24 and Ex. 10.[21] That does not transform the thickening agent in Taro's Product from Carbomer to Carbomer plus the Oil-Phase Excipients.

108. In my long career, I have never heard anyone calling Carbomer, oil and surfactants in a formulation a "thickening agent." Dr. Lane has given no justification for the combination other than to say she does so based on her understanding of the ingredients in the Sepineo P600 product used as a thickening agent used in Aczone® 7.5% Gel and its being a "[polymer-based thickening agent] comprising [A/SA]." I do not agree with Dr. Lane's reasoning. A POSA would understand based on the prosecution history that Sepineo P 600 was an example of a polymer-based thickening agent comprising A/SA as recited in the claims. (Moreover, it would have been understood Sepineo P 600 was simply a product marketed as a thickening agent that did not have the drawbacks of more traditional thickening agents like Carbomer. *See e.g.* ALG_ACZ0264309 (explaining selection of Sepineo P 600 was based, in

[20] There is nothing unusual about a pharmaceutical company attempting to match the reference listed drug as closely as possible. Not only does FDA encourage use of the same excipients in the same concentrations, but it is more helpful to patients who may be switching from a brand to generic to be familiar with the form and feel of the medication. It is well documented that patients have become confused when the form of generic pills differ from the brand, especially where patients receive tablets from different manufacturers at different times. [redacted]

[21] Neither formulation contained A/SA, and that is the claim element at issue.

part, on the ease of processing relative to Carbomer).) However, as stated above, the claims are not drawn to Sepineo P600. Instead, they are drawn to any polymer or polymer-based thickening agent comprising A/SA. Given the breadth of the claim, A/SA alone would be a polymer thickening agent pursuant to the claims, a fact Almirall does not appear to dispute. *See* Markman Hearing Transcript at 9:14-21. Furthermore, not a single ingredient other than A/SA in the Sepineo P 600 product is claimed in the patent. The only reference to any of these excipients is in a reference at column 5 wherein it is stated a PVB that is A/SA can *optionally* include other excipients. As such, whether Taro's Product has one or more of these excipients or does not, it has no relevance to any claim limitation.

109. During prosecution, the applicants conceded Carbomer alone was the thickening agent used in other dapsone formulations and distinguished Sepineo P 600 as being a better thickener. The Garrett reference the applicants distinguished during prosecution described Carbomer formulations that additional could include other excipients, like sodium monooleate, mineral oil and other emulsifiers. It is well-known by those skilled in the art that Carbomer is a thickening agent and that oil and emulsifiers in combination create an oil-phase in topical gel products.[22]

110. The Inactive Ingredient Database ("IID") is a database maintained by FDA to identify inactive ingredients used in approved drug products. The IID identifies Carbomer use in many approved topical formulations, including gels and ointments. In each of those cases, based on the concentrations used, I am confident Carbomer is being used as a polymer thickening agent, just as Taro has done. Similarly, the IID identifies a single use of Sepineo P 600 in an

[22] For clarity, in my report I have applied the definition of a person of skill in the art articulated by Dr. Constantinides. Opening Expert Report of Panayiotis P. Constantinides, Sept. 11, 2018, at Section IV. My opinions would not change were I to use the definition offered by Dr. Lane. *See* Lane Report at ¶¶ 32-35.

approved gel product. Based on the concentration it is my full expectation the gel product identified is Aczone® 7.5% Gel.

111. The IID database confirms what any person of ordinary skill in the art would understand, namely that Carbomer *alone* is the polymer thickening agent in Taro's Product and Sepineo P 600 alone is the polymer-based thickening agent in Aczone® 7.5% Gel. Thickening agents are just that, agents. They are polymer or polymer based products used to thicken topical pharmaceutical formulations. There is absolutely no justification in the patent or otherwise to look at other excipients in a formulation and label them a thickening agent. The fact Sepineo P 600 is a commercial product sold to thicken formulations is irrelevant. Almirall's NDA makes absolutely clear it is a single agent added to its formulation, unlike the Taro Product. *See* ALG_ACZ0004101-2.

112. In summary, I fundamentally disagree with Dr. Lane's opinion that the Oil-Phase Excipients in Taro's Product combine with Carbomer to create a polymeric thickening agent. Carbomer serves that function alone. The Oil-Phase Excipients are present purely to create an oil-phase in the gel, *i.e.* to create an emulgel. The claims don't require the topical formulations of the claims be emulgels and the term PVB in the patents doesn't incorporate that requirement, as discussed in detail above.

C. Taro's Product Does Not Literally Meet The Claim Limitations of Claim 1 of the '219 Patent And Therefore Taro Cannot Induce Literal Direct Infringement of Claim 1

113. It is my understanding Almirall is not alleging Taro induces direct literal infringement of claim 1 of the '219 patent, and Dr. Lane does not offer an opinion on direct literal infringement in her report.[23] Nevertheless, for completeness I note Taro's Product does

[23] *See also*, Nov. 16, 2017, Initial Infringement Contentions and Sept. 11, 2018, Final Infringement Contentions, wherein Almirall relies solely upon the doctrine of equivalents.

not meet each element of the topical pharmaceutical composition described in claim 1. Specifically, Taro's Product does not contain A/SA in any amount. Therefore, it is my opinion Taro will not induce direct literal infringement of claim 1 of the '219 patent irrespective of the labeling indicated in Taro's ANDA.

D. Taro's Product Does Not Infringe Claim 1 of the '219 Patent Under the Doctrine of Equivalents

114. As has been explained in detail above, Dr. Lane claims Carbomer and the Oil-Phase Excipients in Taro's Product are equivalent to Sepineo P 600. Dr. Lane's framing of the analysis is incorrect, both because it is inconsistent with the express language of Claim 1 and improperly identifies the thickening agent in Taro's Product. Dr. Lane's argument is also barred pursuant to the doctrines of prosecution history estoppel, commitment to the public and ensnarement. As discussed below, the thickening agent and concentrations in Taro's Product are not equivalent to "about 2% w/w to about 6% w/w of a polymeric viscosity builder comprising [A/SA]."

1. One Percent of a PVB is Not Equivalent to Two to Six Percent of a PVB

115. The claims require "about 2% w/w to about 6% w/w of a polymeric viscosity builder." Taro's Product contains [redacted] w/w of Carbomer, the sole thickening agent in the formulation. The difference between [redacted] and about 2% w/w is not an insubstantial difference. The amount of thickening agent included in a product impact viscosity, drug dissolution, bioavailability and other clinical drug attributes. The '219 patent includes numerous examples of various thickening agents being used across a range of concentrations, demonstrating small incremental differences in the amount of a thickening agent matter. This is consistent with my own experience. Further, I do not believe a formulation containing Carbomer at about 6% w/w would be viable due to the potential for Carbomer to precipitate out of the formulation.

116. During prosecution, the applicants conceded the difference between at least 0.85% w/w and about 2% w/w and 6% w/w was significant. As explained, the patent office rejected the proposed claims in the Divisional Application as being obvious over Garrett, which taught the use of Carbomer as a thickening agent. *See* Section XX, *supra.* In response, applicants argued:

> Garrett teaches that a preferred composition comprises … about 0.85% w/w/ carbopol 980 is used as a thickening agent. … The new formulation of the instant claims does not include carbomer such as Carbopol®, but instead utilizes as [A/SA] … and *at a much higher concentration* (about 2% to about 6% w/w) as compared to what Garrett teaches for its thickening agent.

ALG_ACZ0000284 (Emphasis added). This argument is consistent with my own opinion, namely that the difference between [redacted] and "about 2% w/w to 6% w/w" of a polymer or polymer-based thickening agent is not insubstantial, and therefore not equivalent.

117. Taro's Product does not have an equivalent concentration of a thickening agent to the claimed ranges, and therefore does not meet all limitations of the '219 patent, either literally or under the doctrine of equivalents. As such, Taro's Product, if sold pursuant to its labeling cannot infringe Claim 1 of the '219 patent.

a. Carbomer Is Not Equivalent to A/SA or Sepineo P 600

118. Carbomer is a cross-linked polyacrylic acid resin. To dissolve Carbomer in water a neutralizing agent, such as a sodium hydroxide solution, must be added to adjust pH. Neutralizing a Carbomer solution above pH 5 resulted in ionization of the carboxylic acid groups in the polymers, the creation of ion-dipole interactions within the dissolution medium and dissolution of the polymer.

119. Mixing Carbomer must be carefully controlled to avoid clumping and/or precipitation of the polymer. Once the Carbomer is reconstituted, it is carefully added to the remaining excipients. At each step, the temperature, rate of addition of the polymer and mixing

rate must be monitored and controlled. An example of this manufacturing process is described above, at Section XX describing the manufacturing of Taro's Product.

120. A/SA is not insubstantially different from Carbomer. As described above, A/SA has a completely different chemical structure compared to Carbomer. Additionally, A/SA is a "copolymer", meaning it consist of two different polymers cross-linked. (Carbomer is a single polymer.) The fact A/SA is a copolymer is important because the ratio of one polymer to other can change the characteristics of the product. The inventors controlled this aspect by purchasing the Sepineo P 600 product from Seppic. At the time of the invention, and now, Seppic marketed the Sepineo P 600 product as being simpler than other polymeric thickening agents because (1) it was simpler to mix; and (2) did not require neutralization. (Seppic Sepineo™ P 600 Brochure (2008) (ALG_ACZ0375156-57)). These advantages were similarly important to Almirall, as stated in its NDA: "Sepineo P 600 was chosen as a gelling agent for … ease of processing relative to Carbopol 980." ALG_ACZ0264309.

121. The difference in manufacturing between Taro's Product and Aczone® 7.5% Gel is stark. Unlike Taro's process, Aczone® 7.5% Gel is manufactured by combining dapsone, methylparaben and DGME, mixing Sepineo P600 with water and then combining the two and mixing. *See* ALG_ACZ0004101-103. The differences between these two processes are not insubstantial. It is clear Carbomer is neither performing the same function as A/SA (or Sepineo P 600) nor is it performing its function in the same way.

122. The Warner Declaration submitted in connection with prosecution of both the Parent Application and the Divisional Application unequivocally stated the A/SA copolymer emulsion was selected over Carbomer because Carbomer was seen to precipitate at higher DGME concentrations and it was concluded the A/SA polymer was more robust.

ALG_ACZ_0000291-292. This is repeated in the NDA describing thickener selection. *See* ALG_ACZ-264306. Dr. Warner also explained in his deposition why he believed, and continues to believe presumably, Carbomer is not as robust a thickening agent. Warner Dep, 76:6-77:16 and 114:15-119:20.

123. Dr. Lane does not address how, if at all, Carbomer in Taro's Product is as "robust" as either A/SA or Sepineo P 600. To the extent it is more "robust", clearly that would constitute a solution to problem the inventors were not able to solve. In any event, it demonstrates an additional reason why the use of Carbomer in Taro's Product is not an insubstantial difference from the use of a thickening agent comprising A/SA. (Certainly, the more difficult manufacturing associated with the use of Carbopol relative to Sepineo P 600 remains.)

124. The only evidence Dr. Lane purports to offer supporting an argument that Carbomer and A/SA are similar is to state: "[Carbomer] and A/SA are both polymers that act in the same way to create a three-dimensional gel-like structure." Lane Report at ¶ 87. She goes on to state both "swell to increase the viscosity of the formulation in the same way." *Id.* Her arguments are not convincing for a number of reasons. First, if the fact both are polymers creating a three-dimensional gel like structure is the standard, it makes little sense the inventors claimed A/SA, argued A/SA was superior to the prior art and received a patent covering the use of A/SA as the "sole thickening agent." *See*, TARO-DG-00064186. Furthermore, although both act to increase viscosity, as discussed above, they do not do so in the same way. Carbomer is pH dependent whereas the A/SA product used by Almirall is not. As such, Dr. Lane's brief attempt to argue equivalence of Carbomer to A/SA is not convincing and I disagree with her opinion.

125. In short, the inventors were issued a patent based on the argument their PVB was different from Carbomer and that Carbomer was unexpectedly not as robust. Both during prosecution of the Divisional Application and in the NDA, the benefits of A/SA (and Sepineo P 600) over Carbopol were repeatedly argued. I see nothing in Taro's Product, formulation or manufacturing suggesting Taro somehow overcame these differences. Carbomer is not insubstantially different from a PVB comprising A/SA, it does not function in the same way and does not render the same results.

b. The Comparisons of Clinical and Non-Clinical Attributes of Aczone® 7.5% Gel and Taro's Product Do Not Evidence an Insubstantial Difference Between Taro's Thickening Agent and A/SA or Sepineo P 600

126. Dr. Lane seeks to show equivalency between Taro's thickening agent and Sepineo P 600 through clinical and non-clinical comparisons between Aczone® 7.5% Gel and Taro's Product characteristics. These comparisons are flawed based on Dr. Lane's incorrect identification of the thickening agent in Taro's Product. Furthermore, the comparisons she makes draw no connection between Carbomer on the one hand and A/SA on the other. Because she never demonstrates any attribute is attributable to a claimed feature in the '219 patent, *i.e.* A/SA, her comparisons are of little value.

127. The first comparison Dr. Lane seeks to make, at Section 5(b)(2) of her report, relates to the rheological profiles of the two products. Many of the properties tested are impacted by Taro's thickening agent, Carbomer (i.e. the viscosity and shear stress). However, it is not surprising two different products can have similar rheological profiles, even achieving them in different ways. Based on my review of Almirall's development documents and the deposition of Kevin Warner, the goals in formulating a 7.5% dapsone product at Almirall was that the product would have similar characteristics to the Aczone® 5% Product.

128. However, the claims do not require a specific rheological profile in any event. A person of skill in the art would not know the rheological profile of *any* of the tens of embodiments disclosed in the patent. Furthermore, the patent explicitly states the compositions can be modified in different ways to achieve different composition characteristics. A skilled person would have known the inventors were not claiming any specific rheological profile and therefore Dr. Lane's reliance on this information is misplaced.

129. The same is true of other data Dr. Lane relies on, including solubility, particle size, and release rates. The '219 patent includes absolutely no disclosure, not in the patent itself and none was submitted during prosecution, to lead a skilled artisan to believe specific characteristics of solubility, particle size and release rates were being claimed as a benefit of the invention. All of these characteristics can be influenced in innumerable ways by the addition and removal of excipients and also by controlling the concentrations of excipients. The claims of the '219 patent simply do not speak to any of these results. Furthermore, Dr. Lane has made no showing that specific characteristics of Aczone® 7.5% Gel are attributable to the only thickening agent claimed, namely A/SA. In fact, it is clear from her report she attributes many, if not all, the product characteristics to unclaimed elements of the Aczone® product. In short, any similarity of characteristics between Taro's and Almirall's products can be achieved in any number of ways that have nothing to do with the '219 patent claims and, specifically, A/SA.

130. An additional reason Dr. Lane's comparisons are unconvincing relates to studies Almirall performed with Carbomer formulations containing Polysorbate 80. It my understanding, based on information I have reviewed, Almirall studies the impact of Polysorbate 80 in Carbomer formulations to determine the impact on particle size. The results were interpreted by Almirall to mean addition of Polysorbate 80 did not result in a formulation with particle size seen

with the Sepineo P 600 formulations tested. (The comparisons are problematic in that too many of the excipients and concentrations differ between formulations making it near impossible to determine how characteristics of the formulations are impacted by the multiple formulation factors). [redacted] This further supports my opinion Taro's thickening agent is not equivalent to a PVB comprising A/SA.

131. The '219 patent, in any event, is not convincing in its attempt to evidence particle size differences between Carbomer versus A/SA formulations. Figure 2 is not labeled to identify A1 through A4. However, it is my understanding A1 and A4 are Carbomer formulations and A3 and A2 are A/SA formulations. (A4 appears to be the formulation containing 1.25% Carbomer and .2% Polysorbate 80.) Looking at the images, it appears the particle size of one of the Carbomer formulations, namely A1, may be smaller than one of the A/SA formulations, namely A3. As such, I do not find particle size comparisons to the product convincing as they have not been demonstrated to be attributable to the Carbomer and/or A/SA.

E. Taro's Does Not Infringe Dependent Claims 2, 4 and 5 of the '219 Patent

132. The only independent claim asserted against Taro is Claim 1. As explained in detail above, it is my opinion Taro's Product does not meet all the claim limitations of the only independent claim, either literally or under the doctrine of equivalents. As such, it would be impossible for Taro's Product, if sold according to its label, to induce infringement of any claim depending on Claim 1. For this reason, it is my opinion Taro does not infringe the asserted dependent claims 2, 4 and 5.

XI. CONCLUSION

133. In my opinion, Taro's Product, if sold, would not infringe claims 1, 2, 4 or 5 of the '219 patent.

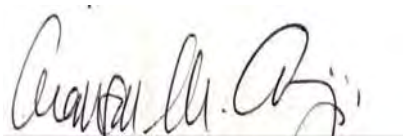
X. RESERVATION OF RIGHTS

134. I have based my opinions and analysis on documents and information available to me at the time I signed this report. If and when any new evidence arises, I reserve the right to supplement or modify my opinions to reflect that evidence.

135. In the event Plaintiff submits any reply to this expert report, I reserve the right to respond to any issues raised by such a reply.

136. If called to testify, my testimony may include an explanation of the scientific principles that underlie the opinions expressed in this report.

137. I reserve the right to make and use demonstratives to help explain my opinions.



November 6th, 2018 Mansoor M. Amiji, Ph.D., R.Ph.

EXHIBIT 4

IN THE UNITED STATES DISTRICT COURT
DISTRICT OF DELAWARE

ALMIRALL, LLC, Plaintiff,	)	
vs.	)	Civil Action No. 17-0663
TARO PHARMACEUTICALS, LTD., et al., Defendants.	)	

VIDEOTAPED DEPOSITION OF MANSOOR AMIJI, Ph.D.
Chicago, Illinois
Wednesday, December 19, 2018

Reported by:
RACHEL F. GARD, CSR, RPR, CLR, CRR
JOB NO. 152403

applicants.

And my reading of the claim as a skilled artisan shows that the requirement -- that the claim limitation is, looking at about 2 to 6 percent by weight of a polymeric viscosity builder comprising acrylamide, sodium acryloyldimethyltaurate or A/SA copolymer.

Q. Uh-huh.

A. So that's the language of the claim. And so when I look at the specification, the other ingredients that I listed here would be optional.

Q. Uh-huh. Okay. I just -- let's just -- we can get to the claim. We'll get to the claim.

I'm asking you in the embodiment as it's described, first of all, the question is: At Column 5 beginning on Line 47, would you agree that the inventors are describing what the polymeric viscosity builder of the invention can be in some embodiments, first question?

A. It's possible. Again, you know, that's what's in the specification. That's

what's described here as one particular composition. But what I also refer to as I just stated is the claims and the language of the claim.

Q. But the description in Column 5 you would agree is a description of one embodiment of what the polymeric viscosity builder as claimed here may be?

A. Again, that's -- in the specification it's describing one particular composition. But in the claim, there is nothing in the claim that specifies that they have to have isohexadecane, sodium oleate or polysorbate 80, there's no claim language to those ingredients.

Q. Are you under the impression that when the claim uses the word "comprising," that additional unclaimed matter cannot fall within the scope of that claim?

A. No, that's not what I'm saying. But it doesn't specify that these have to be those additional unclaimed elements. If you want to claim isohexadecane, if that was a requirement of this composition, that has to be in the

claim. There's nothing that says that the composition will have isohexadecane or sorbitan monooleate.

Q. So your view is that all of the excipients described in the embodiment in Column 5 must be claimed in order to fall within the scope of these claims?

MS. BEIS: Objection.

A. No. That's not what I'm saying. What I'm saying is that these are optional excipients, but the word "comprising" means that there could be others as well.

Q. That's right. That's right. Okay. So if I do start with the claims and I try and determine and I want to look for an example of a polymeric viscosity builder and I look to the specification, you would agree with me that one example is described in Column 5, beginning at Line 47?

A. So again, my reading of the claims require that the polymeric viscosity builder BASA, and the word "comprising" suggests there may be other ingredients that could be included. But what you're reading in the

specification is specific to these different ingredients.

You know, my reading of the claim doesn't limit one -- a skilled artisan, to just these three or four additional ingredients.

Q. And I think that's correct. All I'm saying is that one exemplary embodiment that could fall within the PVB claim is described in Column 5 at Line 47, correct?

A. Yeah, I'm not even sure how it -- you know, it would fall -- I mean, I can see the A/SA in combination with isohexadecane, sorbitan oleate and polysorbate 80 because that's the composition of Sepineo, but the inclusion of water there doesn't say anything about a PVB.

Q. So Sepineo is what, to your understanding?

A. It's a product that's sold by SEPPIC, which consists of A/SA, isohexadecane, sorbitan oleate and polysorbate 80.

Q. And Sepineo, do you disagree that the use of Sepineo as a PVB would fall within the scope of claim 1?

M. AMIJI

A. Well, based on the reading of the claim, you know, it has A/SA, so it does comprise A/SA. And it's an agent based on the claim construction. It is one agent, and so it meets the -- the claim construction for a PVB as the Court has construed. So I think Sepineo does meet the claim limitation based on the term that's there.

Q. Okay. Okay.

A. But the claim is directed towards A/SA.

Q. Uh-huh. And what is isohexadecane, do you know?

A. It's an additive that's used in this particular composition.

Q. Were you aware that it is mineral oil and paraffin? No?

A. No, I haven't seen anywhere where isohexadecane has been referred to as mineral oil.

Q. That's something you could determine given your expertise, correct?

A. Yes. I mean, I know what mineral oil is and I know what isohexadecane is, and

M. AMIJI

they're not -- definitely not the same thing.

Q. Well, I asked you if you're aware that it was mineral oil and paraffin, and I think the answer was no?

A. No, I'm not aware.

Q. Okay. In any event, would you agree that mineral oil and isohexadecane are both derivatives of petroleum?

A. There's so many different derivatives of petroleum. Again, you know, I don't know how one could make a -- you know, just because something is derived from petroleum that they are inherently alike or anything like that. I don't think you can -- you can -- I mean, there are so many different ingredients that are made from petroleum.

Q. Okay. Well, now I'll just ask you as an expert, as I may, to assume that isohexadecane contains mineral oil, and assume that for purposes of my hypothetical.

That being the case, would it surprise you if isohexadecane served to create the oil phase of an embodiment like the one described in Column 5?

M. AMIJI

MS. BEIS: Objection.

A. Again, you know, I have to look at the final composition to be able to specify whether it's forming an oil phase.

Q. Sure.

A. It's how much water is there, how much emulsion formation you have.

Q. Okay. Are you familiar with the Aczone 7 and a half percent formulation?

A. I'm familiar, but if you have something that shows how much...

Q. Yeah. I have two forms of these. Let me just go to a different subject for the moment, because that's beyond bizarre.

Okay. I'll be able to show you the formulation after a break. But just sitting here, you're not sure what is it in the Aczone 7 and a half percent formulation that forms the oil phase of that product?

MS. BEIS: Objection.

A. Yeah, I would need -- I mean, I have a vague understanding of what's in the composition, but it will really help if I had the document in front of me.

M. AMIJI

Q. All right.

MR. TRAINOR: Do we -- do you have that extra copy of Garrett I?

MS. BEIS: I do. I just need to run to another room to grab it. Stephen can grab it if that would be helpful.

MR. TRAINOR: That's all right. We can get it afterwards. Let's just continue with the report then. I'm sorry.

Q. So do you have a view as to -- well, Sepineo, I think you've just testified, and please correct me if I'm wrong, but if Sepineo was the PVB in the claims of the patent, for example, claim 1, can you tell me what function you believe it serves in the -- in the context of the overall method that's claimed?

A. You mean --

MS. BEIS: Objection.

A. You mean the claim was rewritten such that one of the element instead of A/SA was Sepineo?

Q. Well, let me ask it this way: The formulation of the method that's claimed there, right, the formulation that's employed in the

Q. Okay. Now, among the materials you considered and I think you referenced in your report were the Court's claim construction and some of the underlying documents, and I think you point out in a chart -- I can bring you there if you want, but that in this case, Taro proposed the construction which was ultimately decided by the Court to be appropriate, and that is a polymer or a polymer-based thickening agent. Do you recall that? Yes, you have it quicker than me.

A. Yes.

Q. Yes. So I'd have to ask then: What would be the meaning of polymer-based if you don't believe that you can ever have any agents within the PVB other than the polymer that's responsible for the thickening?

MS. BEIS: Objection.

A. Well, again, if you look at the construction, the word -- the important word is "agent," the singular. So it is -- even if it's polymer-based, it's still a singular. And I think the Court incorrectly saw in this case is describing Sepineo as this polymer-based

single entity. And that's why the construction is based on that idea.

So you could have one --- in the case of Sepineo, one particular agent, even though it has polymer and other excipients.

The viscosity building effect is coming from the polymer, but the construction here allows for this idea of having one agent which can have other ingredients in it.

Q. Okay. So it is possible, then, under the construction anyway, that the PVB of the claims can comprise a polymer plus other agents as an entity and be considered collectively the PVB?

MS. BEIS: Objection.

A. Again, it's not an agents, it's not plural. It's agent. It's one. So, therefore, you have -- and I think here encompassing Sepineo specifically, that it has A/SA, it has isohexadecane, polysorbate 80 and sorbitan monooleate, and that's why it's a polymer-based agent. But other than that, all the other like Carbopol and every other excipient that will be used as a polymer viscosity builder will just

be a polymer.

Q. Okay. Okay. But just so that I'm clear, under the Court's construction, it is possible to have a polymer viscosity builder similar to the Sepineo agent which is multicomponent, including the single polymer, correct?

A. But again, it has to be just a single agent when, you know -- if you are looking at, in this context, in Sepineo's case, it's one entity that comes as a commercial product. It's not mixed by any formulator.

Q. Okay. But doesn't that view suggest that if I buy it as a package, it can be a PVB, but if I assemble the same package myself, it's not a single agent?

A. No. I think as I said in my testimony, that in Sepineo's case, this is -- that's the only product that comes as one thickening agent in one formulation. Every other polymeric viscosity builder is just available as polymer itself.

Q. Okay. Okay. But if another Sepineo-like agent comes along, then it could

also fit within the claim construction, you're saying?

A. Again, if it is created with, you know, a polymeric viscosity and has the properties in that hypothetical sense, yeah.

Q. Well, it would have to have the properties collectively because the other part of the construction is it has to thicken, correct?

A. Well, that's what it says, yeah, the polymer-based thickening agent.

Q. Okay. Now, let me -- okay. And so you accept that Sepineo meets the construction of a PVB in this case?

A. Well, I mean, I look at the claims. And so Sepineo has the A/SA and the claim comprising -- the comprising term is that it has these optional ingredients, so all the other ingredients that are in Sepineo are within the scope of the claims. Sepineo can meet the claim limitation based on the fact that there's this comprising term to it.

Q. Okay. And why do you accept that Sepineo can meet the claims under the Court's

M. AMIJI

construction if you insist that the other agents other than A/SA don't contribute to the thickening activity of it?

A. Because I think during the claim construction in the Markman hearing, the position was that in order to have Sepineo be incorporated and the fact that Sepineo has been described and there's examples that utilize Sepineo, and therefore, the other ingredients in Sepineo would be within the scope of the claims because the claim requires that the polymeric viscosity builder be comprised of A/SA.

Q. Okay. All right. Now, in your list of materials considered, which is Exhibit 3, and we established this earlier, so I'm sorry, but again, you considered the opening expert report of Dr. Constantinides; is that right?

A. Yes. Yes, I did.

Q. Okay. Now, I finally -- I'm going to introduce that in one second. Oh, I have one clean copy. Is that all right? Sorry.

MS. BEIS: Are you -- is it the Constantinides opening?

M. AMIJI

MR. TRAINOR: Yes.

MS. BEIS: Okay. I have yesterday's copy.

MR. TRAINOR: Okay. Great. Thank you. So this is No. 5? Oh, 4, thank you.

(Amiji Exhibit Number 4 marked for identification.)

Q. I asked the court reporter to mark as Amiji Exhibit 4 the expert -- the Opening Expert Report of Dr. Panayiotis Constantinides submitted in this case on or about September 11, 2018.

Dr. Amiji, since submitting your report, have you reviewed Dr. Constantinides' report again?

A. Submitting which one? I mean, after submitting the rebuttal report?

Q. After submitting your report, in other words, you reviewed his report and submitted your report. Have you reviewed it since --

A. No.

Q. -- for example, in preparation for this deposition?

M. AMIJI

A. No.

Q. You understand that in considerable part, Dr. Constantinides' opinion is that the patent -- the '219 patent is invalid as obvious in this case, correct?

A. Yes, yes.

Q. And do you -- and I mean, I could take you to just even the table of contents just to orient you under Section 8. The letter C under Section 8 says: Claims 1 through 8 are obvious over Garrett in view of Bonacucina.

Do you see that?

A. Yes.

Q. And then Subsection D, Claims 1 through 8 are obvious over Garrett I in view of Nadau-Fourcade. Do you see that?

A. Yes.

Q. You reviewed the Garrett I reference, I take it?

A. Yes.

Q. Okay. Did you review the secondary references that I just read into the record, the Bonacucina and the Nadau-Fourcade reference?

M. AMIJI

A. I believe I reviewed -- at least, you know, a cursory review. I haven't gone into detailed analysis of each of these prior art references that he's citing, but I did certainly look at the exhibits to his report.

Q. Okay. Oh, I see. Because you reviewed the exhibits to his report, so you may have -- does that mean you reviewed those references at some point?

A. Yeah. Again, as I said, I looked at it from a cursory review. I haven't had -- didn't spend a lot of time looking at each and every exhibit.

Q. That's okay. You can put that aside for a moment, and I'm going to introduce another one.

MR. TRAINOR: I'll have you mark this next one, please.

(Amiji Exhibit Number 5 marked for identification.)

Q. Okay. I've asked the court reporter to mark as Amiji Exhibit 5, United States Patent Application Publication 2012/0004200 to first inventor Nadau-Fourcade. This also bears

Plaintiff's Opposition to Defendant's Motion *in Limine* No. 2

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ALMIRALL, LLC, Plaintiff, v. TARO PHARMACEUTICAL INDUSTRIES LTD. and TARO PHARMACEUTICALS, INC., Defendants.	C.A. No. 17-663 (JFB) (SRF) CONSOLIDATED

PLAINTIFF'S OPPOSITION TO DEFENDANTS' DAUBERT MOTION TO EXCLUDE DR. MAJELLA E. LANE FROM OFFERING THE OPINION TARO'S THICKENING AGENT IS EQUIVALENT TO A/SA COPOLYMER

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Taro moves to exclude testimony from Plaintiff's infringement expert, Dr. Majella Lane, that "the thickening agent in Taro's proposed product is equivalent to the missing claim element, [A/SA]." Taro's Motion *in Limine* ("MIL") at 1. Taro's motion is misguided on two fronts: (1) the disputed claim element is "about 2% w/w to about 6% w/w of a polymeric viscosity builder comprising [A/SA] copolymer," ***not*** "A/SA" alone; and (2) Taro's disagreement with Dr. Lane's opinions and the bases for them is no basis for exclusion. The issues raised in Taro's "*Daubert*" motion go, at best, to the weight, and not the admissibility, of Dr. Lane's testimony. This motion should be denied accordingly.

It is undisputed that Taro's ANDA Product literally meets all but one element of the asserted claims: "about 2% w/w to about 6% w/w of a polymeric viscosity builder comprising [A/SA] copolymer." Taro selectively reduces the claim element at issue to A/SA copolymer ***alone***, improperly ignoring the claims' plain language and the context provided in the '219 Patent. *Graver Tank & Mfg Co. v. Linde Aire Products Co.*, 339 U.S. 605, 609 (1950). Taro's interpretation is further inconsistent with:

- The term "comprising," which allows for other elements in addition to those explicitly named in the claim. *See Genentech, Inc. v. Chiron Corp*., 112 F.3d 495, 501 (Fed. Cir. 1997);
- The Court's construction of the term "polymeric viscosity builder" ("PVB") as "a polymer or polymer-***based*** thickening agent." Report & Recommendation at 6, June 6, 2018, D.I. 87 (emphasis added); Mem. & Order at 8, Aug. 23, 2018, D.I. 107;
- The parties' agreement that the claimed PVB can have multiple components. Report & Recommendation at 6, n.1, June 6, 2018, D.I. 87;
- The '219 Patent's disclosure of, as embodiments of the invention, PVBs that "comprise" A/SA copolymer and that are multi-component thickeners or emulsions with an A/SA copolymer base. *See, e.g*., Ex. 1, '219 Patent at 8:12–16, 10:49–54, tables 1–4, 6. The specification explicitly describes the combination of A/SA copolymer, isohexadecane, sorbitan monooleate, and Polysorbate 80 (also referred to

by its commercial name, Sepineo P 600), as the one and only embodiment of the claimed PVB. *See, e.g.*, *id.* at 5:47–50, table 7;

- Testimony from both parties' experts that the multi-component Sepineo P 600 is an embodiment of the disputed claim element. *See* Ex. 2, Amiji Rpt. ¶ 108; Ex. B to Taro's MIL, Lane Opening Rpt. ¶¶ 69, 71; and
- Dr. Lane's opinion that "[a] POSA would understand that in an accused product such as an emulgel, the polymer, oil and emulsifiers ***together*** function as the [disputed claim element]." Ex. 3, Lane Reply Rpt. ¶ 27.

The foregoing renders it inarguable that the disputed element in the doctrine of equivalents case is "about 2% w/w to about 6% w/w of a [PVB] comprising [A/SA] copolymer," ***not*** A/SA copolymer alone, as Taro misleadingly styles it to premise its motion.

The scope of the disputed claim element being correctly articulated, it is indisputable that Dr. Lane properly considered it in formulating the opinions Almirall will offer at trial. Even assuming Taro believes Dr. Lane did not, that would only go to Dr. Lane's credibility—*i.e.*, the weight of her testimony—***not*** its admissibility. In any case, Dr. Lane testified at her deposition that she compared Taro's PVB to the term "about 2% w/w to about 6% w/w of a [PVB] comprising [A/SA] copolymer," and that correct approach is reflected in her analysis. *See, e.g.*, Ex. 4, Lane Dep. Tr. at 261:22–262:8 ("The analysis I performed was the [PVB] that's the embodiment of claim 1 and the [PVB] that's in the Taro product."); *see also* Ex. 3, Lane Reply Rpt. ¶ 29 ("The relevant comparison is between Taro's [PVB] and the claim term 'about 2% w/w to about 6% w/w of a polymeric viscosity builder comprising [A/SA]', and that is the comparison I applied in my analysis.") and ¶¶ 5, 27–29, 37–41; Ex. B to Taro's MIL, Lane Opening Rpt. ¶¶ 67–131.

Taro argues that Dr. Lane improperly relied on bioequivalence data and referred to unclaimed elements of the '219 Patent that are found in a commercial embodiment of the invention. Taro's apparent dispute with Dr. Lane's reference to other elements, including the context provided by the '219 Patent, cannot stand in view of binding legal precedent. *See*

Graver Tank, 339 U.S. at 609 ("What constitutes equivalency must be determined against the context of the patent, the prior art, and the particular circumstances of the case."). Moreover, bioequivalence ***can be*** relevant to the doctrine of equivalents, and comparison to a commercial product meeting every claim limitation ***is*** appropriate. *See, e.g.*, *Allergan, Inc. v. Teva Pharms. USA, Inc.*, No. 2:15-cv-1455-WCB, 2017 U.S. Dist. LEXIS 4535, at *7–8 (E.D. Tex., Jan. 12, 2017); *Adams Respiratory Therapeutics, Inc. v. Perrigo Co.*, 616 F.3d 1283, 1288-89 (Fed. Cir. 2010); *Abbott Labs. v. Sandoz, Inc.*, 566 F.3d 1282, 1298 (Fed. Cir. 2009).

Taro also dismisses Dr. Lane's opinions as "unsubstantiated conclusions" that certain properties are attributable to the PVB. *See* Taro's MIL at 2-3. Not only does the '219 Patent itself explicitly describe many of these properties as being influenced by the PVB of the invention (*see* Ex. 1, '219 Patent at Abstract, 2:54-61), but Dr. Lane's testimony sets forth in detail the bases for her opinion that a POSA would understand them to be attributable to the PVB. *See, e.g.*, Ex. B to Taro's MIL, Lane Opening Rpt. ¶ 97 (explaining how "Sepineo P 600 and the [PVB] in Taro's ANDA Product each contribute to provide uniform distribution of dapsone in at least two ways. . ."); *see also* ¶¶ 74-78, 83-128; Ex. 3, Lane Reply Rpt. ¶ 27, 31, 34, 38. Taro is free to cross-examine Dr. Lane concerning these bases at trial.

Taro's motion is, in essence, a recitation of its unremarkable disagreement with Plaintiff's position. Disagreement between the parties and their experts is not grounds for excluding Dr. Lane's opinion. A POSA's understanding of which excipients form the claimed PVB, its properties, and whether Taro's PVB is equivalent to the claimed PVB are all decidedly questions of fact for this Court to resolve based on the claims, the specification, and the competing expert testimony. *See Abraxis*, 467 F.3d at 1379; *Intendis GmbH v. Glenmark Pharms., Inc.*, 822 F.3d 1355, 1361–62 (Fed. Cir. 2016). This Court can and should hear all the evidence, including Dr. Lane's testimony, and evaluate the credibility of its sources before deciding the merits of Plaintiff's infringement case.

In sum, Taro's motion is both legally flawed and a conspicuous attempt to obtain a finding on infringement without a trial. It should be denied.

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January 7, 2019

EXHIBIT 1

U 7697471

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

June 06, 2017

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF:

U.S. PATENT: *9,517,219*
ISSUE DATE: *December 13, 2016*

By Authority of the
Under Secretary of Commerce for Intellectual Property
and Director of the United States Patent and Trademark Office

P. SWAIN
Certifying Officer

(12) **United States Patent**
Warner et al.

(10) **Patent No.: US 9,517,219 B2**
(45) **Date of Patent: Dec. 13, 2016**

(54) **TOPICAL DAPSONE AND DAPSONE/ADAPALENE COMPOSITIONS AND METHODS FOR USE THEREOF**

(71) Applicant: **Allergan, Inc.**, Irvine, CA (US)

(72) Inventors: **Kevin S. Warner**, Anaheim, CA (US); **Ajay P. Parashar**, Fairfax, VA (US); **Vijaya Swaminathan**, San Francisco, CA (US); **Varsha Bhatt**, San Francisco, CA (US)

(73) Assignee: **Allergan, Inc.**, Irvine, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **14/885,805**

(22) Filed: **Oct. 16, 2015**

(65) **Prior Publication Data**

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Related U.S. Application Data

(62) Division of application No. 14/082,955, filed on Nov. 18, 2013, now Pat. No. 9,161,926.

(60) Provisional application No. 61/728,403, filed on Nov. 20, 2012, provisional application No. 61/770,768, filed on Feb. 28, 2013.

(51) **Int. Cl.**

A61K 31/136	(2006.01)
A61K 31/192	(2006.01)
A61K 9/00	(2006.01)
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A61K 47/10	(2006.01)
A61K 47/14	(2006.01)
A61K 47/18	(2006.01)
A61K 47/34	(2006.01)

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CPC ***A61K 31/192*** (2013.01); ***A61K 9/0014*** (2013.01); ***A61K 31/136*** (2013.01); ***A61K 31/145*** (2013.01); ***A61K 47/10*** (2013.01); ***A61K 47/14*** (2013.01); ***A61K 47/183*** (2013.01); ***A61K 47/32*** (2013.01); ***A61K 47/34*** (2013.01)

(58) **Field of Classification Search**

None

See application file for complete search history.

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Notification of Transmittal of the International Search Report and the Written Opinion of the International Searching Authority, or the Declaration, International Application No. PCT/US2013/070613, International Filing Date, Nov. 18, 2013, Date of Mailing Feb. 12, 2014.

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(57) **ABSTRACT**

Dapsone and dapsone/adapalene compositions can be useful for treating a variety of dermatological conditions. The compositions of this disclosure include dapsone and/or adapalene in a polymeric viscosity builder. Subject compositions can be adjusted to optimize the dermal delivery profile of dapsone to effectively treat dermatological conditions and improve the efficiency of pharmaceutical products applied to the skin. Use of the polymeric viscosity builder provides compositions with increased concentrations of diethylene glycol monoethyl ether relative to compositions without the polymeric viscosity builder.

8 Claims, 3 Drawing Sheets

Figure 1. Appearance of formulations following 4 weeks of storage

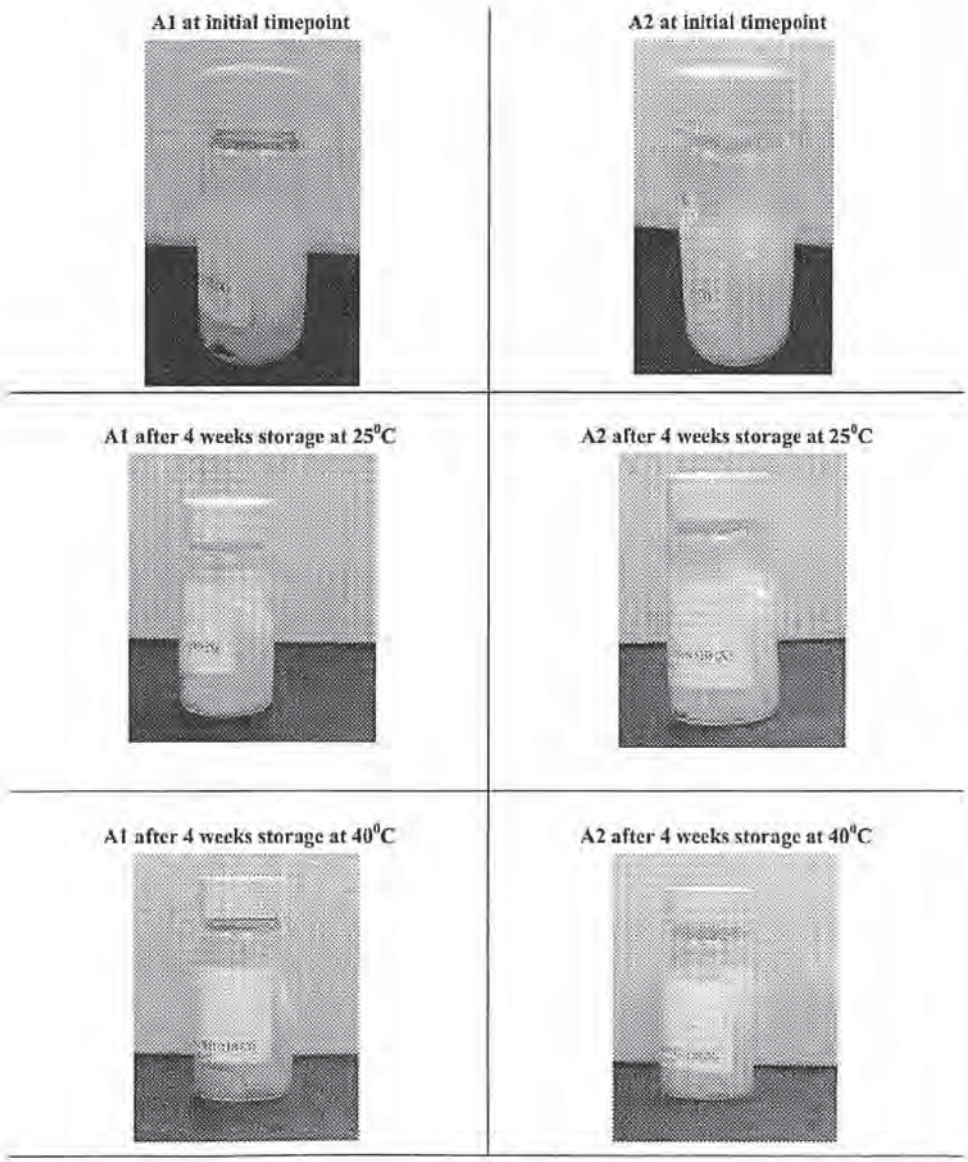


Figure 2. Polarized light images of dapsone in suspension formulations

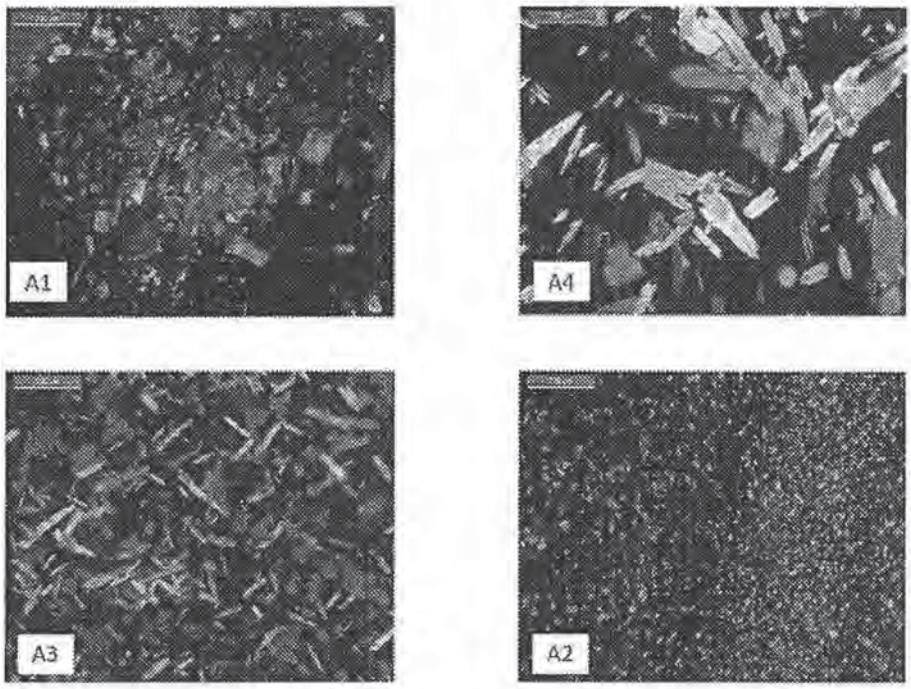
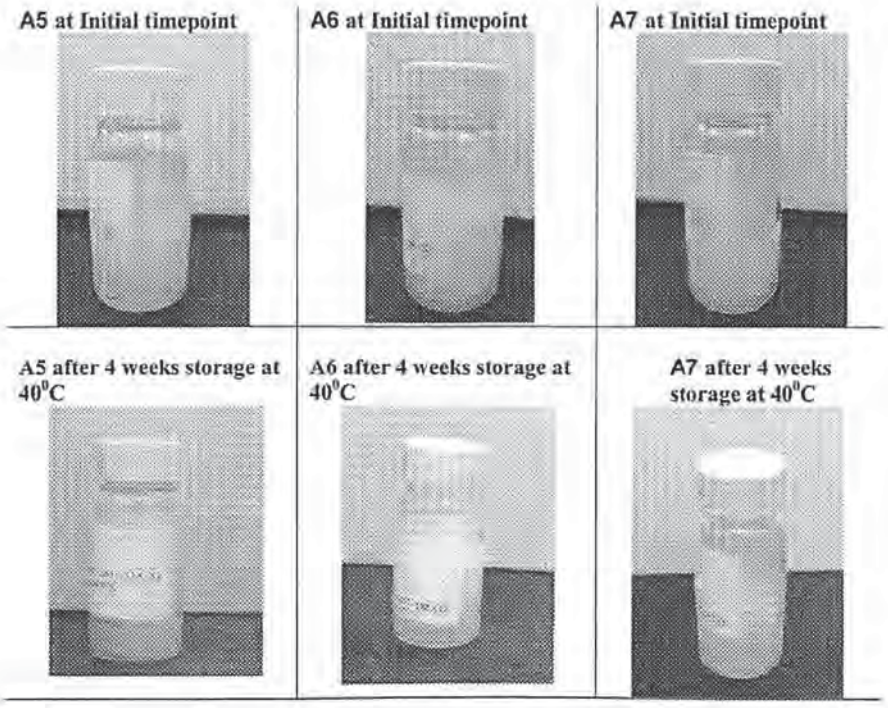


Figure 3. Appearance of formulations with antioxidants or chelating agents over 4 weeks



TOPICAL DAPSONE AND DAPSONE/ADAPALENE COMPOSITIONS AND METHODS FOR USE THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a divisional of copending U.S. patent application Ser. No. 14/082,955, filed on Nov. 18, 2013, which claims the benefit of U.S. Provisional Application Ser. No. 61/728,403 filed on Nov. 20, 2012 and U.S. Provisional Application Ser. No. 61/770,768 filed on Feb. 28, 2013, all of which are incorporated by reference herein in their entirety.

FIELD

The present embodiments relate generally to compositions useful for treating a variety of dermatological conditions. In particular, some embodiments relate to dapsone and dapsone/adapalene compositions and methods for use thereof.

BACKGROUND

Acne is a group of common skin conditions characterized by the so-called "acneiform" or acne-like skin eruptions, which can be contaminated with bacteria, such as *Propionibacterium acnes*, and can also be marked by inflammation. Acne tends to occur in the areas of skin where the sebaceous glands are most active, such as the face. Acne is associated with psychological trauma, and, if left untreated, can lead to scar formation and disfigurement.

Classification and the diagnosis of various acne conditions can be complex, and even contradictory. Given this complexity and unpredictability, medication and other therapies, are often developed on a trial-and-error basis in order to determine the most effective course of treatment for a particular patient. The outcome of any particular acne treatment regimen greatly varies from patient to patient, as well as throughout treatment of a particular patient. In addition to the complexity and variability of acne conditions, treatment efficacy can be greatly affected by a patient's compliance with the treatment regimen. Patient compliance during acne treatment may be influenced by side effects, which, for topical medications, commonly include redness, itching, and skin peeling. The complexity of the drug regimen can also negatively affect patient compliance, particularly where two or more different topical medications are prescribed simultaneously. Another factor that negatively affects patient compliance is the cost of a drug regiment, which is considerably higher when multiple medications are prescribed. In some countries, acne is considered a cosmetic problem, and acne treatments are not covered by insurance plans, thus further increasing patient's treatment costs. Certain compositions for treatment of acne are available. Many of the available compositions include one active agent known to have anti-acne activity. Stability of compositions with multiple anti-acne agents can be problematic. Also, these compositions can be difficult to manufacture.

The problems described above are not confined to the treatment or acne, but are also applicable to a variety of other skin conditions, including, but not limited, to conditions or classes of conditions with complex or unknown etiology and that are difficult to classify or diagnose, in which, nevertheless, topical application of agents are known to be effective

at least in some cases. Examples of such conditions or classes of conditions include psoriasis, rosacea and ichthyosis.

Accordingly, there is a continuing need for compositions and methods used in a treatment of a variety of skin conditions, such as acne, in which topical application is potentially effective. The compositions and methods provided herein address these and other needs in the art.

SUMMARY

Dapsone, (4,4'-diaminodiphenyl sulfone) is a medicament possessing several beneficial medicinal activities. Dapsone is typically administered as one of the medicinal agents used in the treatment of leprosy. Dapsone and its derivatives are also effective for treatment of bacterial infections, protozoal infections such as malaria, *pneumocystis carinii*, and plasmonic infections such as toxoplasmosis.

Dapsone is also useful as an anti-inflammatory agent. It has been used to treat skin diseases characterized by the abnormal infiltration of neutrophils, such as Dermatitis herpetiformis, linear IgA dermatosis, pustular psoriasis, pyoderma gangrenosum, acne vulgaris, and Sweet's Syndrome.

Use of topical compositions of dapsone can be problematic. Topical compositions may act as drying agents for the skin. They remove essential oils and natural skin softeners from the skin thus causing it to be dry, itch and crack. Inclusion of exogenous skin emollients, oils and the like, however, causes phase separation and precipitation of dapsone. Use of typical emulsifiers does not solve the dapsone precipitation owing to the lowered dapsone solubility and conflicting physical characteristics of the phases of the resulting composition. In particular, topical compositions including dapsone and methods are needed that would, for example, exhibit improved effectiveness, reduced side effects, or both, when used in a particular patient with a skin condition. Such improved topical compositions including dapsone and methods of their uses are also needed to improve treatment of patients with acne or suspected acne. The present dapsone and dapsone/adapalene compositions can be useful for treating a variety of dermatological conditions. Some useful compositions include dapsone and/or adapalene in a polymeric viscosity builder. Some compositions can be adjusted to optimize the dermal delivery profile of dapsone to effectively treat dermatological conditions and improve the efficiency of pharmaceutical products applied to the skin. Diethylene glycol monoethyl ether is a solubilizer for dapsone, thereby allowing compositions to be prepared with increased solubilized concentrations of dapsone. As a result, the compositions described herein are effective in treating dermatological conditions in a subject in need thereof.

Moreover, it has been found that use of a polymeric viscosity builder minimizes the intensity of yellowing of the composition caused by the increased solubility of dapsone in diethylene glycol monoethyl ether. In addition, the polymeric viscosity builder influences dapsone crystallization. This, in turn, results in compositions with improved aesthetics (i.e., reduction in particle size which minimizes "gritty" feeling upon application).

In one embodiment, there are provided compositions including dapsone, a first solubilizing agent which is diethylene glycol monoethyl ether, optionally at least one second solubilizing agent, a polymeric viscosity builder, and water, wherein the dapsone is present at a concentration of about 5% w/w to about 10% w/w.

In one embodiment, there are provided compositions including dapsone, a first solubilizing agent which is diethylene glycol monoethyl ether, optionally at least one second solubilizing agent, a polymeric viscosity builder, and water, wherein the dapsone is present at a concentration of about 3% w/w to 8% w/w.

In another embodiment, there are provided methods for treating a dermatological condition. Such methods can be performed, for example, by administering to a subject in need thereof a therapeutically effective amount of a pharmaceutical composition described herein.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 presents the impact of an acrylamide/sodium acryloyldimethyltaurate copolymer emulsion viscosity builder on color change.

FIG. 2 presents the impact of an acrylamide/sodium acryloyldimethyltaurate copolymer emulsion viscosity builder on dapsone crystal growth.

FIG. 3 presents the impact of anti-oxidants and chelating agents on color change.

DETAILED DESCRIPTION

It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and do not restrict the claims. As used herein, the use of the singular includes the plural unless specifically stated otherwise. As used herein, "or" means "and/or" unless stated otherwise. Furthermore, use of the term "including" as well as other forms, such as "includes," and "included," is not limiting. The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

Some embodiments include compositions and products for treatment of skin conditions and methods of treating skin conditions. The term "skin condition" as used herein encompasses human and animal conditions, disorders, or diseases affecting skin. Such skin conditions include, but are not limited to, conditions involving skin inflammation, conditions involving sebaceous glands and hair follicles, conditions characterized by acneiform symptoms, and conditions involving skin dryness, skin thickening, skin scaling or skin flaking. Skin conditions that can be treated using some compositions, products and methods described herein include, but are not limited to, acne, rosacea, folliculitis, perioral dermatitis, photodamage, skin aging, psoriasis, ichthyosis, atopic dermatitis, treatment of chronic wounds, bed sores, keratosis pilaris scars, including surgical and acne scars, sebaceous cysts, inflammatory dermatoses, post inflammatory hyperpigmentation, eczema, xerosis, pruritus, lichen planus, nodular prurigo, eczema, and miliaria.

The term "acne," as used herein, encompasses skin conditions involving acneiform or acne-like symptoms. For example, a skin condition characterized by follicular eruptions, such as papules and pustules resembling acne, can be categorized as acne. It is to be understood that the term "acne" is not to be limited to diseases and conditions characterized by papules and pustules, but can be characterized by a variety of symptoms. It is also to be understood that a particular patient having acne can be in remission, or the patient's acne can be controlled by continuing treatments, and therefore the patient can exhibit reduced symptoms or be asymptomatic. Nevertheless, continuing treatment of acne can be recommended in such a patient in order to reduce the probability of the return of the acne symptoms.

Symptoms of acne or acne-like conditions include, but are not limited to, the appearance of various skin lesions. The term "lesion" is generally used to denote an infected or diseased patch of skin. A lesion can involve an infected sebaceous gland. Some lesions are more severe than others. Examples of skin lesions are comedones, macules, papules, pustules, nodules and cysts. The term "comedo" (plural "comedones") is used to describe a sebaceous follicle plugged with dirt, other cells, tiny hairs, or bacteria. Comedones include the so-called "blackheads," which can also refer to as "open comedones," which have a spot or a surface that appears black. Comedones also include slightly inflamed, skin colored bumps, as well as "whiteheads," which have a spot or a surface that appears white. The term "macule" generally refers to a flat spot or area of the skin with a changed color, such as a red spot. The term "pustule" is generally used to refer to an inflamed, pus-filled lesion, or a small inflamed elevation of the skin that is filled with pus. The term "papule" is generally used to refer to a small, solid, usually inflammatory elevation of the skin that does not contain pus. The term "nodule" is generally used to refer to an elevation of a skin that is similar to a papule but is white and dome-shaped. Colloquially, a papule, a pustule or a nodule can be referred to as "a pimple" or "a zit." The term "cyst" generally refers to an abnormal membranous sac containing a liquid or semi-liquid substance containing white blood cells, dead cells, and bacteria. Cysts can be painful and extend to deeper layers of skin.

In dermatological science and dermatological and cosmetology practice, acne can be classified or categorized into one or more types or categories, according to one or more lines of categorization, such as a predominantly observed type of symptoms, severity of condition or predominant localization. It is to be understood that classification of acne into one of the subtypes does not mean that the characteristics of the classified condition are limited to the symptoms associated with the specific type.

Comedonal acne is characterized by the appearance of non-inflammatory lesions, such as blackheads and whiteheads. Localized cystic acne is characterized by appearance of a few cysts on face, chest and back. Diffuse cystic acne is characterized by the appearance of cysts on wide areas of face, chest and back. Nodular acne is characterized by the appearance of nodules. Nodulocystic acne is characterized by appearance of nodules and cysts. Acne vulgaris is a common form of acne characterized by the appearance of several types of lesions, which may appear together or separately. Individual acne lesions usually last less than two weeks but the deeper papules and nodules may persist for months. Acne vulgaris commonly affects adolescents, but it may also appear, persist or become more severe in adulthood. Acne vulgaris may occur on the face, chest, back and sometimes even more extensively.

Depending on severity, acne can be mild, moderate or severe. Mild acne is generally categorized by the appearance of with blackheads and whiteheads, but can also include papules and pustules. Moderate acne is generally characterized by appearance of more painful, deep-rooted, inflamed lesions, which can result in scarring. Severe acne is characterized by the appearance of deep-rooted inflammatory lesions, including cysts and nodules which can be painful and can produce scarring. Acne conglobata is a category of acne characterized by highly inflammatory cysts that communicate under the skin with abscesses and burrowing sinus tracts.

Some other skin conditions exhibiting acne-like symptoms which can be treated by the compositions and methods

described herein are discussed below. Pyoderma faciale, also known as rosacea fulminans, is a condition that appears in females and is characterized by abrupt appearance of inflamed cysts and nodules localized on the face. Rosacea, which can be referred to as acne rosacea, is a condition that can affects both the skin and the eyes and is characterized by redness, bumps, pimples, and, in advanced stages, thickened skin on the nose. In some classification systems, rosacea and acne are considered as separate conditions. Rosacea usually occurs on the face, although the neck and upper chest are also sometimes involved. A mild degree of eye (ocular) involvement occurs in more than fifty percent of people with rosacea. Perioral dermatitis is characterized by the appearance of small tiny papules, pustules, red bumps and scaling with intense itching. It is usually localized to the surrounding area of the mouth and on the chin, or extends to involve the eyelids and the forehead. Gram-negative folliculitis is a bacterial infection characterized by the appearance of pustules and cysts, possibly occurring as a complication resulting from a long term antibiotic treatment of acne vulgaris.

As used herein, the terms "treatment" or "treating" in reference to a skin condition generally mean "having positive effect on a skin condition" and encompass alleviation of at least one symptom of a skin condition, a reduction in the severity of the skin conditions, or delay, prevention, or inhibition of the progression of the skin condition. Treatment need not mean that the condition is totally cured. A composition or a product useful for treatment of a skin condition, or a method of treating a skin condition, needs only to reduce the severity of a skin condition, reduce the severity of symptoms associated therewith, provide improvement to a patient's quality of life, or delay, prevent, or inhibit the onset of symptoms of a skin condition.

In one embodiment, there are provided compositions including dapsone, a first solubilizing agent which is diethylene glycol monoethyl ether, optionally at least one second solubilizing agent, a polymeric viscosity builder, and water, wherein the dapsone is present at a concentration of about 5% w/w to about 10% w/w, about 1% w/w to about 10% w/w, about 3% w/w to about 10% w/w, about 3% w/w to about 8% w/w, about 4% w/w to about 6% w/w, or about 5%. In certain embodiments, dapsone is present in the composition at 5.0%, 5.5%, 6.0%, 6.5%, 7.0%, 7.5%, 8.0%, 8.5%, 9.0%, 9.5%, or 10.0% w/w.

In some embodiments, the polymeric viscosity builder is an acrylamide/sodium acryloyldimethyltaurate copolymer, and further includes isohexadecane, sorbitan oleate, water, and Polysorbate 80. In some embodiments, the polymeric viscosity builder is present at a concentration of about 2% w/w to about 6% w/w. In some embodiments, the polymeric viscosity builder is present at a concentration of about 3% w/w to about 5% w/w. In some embodiments, the polymeric viscosity builder is present in the composition at about 4% w/w.

In some embodiments, diethylene glycol monoethyl ether is present at a concentration of about 25% w/w to about 40% w/w. In some embodiments, diethylene glycol monoethyl ether is present at a concentration of about 30% w/w to about 40% w/w. In some embodiments, diethylene glycol monoethyl ether is present at a concentration of about 35% w/w to about 40% w/w.

In some embodiments, diethylene glycol monoethyl ether is present at a concentration of about 10% w/w to about 40% w/w, about 20% w/w to about 30% w/w, or about 25%.

In another embodiment, there are provided compositions further including adapalene. In some embodiments, adapalene is present at a concentration of about 0.1% w/w to about 0.3% w/w.

In some embodiments, the second solubilizing agent is selected from alcohols, glycols, esters, ethers, or silicones. Such second solubilizing agents include, but are not limited to, PEG 400, lactic acid, dimethyl isosorbide, propylene glycol, propylene carbonate, hexylene glycol, isostearyl alcohol, benzyl alcohol, diethyl sebacate, and ethanol.

In certain embodiments, the second solubilizing agent is propylene glycol. In some embodiments, propylene glycol is present at a concentration of about 2% w/w to 8% w/w. In some embodiments, propylene glycol is present at a concentration of about 3% w/w to 7% w/w. In some embodiments, propylene glycol is present in the composition at about 5% w/w.

In certain embodiments, the second solubilizing agent is propylene carbonate. In some embodiments, propylene carbonate is present at a concentration of about 2% w/w to 8% w/w. In some embodiments, propylene carbonate is present at a concentration of about 3% w/w to 7% w/w. In some embodiments, propylene carbonate is present in the composition at about 5% w/w.

In certain embodiments, the second solubilizing agent is ethanol. In some embodiments, ethanol is present at a concentration of about 1% w/w to about 5% w/w. In some embodiments, ethanol is present at a concentration of about 2% w/w to about 4% w/w. In some embodiments, ethanol is present in the composition at about 3% w/w.

In some embodiments, the compositions further include methyl paraben.

In other embodiments, the compositions further include carbomer homopolymer type C. In some embodiments, carbomer homopolymer type C is present at a concentration of about 0.7% w/w to about 1.5% w/w. In other embodiments, carbomer homopolymer type C is present at a concentration of about 0.85% w/w to about 1.0% w/w.

In some embodiments, the compositions further include a neutralizing agent. In certain embodiments, the neutralizing agent is an ionic or amine buffer. In certain embodiments, the neutralizing agent is sodium hydroxide or triethanolamine. Use of a neutralizing agent results in compositions typically having a pH from 5.5 to 6.5.

In some embodiments, the compositions further include a chelating agent. In some embodiments, the chelating agent is ethylene diamine tetraacetic acid (EDTA). EDTA is typically present in the compositions from about 0.02% w/w to about 0.04% w/w. In certain embodiments, EDTA is present in the compositions at about 0.03% w/w.

Compositions described herein are typically in the form of a gel, an emulsion, a cream, a liquid, a paste, a lotion, a nanoemulsion, a microemulsion, a reverse emulsion, or a liposomal cream.

EMBODIMENTS

The following embodiments are specifically contemplated herein.

Embodiment 1

A composition comprising dapsone, a first solubilizing agent which is diethylene glycol monoethyl ether, optionally at least one second solubilizing agent, a polymeric viscosity

builder, and water, wherein the dapsone is present in the composition at a concentration of about 3% w/w to about 10% w/w.

Embodiment 2

The composition of embodiment 1, wherein the diethylene glycol monoethyl ether is present at a concentration of about 10% w/w to about 40% w/w.

Embodiment 3

The composition of embodiment 1, wherein the diethylene glycol monoethyl ether is present at a concentration of about 20% w/w to about 30% w/w.

Embodiment 4

The composition of embodiment 1, wherein the diethylene glycol monoethyl ether is present in the composition at a concentration of about 25% w/w.

Embodiment 5

The composition of embodiment 1, further comprising adapalene.

Embodiment 6

The composition of embodiment 5, wherein the adapalene is present at a concentration of about 0.1% w/w to about 0.3% w/w.

Embodiment 7

The composition of embodiment 1 wherein the second solubilizing agent is selected an alcohol, a glycol, an ester, or an ether.

Embodiment 8

The composition of embodiment 1, wherein the second solubilizing agent is PEG 400, lactic acid, dimethyl isosorbide, propylene glycol, propylene carbonate, hexylene glycol, isostearyl alcohol, diethyl sebacate, or ethanol.

Embodiment 9

The composition of embodiment 8, wherein the second solubilizing agent is propylene glycol.

Embodiment 10

The composition of embodiment 9, wherein the propylene glycol is present in the composition at a concentration of about 5% w/w.

Embodiment 11

The composition of embodiment 8, wherein the second solubilizing agent is propylene carbonate.

Embodiment 12

The composition of embodiment 11, wherein the propylene carbonate is present in the composition at a concentration of about 5% w/w.

Embodiment 13

The composition of embodiment 8, wherein the second solubilizing agent is ethanol.

Embodiment 14

The composition of embodiment 13, wherein the ethanol is present in the composition at a concentration of about 3% w/w.

Embodiment 15

The composition of embodiment 1, wherein the polymeric viscosity builder comprises an acrylamide/sodium acryloyldimethyltaurate copolymer.

Embodiment 16

The composition of embodiment 1, wherein the polymeric viscosity builder is present at a concentration of about 2% w/w to about 6% w/w.

Embodiment 17

The composition of embodiment 1, wherein the polymeric viscosity builder is present at a concentration of about 4% w/w.

Embodiment 18

The composition of embodiment 1, further comprising methyl paraben.

Embodiment 19

The composition of embodiment 1, further comprising Carbomer interpolymer type A, Carbomer interpolymer type B, or Carbomer Homopolymer Type C.

Embodiment 20

The composition of embodiment 19, wherein the Carbomer Homopolymer Type C is present at a concentration of about 0.7% w/w to about 1.5% w/w.

Embodiment 21

The composition of embodiment 19, wherein the Carbomer Homopolymer Type C is present at a concentration of about 0.85% w/w to about 1.5% w/w.

Embodiment 22

The composition of embodiment 19, wherein the Carbomer interpolymer Type A is present at a concentration of about 1% w/w to 2% w/w.

Embodiment 23

The composition of embodiment 19, wherein the Carbomer interpolymer Type B is present at a concentration of about 0.1% w/w to about 0.5% w/w.

Embodiment 24

The composition of embodiment 1, further comprising a neutralizing agent.

Embodiment 25

The composition of embodiment 24 wherein the neutralizing agent is NaOH or triethanolamine.

Embodiment 26

The composition of embodiment 1 further comprising a chelating agent.

Embodiment 27

The composition of embodiment 26, wherein the chelating agent is ethylene diamine tetraacetic acid.

Embodiment 28

The composition of embodiment 27, wherein the ethylene diamine tetraacetic acid is present at a concentration of about 0.02% w/w to about 0.04% w/w.

Embodiment 29

The composition of embodiment 27, wherein the ethylene diamine tetraacetic acid is present in the composition at about 0.03% w/w.

Embodiment 30

The composition of embodiment 1 wherein the composition is in the form of a gel, a suspension, an emulsion, a cream, a liquid, a paste, a lotion, a nanoemulsion, a microemulsion, a reverse emulsion, or a liposomal cream.

Embodiment 31

A method for treating a dermatological condition comprising administering to a subject in need thereof a therapeutically effective amount of a composition of embodiment 1.

Embodiment 32

The method of embodiment 31 wherein the condition is acne vulgaris, rosacea, atopic dermatitis, treatment of chronic wounds, bed sores, keratosis pilaris, sebaceous cysts, inflammatory dermatoses, post inflammatory hyperpigmentation, eczema, xerosis, pruritus, lichen planus, nodular prurigo, dermatitis, eczema, or miliaria.

Embodiment 33

The method of embodiment 32 wherein the condition is acne vulgaris.

Embodiment 34

The composition of embodiment 1, 2, 3, or 4, further comprising adapalene.

Embodiment 35

The composition of embodiment 34, wherein the adapalene is present at a concentration of about 0.1% w/w to about 0.3% w/w.

Embodiment 36

The composition of embodiment 1, 2, 3, 4, 34, or 35, wherein the second solubilizing agent is selected an alcohol, a glycol, an ester, or an ether.

Embodiment 37

The composition of embodiment 1, 2, 3, 4, 34, 35, or 36, wherein the second solubilizing agent is PEG 400, lactic acid, dimethyl isosorbide, propylene glycol, propylene carbonate, hexylene glycol, isostearyl alcohol, diethyl sebacate, or ethanol.

Embodiment 38

The composition of embodiment 37, wherein the second solubilizing agent is propylene glycol.

Embodiment 39

The composition of embodiment 38, wherein the propylene glycol is present in the composition at a concentration of about 5% w/w.

Embodiment 40

The composition of embodiment 37, wherein the second solubilizing agent is propylene carbonate.

Embodiment 41

The composition of embodiment 40, wherein the propylene carbonate is present in the composition at a concentration of about 5% w/w.

Embodiment 42

The composition of embodiment 37, wherein the second solubilizing agent is ethanol.

Embodiment 43

The composition of embodiment 42, wherein the ethanol is present in the composition at a concentration of about 3% w/w.

Embodiment 44

The composition of embodiment 1, 2, 3, 4, 34, 35, 36, 37, 38, 39, 40, 41, 42, or 43, wherein the polymeric viscosity builder comprises an acrylamide/sodium acryloyldimethyltaurate copolymer.

Embodiment 45

The composition of embodiment 1, 2, 3, 4, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, or 44, wherein the polymeric viscosity builder is present at a concentration of about 2% w/w to about 6% w/w.

Embodiment 46

The composition of embodiment 45, wherein the polymeric viscosity builder is present at a concentration of about 4% w/w.

Embodiment 47

The composition of embodiment 1, 2, 3, 4, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, or 46, further comprising methyl paraben.

Embodiment 48

The composition of embodiment 1, 2, 3, 4, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, or 47, further comprising Carbomer interpolymer type A, Carbomer interpolymer type B, or Carbomer Homopolymer Type C.

Embodiment 49

The composition of embodiment 48, wherein the Carbomer Homopolymer Type C is present at a concentration of about 0.7% w/w to about 1.5% w/w.

Embodiment 50

The composition of embodiment 48, wherein the Carbomer Homopolymer Type C is present at a concentration of about 0.85% w/w to about 1.5% w/w.

Embodiment 51

The composition of embodiment 48, wherein the Carbomer interpolymer Type A is present at a concentration of about 1% w/w to 2% w/w.

Embodiment 52

The composition of embodiment 48, wherein the Carbomer interpolymer Type B is present at a concentration of about 0.1% w/w to about 0.5% w/w.

Embodiment 53

The composition of embodiment 1, 2, 3, 4, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, or 52, further comprising a neutralizing agent.

Embodiment 54

The composition of embodiment 53 wherein the neutralizing agent is NaOH or triethanolamine.

Embodiment 55

The composition of embodiment 1, 2, 3, 4, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, or 54, further comprising a chelating agent.

Embodiment 56

The composition of embodiment 55, wherein the chelating agent is ethylene diamine tetraacetic acid.

Embodiment 57

The composition of embodiment 56, wherein the ethylene diamine tetraacetic acid is present at a concentration of about 0.02% w/w to about 0.04% w/w.

Embodiment 58

The composition of embodiment 56, wherein the ethylene diamine tetraacetic acid is present in the composition at about 0.03% w/w.

Embodiment 59

The composition of embodiment 1, 2, 3, 4, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, or 58, wherein the composition is in the form of a gel, a suspension, an emulsion, a cream, a liquid, a paste, a lotion, a nanoemulsion, a microemulsion, a reverse emulsion, or a liposomal cream.

Embodiment 60

A method for treating a dermatological condition comprising administering to a subject in need thereof a therapeutically effective amount of a composition of embodiment 1, 2, 3, 4, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, or 59.

Embodiment 61

The method of embodiment 60 wherein the condition is acne vulgaris, rosacea, atopic dermatitis, treatment of chronic wounds, bed sores, keratosis pilaris, sebaceous cysts, inflammatory dermatoses, post inflammatory hyperpigmentation, eczema, xerosis, pruritus, lichen planus, nodular prurigo, dermatitis, eczema, or miliaria.

Embodiment 62

The method of embodiment 60 wherein the condition is acne vulgaris.

The following examples are intended only to illustrate the some embodiments and should in no way be construed as limiting the claims.

EXAMPLES

Example 1

Table 1 lists two formulations (containing equivalent levels of diethylene glycol monoethyl ether) that show the impact of acrylamide/sodium acryloyldimethyltaurate copolymer based thickener on dapsone particle size. FIG. 2 presents impact of acrylamide/sodium acryloyldimethyltaurate copolymer based thickener on dapsone crystal growth. The microscopic image of ENA (30% diethylene glycol monoethyl ether, 4% acrylamide/sodium acryloyldimethyltaurate copolymer based thickener) in comparison to ENC (30% diethylene glycol monoethyl ether, 1% Carbopol 980) shows a clear difference in particle size of the dapsone. Larger crystals were observed in the sample with carbomer homopolymer type C (ENC vs. ENA).

TABLE 1

Formulations Tested For Dapsone Crystal Size

Formulation #	ENA	ENC
Dapsone	7.5	7.5
Diethylene glycol monoethyl ether	30	30
Carbomer homopolymer type C	—	1

TABLE 1-continued

Formulations Tested For Dapsone Crystal Size

Formulation #	ENA	ENC
acrylamide/sodium acryloyldimethyltaurate copolymer based thickener	4	—
Methyl paraben	0.2	0.2
pH adjusting solution	pH 5.5-7	pH 5.5-7
Purified Water	Q.S 100	Q.S 100

Example 2

Example compositions contemplated for use as described herein are set forth in Table 2 below:

TABLE 2

Composition #	1	2	3	4	5	6	7	8	9	10
Dapsone	5-10									
Adapalene	—						0.1-0.3			
Diethylene glycol monoethyl ether	30	35	40	30	35	30	35	40	30	35
Carbomer homopolymer type C	—			0.85-1.5		—	—	—	0.85-1.5	
Acrylamide/sodium acryloyldimethyltaurate copolymer emulsion	4			—		4			—	
Methyl paraben	0.2									
NaOH/pH adjusting solution	pH 5.5-6.5									
Purified Water	Q.S 100									

Example 3

Anti-oxidants and chelating agents such as sodium metabisulfite, citric acid and EDTA were added to formulations to help slow down or completely stop any impurity formation. Table 3 presents the composition of formulations tested. Formulation A7 with sodium metabisulfite minimized the intensity of yellow color caused by the increased solubility of dapsone in diethylene glycol monoethyl ether and maintained the low color intensity over time at accelerated condition (40° C.). See FIG. 3 for appearance of the formulations over 4 weeks. Table 4 presents the formulation panel summarizing other formulation options with chelating agents and antioxidants.

TABLE 3

Compositions Tested containing Antioxidants or Chelating Agents

Composition #	A5	A6	A7
Dapsone	7.5		
Diethylene glycol monoethyl ether	35	40	35
carbomer homopolymer type C	1.25	—	1.25
Acrylamide/sodium acryloyldimethyltaurate copolymer emulsion	—	4	—
EDTA	0.05		—
Anhydrous Citric Acid	0.1		—
Sodium Metabisulfite	—		0.2
Methyl paraben	0.17		0.2
Propyl paraben	0.03		—
NaOH/pH adjusting solution	pH 5.5-6.5		
Purified Water	Q.S 100		

TABLE 4

Formulation panel summarizing other formulation options

Composition #	1	2	3	4	5	6	7	8	9	10
Dapsone	5-10									
Adapalene	—						0.1-0.3			
Diethylene glycol monoethyl ether	30	35	40	30	35	30	35	40	30	35
carbomer homo-polymer type C	—			0.85-1.5		—			0.85-1.5	
Acrylamide/sodium Acryloyl - dimethyltaurate copolymer emulsion	4			—		4			—	
EDTA	0-0.1									
Citric Acid	0-0.1									
Sodium Metabisulfite	0-0.5									
Methyl paraben	0.2									
NaOH/pH adjusting solution	pH 5.5-6.5									
Purified Water	Q.S 100									

Example 4

Additional example compositions contemplated for use as described herein are set forth in Table 5 below.

TABLE 5

Additional examples containing alternate neutralizer

Materials	% w/w					
	5-1	5-2	5-3	5-4	5-5	5-6
Dapsone	7.5					
Adapalene	—			0.3		—
Diethylene glycol monoethyl ether	30	35	40	30	40	25
carbomer homopolymer type C	1					
Methylparaben	0.2					
Triethanolamine (TEA) Q.S.	pH 5.5-6.5					
Hydrochloric Acid Q.S	pH 5.5-6.5					
Purified Water	q.s.a.d. 100					

Example 4

Additional example compositions contemplated for use as described herein are set forth in Table 6 below.

TABLE 6

Additional examples (containing co-solvents, stabilizer and alternate thickener)

Materials	% w/w					
	6-1	6-2	6-3	6-4	6-5	6-6
Dapsone	7.5		10		7.5	
Adapalene	—			0.3		
Diethylene glycol monoethyl ether	25	35	35	25	30	40
Propylene glycol				5		
Propylene Carbonate			5			
Ethanol (absolute)		3		—	3	
EDTA				0.03		
Carbomer Interpolymer Type A		—		1.5		
Carbomer Interpolymer Type B		—		0.3		
Acrylamide/sodium acryloyldimethyltaurate copolymer emulsion		4		—		4
Methyl Paraben				0.2		
Triethanolamine		—		Q.S. pH 5.5-6.5		
Purified Water				q.s.a.d. 100		

Example 5

Another useful composition is depicted in Table 7.

TABLE 7

Ingredient	Amount (% w/w)
Dapsone	5-8
Adapalene	0.1-0.3
Diethylene glycol monoethyl ether	40.00
Propylene glycol	5.00
Ethanol (absolute)	3.00
Ethylene Diamine Tetraacetic acid (EDTA)	0.03
Methyl Paraben	0.20
Sepineo P 600	4.00
Purified Water	Q.S.

Example 6

Another useful composition is depicted in Table 8.

TABLE 8

Ingredient	Amount (% w/w)
Dapsone	5.0
Diethylene glycol monoethyl ether	25
Methyl Paraben	0.2
Carbopol 980	0.85
Sodium Hydroxide	0.2
Purified Water	Q.S.

While this some embodiments have been described with respect to these specific examples, it is understood that other modifications and variations are possible without departing from the spirit of the invention. Each and every reference identified herein is incorporated by reference in its entirety.

What is claimed is:

1. A method for treating a dermatological condition selected from the group consisting of acne vulgaris and rosacea comprising administering to a subject having the dermatological condition selected from the group consisting of acne vulgaris and rosacea a topical pharmaceutical composition comprising:

about 7.5% w/w dapsone;

about 30% w/w to about 40% w/w diethylene glycol monoethyl ether;

about 2% w/w to about 6% w/w of a polymeric viscosity builder comprising acrylamide/sodium acryloyldimethyl taurate copolymer; and

water;

wherein the topical pharmaceutical composition does not comprise adapalene.

2. The method of claim 1, wherein the diethylene glycol monoethyl ether is present at a concentration of about 30% w/w.

3. The method of claim 1, wherein the polymeric viscosity builder is present at a concentration of about 4% w/w.

4. The method of claim 1, wherein the topical pharmaceutical composition further comprises methyl paraben.

5. The method of claim 1 wherein the dermatological condition is acne vulgaris.

6. A method for treating a dermatological condition selected from the group consisting of acne vulgaris and rosacea comprising administering to a subject having the dermatological condition selected from the group consisting of acne vulgaris and rosacea a topical pharmaceutical composition comprising:

about 7.5% w/w dapsone;

about 30% w/w diethylene glycol monoethyl ether;

about 4% w/w of a polymeric viscosity builder comprising acrylamide/sodium acryloyldimethyl taurate copolymer; and

water;

wherein the topical pharmaceutical composition does not comprise adapalene.

7. The method of claim 6, wherein the topical pharmaceutical composition further comprises methyl paraben.

8. The method of claim 6 wherein the dermatological condition is acne vulgaris.

* * * * *

EXHIBIT 2

CONFIDENTIAL

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ALMIRALL, LLC, Plaintiff, v. TARO PHARMACEUTICAL INDUSTRIES LTD. and TARO PHARMACEUTICALS, INC., Defendants.	)	C.A. No. 17-663 (JFB) (SRF) CONSOLIDATED

[CONFIDENTIAL]

REBUTTAL EXPERT REPORT OF MANSOOR M. AMIJI, PH.D, R.PH.

I. INTRODUCTION

1. I, Mansoor M. Amiji, Ph.D., R.Ph. submit my expert report in the above-captioned case on behalf of Defendants Taro Pharmaceutical Industries Ltd. and Taro Pharmaceuticals Inc. (collectively, "Taro").

2. I have been asked to respond to the report submitted on behalf of Plaintiff[1] by Majella E. Lane, Ph.D. alleging that the product described in Taro's ANDA No. 21-0191, if sold and used according to its label, would induce infringement of certain claims of U.S. Patent No. 9,517,219 ("the '219 patent"). In particular, I have been asked for my opinions regarding alleged infringement of claims 1, 2, 4 and 5 of the '219 patent (collectively the "asserted claims") pursuant to the Doctrine of Equivalents ("DOE").

II. QUALIFICATIONS

3. In 1988, I graduated with honors from Northeastern University and received a Bachelor of Science degree in Pharmacy and became a Registered Pharmacist in Massachusetts. In 1992, I received a Ph.D. in Pharmaceutical Science/Pharmaceutics from the School of Pharmacy and Pharmacal Sciences at Purdue University, under the supervision of Professor Kinam Park. My dissertation focused on biomaterials and water-soluble polymers. During my graduate studies at Purdue University, I took several industrial pharmaceutics courses and had hands-on training pharmaceutical formulations.

4. I am currently a University Distinguished Professor and Professor of Pharmaceutical Sciences in the School of Pharmacy, Bouve College of Health Sciences at Northeastern University in Boston, Massachusetts. I am also jointly appointed as a Professor of Chemical Engineering in the College of Engineering at Northeastern University. I am also

[1] I understand Almirall has been substituted for Allergan as the Plaintiff in this action. I also understand I am to respond to Dr. Lane's report and refer to any prior submissions, opinions, statements, etc. as if they were provided by Almirall as opposed to Allergan.

currently an Affiliate Faculty Member in the Department of Biomedical Engineering at Northeastern University. I have taught and carried out research in pharmaceutical sciences at Northeastern University since 1993, and from 2010 to 2016, I served as the Chairman of the Department of Pharmaceutical Sciences. In 2000, I was a Visiting Research Scholar in the Department of Chemical Engineering at the Massachusetts Institute of Technology (MIT) in Cambridge, Massachusetts in the laboratory of Professor Robert Langer.

5. As a tenured faculty member at Northeastern University, I have over 25 years of experience in teaching drug formulations to both graduate and undergraduate students. In theory and laboratory courses that I have taught and continue to teach, I extensively cover the manufacturing and composition of pharmaceutical formulations. I also serve as a consultant to several pharmaceutical, biotechnology, and medical device companies regarding product development and drug delivery.

6. Over the course of my career I have published extensively and am ranked as a Thompson-Reuters Highly Cited (top 1%) author in Pharmacology and Toxicology. I have coauthored over 60 book chapters and more than 300 peer reviewed scientific articles. I am also an inventor on several issued United States patents covering pharmaceutical devices, materials and methods. I have taught courses in pharmaceutics; drug design, evaluation, and development; dosage forms; and pharmacokinetics.

7. I have served as a grant reviewer for the National Institutes of Health, the Department of Defense, the United States Department of Agriculture, and the American Chemical Society. I am a member of several professional and industrial societies, including the American Association of Pharmaceutical Scientists (AAPS) and the Controlled Release Society (CRS), and have participated as a reviewer for more than 50 scientific journals. I have also

received a number of professional awards and honors, including the Nano Science and Technology Institute (NSTI) Fellowship Award for Outstanding Contributions towards the Advancement in Nanotechnology, Microtechnology, and Biotechnology in 2006; a Fellowship and Meritorious Manuscript Award from the AAPS in 2007; the Tsuneji Nagai Award from the CRS in 2012; and the Northeastern University School of Pharmacy Distinguished Alumni Award in 2016. Over the course of my career, I have advised numerous post-doctoral associates, doctoral students, master's students, visiting scientists, and research fellows.

8. A true and correct copy of my curriculum vitae, which includes a list of the published papers that I have written, professional honors and memberships, and presentations that I have given, is attached to this report as Exhibit A. The matters in which I have testified in the past four years are included in Exhibit B.

9. I am being compensated at a rate of $850 per hour for testimony.

III. OVERVIEW OF OPINION

10. In formulating and providing my opinions herein, I reviewed relevant portions of Taro's ANDA, the expert reports of Dr. Lane and Dr. Panayiotis P. Constantinides, the '219 patent and prosecution history, the patent and prosecution history of U.S. Patent No. 9,161,926, as well as background literature and other documents cited throughout this report, including the documents set forth in Exhibit C. The bases for my opinions include the references and observations cited in this report, my education, and my many years of experience in industry and academia, including the development of formulations of pharmaceutical products.

11. The product described in Taro's ANDA will not infringe any of the asserted claims of the '219 patent. Taro's ANDA describes a product that does not include "about 2% w/w to 6% w/w of a polymeric viscosity agent comprising A/SA". Because each asserted claim

of the ’219 patent requires treatment with a formulation containing A/SA, Taro’s Product if sold doctrine of equivalents.

IV. LEGAL STANDARDS

12. I am not a patent attorney, nor have I independently researched the law of patent validity. I have been informed of certain legal standards below that I have relied on in forming my opinions in my report.

13. I understand that for a claim to be found to be infringed, Plaintiff bears the burden of establishing by a preponderance of the evidence that each and every claim limitation is present in the accused product or method. I understand that each claim is to be evaluated individually.

14. I understand that patent claims can be independent or dependent. Dependent claims incorporate all the limitations of an identified independent claim, and then further narrow the claim through additional limitations. I understand that if an independent claim is not infringed by an accused product, then all claims that depend from that claim are also not infringed because each would be missing a shared limitation.

15. I understand that the process for determining infringement requires two steps. First, I have been instructed to apply the Court’s claim construction to those identified terms, then, for the remaining terms, use the plain and ordinary meaning to a person of ordinary skill in the art (“POSA”) at the time of the invention. Second, I have been informed that I should compare the construed claims to the identified accused product or method to determine if all elements are present. I understand that if any claim element is not present in the accused product or method, then the overall product or method does not infringe the claim.

16. I understand that a claim element that is not literally present in the accused product or method may still infringe under the legal doctrine of equivalents. I understand the doctrine of equivalents exists so that an accused infringer may not avoid infringement because of

minor or insubstantial changes that take a product or method outside the literal scope of the claims. I understand that the doctrine of equivalents applies when there are insubstantial differences between the claim element that is not literally present and the accused equivalent structure or method step in the accused device or process.

17. I understand that one test to determine whether an accused equivalent element is insubstantially different from a claim limitation is the "function-way-result" test. I understand that under that test, an accused equivalent infringes if it performs substantially the same function in substantially the same way to achieve substantially the same result as the claim element in question. I also understand that this is only one way of determining equivalence, and that it may not be appropriate in all situations.

18. I understand that the doctrine of equivalents is applied on a claim element-by-element basis. In other words, I understand that I am not to consider the claim as a whole when analyzing whether a claim element is present under the doctrine of equivalents.

19. I also understand that there are situations where the doctrine of equivalents is not allowed to be applied at all.

20. I have been informed and understand there is a doctrine referred to as prosecution history estoppel. It is my understanding prosecution history estoppel prevents a patentee from recapturing subject matter is surrendered during the prosecution of the patent. I understand the surrender of the subject matter does not need to be explicit, but that it must be clear and unequivocal.

21. I have also been informed and understand there is a doctrine referred to as the "dedication to the public" or the "dedication-disclosure" rule, which generally means if a patent

drafter discloses but declines to or does not claim certain subject matter, that unclaimed subject matter is dedicated to the public and its use will not infringe the patent.

22. I also understand under the doctrine of ensnarement a patentee is barred from asserting a scope of equivalents that would encompass or "ensnare" the prior art to find an accused product infringes.

V. TECHNOLOGY BACKGROUND

23. The '219 patent generally claims methods of treating acne with a formulation containing 7.5% dapsone, a solubilizing agent and a polymeric viscosity builder ("PVB" or "thickening agent"). The '219 patent was distinguishing from the prior art during prosecution because the formulation used a polymeric thickening agent called acrylamide/sodium acryloyldimethyl taurate copolymer ("A/SA") instead of the prior used carbomer homopolymer type C ("Carbomer"). Carbomer is commercially available as Carbopol 980.

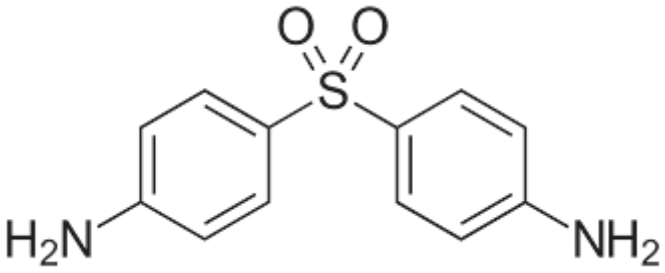
24. The '219 patent, along with the prosecution history of the patent inclusive of the references cited in those documents, include descriptions and evidence of background relevant to the technology claimed in the patents-in-issue. The background information relates, for example, to dapsone, formulations of dapsone at varying concentrations, including formulations containing Carbomer as the thickening agent. If asked, I am prepared to discuss the background of the invention claimed in the '219 patent, in particular with reference to the patent-in-suit, prosecution histories of the patent, and art cited within that document. I will also reference the parent application to the '219 patent, including its prosecution history. Finally, I will also rely on my own personal knowledge and experience.

25. Basic topical drug formulation relevant to the '219 patent can be found in established references such as Remington's Pharmaceutical Sciences. Basic information on pharmaceutical excipients can be found in the references such as the Handbook for

Pharmaceutical Excipients. In describing the basic background of the patent-in-suit, I may additionally rely on these texts along with my own knowledge gained from a career designing pharmaceutical dosage forms, including topical formulations utilizing thickening agents.

A. Dapsone as a Topical Anti-inflammatory Agent

26. Dapsone, whose chemical name is diaminodiphenyl sulfone (chemical structure shown below) was first synthesized in 1908 and was available as an antibacterial and antiprotozoal antibiotic in 1937 and was commonly used in combination with other drugs, such as rifampicin and clofazimine, for the treatment of leprosy. Additionally, it is a second-line medication for the treatment and prevention of Pneumocystis carinii pneumonia and for the prevention of toxoplasmosis in HIV positive patients and those who have poor immune function.



27. Dapsone has intrinsic anti-inflammatory properties and has been indicated topically for treatment of many different types of skin conditions such as for acne, dermatitis herpetiformis and others. The anti-inflammatory effects of dapsone resemble those seen with non-steroidal anti-inflammatory agents such as ibuprofen or meloxicam. Dapsone is poorly soluble in water (solubility = 0.2 mg/mL), but can dissolve readily in organic solvents such as methanol (solubility = 50 mg/mL).

28. The first animal tests for the anti-inflammatory effects of dapsone were carried out in 1970's using various rodent models of inflammatory diseases. Although the exact mechanisms of anti-inflammatory effects of dapsone has not been well understood, the drug

tends to inhibit inflammatory conditions through multiple biological processes including decrease in reactive oxygen species generation, inhibition of specific enzymes, as well as lowering pro-inflammatory cytokine levels.

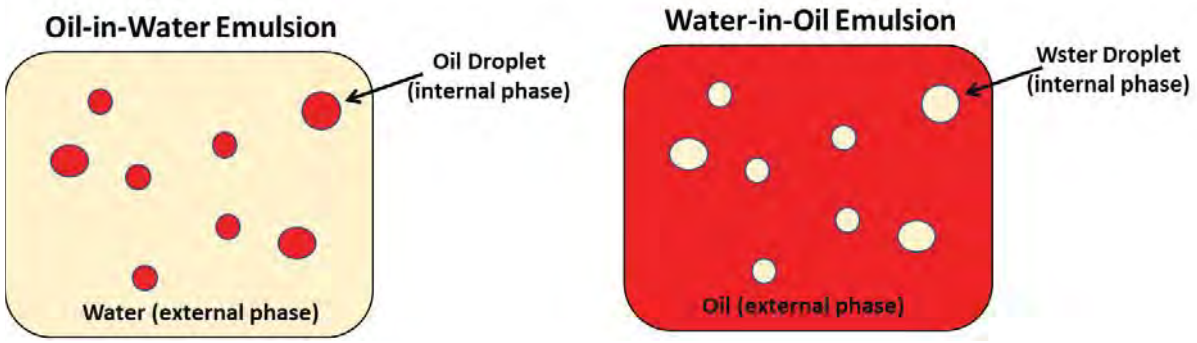
29. When ingested for antimicrobial effects, dapsone has significant issues with toxicity in the liver and other organs in the body. As such, dapsone use as an anti-inflammatory agent is generally restricted to topical administration, such as on the skin, in order to decrease systemic availability and side effects.

B. Topical Drug Products

30. As opposed to systemic administration where the drug products are given by oral or injectable route of administration, a drug product is administered topically for local treatment of diseases of the skin and mucosal surfaces that are accessible. The main advantage of topical drug administration is achievement of maximum benefits of treating the disease condition locally without systemic side effects. Many different diseases of the skin, such as dry skin, eczema, hives, acne, etc., benefit from topical products that confine the medication to the affected area.

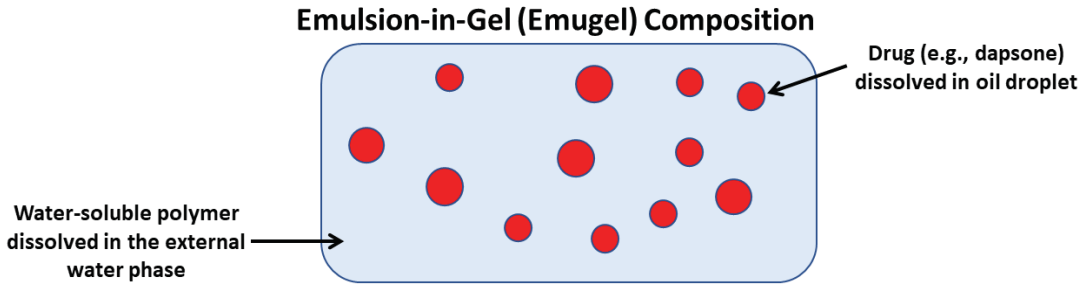
31. Skin is the largest organ in the body and provides the greatest surface area for topical drug administration. In order to achieve maximum benefit for local treatment of skin diseases, a topical drug product needs to have desired attributes that can provide therapeutic benefits in a safe and effective manner. For example, the drug product should be formulated to give the required dose of the active agent in an amount sufficient to cover the affected area and remain at the site for a reasonable period of time. Additionally, the product consistency should be such that it is easy to spread on the skin surface, but not too thin to have poor residence. The formulation should also maintain drug stability over the course of the shelf-life of the product.

32. For these formulation attributes to be met, a person of skill in the art ("POSA") would develop a topical drug product in an ointment, cream, lotions, foams or gel composition. An ointment is a lipid product intended for application on the skin that is usually prepared with petrolatum base. Creams and lotions are prepared by mixing oil and water to form emulsions. These simple emulsions can be either oil-in-water (O/W) or water-in-oil (W/O) depending on the relative percentage by weight of the oil and water phases and the choice of the emulsifier or surfactant used (see figure below). Common household examples of O/W and W/O emulsions are salad dressings and margarine, respectively. Foams are prepared by incorporation of a propellant that aerosolizes upon release, such as in shaving cream. Lastly, gels are made using water-soluble polymers that at a specific concentration will create a product with gel-like consistency that is required to have a product spread easily on the skin. In contrast to ointment, which generally do not absorb or dissolve in water, emulsions and gel products would be able to either imbibe water or completely dissolve in water.



33. Emulsion-gel hybrid or "emugels" are topical drug products that combine the properties of O/W emulsion with a water-soluble polymer gel incorporated to increase the viscosity of the final product (Vivek Sharma, et al, Polymeric Gels, Characterization, Properties and Biomedical Applications, Chapter 9, Emulgels,, pp. 251 – 264 (2018)). The water-soluble polymers used to prepare emugels are also referred to as "polymeric viscosity builders" (PVB).

As shown in the figure below, an emugel will consist of oil droplets (internal phase) surrounded by water (external phase) of an emulsion. A water-soluble polymer is dissolved in the external water phase to create a hydrogel, such that the final product is useful for topical drug administration. Based on the properties of the active drug, it could be dissolved either in the internal oil phase or the external water phase. Dapsone, for example, is water-insoluble and would preferentially dissolve in the oil phase of the emulsion. Additionally, water-soluble and oil-soluble excipients can be incorporated in the respective phases of the emulsion.



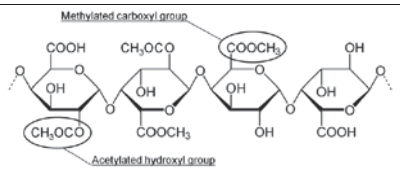
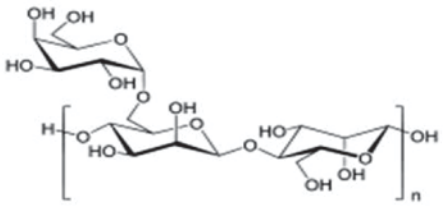
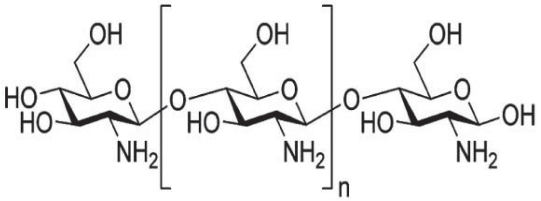
C. Viscosity Enhancement in Topical Emugels

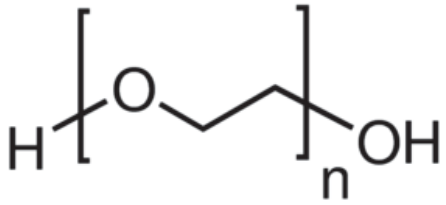
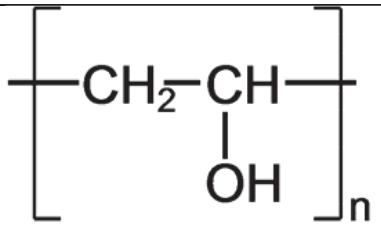
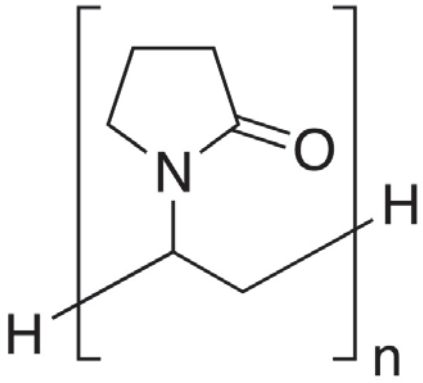
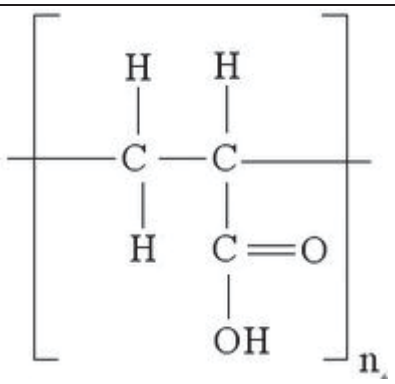
34. There are many benefits of emulsions, gels, and emugels as a topical drug product, including aesthetic appeal, ease of incorporation of diverse types of water-soluble and oil-soluble drugs and excipients, as well as the possibility of washing the product off of the skin when needed. However, since emulsions are heterogenous formulations with oil and water, they are also susceptible to stability issues such as phase separation and creaming as well as stability and homogeneity of drug dispersion within the formulation. Increasing the viscosity of the water phase in an O/W emulsion ensures that the final product will be dispensed as a semi-solid composition that will be easier to spread, will remain on the skin, and will have other desired properties as opposed to liquid emulsions.

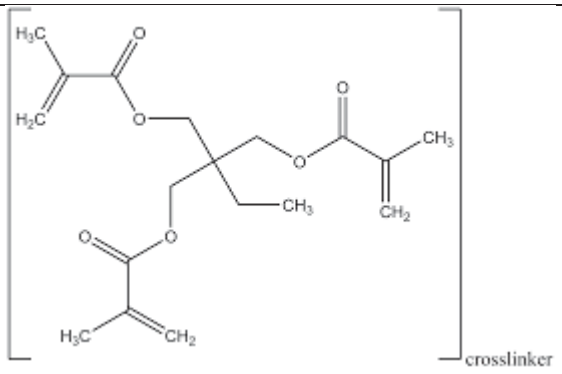
D. Polymeric Viscosity Builders

35. To increase the viscosity of the external water phase in an O/W emulsion of an emugel, water-soluble polymers can be added to induce gelation. In the context of pharmaceutical products, these polymeric viscosity builders (PVB) or gelators are pharmaceutical excipients that can create interconnecting networks in solution to imbibe water and increase viscosity of the final product. Both natural and synthetic water-soluble polymers are used to increase viscosity of the emugels.

36. The Table below shows some illustrative examples and structures of natural and synthetic water-soluble polymers used in pharmaceutical products to increase viscosity. The final viscosity of the formulation is determined by the type of polymer, the molecular weight, and the concentration in the final composition.

Polymer Type	**Name**	**Chemical Structure**
Natural	Pectin	
	Guar gum	
	Chitosan	

Synthetic		
	Poly(ethylene glycol) (PEG) or poly(ethylene oxide) (PEO	
	Poly(vinyl alcohol) (PVA)	
	Poly(N-vinylpyrrolidone) (PVP)	
	Crosslinked polyacrylic acid resins (Carbopol, Carbomer)	

	Acrylamide/sodium acryloyldimethyl taurate copolymer (e.g., Sepineo P600)	

37. Neutral polymers such as PEG or PVA dissolve in water by hydrogen bonding. However, charged polymers, such as Carbopol will dissolve through ion-dipole interactions especially when the pH is increased to above 5.0 when the carboxylic acid group is ionized. Since the ion-dipole interaction is stronger than hydrogen bonding, Carbopol tends to provide greater increase in viscosity when the pH is raised to between 5.0 to 7.0.

VI. TARO'S ANDA PRODUCT AND MANUFACTURING METHOD

38. Taro has submitted ANDA No. 210191 for Dapsone Gel 7.5% ("Taro's ANDA"). I have reviewed relevant portions of Taro's ANDA to analyze whether the product described therein ("Taro's Product") if used according to its labeling would cause infringement of any of the Asserted Claims.

39. Taro's ANDA describes the composition and manufacturing process to create Taro's Product. In the "Description and Composition of the Drug Product" of Taro's ANDA (Section 3.2.P.1), the Quantitative Formulation and Functions of Ingredients tables for Taro's Product are included. TARO-DG-00000610. These tables describing the composition of Taro's Product are reproduced below:

Table 2: Quantitative Formula

Strength (Label claim):	7.5% Dapsone	
Component and Quality Standard	**Quantity per unit** (mg/g)	**%** (w/w)
Dapsone, USP	75.00	7.50
Purified Water, USP	596.5	Calculated 59.65[1]
[redacted]		

Table 3: Functions of Ingredients

Component	**Intended Functions**
Dapsone, USP	Active Pharmaceutical Ingredient (API)
Purified Water, USP	Vehicle/anti-solvent
[redacted]	

40. Dapsone is the sole active ingredient in Taro's Product.[2] The product additionally includes water, [redacted]

[2] The excipients of Taro's Product, including commonly known uses of the same are indicated at TARO-DG-00000679-80.

[redacted] These excipients in combination constitute an aqueous phase of Taro's Product.[3]

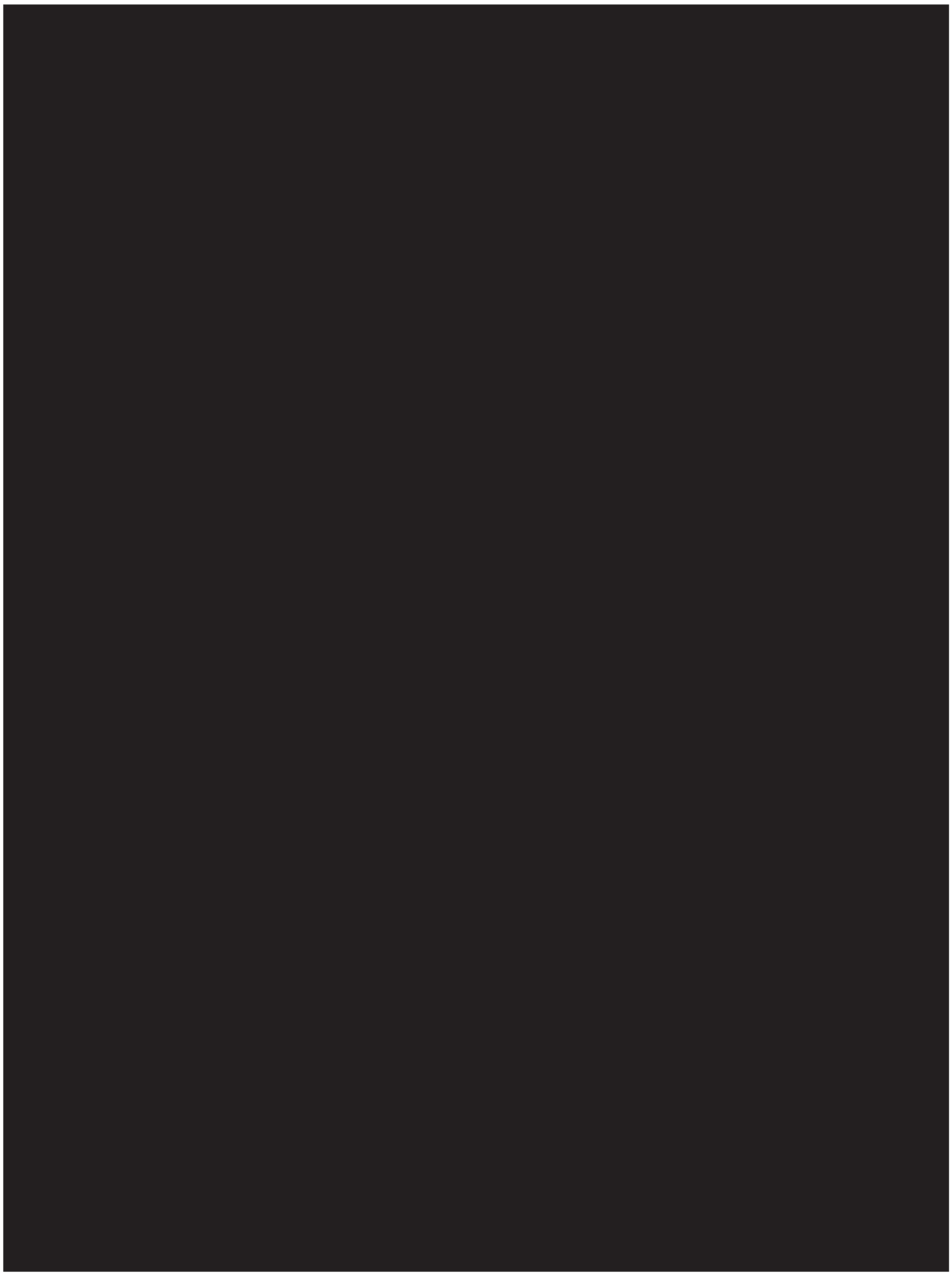
41. Taro's Product additionally includes [redacted]

42. Lastly, Taro's Product includes Carbomer Homopolymer Type C, also commonly referred to as Carbopol 980 or simply "Carbomer." *See* Lubrizol, Viscosity of Carbopol Polymers in Aqueous Systems (2010). Carbomer is a polymeric thickening (or "gelling") agent consisting of a single synthetic high-molecular-weight polymer of acrylic acid. Carbomer is used in Taro's Product to increase the viscosity of the gel and it is the sole thickening agent in Taro's formulation. As described below with reference to the manufacturing protocol for Taro's Product, Carbomer must be carefully mixed with water followed by activation using some form of neutralizing agent, in this case sodium hydroxide. Addition of Carbomer to topical pharmaceutical products must be carefully controlled to prevent clumping of the polymer.

43. Taro's ANDA describes Taro's Manufacturing Process in detail. The Manufacture section of Taro's ANDA (3.2.P.3) contains a subsection entitled, "Description of manufacturing process and process control" (3.2.P.3.3) which provides narrative and graphical information about the manufacturing process. This section also describes what controls are implemented by Taro to ensure adherence to the product and manufacturing specifications.

[3] As described below, Taro's Product additionally includes an oil phase. Topical formulations having an aqueous and oil phase are common.

Section 3.2.P.3.3 contains a "Flow Diagram" that shows a graphical representation of the full manufacturing process for Taro's ANDA Product. TARO-DG-00000769. The Flow Diagram identifies [redacted] *Id.* The Flow Diagram is reproduced in full below:



44. In addition to the graphical description, Section 3.2.P.3.3 contains a Narrative Summary of the manufacturing process. TARO-DG-00000770-71. This narrative provides more detail about each step of the manufacturing process shown in the Flow Diagram.[4]

45. The Narrative Summary describes [redacted]

46. At this point, [redacted] Thereafter, water is added to the mixture to arrive at the target weight and the product is packaged in airless pump containers of 30, 60 and 90 gram sizes. *Id.*

47. As clearly stated in Flow Diagram and the Narrative Summary, Taro does not [redacted] and Carbomer to create a polymeric thickening agent. Instead, Carbomer is added separate from all other ingredients in a

[4] Batch Records for Taro's Product are also a good source for learning the manufacturing protocol. *See* TARO-DG-00000798-821.

time consuming and carefully managed process as is typical with topical pharmaceutical formulations containing Carbomer.

VII. PATENTS-IN-SUIT

A. Disclosures of the '219 and '926 Patents

a. The '219 Patent

48. For the purposes of my report, I separately refer to the Abstract, Specification and Claims of the '219 patent as issued.

49. The Abstract is presented on the face of the '219 patent. It is my understanding the purpose of an abstract is to enable the public to determine quickly from a cursory inspection the nature and gist of the technical disclosure in the specification. *See* 37 CFR § 1.72(b). The abstract reads:

> Dapsone and dapsone/adapalene compositions can be useful for treating a variety of dermatological conditions. The compositions of this disclosure include dapsone and/or adapalene in a polymeric viscosity builder. Subject compositions can be adjusted to optimize the dermal delivery profile of dapsone to effectively treat dermatological conditions and improve the efficiency of pharmaceutical products applied to the skin. Use of the polymeric viscosity builder provides compositions with increased concentrations of diethylene glycol monoethyl ether relative to compositions without the polymeric viscosity builder.

50. In my opinion, the Abstract of the '219 patent provides very little to apprise the public the nature of the invention. At most, the abstract describes dapsone and/or adapalene compositions with a PVB and that the use of the PVB somehow allows for higher concentrations of DGME. It is important to note the abstract does not specifically identify A/SA and also describes adapalene compositions that are explicitly excluded from the claims. See Claims 1 and 6. In my opinion, a person reading the abstract in combination with the claims (described in more detail below) would understand the patent disclosed subject matter that was not claimed and

therefore could be practiced without infringing the issued claims. This understanding would be reinforced by further examination of the Specification and Claims, as described below.

51. It is my understanding the specification of a patent is a written description of the invention and of the manner and process of making and using the invention. *See* 37 CFR § 1.71. It is my further understanding the specification must be in such full, clear, concise, and exact terms as to enable any person skilled in the relevant art to make and use the same. *Id.* It is also my understanding the specification must set out the precise invention in a manner to distinguish it from other inventions and from what is old. *Id.* In my report I refer to the "Field and Background of the Invention", the "Summary of the Invention" and the "Description of the Preferred Embodiments" as the specification of the '219 patent.[5]

52. The Field and Background of the Invention (the "Background") begin with general reference to compositions useful for treating dermatological conditions, with a focus on acne, using dapsone and dapsone/adapalene compositions. Col. 1, ln. 19- Col. 2, ln. 8. The Background generally discusses challenges associated with the treatment of acne, including the need for trial-and-error in determining the most effective treatment, efficacy being affected by patient compliance with treatment, side effects associated with available treatment and cost. The Background also notes the availability of compositions with multiple-anti-acne agents having stability concerns as well as difficult with manufacture.

53. The inventors conclude the Background by stating there is a "continuing need for compositions and methods used in treatment of a variety of skin conditions, such as acne, in which topical application is potentially effective" and that the compositions and methods of the '219 patent address those needs. Col. 2, ln. 4-8. In my opinion, the concluding statement makes

[5] It is my understanding original claims as filed with the patent application are part of the invention disclosure.

clear the inventors were not purporting to solve the foregoing problems, but were offering compositions that were "potentially effective." *Id.* This conclusion would be confirmed by further reading of the Specification, as discussed below. In example, "treating" or "treatment" is defined in the patent as simply having some positive effect on a skin condition. *See* Col. 5:22-34. That is an extremely low bar for compositions comprising active ingredients well-known to provide benefits to patients having acne.

54. The Summary of the Invention begins with a somewhat generic discussion of dermatological issues, including acne and the prior treatments thereof. It is my understanding the Summary of the Invention should be "commensurate with the invention as claimed and any object recited should be that of the invention as claimed." *See* 37 CFR 1.73. The summary states a problem with prior dapsone compositions is they cause drying of skin, itching and cracking. Col 2:25-28. It is stated inclusion of skin emollients and oils in the composition causes "phase separation and precipitation of dapsone." Col 2:29-31. It is further stated improved compositions would improve treatment options and minimize problems with prior formulations and the compositions of the invention include dapsone solubilized with DGME and optionally include a PVB. It is further stated the compositions can be "adjusted to optimize the dermal delivery profile of dapsone[.]" Col 2:44-48. In view of the fact the prior art described dapsone formulations with DGME and a PVB, a person of skill in the art reading this conclusion would not understand the nature of the invention. More specifically, such a person would have noted the complete absence of clinical information of any kind in the patent suggesting improved treatment or reduction in side effects associated with the methods of the invention. (Clinical information or data also was not included during prosecution of the application resulting in the '219 patent.)

55. At the conclusion of the Summary the patent stated that use of a PVB reduces yellowing and the particle size of dapsone in formulations, thereby reducing the feeling of grittiness. Col 2:54-61. The specification does provide information about yellowing and grittiness, specifically at Figures 1 and 3 (yellowing) and 2 (particle size). The Figures are of very little help, however, as there is no way of discerning the "yellowing" in the images of Figures 1 and 3 and Figure 2 does not include information about the formulations at issue. As such, it is impossible to know what formulations are being compared. In conclusion, a POSA would understand the inventors were alleging some benefit of compositions with respect to yellowing and particle size, but the support for those benefits is of almost no value.

56. The Detailed Description and Embodiments (the "Detailed Description") begins with two columns focused on general information relating to dermatological conditions, none of which have any obvious pertinence to the invention disclosed. Cols. 3-4. The conclusion of the clinical information defines the term "treating" or "treat" in the context of the invention as previously described, namely by setting a very low bar of efficacy. Col 5:22-34.

57. The Detailed Description next generally disclose compositions of the invention, such compositions containing dapsone in the ranges of 5 to 10% w/w, DGME in the range of 10 to 40% w/w and the use of different PVBs, including A/SA and Carbomer. Cols. 5-6. There is no representation that the compositions solve any of the foregoing treatment challenges or have any particular clinical benefit beyond being dapsone formulations. Instead, a list of embodiments of the invention follows. The first embodiment is extremely broad, covering a composition with dapsone between 3 and 10% w/w, a first solubilizing agent, a second optional solubilizing agent, a PVB and water. Col 6:65-Col 7:3. Many of the subsequent embodiments refer to this first embodiment, including Embodiment 20 wherein Embodiment 1 is further defined as including

Carbomer between 0.7 and 1.5% w/w. A specific formulation falling under Embodiment 20 appears in Table 5 wherein compositions contemplated for use according to the invention are disclosed. The composition includes 7.5% w/w dapsone, DGME and 1% w/w Carbomer. In view of this, and other information in the patent, a person of skill in the art would have understood the Detailed Description was disclosing dapsone compositions having Carbomer as the PVB in 1% w/w concentration. The claims of the patent, however, do not encompass such compositions.

58. The patent disclosed many other formulations wherein Carbomer was used in combination with dapsone and/or adapalene. A further example is found, for instance, at Example 1 comparing A/SA with 1% w/w Carbomer and noting a larger crystal size with Carbomer formulations than with A/SA (Col. 12, l. 55). Tables 1, 2, 5, 6, and 8 also disclose Carbomer containing formulations. As such, a person reading the specification and examining the claims would have understood Carbomer formulations were disclosed as being part of the invention, but not subsequently claimed. As described below, the reason those formulations were not claimed is due to the applicant specifically disavowing formulations wherein the thickening agent was Carbomer in response to a rejection by the patent office.[6] Similarly, adapalene formulations are described as being part of the invention, but those formulations are expressly precluded by the claims. The only polymeric viscosity builder or thickener referenced in the claims themselves is A/SA.[7]

[6] I have reviewed the deposition of inventor Kevin Warner and understand Carbomer formulations were proposed for Phase I clinical studies along with the formulation that eventually became Aczone® 7.5% gel. Warner Dep. 245:15-248:19. The eventual formulation was selected, but Dr. Warner does not know if the Carbomer formulations would have succeeded if pursued. 266:13-270:3.

[7] It is interesting the applicant claimed A/SA as opposed to Sepineo P 600, as that is what they claim to be the PVB in its Aczone 7.5% Gel product and the only form of A/SA that was ever considered.

59. If asked, I am prepared to talk about the '219 patent, including the Background, Summary and Detailed Description. I am also prepared to discuss how a person of ordinary skill in the art would have understood the disclosure of the '219 patent alone and in view of the prosecution history (described in detail below). Finally, I am prepared to talk about the claims and claim scope.

B. The Parent Application No. 14/082,955

60. It is my understanding the application that resulted in the '219 patent was a division of Application No. 14/082,955. I refer to Application No. 14/082,955 as the "Parent Application" as I understand that to be the proper designation to indicate its relation to the application that resulted in the '219 patent (the "Divisional Application"). The Parent Application issued as U.S. Patent No. 9,161,926 ("the '926 Patent"). It is my understanding the '926 Patent has not been asserted against Taro. Nevertheless, I have been informed the prosecution of the Parent Application can be relevant to an understanding of the subject matter of a divisional application and the claims of a patent issuing from such a divisional application. For this reason, I have reviewed the prosecution history of the '926 patent and, if asked, am prepared to describe the prosecution history for the Court.

61. The Parent Application was submitted with an original twenty (20) proposed claims. The original proposed claim 1 stated the following:

> A composition comprising dapsone, a first solubilizing agent which is diethylene glycol monoethyl ether, optionally at least one second solubilizing agent, a polymeric viscosity building, and water, wherein the dapsone is preset in the composition at a concentration of about 3% w/w to about 10% w/w. TARO-DG-00063859

The original proposed dependent claim 10 claimed:

> The composition of claim 1, wherein the polymeric viscosity building comprising an acrylamide/sodium acryloyldimethyl taurate copolymer. *Id*.

And dependent claim 11 and 12 claim the PVB present at a concentration of about 2% w/w to about 6% w/w and a concentration of about 4% w/w respectively. *Id.* These claims are consistent with embodiments in the specification of the '219 patent, as previously discussed.

62. The original proposed dependent claim 14 claims:

> The composition of claim 1, further comprising Carbomer interpolymer type A, carbomer interpolymer type B or Carbomer Homopolymer Type C. TARO-DG-00063860.

Claim 14 is a claim covering a composition with 7.5% dapsone, 30% DGME, 1% Carbomer and water. It would also cover the same composition additionally including Polysorbate 80, sorbitan monooleate, light mineral oil and a neutralizing agent. That claim was withdrawn based on an examiner's patentability rejection.

63. In a January 14, 2014 Office Action, the patent examiner noted the applicants claimed two separate inventions (composition and method) and required the applicant to choose which invention the applicant wished to have examined. TARO-DG-00063901-63902. Further, the applicant was required to make an election of a single disclosed species for, among other things, claim 14. TARO-DG-00063902-63904. In a February 20, 2014, Response to the Restriction Requirement and Election of Species, the applicant elected invention 1 (the composition). Further, the applicant elected carbomer homopolymer type C as the carbomer polymer listed in Claim 14. TARO-DG-00063911.

64. In the next Office Action dated March 18, 2014, the Examiner issued claim rejections as, among other references, being anticipated by both Lathrop and Ahluwalia. TARO-DG-00063918-63923. I understand Lathrop teaches topical emulsive compositions of dapsone, and claims a composition containing both dapsone and Carbomer. TARO-DG-00063918-919. Ahluwalia teaches topical compositions with dapsone and adapalene for the treatment of acne.

Ahluwalia teaches exemplary compositions such as 5% w/w dapsone; .1% w/w or .3% w/w adapalene; 25% w/w DGME; 15% w/w propylene glycol; .01% w/w EDTA; .75% w/w Carbopol 980; sodium hydroxide and purified water. TARO-DG-00063919. The Examiner cited Lubrizol advertising literature for the fact Carbopol 980 is a polymeric thickener synonymous with carbomer homopolymer type C. TARO-DG-00063919. The Examiner noted Ahluwalia taught ranges of dapsone, DGME and a polymeric viscosity builder and concluded the ranges clearly encompass the ranges being claimed by the applicant. TARO-DG-00063921-922.

65. In response to the March Office Action, on May 20, 2014, the applicant submitted amended claims limiting, among other things, the polymeric viscosity builder in claim 1 to A/SA and cancelling multiple claims, including claim 14. TARO-DG-00064079.

66. The applicant went on to argue against the prior rejections and specifically noted the "unexpected advantages" of the claimed composition in providing improved aesthetics and noted the particle size improvement using A/SA in comparison to Carbomer. TARO-DG-00064088-64089. The applicant specifically stated and included in bold "the composition comprising [A/SA] thickener has unexpected advantages over a composition where the thickener/viscosity builder in Carbomer homopolymer type C." TARO-DG-00064089.

67. On June 5, 2014, the Examiner again rejected multiple claims as being obvious and unpatentable over the prior art. TARO-DG-00064097-64102. The Examiner further discussed the applicant's claim of "unexpected advantages." The Examiner noted the tested formulations cited by the applicant were not commensurate in scope with the claims presented, and further found "a showing of unexpected results must necessarily be accompanied by a clear indication of what the skilled artisan would have expected, as well as a clear showing of how the claimed invention exceed such expectation so as to provide properties or results that were

unexpected, unobvious and of statistical and practical significance" which the applicant had not done. TARO-DG-00064105-64108.

68. In response to another rejection, on February 2, 2015, the applicant submitted a declaration from Kevin S. Warner, one of the co-inventors of the patent application stating: "Based on the unexpected observation of Carbopol 980 incompatibility with 40% DGME, the thickener was changed from Carbopol 980 to Sepineo P 600 [i.e., A/SA] to mitigate the risk of polymer aggregation in DGME containing formulations." ALG-ACZ0000292. He further stated: [We] selected Sepineo P 600 as the gelling agent for our dapsone 7.5% gel formulation. We made this selection due to Sepineo P 600's compatibility with concentrations of DGME greater than 25% and its improvement in dapsone particle size relative to Carbopol 980." *Id*. This same declaration was submitted again in support of the '219 patent application.

69. After the submission of the declaration the applicant further amended and canceled certain claims and responded to the latest rejection. TARO-DG-00064182-64184. In focusing on unexpected results, the applicant reiterated the "unexpected results" discussed by the co-inventor in his declaration. TARO-DG-00064188. They noted undesirable polymer aggregates during formulations studies (using Carbomer) which lead to the utilization of A/SA. TARO-DG-00064188-64189. The applicant went on to state Sepineo P 600 allowed for higher concentrations of DGME, which were found to be incompatible with Carbomer and that Sepineo P 600 formulations provided smaller particle size as compared to Carbomer formulations, which is why Sepineo P 600 was selected as the gelling agent. TARO-DG-00064189. It was emphasized this result was "entirely unexpected and could not have been predicted" based on the 5% dapsone formulation, which used Carbomer or the prior art formulation. *Id*.

70. After these repeated references to the unexpected superiority of A/SA over the well-known and previously utilized Carbopol 980, the Examiner issued a notice of allowability. TARO-DG-00064344.

C. Prosecution of the '219 Patent

71. I have reviewed the prosecution history of the '219 patent and, if asked, I am prepared to describe the prosecution history for the Court. As explained below, and throughout my report, the applicants' responses and representations made to the patent examiner, both about the basic and novel characteristics of the invention being claimed in the application that led to the '219 patent and the nature of the prior art, are relevant to my non-infringement analysis. As explained in detail below, a full review of the prosecution history makes clear the applicants were focused on the novelty of using A/SA as the thickening agent and expressly disclaimed Carbomer formulations.

72. Originally, all of the claims were rejected as unpatentable over Garrett in view of Hani, a rejection nearly identical to those made during prosecution of the Parent Application. (The claims were also rejected on the ground on nonstatutory double patenting, as being unpatentable over claims 1-6 of the '926 patent.). ALG_ACZ0000052-72. By way of amendment and response to the office action dated February 18, 2016, the applicants argued the amount of dapsone, the use of Sepineo P 600 as the sole thickening agent in a topical dermatological formulation comprising dapsone and the specific amount of Sepineo P 600 recited in the claims made the claims distinct from the prior art.[8] ALG_ACZ0000284. Applicants claimed the combination of Sepineo P 600 with dapsone was not suggested in either Garrett or Hani:

[8] This argument is interesting in that the applicant did not claim Sepineo P 600, but a PVB comprising A/SA. As previously mentioned, the claim is broad enough to cover the use of A/SA *alone* as the PVB.

> First, Garrett teaches that a preferred composition comprises about 5% w/w dapsone wherein about 0.85% w/w carbopol 980 is used as a thickening agent. The instant claims recite new formulations of dapsone wherein the active ingredient is about 7.5% dapsone and an entirely new thickening agent is employed. The new formulation of the instant claims does not include a carbomer such as Carbopol®, but instead utilizes as [A/SA], also known as Sepineo™ P 600, and at a much higher concentration (about 2% to about 6% w/w) as compared to what Garrett teaches for its thickening agent.

ALG_ACZ00000284. In this response, applicants were absolutely clear: "the formulation of the instant claims does not include a carbomer such as Carbopol® …" ALG_ACZ0000283-284. As discussed below, the examiner withdrew its rejection based on Garrett and Hani.

73. In this response the applicant also included the declaration of Kevin Warner previously submitted in connection with prosecution of the Parent Application. Warner Declaration, ALG_ACZ0000290-294. In arguing the unexpected nature of the invention, the applicants argued, for example, Sepineo P 600 was found to be a more robust thickener than Carbomer, which was used in the prior 5% dapsone gel formulations. ALG_ACZ0000292. Applicant further argued Sepineo P 600 allowed for higher concentrations of DGME than with Carbomer and resulted in reduced particle size as compared to Carbomer. *Id*. Applicants concluded: "Sepineo P 600 was therefore selected as the gelling agent for the 7.5% w/w dapsone formulation of the instant claims." Response to Office Action, ALG_ACZ000286.

74. The Examiner determined the Warner Application provided enough support for the unexpected results of A/SA over Carbomer and the rejections for obviousness were withdrawn. ALG_ACZ0000503-505. It was noted by the Examiner in the prosecution of both the '926 and the '219 patents that the testing done with Sepineo and Carbopol did not use the same concentrations, but in this instance, the Examiner noted the inventor's explanation that higher concentrations of Carbopol 980 would have results in even greater aggregation. ALG_ACZ0000504. The Examiner went on to note "The Warner Declaration … provides clear

evidence that the improved properties of the Applicant's claimed 7.5% w/w dapsone formulation … yields directly from the selection of the [A/SA] copolymer as the polymeric thickener of the formulation. ALG-ACZ0000504.

75. I note throughout the prosecution of both the '926 and '219 patents, the applicants noted the superiority of A/SA to Carbomer and the incompatibility of Carbomer with their invention. Such consistent efforts to distinguish the alleged invention from the prior art utilizing, claiming and describing the use of Carbomer put the public and a person of skill in the art on notice that only products containing A/SA could be covered by the claims of the '926 and '219 patents and more specifically the thickening agent Carbomer was not covered by the claims.

VIII. CLAIM CONSTRUCTION

76. I understand the Court has construed the term "polymeric viscosity builder" ("PVB") and that the construction is applicable to my analysis of the '219 patent (Markman Order dated June 6, 2018, C.A. No. 17-663, Docket No. 87). The Parties' proposed constructions and the Court's construction are reproduced below:

Allergan	Taro	Court
"polymer-based system with one or more components that contributes to creating or maintaining the viscosity of the topical pharmaceutical composition"	"a polymer or polymer-based thickening agent"	"a polymer or polymer-based thickening agent"

77. My opinions set forth below apply the Court's claim construction. For all terms that have not been construed by the Court, I apply the plain and ordinary meaning to a POSA as of November 20, 2012.[9]

IX. DR. LANE'S INFRINGEMENT THEORIES ARE BARRED

78. Dr. Lane's infringement analysis requires a finding the 1% Carbomer used as a thickening agent in Taro's Product is equivalent to "about 2% w/w to about 6% w/w of a polymeric viscosity builder comprising [A/SA]". *See* Lane Report at ¶ 67. As explained in more detail below, I disagree with Dr. Lane's opinion regarding the identity of the thickening agent in Taro's Product or that the thickening agent in Taro's Product is equivalent to the missing claim elements. (Furthermore, I disagree with Dr. Lane's attempt to show equivalence between excipients in Taro's Product and unclaimed elements.) Nevertheless, *even if* one were to accept Dr. Lane's construction of the PVB in Taro's Product, numerous limitations on the DOE preclude a finding of infringement. Specifically, Dr. Lane's DOE opinions are precluded under the doctrines of 1) prosecution history estoppel; 2) commitment to the public; and 3) ensnarement. Additionally, it appears Dr. Lane is utilizing a "whole claim" analysis instead of analyzing the specific element at issue. For these reasons alone, it is my opinion Dr. Lane has not demonstrated Taro infringes the '219 patent.

A. Prosecution History Estoppel

79. I have been informed there is a doctrine called prosecution history estoppel which essentially bars a patentee from making narrowing amendments and/or narrowing the scope of the claims during the prosecution of the patent and then broadening the scope of the claims to invoke the doctrine of equivalents.

[9] I understand from Counsel Almirall is asserting a priority date of November 20, 2012. By using this date I am giving no opinion as to whether to this an appropriate priority date for the '219 patent.

80. During prosecution of the Parent Application, the applicant attempted to claim Carbomer and then chose to cancel that claim in direct response to a rejection by the Examiner. Specifically, as noted above in Section VII. B. the original proposed claims in the Parent Application included a claim for multiples types of carbomer, which in response to an Office Action the applicant limited to carbomer homopolymer type C (referred to herein as, Carbomer). The applicant then in response to yet another rejection, canceled the claim in its entirety, thus no longer claiming Carbomer. Based on the applicant's original attempt to claim carbomer homopolymer type C and its subsequent cancelation of that claim a POSA would understand that Carbomer was not claimed in the invention and could not be claimed by the applicant.

81. The claim to Carbomer did not reappear in the Divisional Application that resulted in the '219 patent. However, the patent examiner found the claims obvious in view of Garrett and Hani. As described above, the applicants specifically overcame the objections by arguing the claims did not include Carbomer.

> First, Garrett teaches that a preferred composition comprises about 5% w/w dapsone wherein about 0.85% w/w carbopol 980 is used as a thickening agent. The instant claims recite new formulations of dapsone wherein the active ingredient is about 7.5% dapsone and an entirely new thickening agent is employed. The new formulation of the instant claims does not include a carbomer such as Carbopol®, but instead utilizes as [A/SA], also known as Sepineo™ P 600, and at a much higher concentration (about 2% to about 6% w/w) as compared to what Garrett teaches for its thickening agent.

ALG_ACZ00000284. It bears repeating, applicants were absolutely clear: "the formulation of the instant claims does not include a carbomer such as Carbopol® …" ALG_ACZ0000283-284.

82. In further response to obviousness objections, one of the co-inventors submitted a declaration explaining that Carbomer was unexpectedly not compatible with higher percentages of DGME. The Warner Declaration went on to state the inventors chose A/SA over Carbomer because A/SA was a more robust thickener. These arguments were successful in convincing the

patent examiner to withdraw its objections and allow the patent claims drawn to formulations having thickening agents comprised of A/SA.

83. It is clear to me, as it would be to any skilled person in the pharmaceutical arts, the patentee narrowed the scope of the claims, removing any reference to and claiming superiority over Carbomer during the prosecution of the patent. A person of skill in the art would understand formulations comprising 7.5% dapsone, DGME and Carbomer would not be covered by the claims. It is my opinion Almirall is estopped from bringing its doctrine of equivalents argument to encapsulate Taro's Product.

B. Dedication To The Public

84. I understand there is a rule referred to as the "dedication-disclosure rule" or "dedication to the public." I understand this rule applies when an applicant discloses subject matter but does not then claim the subject matter, thus dedicating it to the public. As discussed above, there are multiple Carbomer formulations disclosed as being consistent with the invention. None of these formulations are claimed, as evidenced by Dr. Lane's opinion Taro's Product does not fall within the literal scope of the patent.

85. For example, the compositions in multiple embodiments listed in the '219 patent include Carbomer. In some embodiments, Carbomer is present at a concentration of about 0.7% w/w to about 1.5% w/w. In other embodiments, Carbomer is present at a concentration of about 0.85% w/w to about 1.0% w/w. This disclosure alone, when read in connection with the claims, would lead a POSA to believe Carbomer, in concentrations from .7 w/w to 1.5% w/w or .85% w/w to about 1.0% w/w had been explicitly disclosed by the patentee and not claimed, and therefore the use thereof would not be considered practicing the patent.

86. Specific examples of Carbomer containing embodiments include 19, 20, 21, 48, 49, 50. Further, Example 2/Table 2, Example 4/Table 5, Example 4/Table 6 and Example 6

/Table 8 all explicitly disclose Carbomer in combination with dapsone and are stated to be consistent with the scope of the invention.

87. The '219 patent also makes clear the inventors believed Carbomer formulations to be inferior to those containing A/SA. In Example 1, the patentee specifically differentiates its invention utilizing A/SA to a composition containing Carbopol, claiming a clear difference in the particle size of the dapsone. The Specification notes larger crystals were observed with Carbomer formulations. So, while the examples include Carbomer as an option, it is not claimed and the examples specifically tout the superiority of A/SA over Carbomer in the invention. This comparison, extolling a purported benefit of A/SA over the well-known and previously utilized Carbomer would lead a POSA to understand Carbomer was disclosed by the patentee, not the preferred thickening agent described by the patentees and, not claimed.

88. A POSA reviewing the specification would understand Carbopol 980 was dedicated to the public through the applicant's decision to repeatedly disclose but not claim Carbopol 980. A POSA would have therefore concluded the use of Carbopol 980 (among other PVBs) would be appropriate to use in a topical pharmaceutical formulation and would not be covered by the claims or inventions of the '926 or '219 patents.

89. Additionally, the applicant repeatedly used A/SA and Sepineo interchangeably in the prosecution of the patent, but in the actual claims the patentee claimed A/SA, not Sepineo. While it appears the, based on the label of ACZONE 7.5%, excipients like polysorbate 80, sorbitan monolete and isohexadecane are utilized in Sepineo P 600, the applicant did not claim Sepineo P 600 – it claimed A/SA. Applicants disclosed some of the additional excipients utilized in Taro's ANDA product [redacted] in the Detailed Description and the Examples but neither those excipients nor Sepineo P 600 not appear

anywhere in the claims. [redacted]

C. The Ensnarement Doctrine Bars Almirall's DOE Theory

90. I have been informed that determining whether an equivalent would impermissibly ensnare the prior art is typically resolved through a hypothetical claim analysis. I understand there are two steps to this analysis. The first step is to construct a hypothetical claim that literally covers the accused product. I understand that while the scope of the hypothetical claim may be broader, it may not add any narrowing limitation.

91. In this case, a hypothetical claim for purposes of an ensnarement analysis would expand the claimed PVB amount to cover [redacted] of a PVB and replace A/SA with Carbomer. That claim would read as follows[10]:

> A method for treating a dermatological condition selected from the group consisting of acne vulgaris and rosacea comprising administering to a subject having the dermatological condition selected from the group consisting of acne vulgaris and rosacea a topical pharmaceutical composition comprising:
>
> about 7.5% w/w dapsone;
>
> about 30% w/w to about 40% w/w diethylene glycol monoethyl ether;
>
> about [[2]][redacted] w/w to about 6% w/w of a polymeric viscosity builder comprising ~~acrylamide/sodium acryloyldimethyl taurate copolymer~~ Carbomer homopolymer type C; and
>
> water;

[10] Insertions appear as underlined text (e.g., insertions) while deletions appear as strikethrough or surrounded by double brackets (e.g., ~~deletions~~ or [[deletions]]).

wherein the topical pharmaceutical composition does not comprise adapalene.

92. Almirall disputes Taro's ANDA Product contains [redacted]

Thus, under Almirall's infringement theory, a hypothetical claim for purposes of an ensnarement analysis would simply replace A/SA with Carbomer. That claim would read as follows:

> A method for treating a dermatological condition selected from the group consisting of acne vulgaris and rosacea comprising administering to a subject having the dermatological condition selected from the group consisting of acne vulgaris and rosacea a topical pharmaceutical composition comprising:
>
> about 7.5% w/w dapsone;
>
> about 30% w/w to about 40% w/w diethylene glycol monoethyl ether;
>
> about 2% w/w to about 6% w/w of a polymeric viscosity builder comprising ~~acrylamide/sodium acryloyldimethyl taurate copolymer~~ Carbomer homopolymer type C; and
>
> water;
>
> wherein the topical pharmaceutical composition does not comprise adapalene.

93. The second step to an ensnarement analysis is to determine whether the PTO would have found the hypothetical claim patentable over the prior art. If such a hypothetical claim would not have been patentable under either 35 U.S.C. §§ 102 (i.e., anticipation) or 103 (i.e., obviousness), then the patentee has overreached and the accused product does not infringe.

94. I have reviewed the Expert Report of Dr. Panayiotis P. Constantinides, Ph.D. in Support of Defendants' Ensnarement Defense served concurrently herewith ("Constantinides Ensnarement Report"), in which he opines that the hypothetical claims I constructed above (including the dependent claims) would have been obvious to a POSA at the time of the alleged

invention. (Constantinides Ensnarement Report ¶¶ 5-22). I agree with Dr. Constantinides' obviousness analysis and ultimate conclusion.

95. Because the hypothetical claim analysis confirms Almirall's equivalents theory impermissibly ensnares the prior art, Almirall should be barred from asserting Taro's ANDA Product infringes under the doctrine of equivalents.

X. THE USE OF TARO'S PRODUCT WILL NOT INDUCE INFRINGEMENT OF ANY ASSERTED CLAIM OF THE '219 PATENT

96. Dr. Lane offers the opinion use of Taro's Product will induce infringement of independent claim 1 and dependent claims 2, 4 and 5 of the '219 patent. Claim 1 of the '219 patent is the sole independent claim being asserted against Taro. As described below, Claim 1 describes a method of treating a dermatological condition with a described topical pharmaceutical formulation. In the event Taro's Product does not meet each element of the topical pharmaceutical formulation set out in Claim 1, either directly or through the doctrine of equivalents, it is my understanding Taro cannot induce infringement of the '219 patent, irrespective of the labeling described in Taro's ANDA. *See* Lane Report at ¶¶ 50-53. Furthermore, it is my understanding if Taro does not infringe, either directly or indirectly, the only asserted independent claim it also cannot infringe any other claim depending on the independent claim.

97. Claim 1 of the '219 patent is reproduced below:

> 1. A method for treating a dermatological condition selected from the group consisting of acne vulgaris and rosacea comprising administering to a subject having the dermatological condition selected from the group consisting of acne vulgaris and rosacea a topical pharmaceutical composition comprising:
>
> about 7.5% w/v dapsone;
>
> about 30% w/w to about 40% w/w diethylene glycol monoethyl ether;

about 2% w/w to about 6% w/w of a polymeric viscosity builder comprising acrylamide sodium acryloyldimethyl taurate copolymer; and

water

wherein the topical pharmaceutical composition does not comprise adapalene.

98. Dr. Lane separates claim 1 into seven different limitations, the fifth being "about 2% w/w to about 6% w/w of a polymeric viscosity builder comprising [A/SA]." Lane Report at ¶ 67.[11] Taro's Product neither includes "about 2% w/w to about 6% w/w of a polymeric viscosity builder" nor a PVB "comprising [A/SA]."[12] Therefore, Taro's Product when used according to its label does not literally infringe independent claim 1 of the '219 patent. Further, as described in detail below, Taro's Product does not infringe independent claim 1 under the doctrine of equivalents, because the [redacted] Carbomer used in Taro's Product is not equivalent to "about 2% w/w to about 6% w/w of a [PVB] comprising [A/SA]."[13] (As described above, Dr. Lane's DOE arguments are also barred.)

A. Dr. Lane Improperly Interprets the Claims

99. Dr. Lane's entire analysis treats the missing claim element as being Sepineo P 600, instead of A/SA. The '219 patent claims a thickening agent "comprising A/SA." It does not claim a thickening agent consisting of Sepineo P 600. The fact Almirall chose to formulate the Aczone® 7.5% gel product by using a purchased product (one that was created by someone other than Almirall) containing Polysorbate 80, sodium monooleate and isohexadecane in addition to

[11] Throughout my report, when responding to Dr. Lane's infringement claims, unless otherwise noted I respond to the limitation conventions she has chosen. By doing so I am in no way conceding she has properly separated the various elements of the claims in the patent-in-suit.
[12] My opinion focuses on the fact Taro's Product is not a topical pharmaceutical composition described in the Asserted Claims. It is not necessary for me to offer an opinion on whether Taro's proposed labeling would induce others to practice the methods of the Asserted Claims *if* Taro's Product was a topical composition described by the claims. *See* Lane Report at ¶¶ 50-53.
[13] For the same reason, Taro's Product, if sold and used according to its label, does not infringe the Asserted Claims depending, either directly or indirectly, on claim 1, namely claims 2, 4 and 5 of the '219 patent.

A/SA does not convert the claim to one reciting those excipients. Dr. Lane repeatedly states Taro's Product is equivalent to "the claimed polymeric viscosity builder, as embodied by Sepineo P 600", but never once shows the polymeric thickening agent in Taro's product, Carbomer, is equivalent to A/SA.[14]

100. At Section 5(a) of Dr. Lane's report, it is clear her understanding of the claims is incorrect. Dr. Lane begins by listing the ingredients of Sepineo P 600 and arguing the Sepineo P 600 product is "an embodiment" of the claims. The remaining portion of her analysis set out in Section 5 is to show equivalency between Sepineo P 600 and Taro's Product. [redacted] *See* Lane Report at ¶¶ 44, 73 and 86. It is my understanding comparing unclaimed features of an embodiment of a claim to an accused product for the purpose of establishing equivalency is improper as it is not comparing a missing claim feature to a corresponding feature in the accused product.

101. Dr. Lane also appears to be taking the position that all thickening agents pursuant to the claims must result in emulgels. *See* Lane Report at ¶¶ 74, 81-88. As an initial matter, I agree the role of a PVB is to thicken a formulation. Lane Report at ¶ 74. I disagree "the polymeric viscosity builder … determines the type of semisolid that is formed – e.g., an emulsion gel (emulgel)." *Id.* As Dr. Lane herself admits in her report, [redacted] *See* Lane Report ¶ 47.[15] The thickening agent

[14] The closest Dr. Lane comes to comparing the two polymers are the basic observations that both Carbomer and A/SA are polymers that serve to thicken formulations. *See* Lane Report at ¶ 87.

[15] The Aczone® 5% gel also was not an emulgel. That formulation is set out at Table 8 in the '219 patent as a "useful composition." It is not an emulgel and uses Carbomer as the thickening agent at 0.85% w/w.

used in that formulation (as in its final formulation) was Carbomer.[16] As Dr. Lane further concedes, [redacted]

102. Nothing in the claims mandates the topical pharmaceutical formulation need be an emulgel. As exemplified by the Garrett reference that was a basis of the patent examiner's obviousness rejections discussed above, it was well understood in the art in 2012 that a topical formulation could be formulated with dapsone, DGME and Carbomer (as the thickening agent) and that such formulations could optionally be formulated as an emulsion by addition of oil and surfactants. TARO-DG-00065190. This is similarly set out in the '219 patent wherein the inventors state: "Compositions described herein are typically in the form of a gel, an emulsion, a cream, a liquid, a paste, a lotion, a nanoemulsion, a reverse emulsion, or a liposomal cream." '219 patent at Col. 6:53-56. I also disagree with Dr. Lane's surprising statement that the Aczone® 7.5% gel and Taro's Product formulations not included an oil-phase those products would be "simple liquid formulations not suitable for treatment of acne because they would not stay on the skin." Lane Report at ¶ 84. Dr. Lane seems to forget the Aczone® 5% Gel product

[16] It is telling that Dr. Lane's theory appears to be Taro's thickening agent was Carbomer in the first formulation and then Carbomer and the added excipients in the second formulation, all the while conceding the other formulation excipients were not added to thicken Taro's Product, but to create an oil-phase in the product. *See e.g.* Lane Report at Section 5(b)(1). It is worth noting the persons responsible for developing Aczone® 7.5% gel knew Carbomer was the thickening agent in Carbomer formulations. *See e.g.* ALG_ACZ0264306.

[17] I have reviewed the expert declaration of Dr. Klibanov. Dr. Klibanov also appears to concede A/SA in the Aczone® formulation and Carbomer in Taro's Product are the thickening agents in the products. March 1, 2018, Declaration of A. Klibanov, Docket No. 59, at ¶¶ 38 and 43. I agree.

only had an aqueous phase, was deemed suitable for treatment of acne and is currently marketed and sold by Almirall. The formulation is *not* a "simple liquid", but a gel.

103. The problem, inevitably, with Dr. Lane's analysis is she attributes advantages of unclaimed excipients to the missing term "A/SA." Dr. Lane knows the function of Polysorbate 80, sodium monooleate and isohexadecane is creating an emulsion, or emulgel in the formulation. That has nothing to do with the claim element reciting a polymeric thickening agent. Imagine a car company has a patent on a car seat comprising leather and a competitor sells a car seat with vinyl. Now imagine a doctrine of equivalents arguments wherein the patentee seeks to claim equivalence based on the fact its cars have heated seats and the accused product also has heated seats and both are warm in the winter. The fact they both have seat heaters and are warm in the winter would be irrelevant to the claims of the patent. Dr. Lane's argument is no different.

104. In summary, the fact that Almirall purchased a product containing both a polymeric thickening agent and common excipients used to create an emulsion and used that product in its formulation does not transform the missing claim element reciting a thickening agent comprising A/SA into one reciting a thickening agent comprising a polymer and excipients capable of creating an oil-phase in the topical pharmaceutical formulation.[18] The inventors, for whatever reason, chose to claim the polymer A/SA alone and my understanding is they cannot now transform that broad claim into a narrower claim so as to capture Taro's Product.[19] The

[18] It is clear Taro understood A/SA in the Aczone® 7.5% gel was the gelling agent in the product and the other excipients served to create the oil phase. TARO-DG-00000682. Dr. Lane does not disagree.

[19] 3. My understanding is the inventors never tested a formulation with A/SA alone and I have not seen any testing done with Sepineo P 600 at a concentration other than 4% w/w. It appears 4% Sepineo P 600 was chosen because that percentage had previously been approved in the IIG. Warner Dep. 294:22-297:5. The claims are much broader.

claims allow for formulations that are gels and do not contain an oil-phase, as such Dr. Lane is incorrect to attempt to show equivalency of the oil-phase of Taro's Product to the oil-phase of Aczone® 7.5% Gel.

B. Dr. Lane Incorrectly Identifies the Thickening Agent Used in Taro's Product

105. The Court has construed "polymeric viscosity builder" to mean "a polymer or polymer-based thickening agent." *See* Section VIII, *supra*. As explained previously, thickening agents are commonly used in topical pharmaceutical applications. Although not all thickening agents are polymeric, the most common types of polymeric thickeners are acrylamide thickeners. A well-known example of this type thickener is Carbomer Homopolymer Type C, commercially available as Carbopol® 980 from Lubrizol. In this report, for ease of reference I have referred to Carbomer Homopolymer Type C as "Carbomer."

106. Taro's product contains [redacted] Carbomer. *See* Section VI, *supra*. It is the only thickening agent in Taro's Product, which also includes a solubilizer, a preservative, emulsifiers and oil. The fact Carbomer is a thickening agent cannot be argued. *See* Lubrizol, Viscosity of Carbopol Polymers in Aqueous Systems, 2010. Plaintiff's NDA clearly states its own development work included looking at both Carbomer and Sepineo P 600 as thickening agents in developing Aczone® 7.5% Gel. [redacted]

107. Dr. Lane incorrectly identifies other pharmaceutical excipients as being part of Taro's thickening agent so as to arrive at her opinion that Taro's thickening agent is not just Carbomer, but Carbomer in combination [redacted] By combining these other excipients [redacted]

[redacted] Dr. Lane arrives at a "thickening agent" that falls within the concentration range of Claim 1. However, Dr. Lane seems to concede Taro added the Oil-Phase Excipients *not* to act as a "thickening agent", but to create an emulgel that more closely mimicked the reference listed drug.[20] Lane Report at ¶¶ 17-18. Dr. Lane is correct, Taro's addition of the Oil-Phase Excipients function to create an emulsion (it is also correct Taro's product prior to addition of the Oil-Phase Excipients appeared to be an acceptable topical pharmaceutical composition.) Avramoff Dep. 143:17-24 and Ex. 10.[21] That does not transform the thickening agent in Taro's Product from Carbomer to Carbomer plus the Oil-Phase Excipients.

108. In my long career, I have never heard anyone calling Carbomer, oil and surfactants in a formulation a "thickening agent." Dr. Lane has given no justification for the combination other than to say she does so based on her understanding of the ingredients in the Sepineo P600 product used as a thickening agent used in Aczone® 7.5% Gel and its being a "[polymer-based thickening agent] comprising [A/SA]." I do not agree with Dr. Lane's reasoning. A POSA would understand based on the prosecution history that Sepineo P 600 was an example of a polymer-based thickening agent comprising A/SA as recited in the claims. (Moreover, it would have been understood Sepineo P 600 was simply a product marketed as a thickening agent that did not have the drawbacks of more traditional thickening agents like Carbomer. *See e.g.* ALG_ACZ0264309 (explaining selection of Sepineo P 600 was based, in

[20] There is nothing unusual about a pharmaceutical company attempting to match the reference listed drug as closely as possible. Not only does FDA encourage use of the same excipients in the same concentrations, but it is more helpful to patients who may be switching from a brand to generic to be familiar with the form and feel of the medication. It is well documented that patients have become confused when the form of generic pills differ from the brand, especially where patients receive tablets from different manufacturers at different times. [redacted]

[21] Neither formulation contained A/SA, and that is the claim element at issue.

part, on the ease of processing relative to Carbomer).) However, as stated above, the claims are not drawn to Sepineo P600. Instead, they are drawn to any polymer or polymer-based thickening agent comprising A/SA. Given the breadth of the claim, A/SA alone would be a polymer thickening agent pursuant to the claims, a fact Almirall does not appear to dispute. *See* Markman Hearing Transcript at 9:14-21. Furthermore, not a single ingredient other than A/SA in the Sepineo P 600 product is claimed in the patent. The only reference to any of these excipients is in a reference at column 5 wherein it is stated a PVB that is A/SA can *optionally* include other excipients. As such, whether Taro's Product has one or more of these excipients or does not, it has no relevance to any claim limitation.

109. During prosecution, the applicants conceded Carbomer alone was the thickening agent used in other dapsone formulations and distinguished Sepineo P 600 as being a better thickener. The Garrett reference the applicants distinguished during prosecution described Carbomer formulations that additional could include other excipients, like sodium monooleate, mineral oil and other emulsifiers. It is well-known by those skilled in the art that Carbomer is a thickening agent and that oil and emulsifiers in combination create an oil-phase in topical gel products.[22]

110. The Inactive Ingredient Database ("IID") is a database maintained by FDA to identify inactive ingredients used in approved drug products. The IID identifies Carbomer use in many approved topical formulations, including gels and ointments. In each of those cases, based on the concentrations used, I am confident Carbomer is being used as a polymer thickening agent, just as Taro has done. Similarly, the IID identifies a single use of Sepineo P 600 in an

[22] For clarity, in my report I have applied the definition of a person of skill in the art articulated by Dr. Constantinides. Opening Expert Report of Panayiotis P. Constantinides, Sept. 11, 2018, at Section IV. My opinions would not change were I to use the definition offered by Dr. Lane. *See* Lane Report at ¶¶ 32-35.

approved gel product. Based on the concentration it is my full expectation the gel product identified is Aczone® 7.5% Gel.

111. The IID database confirms what any person of ordinary skill in the art would understand, namely that Carbomer *alone* is the polymer thickening agent in Taro's Product and Sepineo P 600 alone is the polymer-based thickening agent in Aczone® 7.5% Gel. Thickening agents are just that, agents. They are polymer or polymer based products used to thicken topical pharmaceutical formulations. There is absolutely no justification in the patent or otherwise to look at other excipients in a formulation and label them a thickening agent. The fact Sepineo P 600 is a commercial product sold to thicken formulations is irrelevant. Almirall's NDA makes absolutely clear it is a single agent added to its formulation, unlike the Taro Product. *See* ALG_ACZ0004101-2.

112. In summary, I fundamentally disagree with Dr. Lane's opinion that the Oil-Phase Excipients in Taro's Product combine with Carbomer to create a polymeric thickening agent. Carbomer serves that function alone. The Oil-Phase Excipients are present purely to create an oil-phase in the gel, *i.e.* to create an emulgel. The claims don't require the topical formulations of the claims be emulgels and the term PVB in the patents doesn't incorporate that requirement, as discussed in detail above.

C. Taro's Product Does Not Literally Meet The Claim Limitations of Claim 1 of the '219 Patent And Therefore Taro Cannot Induce Literal Direct Infringement of Claim 1

113. It is my understanding Almirall is not alleging Taro induces direct literal infringement of claim 1 of the '219 patent, and Dr. Lane does not offer an opinion on direct literal infringement in her report.[23] Nevertheless, for completeness I note Taro's Product does

[23] *See also*, Nov. 16, 2017, Initial Infringement Contentions and Sept. 11, 2018, Final Infringement Contentions, wherein Almirall relies solely upon the doctrine of equivalents.

not meet each element of the topical pharmaceutical composition described in claim 1. Specifically, Taro's Product does not contain A/SA in any amount. Therefore, it is my opinion Taro will not induce direct literal infringement of claim 1 of the '219 patent irrespective of the labeling indicated in Taro's ANDA.

D. Taro's Product Does Not Infringe Claim 1 of the '219 Patent Under the Doctrine of Equivalents

114. As has been explained in detail above, Dr. Lane claims Carbomer and the Oil-Phase Excipients in Taro's Product are equivalent to Sepineo P 600. Dr. Lane's framing of the analysis is incorrect, both because it is inconsistent with the express language of Claim 1 and improperly identifies the thickening agent in Taro's Product. Dr. Lane's argument is also barred pursuant to the doctrines of prosecution history estoppel, commitment to the public and ensnarement. As discussed below, the thickening agent and concentrations in Taro's Product are not equivalent to "about 2% w/w to about 6% w/w of a polymeric viscosity builder comprising [A/SA]."

1. One Percent of a PVB is Not Equivalent to Two to Six Percent of a PVB

115. The claims require "about 2% w/w to about 6% w/w of a polymeric viscosity builder." Taro's Product contains [redacted] w/w of Carbomer, the sole thickening agent in the formulation. The difference between [redacted] and about 2% w/w is not an insubstantial difference. The amount of thickening agent included in a product impact viscosity, drug dissolution, bioavailability and other clinical drug attributes. The '219 patent includes numerous examples of various thickening agents being used across a range of concentrations, demonstrating small incremental differences in the amount of a thickening agent matter. This is consistent with my own experience. Further, I do not believe a formulation containing Carbomer at about 6% w/w would be viable due to the potential for Carbomer to precipitate out of the formulation.

116. During prosecution, the applicants conceded the difference between at least 0.85% w/w and about 2% w/w and 6% w/w was significant. As explained, the patent office rejected the proposed claims in the Divisional Application as being obvious over Garrett, which taught the use of Carbomer as a thickening agent. *See* Section XX, *supra.* In response, applicants argued:

> Garrett teaches that a preferred composition comprises … about 0.85% w/w/ carbopol 980 is used as a thickening agent. … The new formulation of the instant claims does not include carbomer such as Carbopol®, but instead utilizes as [A/SA] … and *at a much higher concentration* (about 2% to about 6% w/w) as compared to what Garrett teaches for its thickening agent.

ALG_ACZ0000284 (Emphasis added). This argument is consistent with my own opinion, namely that the difference between [redacted] and "about 2% w/w to 6% w/w" of a polymer or polymer-based thickening agent is not insubstantial, and therefore not equivalent.

117. Taro's Product does not have an equivalent concentration of a thickening agent to the claimed ranges, and therefore does not meet all limitations of the '219 patent, either literally or under the doctrine of equivalents. As such, Taro's Product, if sold pursuant to its labeling cannot infringe Claim 1 of the '219 patent.

a. Carbomer Is Not Equivalent to A/SA or Sepineo P 600

118. Carbomer is a cross-linked polyacrylic acid resin. To dissolve Carbomer in water a neutralizing agent, such as a sodium hydroxide solution, must be added to adjust pH. Neutralizing a Carbomer solution above pH 5 resulted in ionization of the carboxylic acid groups in the polymers, the creation of ion-dipole interactions within the dissolution medium and dissolution of the polymer.

119. Mixing Carbomer must be carefully controlled to avoid clumping and/or precipitation of the polymer. Once the Carbomer is reconstituted, it is carefully added to the remaining excipients. At each step, the temperature, rate of addition of the polymer and mixing

rate must be monitored and controlled. An example of this manufacturing process is described above, at Section XX describing the manufacturing of Taro's Product.

120. A/SA is not insubstantially different from Carbomer. As described above, A/SA has a completely different chemical structure compared to Carbomer. Additionally, A/SA is a "copolymer", meaning it consist of two different polymers cross-linked. (Carbomer is a single polymer.) The fact A/SA is a copolymer is important because the ratio of one polymer to other can change the characteristics of the product. The inventors controlled this aspect by purchasing the Sepineo P 600 product from Seppic. At the time of the invention, and now, Seppic marketed the Sepineo P 600 product as being simpler than other polymeric thickening agents because (1) it was simpler to mix; and (2) did not require neutralization. (Seppic Sepineo™ P 600 Brochure (2008) (ALG_ACZ0375156-57)). These advantages were similarly important to Almirall, as stated in its NDA: "Sepineo P 600 was chosen as a gelling agent for … ease of processing relative to Carbopol 980." ALG_ACZ0264309.

121. The difference in manufacturing between Taro's Product and Aczone® 7.5% Gel is stark. Unlike Taro's process, Aczone® 7.5% Gel is manufactured by combining dapsone, methylparaben and DGME, mixing Sepineo P600 with water and then combining the two and mixing. *See* ALG_ACZ0004101-103. The differences between these two processes are not insubstantial. It is clear Carbomer is neither performing the same function as A/SA (or Sepineo P 600) nor is it performing its function in the same way.

122. The Warner Declaration submitted in connection with prosecution of both the Parent Application and the Divisional Application unequivocally stated the A/SA copolymer emulsion was selected over Carbomer because Carbomer was seen to precipitate at higher DGME concentrations and it was concluded the A/SA polymer was more robust.

ALG_ACZ_0000291-292. This is repeated in the NDA describing thickener selection. *See* ALG_ACZ-264306. Dr. Warner also explained in his deposition why he believed, and continues to believe presumably, Carbomer is not as robust a thickening agent. Warner Dep, 76:6-77:16 and 114:15-119:20.

123. Dr. Lane does not address how, if at all, Carbomer in Taro's Product is as "robust" as either A/SA or Sepineo P 600. To the extent it is more "robust", clearly that would constitute a solution to problem the inventors were not able to solve. In any event, it demonstrates an additional reason why the use of Carbomer in Taro's Product is not an insubstantial difference from the use of a thickening agent comprising A/SA. (Certainly, the more difficult manufacturing associated with the use of Carbopol relative to Sepineo P 600 remains.)

124. The only evidence Dr. Lane purports to offer supporting an argument that Carbomer and A/SA are similar is to state: "[Carbomer] and A/SA are both polymers that act in the same way to create a three-dimensional gel-like structure." Lane Report at ¶ 87. She goes on to state both "swell to increase the viscosity of the formulation in the same way." *Id.* Her arguments are not convincing for a number of reasons. First, if the fact both are polymers creating a three-dimensional gel like structure is the standard, it makes little sense the inventors claimed A/SA, argued A/SA was superior to the prior art and received a patent covering the use of A/SA as the "sole thickening agent." *See*, TARO-DG-00064186. Furthermore, although both act to increase viscosity, as discussed above, they do not do so in the same way. Carbomer is pH dependent whereas the A/SA product used by Almirall is not. As such, Dr. Lane's brief attempt to argue equivalence of Carbomer to A/SA is not convincing and I disagree with her opinion.

125. In short, the inventors were issued a patent based on the argument their PVB was different from Carbomer and that Carbomer was unexpectedly not as robust. Both during prosecution of the Divisional Application and in the NDA, the benefits of A/SA (and Sepineo P 600) over Carbopol were repeatedly argued. I see nothing in Taro's Product, formulation or manufacturing suggesting Taro somehow overcame these differences. Carbomer is not insubstantially different from a PVB comprising A/SA, it does not function in the same way and does not render the same results.

b. The Comparisons of Clinical and Non-Clinical Attributes of Aczone® 7.5% Gel and Taro's Product Do Not Evidence an Insubstantial Difference Between Taro's Thickening Agent and A/SA or Sepineo P 600

126. Dr. Lane seeks to show equivalency between Taro's thickening agent and Sepineo P 600 through clinical and non-clinical comparisons between Aczone® 7.5% Gel and Taro's Product characteristics. These comparisons are flawed based on Dr. Lane's incorrect identification of the thickening agent in Taro's Product. Furthermore, the comparisons she makes draw no connection between Carbomer on the one hand and A/SA on the other. Because she never demonstrates any attribute is attributable to a claimed feature in the '219 patent, *i.e.* A/SA, her comparisons are of little value.

127. The first comparison Dr. Lane seeks to make, at Section 5(b)(2) of her report, relates to the rheological profiles of the two products. Many of the properties tested are impacted by Taro's thickening agent, Carbomer (i.e. the viscosity and shear stress). However, it is not surprising two different products can have similar rheological profiles, even achieving them in different ways. Based on my review of Almirall's development documents and the deposition of Kevin Warner, the goals in formulating a 7.5% dapsone product at Almirall was that the product would have similar characteristics to the Aczone® 5% Product.

128. However, the claims do not require a specific rheological profile in any event. A person of skill in the art would not know the rheological profile of *any* of the tens of embodiments disclosed in the patent. Furthermore, the patent explicitly states the compositions can be modified in different ways to achieve different composition characteristics. A skilled person would have known the inventors were not claiming any specific rheological profile and therefore Dr. Lane's reliance on this information is misplaced.

129. The same is true of other data Dr. Lane relies on, including solubility, particle size, and release rates. The '219 patent includes absolutely no disclosure, not in the patent itself and none was submitted during prosecution, to lead a skilled artisan to believe specific characteristics of solubility, particle size and release rates were being claimed as a benefit of the invention. All of these characteristics can be influenced in innumerable ways by the addition and removal of excipients and also by controlling the concentrations of excipients. The claims of the '219 patent simply do not speak to any of these results. Furthermore, Dr. Lane has made no showing that specific characteristics of Aczone® 7.5% Gel are attributable to the only thickening agent claimed, namely A/SA. In fact, it is clear from her report she attributes many, if not all, the product characteristics to unclaimed elements of the Aczone® product. In short, any similarity of characteristics between Taro's and Almirall's products can be achieved in any number of ways that have nothing to do with the '219 patent claims and, specifically, A/SA.

130. An additional reason Dr. Lane's comparisons are unconvincing relates to studies Almirall performed with Carbomer formulations containing Polysorbate 80. It my understanding, based on information I have reviewed, Almirall studies the impact of Polysorbate 80 in Carbomer formulations to determine the impact on particle size. The results were interpreted by Almirall to mean addition of Polysorbate 80 did not result in a formulation with particle size seen

with the Sepineo P 600 formulations tested. (The comparisons are problematic in that too many of the excipients and concentrations differ between formulations making it near impossible to determine how characteristics of the formulations are impacted by the multiple formulation factors). [redacted] This further supports my opinion Taro's thickening agent is not equivalent to a PVB comprising A/SA.

131. The '219 patent, in any event, is not convincing in its attempt to evidence particle size differences between Carbomer versus A/SA formulations. Figure 2 is not labeled to identify A1 through A4. However, it is my understanding A1 and A4 are Carbomer formulations and A3 and A2 are A/SA formulations. (A4 appears to be the formulation containing 1.25% Carbomer and .2% Polysorbate 80.) Looking at the images, it appears the particle size of one of the Carbomer formulations, namely A1, may be smaller than one of the A/SA formulations, namely A3. As such, I do not find particle size comparisons to the product convincing as they have not been demonstrated to be attributable to the Carbomer and/or A/SA.

E. Taro's Does Not Infringe Dependent Claims 2, 4 and 5 of the '219 Patent

132. The only independent claim asserted against Taro is Claim 1. As explained in detail above, it is my opinion Taro's Product does not meet all the claim limitations of the only independent claim, either literally or under the doctrine of equivalents. As such, it would be impossible for Taro's Product, if sold according to its label, to induce infringement of any claim depending on Claim 1. For this reason, it is my opinion Taro does not infringe the asserted dependent claims 2, 4 and 5.

XI. CONCLUSION

133. In my opinion, Taro's Product, if sold, would not infringe claims 1, 2, 4 or 5 of the '219 patent.

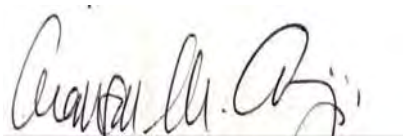
X. RESERVATION OF RIGHTS

134. I have based my opinions and analysis on documents and information available to me at the time I signed this report. If and when any new evidence arises, I reserve the right to supplement or modify my opinions to reflect that evidence.

135. In the event Plaintiff submits any reply to this expert report, I reserve the right to respond to any issues raised by such a reply.

136. If called to testify, my testimony may include an explanation of the scientific principles that underlie the opinions expressed in this report.

137. I reserve the right to make and use demonstratives to help explain my opinions.



November 6th, 2018 Mansoor M. Amiji, Ph.D., R.Ph.

EXHIBIT 3

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ALMIRALL, LLC, Plaintiff, v. TARO PHARMACEUTICAL INDUSTRIES LTD. and TARO PHARMACEUTICALS, INC., Defendants.	C.A. No. 17-663 (JFB) (SRF) (Consolidated)

"CONFIDENTIAL" Under the Protective Order

REPLY EXPERT REPORT OF MAJELLA E. LANE, Ph. D.

I declare under penalty of perjury of the laws of the United States of America that the following is, to the best of my knowledge and belief, true and correct.

Dated: November 20, 2018

Majella E. Lane, Ph.D.

Table of Contents

I. Introduction

1. I am the same Majella E. Lane who previously rendered an expert report on behalf of Plaintiff in the above-captioned case on September 11, 2018 (my "Initial Report").[1] I am a Senior Lecturer and the Director of the Skin Research Group at the University College London School of Pharmacy, United Kingdom. My experience and qualifications are described more fully in my Initial Report.

2. My Initial Report sets out my opinion that the use of Taro's ANDA Product in accordance with its proposed labeling would infringe at least claims 1, 2, 4, and 5 of the '219 patent. I incorporate my Initial Report in its entirety in this, my Reply Report, and use the same defined terms as in my Initial Report.

3. I provide this Reply Report in support of my Initial Report and in response to the Rebuttal Expert Report of Mansoor M. Amiji, Ph.D., R.Ph. ("Amiji Report") on behalf of Defendants. In the Amiji Report, Dr. Amiji opines that Taro's ANDA Product does not infringe the '219 patent under the doctrine of equivalents, and additionally, that Almirall's infringement claims are barred. I disagree with the opinions in the Amiji Report, as I further describe below.

II. Materials Considered

4. In forming my opinions described in this report, I have reviewed and/or relied on: (1) the materials identified in my Initial Report and Exhibit 3 to that report; (2) the Amiji Report; (3) the Expert Report of Panayiotis P. Constantinides, Ph.D. dated November 6, 2018 ("Constantinides Ensnarement Report"); (4) the Responsive Expert Report of Alexander M. Klibanov, Ph.D. dated November 16, 2018 ("Klibanov Ensnarement Report"); (5) the

[1] I understand that Almirall, LLC ("Almirall") has been substituted for the original plaintiff in this lawsuit, Allergan, Inc. My opinions in my Initial Report apply equally as though provided on behalf of Almirall as opposed to Allergan, Inc.

Responsive Expert Report of Julie Harper, M.D. dated November 15, 2018 ("Harper Ensnarement Report"); (6) the prosecution history of the '219 patent; and (7) U.S. Patent No. 9,161,926 ("the '926 patent") and its prosecution history. I have also relied on my knowledge, experience, and education obtained over the last 26 years in the fields of pharmaceutics and pharmaceutical technology.

III. Summary of Opinions

5. In my opinion, and as I explained in my Initial Report, Taro's ANDA Product infringes the asserted claims of the '219 patent. Nothing in the Amiji Report changes my opinion. Further, based on my understanding of the relevant legal principles as they have been explained to me by counsel, it is my opinion that Almirall's infringement claims are not barred. In brief, I disagree with the Amiji Report as follows:

- Taro's ANDA Product infringes under the doctrine of equivalents.
    - Dr. Amiji's opinion that Taro's polymeric viscosity builder is carbomer ***only*** is inconsistent with a POSA's understanding of Taro's product, the claims, the disclosure of the '219 patent, and Taro's own admissions in its ANDA. A POSA would understand that carbomer, [redacted] are all necessarily part of Taro's polymeric viscosity builder as contemplated by the '219 patent, and that therefore, Taro's product contains [redacted] w/w of a polymeric viscosity builder that is equivalent to the claimed "about 2% w/w to about 6% w/w of a polymeric viscosity builder comprising [A/SA]."
- Almirall's claims are not barred by prosecution history estoppel.
    - Because Applicants ***broadened*** the claims during prosecution, there is no narrowing amendment. Therefore, I understand that amendment-based prosecution history estoppel does not apply.
    - Because Applicants never clearly and unmistakably surrendered Taro's polymeric viscosity builder as a possible equivalent of the claim element "a polymeric viscosity builder comprising [A/SA]", I understand that argument-based prosecution history estoppel therefore does not apply. Even assuming as true the premises of the corresponding opinion expressed in Dr. Amiji's report, Dr. Amiji

proposes only that Applicants surrendered polymeric viscosity builders consisting of carbomer ***alone***. He does not propose that Applicants surrendered any carbomer-***based*** polymeric viscosity builder, such as that employed in Taro's ANDA Product, as equivalent to the claimed polymeric viscosity builder. Accordingly, Dr. Amiji's opinions are misguided.

- Almirall's claims are not barred by the disclosure-dedication rule, as I understand it. The statements that Dr. Amiji identifies regarding carbomer ***alone*** are not a precise and clear disclosure of Taro's carbomer-***based*** polymeric viscosity builder, nor do they characterize or otherwise describe it as an alternative to the polymeric viscosity builder element of the asserted claims.

- My opinion with respect to ensnarement is limited to what the hypothetical claim should properly be. I defer to Drs. Harper and/or Klibanov as to any opinion concerning the validity of the hypothetical claim I propose as appropriate.

IV. Legal Standards

A. Prosecution History Estoppel

6. I have been advised by counsel that prosecution history estoppel is a legal limitation on the range of equivalents available to a patentee under the doctrine of equivalents. It prevents a patentee from recapturing subject matter surrendered during patent prosecution.

7. I have been advised by counsel that prosecution history estoppel may arise in two ways: (1) by making a narrowing amendment to the claim ("amendment-based estoppel"); or (2) by surrendering claim scope through argument to the patent examiner ("argument-based estoppel"). I understand that amendment-based estoppel requires an amendment or cancellation during prosecution to ***narrow*** the literal scope of a claim. I understand that argument-based estoppel requires clear assertions or arguments made by the patentee to the examiner during prosecution that show a clear and unmistakable surrender of subject matter.

B. Disclosure-Dedication / Dedication to the Public

8. I have been advised by counsel that a patent applicant who discloses but does not claim subject matter has dedicated that matter to the public and cannot reclaim the disclosed matter under the doctrine of equivalents. The disclosure must be precise and clear, and of such specificity that a POSA could identify the subject matter that had been disclosed and not claimed.

9. I have further been advised by counsel that before unclaimed subject matter is deemed to have been dedicated to the public, that unclaimed subject matter must have been identified by the patentee as an alternative to a claim limitation. Whether a POSA ultimately could employ the disclosures of the patent to implement a purported equivalent does not amount to actually disclosing to a POSA that equivalent as an alternative to a claim limitation.

C. Ensnarement

10. I have been advised by counsel that a patentee cannot assert a doctrine of equivalents theory if it will encompass or "ensnare" the prior art. I have further been advised by counsel that a hypothetical claim analysis is a practical method to determine whether an equivalent would impermissibly ensnare the prior art. Under this analysis, a patentee proposes a hypothetical claim that is sufficiently broad in scope to literally encompass the accused product or process. While slight broadening is permitted, a patentee's hypothetical claim may not add any narrowing limitations. I understand that if the hypothetical claim would have been allowed by the PTO over the prior art, then the prior art does not bar the application of the doctrine of equivalents.

V. The '219 Patent

11. I reviewed the claims and the specification of the '219 patent in my Initial Report. Below, I highlight certain aspects of the claimed polymeric viscosity builder that are relevant to my Reply Report.

12. The '219 patent's specification explains that the claimed polymeric viscosity builder serves specific functions in the topical pharmaceutical composition of the invention. For example, it influences the quality of the formulation by influencing dapsone crystallization and allowing for compositions with increased DGME concentrations.[2] It also improves the aesthetics of the composition by minimizing the intensity of yellowing of the composition as well as the "gritty" feeling upon application.[3]

13. The specification discloses, as embodiments of the invention, polymeric viscosity builders that "comprise" A/SA and that have A/SA as the polymeric base of a multi-component thickener or emulsion.[4] A POSA would understand the '219 patent to disclose, *e.g.*, A/SA-based emulsions formed when the otherwise immiscible oil phase is held in place by surfactants to form a stable composition.[5] The disclosure specifies that "[i]n some embodiments, the polymeric viscosity builder is acrylamide/sodium acryloyldimethyl taurate copolymer, . . . Isohexadecane, Sorbitan Oleate, water, and Polysorbate 80," also referred to in the specification

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[2] Ex. 1, '219 Patent, Abstract, ALG_ACZ0000565, at ALG_ACZ0000566; *id*., col. 2 ll. 54–61, ALG_ACZ0000565, at ALG_ACZ0000570.

[3] *Id*.

[4] *See, e.g*., *id*., col. 8 ll. 12-16, ALG_ACZ0000565, at ALG_ACZ0000573; *id*., col. 10 ll. 49-54, ALG_ACZ0000565, at ACZ0000574; *id*., tbls. 1–4, 6, ALG_ACZ0000565, at ALG_ ALG_ACZ0000575–76 (listing "acrylamide/sodium acryloyldimethyl copolymer based thickener" and "acrylamide/sodium acryloyldimethyl copolymer emulsion").

[5] *See further* Initial Report, paras. 83-87.

as Sepineo P 600.[6] A POSA reading these disclosures in the specification would understand that these elements – a polymer (A/SA), oil (isohexadecane), and surfactants (sorbitan oleate and Polysorbate 80) – collectively form a "polymeric viscosity builder" of the invention.[7]

14. As I explained in my Initial Report, the polymeric viscosity builder in Taro's ANDA Product contains Carbomer homopolymer type C (commercially known as Carbopol 980 and referred to in this report as "carbomer"), as well as [redacted][8] The specification of the '219 patent discloses compositions that include carbomer.[9] Unlike the multi-component A/SA-based thickeners and emulsions described in the specification, carbomer is always named on its own, and never as part of the polymeric viscosity builder of the claims.[10]

VI. The Prosecution History

15. U.S. Patent Application No. 14/885,805 ("the '805 application"), the application that issued as the '219 patent, was filed as a divisional application from U.S. Patent Application No. 14/082,955, which issued as U.S. Patent No. 9,161,926.[11] I have reviewed the prosecution histories of the '219 patent and the parent '926 patent and am prepared to testify regarding how they would be interpreted by a POSA.

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[6] *See, e.g.*, Ex. 1, '219 patent, col. 5 ll. 47–50, ALG_ACZ0000565, at ALG_ACZ0000572; *id.*, tbl. 7, ALG_ACZ0000565, at ALG_ACZ0000577 (listing "Sepineo P 600").

[7] *See further* the discussion below, under "VII.A. The Claims Encompass an Emulgel with a Polymeric Viscosity Builder Comprising A/SA and Non-Polymer Excipients".

[8] Initial Report, para. 68-131.

[9] *See, e.g.,* Ex. 1, '219 patent, col. 6 ll. 34-40, ALG_ACZ0000565, at ALG_ACZ0000572; *id.*, col. 8 ll. 35-51, ALG_ACZ0000565, at ALG_ACZ0000573; *id.*, col. 11 ll. 6-25, ALG_ACZ0000565, at ALG_ACZ0000575.

[10] *Id.*

[11] *See* Ex. 1, '219 patent, Cover at (62), ALG_ACZ0000565, at ALG_ACZ0000566.

16. The Amiji Report describes Dr. Amiji's review of the prosecution history. It includes several critical misstatements and omissions, concluding that "the prosecution history makes clear the applicants were focused on the novelty of using A/SA as the thickening agent and expressly disclaimed Carbomer formulations."[12] To the contrary, the record shows that Applicants were focused on the specific amount (7.5%) of dapsone ***in combination with*** the polymeric viscosity builder (and also with DGME), and that Applicants ***broadened*** the polymeric viscosity builder claim limitation during the prosecution. I provide a short summary of the '219 patent prosecution below.

A. Prosecution of the '219 Patent

17. The '805 application was filed with ten claims covering methods of treating a dermatological condition with topical dapsone compositions. Claim 1 read:[13]

> **1.** A method for treating a dermatological condition comprising administering to a subject in need thereof a topical pharmaceutical composition comprising:
>
> about 7.5% w/w dapsone;
>
> about 30% w/w to about 40% w/w diethylene glycol monoethyl ether;
>
> about 2% w/w to about 6% w/w of a polymeric viscosity builder consisting of acrylamide/sodium acryloyldimethyl taurate copolymer; and
>
> water;
>
> wherein the topical pharmaceutical composition does not comprise adapalene.

18. Importantly, when filed, each of the claims (directly or indirectly) required the use of A/SA ***solely*** as the polymeric viscosity builder, by use of the term "consisting of".[14] It

[12] Amiji Report, para. 71.

[13] *See* '219 prosecution history, ALG_ACZ0000001, at ALG_ACZ0000025–26.

appears that none of the claims as filed – or at any point in the prosecution – referred to carbomer.

19. Among other things, the Examiner rejected the pending claims as obvious over WO 2009/108147 ("Garrett I") in view of WO 2010/105052 ("Hani"), and in further view of WO 2009/061298 ("Garrett II").[15] I note that Garrett I is the same prior art upon which the Amiji Report and the Constantinides Ensnarement Report rely for their ensnarement opinions. The Examiner stated that Garrett I taught topical dapsone compositions with all the features of the claimed invention, ***except***: (1) A/SA and the exact claimed amount of A/SA; (2) the exact claimed amount of DGME; and (3) the exact claimed amount of dapsone.[16] The Examiner noted that Hani taught the use of A/SA as a thickener in topical personal care compositions.[17] The Examiner concluded that the substitution of A/SA (disclosed in Hani) for Carbopol 980 (disclosed in Garrett I) was *prima facie* obvious as they were both well known to be suitable thickening agents for topical personal care products.[18]

20. In response to this obviousness rejection, Applicants submitted a declaration by a co-inventor of the '219 patent, Dr. Kevin Warner (the "Warner Declaration"), and argued that the claims were not obvious.[19] Applicants stated that there were at least three distinctions between the invention and the cited art: (1) the specific amount of dapsone (7.5%);

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[14] *Id.*

[15] *See* Nov. 18, 2015 Office Action, p. 8-12, ALG_ACZ0000001, at ALG_ACZ0000060–64.

[16] *Id*., p. 9, ALG_ACZ0000001, at ALG_ACZ0000061.

[17] *Id.*

[18] *See id*., p. 10, ALG_ACZ0000001, at ALG_ACZ0000062.

[19] *See* Feb. 18, 2016 Response and Warner Dec., ALG_ACZ0000001, at ALG_ACZ0000279–94.

(2) the use of Sepineo P 600 (a multi-component A/SA-based thickener) as the sole thickening agent in a topical dermatological formulation comprising dapsone; and (3) the specific amount of Sepineo P 600.[20] Applicants specifically distinguished Garrett I on the basis that, whereas "Garrett teaches that a preferred composition comprises about 5% w/w dapsone wherein about 0.85% w/w Carbopol 980 [*i.e.*, carbomer alone] is used as a thickening agent," "[t]he instant claims recite a new formulation of dapsone wherein the active ingredient is about 7.5% w/w dapsone and an entirely new thickening agent [*i.e.*, Sepineo P 600] is employed."[21]

21. The Warner Declaration submitted concurrently with Applicants' Response described unexpected results from this new combination of elements.[22] It described the development of a new topical dapsone formulation with a dapsone concentration that was higher (7.5% w/w) than the prior dapsone formulation (5% w/w). According to Dr. Warner, the inventors unexpectedly discovered that Carbopol 980 was incompatible with the increased amount of DGME needed to dissolve the higher concentration of dapsone and resulted in undesirable polymer aggregates.[23] On the other hand, the multi-component Sepineo P 600 was compatible with the DGME concentration and also provided a smaller dapsone particle size distribution.[24] Thus, the inventors selected Sepineo P 600 as the gelling agent for the dapsone 7.5% formulation.[25]

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[20] *See id.*, p. 6, ALG_ACZ0000001, at ALG_ACZ0000284.

[21] *Id*.

[22] *See id.*, Warner Dec., ALG_ACZ0000001, at ALG_ACZ0000290–94.

[23] Warner Dec., paras. 7-8, ALG_ACZ0000001, at ALG_ACZ0000291–92.

[24] Warner Dec., para. 10, ALG_ACZ0000001, at ALG_ACZ0000292.

[25] *Id*.

22. The Examiner accepted Applicants' arguments that the claimed formulation had unexpected properties and withdrew its obviousness rejection.[26] However, the Examiner maintained its rejection for lack of enablement over the range of dermatological conditions claimed and issued a new rejection based on improper claim dependencies.[27]

23. In response, Applicants amended the claims as follows (insertions underlined and bolded; deletions with strikethrough):

> **1.** A method for treating a dermatological condition **selected from the group consisting of acne vulgaris and rosacea** comprising administering to a subject having the dermatological condition **selected from the group consisting of acne vulgaris and rosacea** a topical pharmaceutical composition comprising:
>
> about 7.5% w/w dapsone;
>
> about 30% w/w to about 40% w/w diethylene glycol monoethyl ether;
>
> about 2% w/w to about 6% w/w of a polymeric viscosity builder **comprising** ~~consisting of~~ acrylamide/sodium acryloyldimethyl taurate copolymer; and
>
> water;
>
> wherein the topical pharmaceutical composition does not comprise adapalene.

24. Notably, and as a POSA would understand, Applicants ***broadened*** the polymeric viscosity builder limitation from "a polymeric viscosity builder ***consisting of*** [A/SA]" to one "***comprising*** [A/SA]."[28] This important detail from the file history is ignored by Dr. Amiji in his report. In their Remarks, Applicants highlighted this broadening amendment and

[26] Mar. 7, 2016 Office Action, p. 2-4, ALG_ACZ0000001, at ALG_ACZ0000503–05.

[27] *Id*., p. 4-7, ALG_ACZ0000001, at ALG_ACZ0000505–08.

[28] *Compare* Claims in Feb. 18, 2016 Response, p. 2-3, ALG_ACZ0000001, at ALG_ACZ0000280–81 *with* Claims in Sept. 07, 2016 Response, p. 12-13, ALG_ACZ0000001, at ALG_ACZ0000530–31 (emphasis added).

argued "that the pending Claims are still patentable in view of the cited prior art, and that relevant arguments made in the [prior] response and the [Warner] declaration… still support the patentability of the amended pending claims."[29]

25. Based on Applicants' arguments, the Patent Office allowed the claims on September 30, 2016.[30] The Examiner referred to the evidence from the Warner Declaration and cited the explanation in its prior Office Action as to why the claimed method was nonobvious over the prior art.[31]

VII. Taro's ANDA Product Will Induce Infringement of the Asserted Claims

26. As I explained in my Initial Report, Taro's ANDA product will induce infringement of at least claims 1, 2, 4, and 5 of the '219 patent.[32] In his report, Dr. Amiji appears to concede that every limitation of the asserted claims is literally met, aside from the limitation of "about 2% w/w to about 6% w/w of a polymeric viscosity builder comprising [A/SA]." His only opinion supporting non-infringement is that "the [redacted] w/w Carbomer used in Taro's Product is not equivalent to 'about 2% w/w to about 6% w/w of a polymeric viscosity builder comprising [A/SA]'."[33] However, Dr. Amiji's analysis is flawed and mischaracterizes my opinion, as I describe below. My opinion remains unchanged that Taro's [redacted] % carbomer-based polymeric viscosity builder is equivalent to the polymeric viscosity builder element of the asserted claims, and that therefore, Taro's ANDA Product will induce infringement of the asserted claims.

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[29] *See* Sept. 7, 2016 Response, p. 14, ALG_ACZ0000001, at ALG_ACZ0000532.

[30] Sept. 30, 2016 Notice of Allowability, ALG_ACZ0000001, at ALG_ACZ0000544-46.

[31] *Id.*, p. 2, ALG_ACZ0000001, at ALG_ACZ0000545.

[32] *See* Initial Report, paras. 48-154.

[33] *See* Amiji Report, para. 98.

A. The Claims Encompass an Emulgel With a Polymeric Viscosity Builder Comprising A/SA and Non-Polymer Excipients

27. Dr. Amiji and I fundamentally disagree about the role that non-polymer excipients play in the polymeric viscosity builder element of the asserted claims (and in Taro's ANDA Product, as I describe in the next section). Dr. Amiji states that "the function of Polysorbate 80, sodium monooleate and isohexadecane [*i.e.*, the non-polymer excipients in Sepineo p 600] is creating an emulsion" and that creating that emulsion "has nothing to do with the claim element reciting a polymeric thickening agent."[34] This is incorrect. A POSA would clearly recognize that the addition of an oil phase (such as isohexadecane) to a formulation would alter the viscosity, feel and aesthetic appearance of a topical formulation.[35] A POSA would also know that emulsifiers such as Polysorbate 80 and sorbitan monooleate are necessary to stabilize the oil phase in an aqueous phase.[36] Thus, the oil and emulsifiers do not ***only*** create an emulgel; they create a system that is stable and that has a different appearance and feel than in their absence. A POSA would understand that in an accused product such as an emulgel, the polymer, oil and emulsifiers ***together*** function as the claim element "a polymeric viscosity

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[34] Amiji Report, para. 103.

[35] Dr. Amiji mischaracterizes my report when he describes my opinion as "that the Aczone® 7.5% gel and Taro's Product formulations not included an oil-phase those products would be "simple liquid formulations not suitable for treatment of acne because they would not stay on the skin." *See* Amiji Report, para. 102. To clarify, the exact statement I made in paragraph 84 of my report was: "***Without their respective polymeric viscosity builders***, both Taro's ANDA Product and ACZONE Gel, 7.5% would include only an aqueous phase and would be simple liquid formulations not suitable for treatment of acne because they would not stay on the skin". (Emphasis added).

[36] *See, e.g.,* Ex. A, Giulia Bonacucina et al., "Characterization and Stability of Emulsion Gels Based on Acrylamide/Sodium Acryloyldimethyl Taurate Copolymer," *AAPS PharmaSciTech*, vol. 10, no. 2 (June 2009) ("Bonacucina"), p. 369; Ex. B, Excerpts from Raymond C. Rowe et al., *Handbook of Pharmaceutical Excipients,* 6th ed. (2009) ("HPE"), p. 550 (discussing the Polyoxyethylene Sorbitan Fatty Acid Esters family); *id.*, p. 675 (discussing the Sorbitan Esters family).

builder comprising [A/SA]". This is not to say "that all thickening agents pursuant to the claims must result in emulgels," as Dr. Amiji asserts;[37] while the asserted claims are broader than emulgels, they do encompass emulgels, including Taro's ANDA Product.

28. In addition to being contrary to a POSA's understanding, Dr. Amiji's position is inconsistent with the '219 patent's specification, which describes an embodiment of the claimed invention where the polymeric viscosity builder is an "emulsion" or "[A/SA-]***based*** thickener" comprising isohexadecane, sorbitan monooleate, and Polysorbate 80[38] – the exact excipients Dr. Amiji states "ha[ve] nothing to do with the claim element reciting polymeric viscosity builder."[39]

29. Dr. Amiji mischaracterizes my opinion when he says, "Dr. Lane's entire analysis treats the missing claim element as being Sepineo P 600, instead of A/SA."[40] As I described in my Initial Report, Sepineo P 600 is an embodiment of the invention, well-known in the art, and specifically identified to the POSA in the '219 patent's specification. The relevant comparison is between Taro's polymeric viscosity builder and the claim term "about 2% w/w to about 6% w/w of a polymeric viscosity builder comprising [A/SA]", and that is the comparison I applied in my analysis.

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[37] Amiji Report, para. 101.

[38] *See, e.g.*, Ex. 1, '219 Patent, tbls. 1–4, 6, ALG_ACZ0000565, at ALG_ACZ0000575–76 (listing "acrylamide/sodium acryloyldimethyl copolymer based thickener" and "acrylamide/sodium acryloyldimethyl copolymer emulsion") (emphasis added); *id.*, col. 5 ll. 47–50, ALG_ACZ0000565, at ALG_ACZ0000572 ("[i]n some embodiments, the polymeric viscosity builder is acrylamide/sodium acryloyldimethyl taurate copolymer, . . . Isohexadecane, Sorbitan Oleate, water, and Polysorbate 80."); *id.*, tbl. 7, ALG_ACZ0000565, at ALG_ACZ0000577 (listing "Sepineo P 600").

[39] Amiji Report, para. 103.

[40] *Id.*, para. 99.

B. Taro's Polymeric Viscosity Builder Comprises Carbomer and [redacted]

30. In my Initial Report, I explained the POSA's understanding that the [redacted] is Taro's polymeric viscosity builder.[41] Dr. Amiji's insistence that "Carbomer… is the sole thickening agent in Taro's formulation"[42] ignores that Taro's polymeric viscosity builder serves substantially the same function, acts in substantially the same way, and achieves substantially the same result as the polymeric viscosity builder of the claimed invention and is insubstantially different from it.[43] Furthermore, it is inconsistent with a POSA's understanding of Taro's ANDA Product, the claim terms, the '219 patent's specification, and Taro's own representations in their ANDA, as I describe below.

31. As I explained above and in my Initial Report, a POSA would understand that the [redacted][44] Dr. Amiji dismisses the non-carbomer excipients (which he misleadingly calls the '[redacted]') as [redacted] As described above, the addition of an oil phase to an aqueous phase increases the viscosity of a formulation. A POSA would clearly understand that in order to stabilize the oil phase in the aqueous phase, emulsifiers

[41] *See* Initial Report, paras. 67-131.

[42] Amiji Report, para. 42; *see also id.*, para. 106.

[43] *See* Initial Report, paras. 67-131.

[44] *See id.*, paras. 71-131.

such as [redacted] would be needed.[45] Additionally, a POSA would know that both [redacted] are viscous liquids, as characterized by the Handbook of Pharmaceutical Excipients.[46] A POSA would understand that in all these ways, [redacted] are contributing to the increase in viscosity of the formulation compared with a simple aqueous formulation.

32. Dr. Amiji argues that the amount of thickener can significantly affect a product's viscosity, drug dissolution, bioavailability and other clinical drug attributes.[47] This only further demonstrates that Taro's polymeric viscosity builder is the ***combined*** [redacted] as opposed to simpl [redacted] wt. % carbomer, as Dr. Amiji suggests. If "[redacted]", as Dr. Amiji contends, then one would expect Taro's ANDA Product and ACZONE 7.5% product to exhibit different properties. However, as I demonstrate in my Initial Report and as Taro's ANDA shows, Taro's ANDA Product and Almirall's ACZONE 7.5% product are equivalent in all relevant aspects.[48] The only explanation is that Taro's ANDA Product does [redacted]

33. Dr. Amiji's opinion that carbomer [redacted] in Taro's ANDA Product is also inconsistent with a POSA's understanding of the claims.

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[45] *See* Ex. A, Bonacucina, p. 369; Ex. B, HPE, p. 550 (discussing the Polyoxyethylene Sorbitan Fatty Acid Esters family); *id.*, p. 675 (discussing the Sorbitan Esters family).

[46] *See* Ex. B, HPE, p. 551 (describing Polysorbate 80 as aa "Yellow oily liquid" and listing a viscosity of 425 mPas); *id.*, p. 676 (describing sorbitan monooleate as "Yellow viscous liquid" and listing a viscosity of 970-1080 mPas at 25° C).

[47] Amiji Report, paras. 115-117.

[48] Initial Report, paras. 71-131.

The Court has construed the term "polymeric viscosity builder" as "a polymer ***or polymer-based*** thickening agent."[49] The parties themselves have agreed that this claim term can include one or more components.[50]

34. The '219 patent's specification further proves that a POSA would understand [redacted] The specification explains that the polymeric viscosity builder of the invention is an ***emulsion*** (*i.e.*, involves an oil phase) and ***can contain oil and surfactants***.[51] The specification explains how the polymeric viscosity builder influences dapsone crystallization, allows for compositions with increased DGME concentrations, minimizes the yellowing of the composition, and reduces its "gritty" feeling.[52] A POSA knows [redacted][53] Even though these components are not claimed, a POSA would be able to identify them in Taro's ANDA Product based on this description in the specification.

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[49] Report and Recommendation at 6, June 6, 2018, D.I. 87 (emphasis added); Memorandum and Order at 8, Aug. 23, 2018, D.I. 107.

[50] Report and Recommendation at 6 n.1, June 6, 2018, D.I. 87.

[51] *See, e.g.*, Ex. 1, '219 Patent, tbls. 1–4, 6, ALG_ACZ0000565, at ALG_ACZ0000575–76 (listing "acrylamide/sodium acryloyldimethyl copolymer based thickener" and "acrylamide/sodium acryloyldimethyl copolymer emulsion"); *id.,* col. 5 ll. 47–50, ALG_ACZ0000565, at ALG_ACZ0000572 ("[i]n some embodiments, the polymeric viscosity builder is acrylamide/sodium acryloyldimethyl taurate copolymer, . . . Isohexadecane, Sorbitan Oleate, water, and Polysorbate 80."); *id.*, tbl. 7, ALG_ACZ0000565, at ALG_ACZ0000577 (listing "Sepineo P 600").

[52] Ex. 1, '219 Patent, Abstract, ALG_ACZ0000565, at ALG_ACZ0000566; *id.*, col. 2 ll. 54–61, ALG_ACZ0000565, at ALG_ACZ0000570.

[53] *See also* Initial Report, paras. 101-104.

35. Dr. Amiji states that "[i]n [his] long career, [he] [has] never heard anyone calling Carbomer, oil and surfactants in a formulation a 'thickening agent'."[54] Dr. Amiji's understanding is inconsistent with Taro's own representations to the FDA. Taro's ANDA states that Taro '[redacted][55] These unequivocal statements demonstrate that Taro itself viewed the combination of [redacted]

36. For at least these reasons, a POSA would know that the [redacted] in Taro's ANDA Product are not only present [redacted]

C. Taro's Polymeric Viscosity Builder is Equivalent to the Polymeric Viscosity Builder Element of the Asserted Claims

37. In my Initial Report, I outlined in detail how Taro's carbomer-based polymeric viscosity builder performs substantially the same function, in substantially the same way, to achieve substantially the same result as the claimed polymeric viscosity builder comprising A/SA.[56] In an attempt to distinguish these facts, Dr. Amiji makes numerous comparisons between carbomer ***alone*** and A/SA or Sepineo. The differences Dr. Amiji

[54] Amiji Report, para. 108.

[55] Ex. 11, Dapsone Gel, 7.5% Product Development Summary, TARO-DG-00000655, at TARO-DG-00000671; Ex. 15, Avramoff Dep. 42:7-43:12; *see also* Ex. 16, Final Formula Review Form, dated June 8, 2016, TARO-DG-00111048, at TARO-DG-00111049[redacted] *See further* Initial Report, paras. 45-47.

[56] *See* Initial Report, paras. 71-131.

highlights would be irrelevant to a POSA in the context of the claimed invention, for the following reasons.

38. Although carbomer and A/SA have different structural features, they are both polymeric thickening agents, *i.e.*, they are polymers that swell in the aqueous phase to create a three-dimensional network in which drug and solvent are entrapped. The manufacturing process would also not be relevant to a POSA, as it does not change how the polymer or copolymer behave when in contact with an aqueous phase. By contrast, a POSA, upon reading the patent and assessing whether an accused product infringes, would understand that the rheological characteristics of a topical formulation are critical for its stability, residence time on the skin and drug release profile. Dr. Amiji admits that Taro's ANDA Product and the ACZONE 7.5% product have similar rheological profiles.[57]

39. Dr. Amiji's analysis is flawed to the extent that he requires that these relevant characteristics be solely "attributable to a claimed feature in the '219 patent, *i.e.* A/SA".[58] They are attributable to the polymeric viscosity builder as a ***whole***. In any event, the relevant comparison is between Taro's carbomer-based polymeric viscosity builder and the claim element "a polymeric viscosity builder comprising A/SA" and the question is one of equivalence.

40. To further support his opinion, Dr. Amiji refers to statements in the Warner Declaration comparing Sepineo P 600 to carbomer as thickeners in 7.5 wt. % dapsone formulations.[59] While the Warner Declaration highlights certain advantages of Sepineo P 600 over carbomer ***alone***, it never says carbomer ***cannot*** be included as part of a greater polymeric

[57] Amiji Report, para. 127.

[58] *Id.*, para. 126.

[59] Amiji Report, paras 122-123.

viscosity builder – or even that a polymeric viscosity builder cannot be carbomer-***based***. Furthermore, Dr. Amiji obscures the intrinsic record in characterizing the '219 patent prosecution history when he says the inventors "argued ***A/SA*** was superior to the prior art and received a patent covering the use of ***A/SA*** as the sole thickening agent'."[60] In fact, Dr. Warner described advantages of the multi-component A/SA-based thickener Sepineo P 600, and the '219 patent correspondingly encompasses polymeric viscosity builders comprising A/SA and other components.

41. In sum, neither Applicants' arguments during prosecution nor the irrelevant differences Dr. Amiji highlights would change a POSA's understanding that Taro's carbomer-based polymeric viscosity builder comprising [redacted] is equivalent to the polymeric viscosity builder claim element of the asserted claims.

D. Taro's ANDA Product Will Contain the Claimed Amount of a Polymeric Viscosity Builder

42. Dr. Amiji's opinion that Taro's ANDA Product will contain [redacted] wt. % of a polymeric viscosity builder is based on his erroneous conclusion that [redacted][61] As described above, Taro's polymeric viscosity builder is [redacted][62] This falls within the claimed range of "about 2% w/w to about 6% w/w" and therefore meets the polymeric viscosity builder limitation of the asserted claims.

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[60] *Id.*, para. 124 (emphasis added).

[61] *See id.*, paras. 115-117.

[62] Ex. 15, Avramoff Dep. 22:23.

VIII. Almirall's Infringement Claims Are Not Barred

43. I disagree with Dr. Amiji that Almirall's doctrine of equivalents claims are barred by three legal doctrines: prosecution history estoppel, disclosure-dedication, and ensnarement.[63] I have been advised by counsel that whether any of these three legal doctrines applies is primarily a legal question and properly the subject of attorney argument. Below, I provide the relevant factual context from the perspective of a POSA.

A. Prosecution History Estoppel

44. I have been advised by counsel that there are two types of prosecution history estoppel: "amendment-based" and "argument-based". Based on my reading of the prosecution history from the perspective of a POSA, neither of these doctrines applies.

45. First, there is no amendment-based prosecution history estoppel because Applicants never made a narrowing amendment to the "polymeric viscosity builder" claim limitation during the prosecution of the '219 patent. To the contrary, a POSA would understand that the "polymeric viscosity builder" limitation was ***broadened***, not narrowed, when Applicants replaced the close-ended "***consisting of*** [A/SA]" language with the open-ended "***comprising*** [A/SA]" language.[64] Dr. Amiji does not mention this broadening amendment in his report. Instead, he focuses on the removal of carbomer-specific claims early in the prosecution of the parent application.[65]

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[63] Regarding ensnarement, I defer to Drs. Harper and/or Klibanov as to any opinion concerning the validity of the hypothetical claim I propose below.

[64] *Compare* Claims in Feb. 18, 2016 Response, p. 2-3, ALG_ACZ0000001, at ALG_ACZ0000280–81 *with* Claims in Sept. 07, 2016 Response, p. 12-13, ALG_ACZ0000001, at ALG_ACZ0000530–31 (emphasis added).

[65] Amiji Report, para. 80.

46. Second, there is no argument-based prosecution history estoppel. The prosecution history does not evidence to a POSA that Applicants surrendered the right to assert Taro's polymeric viscosity builder as an equivalent to the corresponding claim element, let alone that they did so clearly and unmistakably.

47. Dr. Amiji relies on Applicants' submissions to the Patent Office distinguishing Garrett I from the claimed invention.[66] He also refers to the Warner Declaration that described unexpected hurdles when using Carbopol 980 (*i.e.* carbomer alone), as opposed to Sepineo P 600.[67] A POSA reading these statements, and the rest of the file wrapper, would understand that Applicants believed that thickening agents comprising A/SA, such as Sepineo P 600, had certain advantages when used in combination with an increased (7.5%) dapsone concentration. A POSA would take note of Applicants' broadening amendment from "consisting of [A/SA]" to "comprising [A/SA]", which Applicants argued, and the Patent Office agreed, was still patentable over the cited art. A POSA would understand that, if ***anything***, Applicants were distinguishing the polymeric viscosity builder of the invention from polymeric viscosity builders consisting of carbomer ***alone***, as discussed in Garrett I, which was being cited in support of the Examiner's then-pending rejections of the claims. A POSA would readily understand this context and would not conclude that Applicants clearly and unmistakably surrendered any carbomer-***based*** polymeric viscosity builder, including the one employed in Taro's ANDA Product, as the functional equivalent of the corresponding claim element.

48. Furthermore, Dr. Amiji's opinion that Applicants' statements regarding carbomer ***alone*** evidences a clear and unmistakable surrender of the claimed subject matter is

[66] *See id*., citing Feb. 18, 2016 Response, p. 6, ALG_ACZ0000001, at ALG_ACZ0000284.

[67] Amiji Report, para. 82.

inconsistent with the Court's construction of the term "polymeric viscosity builder" as "a polymer ***or polymer-based*** thickening agent."[68] It is also inconsistent with the parties' agreement that the term comprising means that the polymeric viscosity builder can have one or more components.[69] It cannot be correct.

49. Thus, based on my understanding of this legal doctrine, argument-based prosecution history estoppel does not apply.

B. Disclosure-Dedication / Dedication to the Public

50. I disagree with Dr. Amiji that the disclosure-dedication rule bars Almirall's infringement claims.[70] I do not see any precise or clear disclosure in the '219 patent, or elsewhere, that would indicate to a POSA that a formulation employing [redacted] such as Taro's ANDA Product, had been disclosed but not claimed.

51. Dr. Amiji's only support for his opinion on this point are disclosures regarding carbomer ***alone***.[71] As I have explained, Taro's product will not use carbomer ***alone*** as

[68] Report and Recommendation at 6, June 6, 2018, D.I. 87 (emphasis added); Memorandum and Order at 8, Aug. 23, 2018, D.I. 107.

[69] Report and Recommendation at 6 n.1, June 6, 2018, D.I. 87.

[70] I note that Dr. Amiji appears to be arguing that aspects of the '926 patent have also been dedicated to the public. He says, at para. 88, "A POSA would have therefore concluded the use of Carbopol 980 (among other PVBs) would be appropriate to use in a topical pharmaceutical formulation and would not be covered by the claims or inventions of the '926 or '219 patents." I have reviewed the prosecution history of the application that issued as the '926 patent, and on the same reasoning I provide with respect to the '219 patent-in-suit, I disagree that any statement in the '926 file history gives rise to disclosure-dedication of a formulation employing a multi-component, carbomer-based polymeric viscosity builder.

[71] Amiji Report, paras. 85-88, citing Embodiments 19-21 and 48-50 (which appear in Ex. 1, '219 patent, at col. 8 ll. 35-51, ALG_ACZ0000565, at ALG_ACZ0000573) and Examples 1, 2, 4, and 6 (*see id.*, col. 12 ll. 45-col. 15 ll. 32, ALG_ACZ0000565, at ALG_ACZ0000575-577).

the polymeric viscosity builder; it will use [redacted] that are either identical or equivalent to the polymeric viscosity builder in the claims and in Almirall's ACZONE 7.5% product. A [redacted] like Taro's is not described anywhere in the '219 patent's specification – a fact that Dr. Amiji does not appear to dispute. Moreover, a POSA would not extrapolate from the statements regarding carbomer alone that Taro's [redacted] had been dedicated to the public. The patent's references to carbomer alone are in sharp contrast to the description of the polymeric viscosity builder as having multiple components (*i.e.*, "compris[ing] an [A/SA]" and "further includ[ing] isohexadecane, sorbitan oleate, water and Polysorbate 80").[72] The Examples in the specification compare carbomer alone with A/SA-based thickeners or A/SA emulsions, which a POSA would understand would comprise A/SA with oil and surfactants.[73] As I described above regarding prosecution history estoppel, the disclosure that an embodiment of the invention with A/SA had certain advantages over one with carbomer alone would not indicate to a POSA that all embodiments including carbomer were thereby surrendered as equivalents. Dr. Amiji's opinion to that effect is inconsistent with the Court's construction of the term "polymeric viscosity builder" as "a polymer ***or polymer-based*** thickening agent"[74] and with the parties'

[72] *See, e.g.*, Ex. 1, '219 patent, col. 8 ll. 12-16, ALG_ACZ0000565, at ALG_ACZ0000573; *id.*, col. 10 ll. 49-54, ALG_ACZ0000565, at ACZ0000574; *id.*, col. 5 ll. 47–50, ALG_ACZ0000565, at ALG_ACZ0000572; *id.*, tbl. 7, ALG_ACZ0000565, at ALG_ACZ0000577 (listing "Sepineo P 600"); *see also id.*, tbls. 1–4, 6, ALG_ACZ0000565, at ALG_ ALG_ACZ0000575–76 (listing "acrylamide/sodium acryloyldimethyl copolymer based thickener" and "acrylamide/sodium acryloyldimethyl copolymer emulsion").

[73] *See id.*, col. 12 ll. 46-col. 14 ll. 20, ALG_ACZ0000565, at ALG_ ALG_ACZ0000575–76.

[74] Report and Recommendation at 6, June 6, 2018, D.I. 87; Memorandum and Order at 8, Aug. 23, 2018, D.I. 107.

agreement that the term can include one or more components.[75] Thus, the statements Dr. Amiji identifies do not convey to a POSA, with the requisite specificity or otherwise [redacted] ike Taro's is disclosed but not claimed in the '219 patent.

52. Nor is Taro's equivalent polymeric viscosity builder identified in the specification or elsewhere as an alternative to the polymeric viscosity builder claim limitation. In contrast to the disclosure regarding A/SA-based thickeners, the specification discloses no embodiment where carbomer – alone or in combination – comprises the polymeric viscosity builder of the claimed invention.[76] Given that there is no embodiment having a carbomer-comprising polymeric viscosity builder at all, the '219 patent necessarily does not disclose such an embodiment as an alternative to the claimed formulations.

53. To the extent that Dr. Amiji is suggesting that [redacted] have been dedicated to the public, I disagree with that opinion as well. The specification discloses the use of those excipients as part of a polymeric viscosity builder comprising A/SA, but never as part of one comprising carbomer.[77] A POSA reading the specification would not see any precise or clear intention to dedicate [redacted] o the public as part of Taro's carbomer-based polymeric viscosity builder; nor would a POSA understand that they had been identified as an alternative to the polymeric viscosity builder claim element.

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[75] Report and Recommendation at 6 n.1, June 6, 2018, D.I. 87.

[76] *See, e.g.*, *id.*, col. 8 ll. 35-51, ALG_ACZ0000565, at ALG_ACZ0000573; *id.*, col. 11 ll. 6-25, ALG_ACZ0000565, at ALG_ACZ0000575.

[77] *See id.*, col. 5:47-50, ALG_ACZ0000565, at ALG_ACZ0000572.

54. In sum, a POSA reading the specification would not understand that the patentee was dedicating Taro's polymeric viscosity builder to the public and the disclosure-dedication rule does not bar Almirall's infringement claim.

C. Ensnarement

55. I have been asked to construct a hypothetical Claim 1 that covers the literal claim scope in addition to Taro's ANDA Product. In my opinion, the proper hypothetical claim reads as follows (additions underlined and bolded):

> **1**. A method for treating a dermatological condition selected from the group consisting of acne vulgaris and rosacea comprising administering to a subject having the dermatological condition selected from the group consisting of acne vulgaris and rosacea a topical pharmaceutical composition comprising:
>
> about 7.5% w/w dapsone;
>
> about 30% w/w to about 40% w/w diethylene glycol monoethyl ether;
>
> about 2% w/w to about 6% w/w of a polymeric viscosity builder comprising acrylamide/sodium acryloyldimethyl taurate copolymer **or Carbomer homopolymer type C**;
>
> and water;
>
> wherein the topical pharmaceutical composition does not comprise adapalene.

56. In his report, Dr. Amiji offers two hypothetical claims: one that expands the polymeric viscosity builder range to "about [redacted]% w/w to about 6% w/w" (as opposed to the claimed range of about 2-6% w/w) and replaces A/SA with Carbomer homopolymer type C; and one that merely replaces A/SA with Carbomer homopolymer type C.[78] In my view, neither of those two hypotheticals is correct. Removing A/SA from the claim changes (and potentially

[78] Amiji Report, paras. 91-92.

narrows) the literal claim scope, which I understand is legally improper. The proper hypothetical claim extends the polymeric viscosity builder claim element to ***include*** either or both of A/SA and carbomer as alternative polymers upon which the polymeric viscosity builder may be based.

57. Furthermore, there is no basis for expanding the range to "about [redacted]% w/w to about 6% w/w". As I explained in my Initial Report, Taro's polymeric viscosity builder contains [redacted]wt. % polymeric viscosity builder and falls squarely within the claimed range. Dr. Amiji concedes that a range of "about 2% w/w to about 6% w/w" is consistent with Almirall's infringement theory.[79] I note that both the Harper Ensnarement Report and the Klibanov Ensnarement Report provide that the claim is non-obvious regardless of whether the lower limit is [redacted]% or 2 wt. %.[80]

58. I have not been asked to offer an opinion as to the validity of the proper hypothetical claim in view of the cited prior art, and I have not formed one. My opinion here is limited to the threshold issue of what constitutes a proper hypothetical claim. I defer to Drs. Harper and/or Klibanov as to any opinion concerning the validity of the hypothetical claim I propose as appropriate.

IX. Conclusion

59. In my opinion, Taro's ANDA Product, if marketed, would infringe claims 1, 2, 4, and 5 of the '219 patent, and Almirall's infringement claims are not barred.

X. Supplementation

60. I may utilize the documents cited and/or listed herein as exhibits at any hearing or trial in this litigation. I may further prepare and use exhibits that summarize portions

[79] *Id.*, para. 92.

[80] Harper Ensnarement Report, para. 12; Klibanov Ensnarement Report, para. 13.

of my testimony, or key terms or concepts presented herein, at any hearing or trial in this litigation.

61. I reserve the right to supplement any testimony in this report in response to any judicial determinations including, but not limited to, the opinions of Defendants' experts, and/or in light of additional evidence (including graphic or demonstrative materials) or testimony brought forth at trial or otherwise brought to my attention after the date of my signature on the cover of this report.

EXHIBIT 4

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

C.A. NO. 17-633 (JFB)(SRF) (Consolidated)

----------x

ALMIRALL, LLC,

Plaintiff,

vs.

TARO PHARMACEUTICAL INDUSTRIES LTD. and TARO PHARMACEUTICALS, INC.,

Defendants.

----------x

December 21, 2018

9:25 a.m.

Videotaped deposition of MAJELLA E. LANE, Ph.D., held at the offices of Fenwick & West, LLP, 902 Broadway, Suite 14, New York, New York 10010, before Suzanne J. Stotz, Certified Realtime Reporter, Registered Professional Reporter, and a Notary Public of the State of New York.

**** Job No. 29325

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gelling agents, right?
A. That's what the words say, yes.
Q. Okay. So they are using gelling agent -- or at least this -- the inventor is using, you know, thickeners kind of interchangeably with gelling agent, right?
A. Well, he says that both Carbopol and Sepineo are promising gelling agents. But he doesn't say -- he actually says, you know, they were evaluated to thicken the proposed formulation.
Q. Well, he calls them thickeners, right, early in paragraph 6?
A. Yes. He does.
Q. Yeah. So he's kind of using thickeners and gelling agents interchangeably. Wouldn't you agree?
A. He is using the terms to describe -- he is using two different terms to describe the same -- same -- Carbopol 980, Sepineo P 600, yes.
Q. Okay. So I guess, you know, my question for you is, you know, if persons of ordinary skill in the art knew you could take an emulsion, just like Taro had here in their

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own manufacturing step, and you could add a thickening agent to that to create an emulgel, what is the basis of your own opinion that, in the context of Taro's product, when you add the thickener, the thickener suddenly becomes defined not just b the Carbopol 980 but also b the [redacted]
A. So I explain that on page 12 of my second report. So I'll just go to that.
So the oil phase when added to the formulation is going to alter the thickness, the viscosity, and we talk about the feel and aesthetic appearance. The -- not on page 12, but I know I have referred elsewhere in the second report to the other functions of [redacted]
Q. But those other functions of those excipients would be shared by the emulsions described in the emulgel reference we were just looking at, too, right? I mean, it's not something unique to the dapsone formulations, right?
A. I'm sorry. I'm not sure what you mean.

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Q. Well, you know, these different functions of surfactants, emulsifiers, oils -- I mean, those different functions exist with respect to the emulsions described in the reference from the Journal of Controlled Release, right?
A. We have seen Carbopol described there, but I am not quite sure what the second part of your question is.
Q. Well, like -- well, they talk about emulsions, right, and that an emulgel is simply an emulsion, and you add in a thickener, right?
A. They are describing these as gelling agents.
Q. Yes.
A. But again, it's important to remember that the emulsifiers are also viscous substances.
Q. Yeah, but they're not -- they don't create that three-dimensional structure that is -- that you talked with respect to AS/A and Carbopol, right?
A. They contribute to the viscosity of the formulation.
Q. Yeah, but nobody in this article

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here with emulgels -- they don't call those thickeners, right?
A. In the patent we talk about the polymeric viscosity builder. So that's -- so it's in column 5 towards the end of the column. And, you know, there is an understanding that a polymeric viscosity builder has AS/A and Isohexadecane, Sorbitan Monooleate, water and Polysorbate 80.
So there is an understanding that they are part of the viscosity of the product. They are contributing to the thickness of the product.
Q. But you admit claim 1 can just be a gel; it doesn't have to be an emulgel, right? Like the formulations described in claim 1 can be gels; they don't have to be Emulgels, right?
A. I'm just looking at claim 1.
Yes. As I discussed earlier, I believe that gels are within the scope of claim 1.
Q. So with respect to what you regard as being Taro's PVB, you've never done an analysis to determine whether or not that PVB, as you describe it, that -- those four

excipients working together, whether those excipients working together are equivalent to AS/A copolymer.

A. The analysis I performed was the polymeric viscosity builder that's the embodiment of claim 1 and the polymeric viscosity builder that's in the Taro product. So that was my analysis.

Q. Okay. So just, you know, yes or no, did -- well, just confirm for me with either yes or no, you did not undertake to analyze whether or not Taro's PVB, as you define it, was equivalent to AS/A alone, right?

A. That's not something I was asked to do.

Q. Okay. That's fair.

Dr. Lane, I appreciate your time. I have no further questions for you.

A. Thank you.

MR. TRAINOR: I have no questions.

THE VIDEOGRAPHER: This marks the end of media number 4 in the video deposition of Majella Lane. We are going off the record. The time is 4:29 p.m.

(The witness is excused.)

(Deposition of Majella E. Lane, Ph.D., concluded at 4:29 p.m.)

C E R T I F I C A T E

I, SUZANNE J. STOTZ, a Registered Professional Reporter, Certified Realtime Reporter, and Notary Public in and for the State of New York, do hereby certify that the foregoing is a true and accurate transcript of the stenographic above-captioned matter.

Suzanne Stotz

SUZANNE J. STOTZ, RPR, CRR

My Commission Expires October 17, 2021

DATED: DECEMBER 31, 2018

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E R R A T A S H E E T

I have read my testimony in the foregoing transcript and believe it to be true and correct to the best of my knowledge and belief with the following changes:

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WITNESS SIGNATURE DATE

Sworn and subscribed to before me this _____ day of _____ , 2019.

Notary Public of the State of _____.