

**IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE**

LEO PHARMA A/S, LEO)
LABORATORIES LIMITED, AND LEO)
PHARMA, INC.,)

Plaintiffs,)

v.)

ACTAVIS LABORATORIES UT, INC.,)
AND ACTAVIS, INC.,)

Defendants.)

Civil Action No. 16-333-JFB-SRF

UNDER SEAL

LEO PHARMA A/S, LEO)
LABORATORIES LIMITED, AND LEO)
PHARMA, INC.,)

Plaintiffs,)

v.)

PERRIGO UK FINCO LIMITED)
PARTNERSHIP AND PERRIGO)
COMPANY,)

Defendants.)

Civil Action No. 16-430-JFB-SRF

UNDER SEAL

REPORT AND RECOMMENDATION

I. INTRODUCTION

In these patent infringement actions filed under the Hatch-Waxman Act by plaintiffs LEO Pharma A/S (“LEO Pharma”), LEO Laboratories Limited (“LEO Labs”), and LEO Pharma, Inc. (“LEO, Inc.”) (collectively, “LEO”) against defendants Actavis Laboratories UT, Inc. and Actavis, Inc. (together, “Actavis”) and Perrigo UK Finco Limited Partnership and Perrigo Company (together, “Perrigo”), LEO alleges infringement of numerous patents directed to LEO’s Picato® drug. Against Actavis, LEO filed a second amended complaint alleging

infringement of United States Patent Nos. 7,410,656 (“the ‘656 patent”), 8,278,292 (“the ‘292 patent”), 8,372,827 (“the ‘827 patent”), 8,372,828 (“the ‘828 patent”), 8,377,919 (“the ‘919 patent”), 8,536,163 (“the ‘163 patent”), 8,716,271 (“the ‘271 patent”), 8,735,375 (“the ‘375 patent”), 9,676,698 (“the ‘698 patent”), and 9,416,084 (“the ‘084 patent”). (C.A. No. 16-333-JFB-SRF, D.I. 73) Against Perrigo, LEO filed a first amended complaint alleging infringement of United States Patent Nos. 6,787,161 (“the ‘161 patent”) and 6,844,013 (“the ‘013 patent), as well as the ‘656 patent, the ‘292 patent, the ‘827 patent, the ‘828 patent, the ‘919 patent, the ‘163 patent, the ‘271 patent, the ‘375 patent, the ‘698 patent, and the ‘084 patent. (C.A. No. 16-430-JFB-SRF, D.I. 99) Presently before the court is the matter of claim construction. This decision sets forth the court’s recommendations of constructions for the disputed claim terms discussed in the briefing and at the *Markman* hearing held on September 15, 2017.

II. BACKGROUND

A. Parties

LEO is the holder of New Drug Application (“NDA”) No. 202833 for ingenol mebutate gel, 0.015% and 0.05%, which was approved by the FDA on January 23, 2012. (D.I. 73 at ¶ 13)¹ LEO markets the drug under the trade name Picato®. (*Id.*) The active pharmaceutical ingredient (“API”) in Picato® is ingenol mebutate, or ingenol-3-angelate. (*Id.* at ¶ 14)

Actavis manufactures and sells generic copies of branded pharmaceutical products throughout the United States. (*Id.* at ¶ 6) Actavis has submitted two Abbreviated New Drug Applications (“ANDA”) to the FDA for approval of a generic version of Picato®: ANDA No. 208807 and ANDA No. 209086. (*Id.* at ¶¶ 32-33)

¹ All references to docket entries in this ruling will reflect the docket in Civil Action No. 16-333-JFB-SRF, unless otherwise noted.

Perrigo manufactures and sells generic copies of branded pharmaceutical products.

Perrigo has submitted two ANDAs to the FDA for approval of a generic version of Picato®: ANDA No. 209018 and ANDA No. 209019. (*Id.* at ¶¶ 45-46)

B. Technology of the Patents-In-Suit

1. The Aylward Patents

The Aylward patents² are a group of related patents sharing a common specification and having one named inventor, James Harrison Aylward. The Aylward patents are directed to methods of treating various cancerous conditions using certain ingenane compounds, including ingenol mebutate. ('656 patent, Abstract; col. 34:23-24) Dr. Aylward isolated compounds from certain species of Euphorbia, a genus of flowering plants used for traditional medicinal remedies, and discovered that angeloyl-substituted ingenanes could selectively kill cancer cells. (*Id.* at 4:62-5:1; 6:8-38) The claims of the '161 and '013 patents are directed to treating cancerous conditions with specific compounds obtained from the sap of Euphorbia species. ('161 patent, col. 31:22-32:35; '013 patent, col. 32:8-60) The claims of the '656 patent are more generally directed to isolated compounds. ('656 patent, col. 34:13-34)

2. The Brown Patents

The Brown patents³ share a common specification and name as inventors Marc Barry Brown, Michael Edwards Crothers, and Tahir Nazir. The Brown patents are directed to topical skin cancer treatments. Specifically, the Brown patents claim pharmaceutically acceptable

² The Aylward patents include the '656 patent, the '013 patent, and the '161 patent. (D.I. 142, Ex. A at 1)

³ The Brown patents include the '292 patent, the '827 patent, the '828 patent, the '919 patent, the '163 patent, the '271 patent, and the '375 patent. (D.I. 142, Ex. A at 3)

formulations of ingenol-3-angelate combined with pharmaceutical solvents and excipients to achieve a stable form. (‘292 patent, col. 1:60-67)

III. LEGAL STANDARD

Construing the claims of a patent presents a question of law, although subsidiary fact finding is sometimes necessary. *Teva Pharms. USA, Inc. v. Sandoz, Inc.*, 135 S. Ct. 831, 837-38 (2015) (citing *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 977-78 (Fed. Cir. 1995), *aff’d*, 517 U.S. 370, 388-90 (1996)). “It is a bedrock principle of patent law that the claims of a patent define the invention to which the patentee is entitled the right to exclude.” *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005) (internal quotation marks omitted). “[T]here is no magic formula or catechism for conducting claim construction.” *Id.* at 1324. Instead, the court may attach the appropriate weight to appropriate sources “in light of the statutes and policies that inform patent law.” *Id.*

The words of the claims “are generally given their ordinary and customary meaning,” which is “the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application.” *Phillips*, 415 F.3d at 1312-13 (internal citations and quotation marks omitted). “[T]he ordinary meaning of a claim term is its meaning to the ordinary artisan after reading the entire patent.” *Id.* at 1321 (internal quotation marks omitted); *see also Eon Corp. IP Holdings v. Silver Spring Networks, Inc.*, 815 F.3d 1314, 1320 (Fed. Cir. 2016). Claim terms are typically used consistently throughout the patent, and “usage of a term in one claim can often illuminate the meaning of the same term in other claims.” *Phillips*, 415 F.3d at 1314 (observing that “[o]ther claims of the patent in question, both asserted and unasserted, can also be valuable sources of enlightenment . . . [b]ecause claim terms are normally used consistently throughout the patent . . .”).

It is likewise true that “[d]ifferences among claims can also be a useful guide For example, the presence of a dependent claim that adds a particular limitation gives rise to a presumption that the limitation in question is not present in the independent claim.” *Id.* at 1314-15 (internal citation omitted). This “presumption is especially strong when the limitation in dispute is the only meaningful difference between an independent and dependent claim, and one party is urging that the limitation in the dependent claim should be read into the independent claim.” *SunRace Roots Enter. Co., Ltd. v. SRAM Corp.*, 336 F.3d 1298, 1303 (Fed. Cir. 2003) (citing *Ecolab Inc. v. Paraclipse, Inc.*, 285 F.3d 1362, 1375 (Fed. Cir. 2002)).

Other intrinsic evidence, including the patent specification, “is always highly relevant to the claim construction analysis. Usually, it is dispositive; it is the single best guide to the meaning of a disputed term.” *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996). “[T]he specification may reveal a special definition given to a claim term by the patentee that differs from the meaning it would otherwise possess. In such cases, the inventor’s lexicography governs.” *Phillips*, 415 F.3d at 1316 (citing *CCS Fitness, Inc. v. Brunswick Corp.*, 288 F.3d 1359, 1366 (Fed. Cir. 2002)). It bears emphasis that “[e]ven when the specification describes only a single embodiment, the claims of the patent will not be read restrictively unless the patentee has demonstrated a clear intention to limit the claim scope using words or expressions of manifest exclusion or restriction.” *Liebel-Flarsheim Co. v. Medrad, Inc.*, 358 F.3d 898, 906 (Fed. Cir. 2004) (internal quotation marks omitted), *aff’d*, 481 F.3d 1371 (Fed. Cir. 2007). The specification “is not a substitute for, nor can it be used to rewrite, the chosen claim language.” *SuperGuide Corp. v. DirecTV Enters., Inc.*, 358 F.3d 870, 875 (Fed. Cir. 2004).

In addition to the specification, a court “should also consider the patent’s prosecution history, if it is in evidence.” *Markman*, 52 F.3d at 980. The prosecution history, which is also “intrinsic evidence,” “consists of the complete record of the proceedings before the PTO [Patent and Trademark Office] and includes the prior art cited during the examination of the patent.” *Phillips*, 415 F.3d at 1317. “[T]he prosecution history can often inform the meaning of the claim language by demonstrating how the inventor understood the invention and whether the inventor limited the invention in the course of prosecution, making the claim scope narrower than it would otherwise be.” *Id.*

A court also may rely on “extrinsic evidence,” which “consists of all evidence external to the patent and prosecution history, including expert and inventor testimony, dictionaries, and learned treatises.” *Markman*, 52 F.3d at 980. For instance, technical dictionaries can assist the court in determining the meaning of a term to those of skill in the relevant art because such dictionaries “endeavor to collect the accepted meanings of terms used in various fields of science and technology.” *Phillips*, 415 F.3d at 1318. In addition, expert testimony can be useful “to ensure that the court’s understanding of the technical aspects of the patent is consistent with that of a person of skill in the art, or to establish that a particular term in the patent or the prior art has a particular meaning in the pertinent field.” *Id.* Nonetheless, courts must not lose sight of the fact that “expert reports and testimony [are] generated at the time of and for the purpose of litigation and thus can suffer from bias that is not present in intrinsic evidence.” *Id.* (“[C]onclusory, unsupported assertions by experts as to the definition of a claim term are not useful to a court.”). Overall, while extrinsic evidence may be useful to the court, it is less reliable than intrinsic evidence, and its consideration “is unlikely to result in a reliable

interpretation of patent claim scope unless considered in the context of the intrinsic evidence.”

Id. at 1318-19.

Finally, “[t]he construction that stays true to the claim language and most naturally aligns with the patent’s description of the invention will be, in the end, the correct construction.”

Renishaw PLC v. Marposs Societa’ Per Azioni, 158 F.3d 1243, 1250 (Fed. Cir. 1998). It follows that “a claim interpretation that would exclude the inventor’s device is rarely the correct interpretation.” *Osram GmbH v. Int’l Trade Comm’n*, 505 F.3d 1351, 1358 (Fed. Cir. 2007).

IV. CONSTRUCTION OF DISPUTED TERMS⁴

A. Disputed Terms in the Aylward Patents

1. “[an] isolated compound” (“656 patent, claim 1)

LEO	Defendants	Court
“a compound separate from other components, except that a small amount of residual other components may remain”	“a compound purified from a plant”	“a compound purified from a plant”

I recommend that the court adopt defendants’ construction, which is supported by the intrinsic evidence. The parties do not dispute the degree of isolation or purity of the compound.⁵ (9/15/17 Tr. at 44:17-45:2; 54:1-10) Instead, the dispute focuses on whether the compound is

⁴ The parties have reduced the number of terms in dispute to nine. (D.I. 134 at 1 n.1)

⁵ In other words, the dispute is not about whether “a small amount of residual other than components may remain.” In light of the practical limitations of science, district courts have been reluctant to adopt constructions that require 100 percent purity. *See In re Depomed Patent Litig.*, 2016 WL 452312 at *6 (D.N.J. Feb. 5, 2016); *see also Ortho-McNeil, Inc., v. Johnson & Johnson Pharma. Res. & Dev., LLC*, 348 F. Supp. 2d 713, 730 (N.D.W. Va. 2004) (“[A]though one of ordinary skill in the art would have understood the claim to the compound ... to be substantially pure ... the realities of science would have led such a skilled artisan to conclude that purity was not 100 percent.”). Since adoption of defendants’ proposed construction is recommended, it is not necessary to confront whether the “small amount of residual” language in LEO’s proposed construction introduces ambiguity to the claims. (D.I. 70 at 7)

isolated from a plant, as opposed to isolation from either a plant or a reaction mixture, or, more broadly, from “no specific source.” (D.I. 68 at 17-18)

The written description repeatedly identifies plants as the source of “[an] isolated compound.” The Abstract of the ‘656 patent states that “[t]his invention relates to a compound or group of compounds present in an active principle derived from plants of species *Euphorbia peplus*, *Euphorbia hirta* and *Euphorbia drummondii*.” (‘656 Patent, Abstract) The Cross-Reference to Related Applications section also states that “[t]his invention relates to a compound [] present in an active principle derived from the family *Euphorbiaceae*.” (*Id.*, col. 1:15-17) The Summary of the Invention section reiterates that “the invention provides a compound or compounds present in plants of the genus *Euphorbia*.” (*Id.*, col. 6:25-28) Consistent with defendants’ proposed construction, all the disclosed embodiments of the compound in the specification are derived from a plant. Examples 1 to 3 of the specification teach the preparation of “crude sap.” (*Id.*, col. 10:39-63; col. 12:64-13:2; col. 15:11) Examples 4 and 6 to 9 teach various purifications from the crude sap. (*Id.*, col. 16:40-17:26; col. 18:6-24:6)

Other statements made in the specification also lend support to defendants’ proposed construction. First, the Background of the Invention section distinguishes the prior art uses of plant sap on the basis of newly discovered uses. After noting that “there has been no reliable or reproducible report of the use of any extract from *Euphorbia* species” for the treatment of certain skin cancers, (*Id.*, col. 5:40-42), the specification discloses that “[t]he inventor has now surprisingly found that sap of plants from three different *Euphorbia* species [] specifically inhibits growth of three different human tumour cell lines,” (*Id.*, col. 6:9-13), and that “[these anti-skin cancer] results were particularly striking,” (*Id.*, col. 6:19-22). The specification thus confirms that the subject matter of the ‘656 patent covers new methods for using extracted plant

sap, as opposed to methods for synthesizing any plant-sap ingredients. *See Tronzo v. Biomet, Inc.*, 156 F.3d 1154, 1159 (Fed. Cir. 1998) (finding that the statements in the specification, which distinguished the prior art as inferior and touted the advantages of a conical shaped cup for use in an artificial hip device, “make clear that the ‘589 patent discloses only conical shaped cups and nothing further.”).

Moreover, the prosecution history distinguishes claim 1 over prior art methods of obtaining sap extracts on the basis of purification to separate—not reactions to synthesize any angeloyl-substituted ingenane. (D.I. 98, Ex. 11 at 6) The examiner initially rejected claim 1 as anticipated by the Tamas reference, which “describes *Euphorbia Hirta* plants and their extracts as being used to prepare medicaments for tumor therapy.” (D.I. 98, Ex. 11 at 4 and 8) To overcome this rejection, the patentees stressed that “Tamas does not teach, disclose an isolated angeloyl-substituted ingenane, as recited in the claim,” and that “even if an angeloyl-substituted ingenane were present in the extracts, the ingenane would be part of an extract, and not separate therefrom.” (D.I. 98, Ex. 11 at 2, 4 and 6) These statements describe and enable only the compounds “from a plant.”

The specification explicitly addresses any residual uncertainty as to the scope of “various modifications and alterations to the embodiments and methods described herein.” (‘656 patent, col. 32:39-41) The Summary of the Invention section provides that, “while the invention is described in detail with reference to compounds detected in sap or sap extracts, these compounds, when present in or extracted from whole plants or parts thereof, are still within the scope of the invention.” (‘656 patent, col. 6:49-53) The ‘656 patent does not contemplate synthetic or semi-synthetic compounds. *See Wang Labs., Inc. v. America Online, Inc.*, 197 F.3d 1377 1382 (Fed. Cir. 1999) (holding that the “only system that is described and enabled” in the

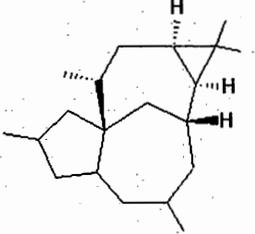
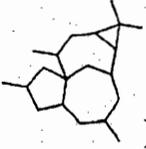
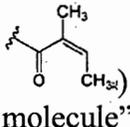
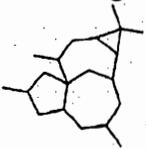
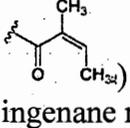
patent specification “uses a character-based protocol,” and that references to bit-mapped protocols did “not describe them as included in the applicant’s invention, and that the specification would not be so understood by a person skilled in the field of the invention.”). Therefore, the entire specification and prosecution history define “[an] isolated compound” as from a specific source—a plant from the *Euphorbia* species.

LEO relies on a single sentence in the specification that “[t]he Promega mRNA isolation kit was used to isolate mRNA.” (‘656 patent, col. 27:15-16) However, this portion of the specification found in Example 13 describes the isolation of mRNA, and not the isolation of the claimed compound. (*Id.*, col. 27:3-5) In other words, while the usage of the term “isolated” in Claim 1 refers to a new preparation method of the claimed compound, the usage of the term “isolating” in Example 13 refers to a routine characterization method for determining the anti-cancer functions of the claimed compound. A person of ordinary skill in the art would not have understood Example 13 to teach that the claimed compound can be isolated by using a commercially available “mRNA isolation kit.”

The extrinsic evidence shows that a person of ordinary skill in the art at the time of the invention would have lacked any knowledge of the “reaction mixture,” and the term “[an] isolated compound” therefore could not encompass “a reaction mixture.” Specifically, LEO’s expert, Dr. Micalizio, explains that “the first synthesis of ingenol was reported” in 2002—four years after the alleged priority date of the ‘656 patent. (D.I. 70 at ¶ 18; Ex. 16 at 54; D.I. 99 at ¶ 15) Moreover, LEO published an article in 2012 “present[ing] the first semi-synthesis of ingenol 3-angelate starting from ingenol (3).” (D.I. 135, Ex. 51) Consequently, LEO’s proposed construction impermissibly expands the scope of the claims beyond “what the specifications

indicate the inventor actually invented.” See *Retractable Techs., Inc. v. Becton, Dickinson & Co.*, 653 F.3d 1296, 1305 (Fed. Cir. 2011).

2. “angeloyl-substituted ingenane” (“656 patent, claim 1)

LEO	Defendants	Court
<p>“the ingenane core substituted with an ester of angelic acid”</p> 	<p>Indefinite; alternatively, “an ingenane molecule (i.e., a hydrocarbon having the following structure: ) in which an angeloyl group ((i.e., an acyl group having the following structure ) is bonded to the ingenane molecule”</p>	<p>“an ingenane molecule (i.e., a hydrocarbon having the following structure: ) in which an angeloyl group ((i.e., an acyl group having the following structure ) is bonded to the ingenane molecule”</p>

To the extent that defendants have failed to show by clear and convincing evidence that claim 1 is indefinite,⁶ I recommend that the court adopt defendants’ alternative construction, which is consistent with the intrinsic record.

To determine the ordinary meaning of the technical term “angeloyl-substituted ingenane,” the Court begins by identifying the structural relationship between the two constituents of the claimed compound: the “angeloyl” group and “ingenane.”⁷ Because the intrinsic evidence does not expressly define the chemical structure, the court considers the international standard for nomenclature, as promulgated by the International Union of Pure and

⁶ The parties reached agreement regarding defendants’ indefiniteness arguments with respect to a number of the disputed claim terms, and defendants have preserved their indefiniteness arguments for trial. (D.I. 142 at 2)

⁷ The parties do not dispute that an ingenane is a multi-cyclic hydrocarbon, because the relevant portions of the parties’ proposed constructions differ only in the stereochemistry of the ingenane. (D.I. 68 at 19; D.I. 70 at 10)

Applied Chemistry (“IUPAC”), and finds that an “angeloyl-substituted ingenane” consists of an “ingenane” core with an “angeloyl” substituent. *See, e.g., Allergan, Inc. v. Athena Cosmetics, Inc.*, 2012 WL 12895366, at *7 (C.D. Cal. Feb. 8, 2012) (“The Court first turns to the IUPAC rules on nomenclature to determine the ordinary meaning.”); *Dow Agrosciences LLC v. Crompton Corp.*, 2004 WL 1087362, at *3 (S.D. Ind. May 12, 2004) (“In [the IUPAC] system, [organic] molecules are named by dividing the structure into a core structure and various substituents”). In light of the IUPAC core-and-substituent classification, the parties’ principal disputes over this term include: (1) whether the ingenane core, as described in claim 1, has a specific three-dimensional stereo-chemical structure; (2) whether the angeloyl substituent is limited to an ester of angelic acid; and (3) whether the substitution position is limited to particular, identifiable sites.

With respect to the stereo-chemical limitation of the ingenane core, LEO contends that a person of ordinary skill in the art would be “familiar” with “the tetracyclic core of ingenanes,” (D.I. 68 at 20), and “would have understood” the stereochemistry as depicted in LEO’s proposed construction, (D.I. 111 at 20). In support of this position, LEO mainly relies on prior art reference Evans and Soper, which discloses a schematic of ingenane stereochemistry, and a list of sixteen examples of ingenane compounds which was submitted to the PTO during prosecution of the parent ‘161 patent. (D.I. 69, Ex. 17; Ex. 18 at ¶ 4 & Table 6) However, the ‘656 patent itself does not place any limitations on the stereochemistry of the multi-cyclic compound. Nor do the sixteen examples of “angeloyl substituted ingenanes from *Euphorbia paralias*, not *peplus*, *hirta* or *drummondii*” disavow any stereo-chemical structures from the subject matter of the ‘656 patent. Indeed, the fact that the inventors were aware of a specific 3D configuration of ingenane suggests that they did not want to impose a stereo-chemical limitation. *See, e.g., Pfizer, Inc. v.*

Ranbaxy Labs. Ltd., 457 F.3d 1284, 1290 (Fed. Cir. 2006) (finding that even if a depiction of an enantiomer “commonly” represents a racemic mixture, it does not “always represents only a racemate”).

LEO’s assertion that a person of ordinary skill would have understood the angeloyl substituent as an ester linkage also lacks support in the intrinsic record. Defendants’ expert, Dr. Williams, indicates that the claimed angeloyl-substitution “may involve a number of functional groups, including esters, amides, and ketones.” (D.I. 99 at ¶ 9) Nothing in the evidence relied on by LEO “indicate[s] a clear intent” to “deviate from the plain and ordinary meaning.” *Hill-Rom Servs., Inc. v. Stryker Corp.*, 755 F.3d 1367, 1372-73 (Fed. Cir. 2014). LEO first points to the recitation of “20-O-acetyl-ingenol-3-angelate” in claim 3 and the specification’s disclosure of the NMR data of 20-O-acetyl-ingenol-3-angelate. (‘656 patent, col. 24:25-62; D.I. at 68 at 19; 9/15/17 Tr. at 29:15-35:13) However, the doctrine of claim differentiation prohibits reading any structural limitations from a dependent claim into an independent claim, and the presumption is “especially strong” in this instance because “the only meaningful difference” among the first three claims concerns the substitution type and position. *See Acumed LLC v. Stryker Corp.*, 483 F.3d 800, 806 (Fed. Cir. 2007). While independent claim 1 is directed to the broad genus “an angeloyl-substituted ingenane,” dependent claim 2 narrows claim 1 by limiting to a subgenus those “with an acylated substitution on or at the C-20 position.” (‘656 patent, col. 34:14-22) Claim 3 further narrows the scope by specifying a species “20-O-acetyl-ingenol-3-angelate.” (*Id.*, col. 34:23-24) Therefore, the “20-O-acetyl-ingenol-3-angelate” recited in claim 3 cannot properly be read to preclude other “angeloyl” derivatives in claim 1.

Moreover, the sixteen examples of ingenane compounds submitted during prosecution of the parent ‘161 patent do not limit the angeloyl substituents claimed in the ‘656 patent to ester

derivatives because they illustrate a different subject matter: “*Euphorbia paralias*, not *peplus*, *hirta* or *drummondii*.” (D.I. 69, Ex. 18 at 19) Even assuming that “angeloyl-substitut[ion]” would “commonly” represent “an ester of angelic acid,” as LEO contends, (D.I. 68 at 19), it does not follow that the term “always represent[s] only” an ester derivative. *See Ranbaxy Labs.*, 457 F.3d at 1290. The evidence also shows that a nomenclature specific to ester derivatives fell within the common knowledge of a person of ordinary skill in the art at the relevant time. LEO’s expert repeated and consistently used the term “angeloyloxy” in naming angeloyl-substituted ingenanes during prosecution of the parent ‘161 patent. (D.I. 69, Ex. 18, Examples 5-8 and 10-20)

With respect to the substitution-position limitation, LEO’s position does not contradict defendants’ proposed construction. LEO argues that “[a]n ingenane core is defined as possessing twenty carbons, many of which could be the site of ‘angeloyl substitution,’” and a person of ordinary skill could identify these sites “based on an examination of the compound’s structure.” (D.I. 111 at 20) The court finds that an “angeloyl-substitute” can be “bonded to the ingenane molecule” at least “at the C-20 position,” because dependent claims 2 and 3 explicitly narrow claim 1 to ingenanes with C-20 substitution.

3. “active derivative of an angeloyl-substituted ingenane” (‘161 patent, claims 1, 5-7; ‘013 patent, claim 1)

LEO	Defendants	Court
“a compound derived from an angeloyl-substituted ingenane, which has activity”	“an acylated angeloyl-substituted ingenane”	“a compound derived from an angeloyl-substituted ingenane, which has activity”

I recommend that the court adopt LEO’s proposed construction, which is consistent with the plain and ordinary meaning of the term and is supported by the intrinsic record. The declaration of LEO’s expert, Dr. Micalizio, explains that a person of ordinary skill would not

have understood an “active derivative of an angeloyl-substituted ingenane” to be limited to only acylated compounds because there are different ways to create derivatives in accordance with the plain and ordinary meaning of the term. (D.I. 70 at ¶¶ 48-52)

Moreover, the prosecution histories of the ‘161 and ‘013 patents and other patents in the family do not contain an express disavowal of claim scope sufficient to limit the claim term to a single example. The ‘161 patent and the ‘013 patent claim priority to parent U.S. Patent No. 6,432,452 (“the ‘452 patent”). During prosecution of the ‘452 patent, the applicant indicated that 20-acetyl-ingenol-3-angelate was an example of an acetylated derivative of an angeloyl-substituted ingenane:

Table 17 at page 50 of the specification, for example, discloses NMR data supporting the bioactive fraction A2 which constitutes 20-acetyl-ingenol-3-angelate, which is an acetylated derivative of an angeloyl-substituted ingenane obtained from the sap of *Euphorbia peplus*, as presently claimed. Notably, in this regard, original Claims 6, 9, 11 and 13, for example, specifically recite angeloyl-substituted ingenane and their derivatives for use in the treatment of skin cancer and related disorders.

(D.I. 98, Ex. 17 at LEO_PCT00000683-84) This statement does not rise to the level of disclaimer, which requires a “clear and unmistakable” disavowal of claim scope. *See Luminara Worldwide, LLC v. Liown Elecs. Co.*, 814 F.3d 1343, 1353 (Fed. Cir. 2016) (“[D]isavowal requires that the specification [or prosecution history] make[] clear that the invention does not include a particular feature.” (internal quotation marks and citations omitted)). Nothing in this passage limits the active derivative to 20-acetyl-ingenol-3-angelate, which is cited as an example of an active derivative. Consequently, the statements made during prosecution of the ‘452 patent do not narrow the scope of the claim term in the ‘161 and ‘013 patents.

The prosecution histories of the ‘161 and ‘013 patents likewise fail to disavow all other derivatives besides 20-acetyl-ingenol-3-angelate. During prosecution of the ‘013 patent, the

applicant submitted a declaration to overcome an indefiniteness rejection, explaining that “[t]he Second Declaration describes the acetylation of ingenanes. Based thereon Applicant respectfully submits that one of ordinary skill in the relevant art would understand the metes and bounds of what was meant by the phrase ‘an angeloyl substituted derivative’ in these claims.” (D.I. 98, Ex. 18 at LEO_PCT00001946) This statement indicates that the acetylation of ingenanes is included in the scope of the term “an angeloyl-substituted derivative,” but falls short of disavowing claim scope. *See Home Diagnostics, Inc. v. LifeScan, Inc.*, 381 F.3d 1352, 1358 (Fed. Cir. 2004) (“Absent a clear disavowal or contrary definition in the specification or the prosecution history, the patentee is entitled to the full scope of its claim language.”). During prosecution of the ‘161 patent, the applicant stated, “[a]n example of a derivative of an angeloyl-substituted ingenane is an acetylated derivative” to overcome an indefiniteness rejection. (D.I. 69, Ex. 22 at LEO_PCT00001521; D.I. 135, Ex. 52 at LEO_PCT00001954) The applicant’s express identification of an acetylated derivative as “[a]n example of a derivative of an angeloyl-substituted ingenane” suggests the existence of other derivatives, and does not limit the term to a single exemplary embodiment. *See Luminara*, 814 F.3d at 1353.

Although the specifications of the ‘161 and ‘013 patents recite 20-acetyl-ingenol-3-angelate as the only identified species within the claimed subgenus, (‘161 patent, col. 23:12-48; ‘013 patent, col. 23:22-58), the law is well-established that patent claims should not be confined to the disclosed embodiments even when the specification only discloses a single embodiment, *see Woods v. DeAngelo Marine Exhaust, Inc.*, 692 F.3d 1272, 1283 (Fed. Cir. 2012) (“The specification need not describe every embodiment of the claimed invention, and the claims should not be confined to the disclosed embodiments—even when the specification discloses

only one embodiment.” (internal citations omitted)). Consequently, I recommend that the court adopt LEO’s proposed construction.

4. “[a] Euphorbia species” (‘161 patent, claims 1-4; ‘013 patent, claims 1-4)

LEO	Defendants	Court
“a species from the plant genus Euphorbia”	“Euphorbia peplus, Euphorbia hirta, and Euphorbia drummondii”	“a species from the plant genus Euphorbia”

I recommend that the court adopt LEO’s proposed construction and construe “[a] Euphorbia species” as “a species from the plant genus Euphorbia.” The specification identifies “Euphorbia” as a genus of plants and lists a number of species within the Euphorbia genus, including “in particular . . . plants of the species *Euphorbia peplus*, *Euphorbia hirta* and *Euphorbia drummondii*.” (‘161 patent, col. 1:15-17; 2:60-62; 3:8-4:30) However, the specification does not limit the definition of the claim term to those species, and repeatedly refers more broadly to Euphorbia species in general. (*Id.* at 1:13-22, 3:8-4:30) The patentee’s choice to focus on compounds isolated from the sap of three particular species of Euphorbia is not adequate to establish disclaimer, particularly in light of the disclosure of other Euphorbia species in Table 1 of the ‘161 and ‘013 patent specifications. (*Id.* at 3:8-4:30) Moreover, Dr. Aylward identified another species, *Euphorbia paralias*, in an example during the prosecution of the ‘161 patent, suggesting an intention not to limit the term to three other species. (D.I. 69, Ex. 18 at LEO_PCT00001491) The law is well-established that disavowal must be clear and unmistakable, and no such disclaimer exists in the intrinsic record of the ‘161 and ‘013 patents regarding limitations on the definition of “[a] Euphorbia species.” *See Luminara*, 814 F.3d at 1353.

5. “inhibiting proliferative activity of neoplastic cells” (‘656 patent, claims 1, 4, 5)

LEO	Defendants	Court
“selectively decreasing the replication rate of neoplastic cells”	Indefinite, or alternatively, to the extent this term can be construed, “inhibiting proliferation of neoplastic cells by direct cytotoxicity, inducing apoptosis, or inhibiting cell division”	“selectively decreasing the replication rate of neoplastic cells”

I recommend that the court adopt LEO’s proposed construction, which is supported by the specification of the ‘656 patent. The parties agree that the disputed term from the ‘656 patent claim preamble is limiting. *See Poly-Am., L.P. v. GSE Lining Tech., Inc.*, 383 F.3d 1303, 1310 (Fed. Cir. 2004). The focus of the dispute centers on whether the “inhibiting proliferative activity of neoplastic cells” limitation of claim 1, when read in light of the specification, requires “selectivity”—in other words, requires “greater inhibition of the proliferation of neoplastic cells than of healthy cells.” (D.I. 111 at 22) Selectivity is emphasized throughout the ‘656 patent specification, and is therefore central to the claims in accordance with LEO’s proposed construction. *See Phillips v. AWH Corp.*, 415 F.3d 1303, 1316 (Fed. Cir. 2005).

Specifically, the Background of the Invention section discloses the challenge facing the inventors by explaining that “an ideal drug would be one that when applied [] selectively necrotizes the tumour cells or induces them to undergo apoptosis, without causing damage to the surrounding healthy skin cells. In practice, this has yet to be achieved. The drugs currently available are neither selective nor penetrative.” (‘656 patent, col. 2:28-33) The Abstract of the ‘656 patent identifies extracts from *Euphorbia* plants, which “show selective cytotoxicity against several different cancer cell lines,” as the solution to this challenge. (*Id.*, Abstract) The specification subsequently repeats that “[e]xtracts from these plants have been found to show selective cytotoxicity.” (*Id.*, col. 1:19-21) The Summary of the Invention section reiterates that

“the invention” is “able to kill or inhibit the growth of cancer cells, but does not significantly affect normal neonatal fibroblasts, or spontaneously transformed keratinocytes.” (*Id.*, col. 6:26-38) Thus, the specification supports LEO’s proposed construction.

Consistent with LEO’s proposed construction, the specification discloses a number of embodiments that achieve selective inhibition effects. Example 1 discloses that, “[a]t a dilution of 1/125, no effect was observed against [normal] NFF cells (rating 0),⁸ but severe inhibition of [malignant melanoma] MM96L cells (rating 4) was observed for one sample.” (*Id.*, col. 12:43-48) Example 3 discloses that, “[a]t dilutions of 1/100 to 1/50 there was no effect on [normal skin fibroblast] NFF cells, but significant inhibition of [malignant melanoma] MM96L cells was observed.” (*Id.*, col. 15:41-55; Table 10)

Defendants contend that the selectivity requirement is not fully supported by the specification, misinterpreting Example 2 by ignoring the description conceding that “some growth inhibition of [normal] NFF cells was seen in this experiment.” (*Id.*, col. 13:15-16) A person skilled in the art would understand that selective inhibition may still harm some normal cells. (D.I. 114 at ¶¶ 42-44, 55-56) Given the vast range of dilutions available for experimentation, a person having ordinary skill in the art would likely regard the disclosed embodiments of various dilutions as efforts to optimize the selectivity.⁹ See *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1576 (Fed. Cir. 1984) (“Experiments were designated ‘failures’ . . . in essence because they were not optimal under all conditions, but such

⁸ According to the ‘656 patent, the inhibition effects are rated on a scale of 0 to 5. A rating of 0 means “no effect to” the tested cells; and a rating of 5 corresponds to “complete cell death.” (‘656 patent, Col. 11:8-9)

⁹ In fact, a person skilled in the art would have understood Example 2, entitled “Effect of Heat or Acetone Trea Bent on Activity of *Euphorbia* Sap,” mainly to show that “[n]either heat nor acetone affected the anti-tumour activity significantly” and that “the compounds responsible are not protein in nature.” (*Id.*, col. 12:61-62 and 13:15-16)

optimality is not required for a valid patent.”) To the extent that LEO’s proposed construction may render a few embodiments inoperative, the mere presence of some inoperative embodiments does not necessarily invalidate the claims. *See id.* at 1576-77; *In re Cook*, 439 F.2d 730, 735 (C.C.P.A. 1971) (noting that although claims may read on some inoperative embodiments, this does not necessarily invalidate the claim if the necessary information to limit the claims to operative embodiments is known to a person of ordinary skill in the art). Here, defendants fail to demonstrate that the claims “read[] on significant numbers of inoperative embodiments” that “one of ordinary skill cannot practice the full scope of the method [of the claims] without undue experimentation.” *See Senju Pharm. Co. Ltd. v. Apotex Inc.*, 717 F. Supp. 2d 404, 429 (D. Del. 2010) (citing *Crown Operations Int’l, Ltd. v. Solutia Inc.*, 289 F.3d 1367, 1380 (Fed. Cir. 2002)).

6. “sap” (‘161 patent, claims 1, 5-7; ‘013 patent, claims 1, 5-7)

LEO	Defendants	Court
“fluid substance in plants”	“the liquid exuded from the plant’s vascular system”	“fluid substance in plants”

I recommend that the court adopt LEO’s proposed construction of sap, which is consistent with the plain and ordinary meaning of the term. The term sap is not defined in the claim language, the specification, or the prosecution history of the ‘161 and ‘013 patents, and the intrinsic record does not definitively identify where or how sap must be obtained from a plant. (‘161 patent, col. 1:19-22; 6:10-13) The court declines to read a limitation into the term which is not found in the intrinsic record and is inconsistent with the meaning of the term to a person of ordinary skill in the art.

“When the intrinsic evidence is silent as to the plain meaning of a term, it is entirely appropriate for the district court to look to dictionaries or other extrinsic sources for context—to aid in arriving at the plain meaning of a claim term.” *Helmsderfer v. Bobrick Washroom Equip.*,

Inc., 527 F.3d 1379, 1382 (Fed. Cir. 2008). The Harper Collins Dictionary of Biology defines “sap” as “a watery liquid found within the vacuole of a plant cell (cell sap) and within conducting tissues of the vascular bundles.” (D.I. 69, Ex. 27 at LEO_PCT00099471)

Defendants do not dispute that the vacuole of a plant cell is not part of the vascular system of a plant. The Random House Unabridged Dictionary defines “sap” as “the juice or vital circulating fluid of a plant, esp. of a woody plant,” and does not specify a particular location in the plant where sap is found. (*Id.*, Ex. 28 at LEO_PCT00099545) The dictionary definitions relied upon by defendants do not contradict LEO’s position. The Dictionary of Plant Sciences defines sap as “[t]he exudate from ruptured tissues emanating from the vascular system or parenchyma,” where “parenchyma” is defined as “tissue composed of the least specialized of plant cells within a system of air spaces running between them.” (D.I. 98, Ex. 21 at PER-ING-0016489; 9/15/17 Tr. at 102:8-22) Although the Academic Press Dictionary of Science and Technology defines sap more narrowly by limiting it to “the vascular fluid of woody plants, containing mineral salts and sugar dissolved in water,” this narrow definition does not control in light of the lack of such limitations in the intrinsic record and the weight of the extrinsic evidence indicating that sap may be found outside of a plant’s vascular system. (*Id.*, Ex. 22 at PER-ING-0016486)

The intrinsic record does not narrow the plain and ordinary meaning of the term by limiting the source of the sap to a plant’s vascular system. The Summary of the Invention states that, “while the invention is described in detail with reference to compounds detected in sap or sap extracts, these compounds, when present in or extracted from whole plants or parts thereof, are still within the scope of the invention.” (‘161 patent, col. 6:37-41) This observation that sap may be extracted from whole plants or parts of plants does not narrow the scope of the term, because it does not identify with specificity any “parts” of the plant from which sap is extracted

that would limit it to the plant’s vascular system. The specification’s description of harvesting sap explains that “[t]he plant stem surface was briefly washed with 70% ethanol, and scissors washed in ethanol were used to cut the stem and release the milky latex sap.” (*Id.* at col. 10:25-28) The fact that sap was harvested from the stem of the plant in this instance does not establish that sap cannot be present in and harvested from other locations, as established by extrinsic evidence showing that sap may also be present in vacuoles and parenchyma, which are outside the vascular system. (D.I. 69, Ex. 27 at LEO_PCT00099471; D.I. 98, Ex. 21 at PER-ING-0016489; 9/15/17 Tr. at 102:8-22) For these reasons, I recommend that the court construe the term “sap” in accordance with LEO’s proposed construction, which is consistent with the plain and ordinary meaning.

B. Disputed Terms in the Brown Patents

1. “pharmaceutically acceptable acidifying agent” (‘292 patent, claims 1, 11, 14, 15)

LEO	Defendants	Court
“agent that lowers pH and is suitable for use in a pharmaceutical formulation”	“an acid, acid preparation, or acidic buffer present in an amount to provide a pharmaceutical formulation pH of less than 4.0”	“agent that lowers pH and is suitable for use in a pharmaceutical formulation”

I recommend that the court adopt LEO’s proposed construction of the disputed term. In accordance with the plain meaning of the term, a person of ordinary skill in the art would understand that an “acidifying agent” is an agent that lowers pH. (D.I. 69, Ex. 11 at 6) (defining an “acidifying agent” as a “substance added to lower the pH of a system under observation.”) The words “pharmaceutically acceptable” modify “acidifying agent.” Defendants’ contention that this modifier narrows the claimed acidifying agent to a pH of less than 4.0 is not supported by the intrinsic record.

The '292 patent specification identifies numerous non-limiting examples of suitable acidifying agents, such as organic acid buffers, and explains that the agents may be used to provide a pH of up to 7.0. ('292 patent, col. 2:33-59) The specification repeatedly refers to "a pharmaceutically acceptable acidifying agent . . . which provides the formulation with an apparent pH of no greater than 4.5." (*Id.*, col. 1:56-67; *see also* col. 4:54-65; col. 5:34-37) Moreover, embodiments reflected in the specification's tables meet the claim limitations and contradict defendants' argument that the pharmaceutically acceptable acidifying agents must provide a pharmaceutical formulation pH of less than 4.0. Specifically, Table 41 discloses a formulation with a pH level of 4.23 which has the stability required by claims 1 and 7 of the '292 patent, retaining 97.74% of the ingenol-3-angelate after twelve months of storage at temperatures between 2° C and 8° C. ('292 patent, col. 47:45-59) Thus, defendants' proposed construction would exclude exemplary embodiments. *In re Papst Licensing Digital Camera Patent Litig.*, 778 F.3d 1255, 1270-71 (Fed. Cir. 2015).

Continuation applications to the Brown patents recently allowed by the PTO are consistent with the court's recommended construction of "pharmaceutically acceptable acidifying agent" in the '292 patent. Consideration of these continuation applications is appropriate in accordance with Federal Circuit precedent, which establishes that when "patents all derive from the same parent application and share many common terms," [a court] must interpret the claims consistently across all asserted patents." *NTP, Inc. v. Research In Motion, Ltd.*, 418 F.3d 1282, 1293 (Fed Cir. 2005). The PTO issued Notices of Allowance for all claims in certain continuation applications to the Brown patents, including U.S. Patent Application Nos. 15/163,390 ("the '390 application"), 15/163,454 ("the '454 application"), 15/163,295 ("the '295 application"), and 14/269,055 ("the '055 application"). (D.I. 185; D.I. 186, Exs. 35-38)

The '390 application, the '454 application, and the '295 application refer to an "acidifying agent" intended to lower pH, but do not impose a limitation that the acidifying agent must have a pH of 4.0 or lower. (D.I. 186, Ex. 35 at claim 51; Ex. 36 at claim 47; Ex. 37 at claim 47) The only restriction on pH levels recited in the dependent claims requires a formulation with a pH of no greater than 4.5, consistent with the specification and claims of the '292 patent. (*Id.*, Ex. 35 at claim 68; Ex. 36 at claim 67; Ex. 37 at claim 51) The '055 application expressly uses the phrase "pharmaceutically acceptable acidifying agent," and independent claim 1 recites "a formulation further comprising a pharmaceutically acceptable acidifying agent which provides the formulation with a pH of no greater than 4.5," consistent with the claims and specification of the '292 patent. (*Id.*, Ex. 38 at claim 1) Nothing in the claim language of these continuation applications requires a pH of below 4.0.

Other issued Brown patents expressly claim a pharmaceutical formulation having a pH of less than 4 when an intention to restrict the pH range exists. ('827 patent, claim 1; '163 patent, claim 1) Neither the '827 patent nor the '163 patent recites the claim term "pharmaceutically acceptable acidifying agent." Consequently, importing a limitation from other patents in the Brown family into the claims of the '292 patent is not proper.

Defendants contend that the prosecution history of the '292 patent demonstrates a clear disavowal of formulations having a pH of 4.0 or greater. The examiner, in the Final Rejection, cited the Ogbourne reference as prior art teaching a formulation of 3-ingenyl angelate "in a [sic] isopropanol-based gel [] with a pH of 4-6." (D.I. 98, Ex. 24 at LEO_PCT00004259) The applicants overcame the obviousness rejection by arguing that "Ogbourne does not teach or suggest ... how to prepare an ingenol-3-angelate formulation with a pharmaceutically acceptable acidifying agent to enhance stability and prevent rearrangement of ingenol-3-angelate (isoform

‘b’) to other isoforms upon storage” (*Id.*, Ex. 25 at LEO_PCT00004293-94) The applicants also indicated that, “as shown in Figure 2, ingenol-3-angelate in a formulation without an acidifying agent undergoes substantial rearrangement from isoform ‘b,’ while a formulation comprising an acidifying agent has much less rearrangement and much greater stability of ingenol-3-angelate (isoform ‘b’), as shown in Figure 3.” (*Id.*) The applicants also omitted a limitation from the claim language reciting “an apparent pH of no greater than 4.5.” (*Id.* at LEO_PCT00004286) Defendants conclude that, because the formulations in Ogbourne have a pH of 4-6, the term “pharmaceutically acceptable acidifying agent” must be limited to those that acidify the formulations to a pH of less than 4.0 so as to meet the claimed stability parameters. (D.I. 134 at 10)

Although the applicants removed the pH limitation from the proposed claims of the ‘292 patent during prosecution prior to allowance, they did not expressly distinguish Ogbourne from the ‘292 patent in terms of pH, and did not expressly tie or relate the claimed stability¹⁰ of the formulation to a pH of less than 4. (D.I. 98, Ex. 25 at LEO_PCT00004294) Moreover, the examiner’s stated reasons for allowance did not identify the pH levels as a contributing factor to overcoming the prior art. (D.I. 112, Ex. 29 at LEO_PCT00004322) Because the applicants distinguished the Ogbourne reference on grounds different than the disputed limitation, and the examiner allowed the ‘292 patent to issue without identifying pH ranges among the list of reasons for allowance, there can be no prosecution disclaimer. *See Grober v. Mako Prods., Inc.*,

¹⁰ The ‘292 patents specification indicates that the pH is not the only factor that improves the formulation’s stability and prevents the isoform rearrangement of ingenol angelate. (‘292 patent, col. 2:35-38) (“it has been established that [the claimed ingenol-3-angelate] can decompose much below about a pH of 3, while rearrangement is likely to occur at above a pH of about 4.5.”) The applicants distinguished Ogbourne on the overall basis of “increased stability” of ingenol-3-angelate after extended storage at particular temperatures. (D.I. 98, Ex. 25 at LEO_PCT00004293-94; ‘292 patent, col. 1:41-47; col. 2:9-13; col. 2:25-29)

686 F.3d 1335, 1342-43 (Fed. Cir. 2012) (rejecting prosecution disclaimer argument where the applicant’s “statements were not an unambiguous disavowal that clearly and unmistakably disclaims claim scope or meaning.”). Thus, the applicants did not disclaim the pH range of 4 or greater during prosecution of the ‘292 patent.

2. “cancerous skin condition” (‘163 patent, claim 13; ‘271 patent, claim 13; ‘375 patent, claim 13)

LEO	Defendants	Court
“condition of the skin which is or can become cancer”	“cancer of the skin”	“condition of the skin which is or can become cancer”

I recommend that the court adopt LEO’s proposed construction, which is consistent with the intrinsic and extrinsic evidence. “Claim construction begins and ends in all cases with the actual words of the claim.” *Becton, Dickinson & Co. v. Tyco Healthcare Grp., LP*, 616 F.3d 1249, 1254 (Fed. Cir. 2010) (internal quotation marks and citations omitted). Claim 13 of the ‘163, ‘271, and ‘375 patents is directed to “[a] method of treating a cancerous skin condition,” which includes “squamous cell carcinoma, basal cell carcinoma, malignant melanoma, and actinic keratosis.” (‘271 patent, col. 53:15-21) LEO’s proposed construction encompasses both skin cancers and precancerous skin conditions, consistent with the language in the claim itself.

A person of ordinary skill in the art would recognize that actinic keratosis may be a precancerous skin condition, but is not necessarily a form of skin cancer by definition. (D.I. 69, Ex. 15) The scientific literature (specifically, the “Mackie reference”) relied upon by LEO defines actinic keratosis as “[a]n area of epidermal dysplasia giving rise to cutaneous scaling usually seen on light-exposed Caucasian skin,” but distinguishes the condition from skin cancer, noting that a small percentage of cases ultimately result in skin cancer. (*Id.* at 78-79) (“Recent work from Australia has shown that . . . 40 per cent of individuals over the age of 40 will have one or more actinic or solar keratosis, and 2-3 percent will have a non-melanoma skin cancer.”)

Thus, equating the claim term to “cancer of the skin” would effectively exclude actinic keratosis from the definition because actinic keratosis is understood to be a precursor to skin cancer:

[I]t is suggested that the patient with actinic keratoses should be regarded as an individual who has had more UV exposure than his epidermis can tolerate and is therefore at risk of future squamous cell carcinoma and basal cell carcinoma, which may not necessarily develop on the actinic keratosis already present, but may be seen on sun-damaged surrounding skin.

(*Id.* at 84; 9/15/17 Tr. at 150:13-18 (“And really the dispute between the parties is Defendants’ contention that a cancerous skin condition may not be actinic keratosis and treatment of cancerous skin conditions may not be treatment of actinic keratosis.”))

Defining the term “cancerous skin condition” in independent claim 13 as “cancer of the skin” in accordance with defendants’ proposed construction would also diminish the distinction between the disputed term and the term “skin cancer” as recited in independent claim 1. *See Comaper Corp. v. Antec, Inc.*, 596 F.3d 1343, 1348 (Fed. Cir. 2010) (“There is an inference . . . that two different terms used in a patent have different meanings.”). The patentee’s use of different terms in independent claims 1 and 13 gives rise to a presumption that the terms have different meanings. *See Becton, Dickinson*, 616 F.3d at 1254 (citing *CAE Screenplates, Inc. v. Heinrich Fiedler GmbH & Co.*, 224 F.3d 1308, 1317 (Fed. Cir. 2000)). The dependent claims reinforce this distinction. The claims depending from claim 1 refer to squamous cell carcinoma, basal cell carcinoma, and malignant melanoma, all of which are forms of skin cancer, but these dependent claims do not mention actinic keratosis. (‘271 patent, col. 52:66-53:4) In contrast, the claims depending from claim 13 include actinic keratosis in addition to squamous cell carcinoma, basal cell carcinoma, and malignant melanoma, supporting a broader construction of “cancerous skin condition” to include precancerous conditions in addition to skin cancers. (*Id.*, col. 54:6-26) LEO’s proposed construction is also consistent with the specification, which does

not use the terms “cancerous skin condition” and “skin cancer” interchangeably. *Compare* ‘271 patent, col. 5:39-40 (“There is further provided the use of a formulation of the invention in the treatment of a skin cancer.”), *with id.* at 5:53-57 (“The present invention also provides a method of treating a subject suffering from a cancerous skin condition.”).

Defendants argue that “cancerous skin condition” is interchangeable with “skin cancer” or “cancer of the skin.” (D.I. 96 at 34-35; D.I. 134 at 13-14) As a result, defendants allege that the addition of the term “actinic keratosis” by amendment after the filing date was an improper addition of new matter intended to expand the definition of “cancerous skin condition” to include precancerous conditions such as actinic keratosis. (D.I. 134 at 14 n.14; 9/15/17 Tr. at 155:3-7) Defendants rely on the declaration of their expert, Dr. Mark Steven Nestor, to establish that a cancerous skin condition is equivalent to skin cancer. (D.I. 97 at ¶¶ 30-32) However, Dr. Nestor’s declaration refutes LEO’s interpretation of the Mackie reference, the specification, and the claim language without offering affirmative evidence supporting Dr. Nestor’s conclusory allegation regarding the understanding of a person of ordinary skill in the art with respect to the term “cancerous skin condition.”

The evidence presented by defendants in support of their construction is not sufficient to overcome the presumption of validity where, as here, the examiner permitted the amendment without issuing a new matter rejection. (D.I. 135, Exs. 57-59) “Whether particular technological information is ‘new matter’ depends on the facts of the case: the nature of the disclosure, the state of the art, and the nature of the added matter. A patent is presumed valid, 35 U.S.C. § 282, and this presumption is based in part on the expertise of patent examiners presumed to have done their job.” *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1574 (Fed. Cir. 1992); *see also In re Smythe*, 480 F.2d 1376, 1385 n.5 (C.C.P.A. 1973) (“[T]he fact that the

Patent Office allows such an amendment without objection thereto as new matter . . . is entitled to an especially weighty presumption of correctness.”).

For the reasons previously stated, the specification and claim language establish that the patentee intended to distinguish the meaning of “cancerous skin condition” and “skin cancer” before the claims were amended to add “actinic keratosis,” and the amendment did not introduce new matter in view of the intrinsic record. Defendants’ position lacks support in the intrinsic record, and would require the court to disregard both the presumption of validity and the inference that two different terms used in a patent have different meanings. (D.I. 134 at 14 n.14; 9/15/17 Tr. at 155:3-7) Consequently, I recommend that the court adopt LEO’s proposed construction of the disputed term.

3. “across the skin” (‘919 patent, claims 17-18)

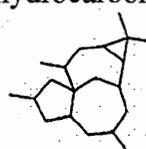
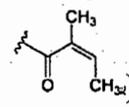
LEO	Defendants	Court
“across the stratum corneum”	“across all layers of the skin”	“across all layers of the skin”

I recommend that the court adopt defendants’ proposed construction, which is consistent with the plain meaning of the term and the intrinsic record. There is no dispute that the skin is a multi-layered organ, and the stratum corneum is one of those layers. (‘919 patent, col. 12:13-36; D.I. 97 at ¶¶ 34-35) The specification does not use the terms “skin” and “stratum corneum” synonymously, describing the skin as a multi-layered organ, (‘919 patent, col. 12:13-36), and identifying the stratum corneum as one layer of the skin, (*id.*, col. 12:19-22). When the patentee sought to describe the diffusion of ingenol-3-angelate across the stratum corneum in the specification, the patentee expressly identified the stratum corneum. (*Id.*, col. 14:55-57) In contrast, claim 17 uses the words “across the skin,” consistent with other uses of the phrase in the specification. (*Id.*, col. 6:41-42)

LEO contends that defendants' proposed construction should be rejected because it would give "skin" different meanings in two places within claim 17. According to LEO, the requirement in claim 17 that the "pharmaceutical formulation is applied to the skin" would be rendered inoperable by defendants' proposed construction because it is not possible to topically apply the pharmaceutical formulation to all layers of the skin. (D.I. 68 at 14-15) The court concludes that the phrase "applied to the skin" in claim 17 does not compel a narrower definition of "skin" in other usages, including "across the skin," because the stratum corneum is indisputably part of the skin. As defendants suggest, "skin" should not be defined as the stratum corneum simply because it includes the stratum corneum. Consequently, construing the disputed term in accordance with defendants' proposed construction does not require an inconsistent interpretation of the term.

V. CONCLUSION

For the reasons set forth above, I recommend that the court construe disputed terms as follows:

Claim Term	Recommended Construction
"[an] isolated compound"	"a compound purified from a plant"
"angeloyl-substituted ingenane"	<p>"an ingenane molecule (i.e., a hydrocarbon</p>  <p>) in having the following structure: which an angeloyl group ((i.e., an acyl group having the following structure</p>  <p>) is bonded to the ingenane molecule"</p>
"active derivative of an angeloyl-substituted ingenane"	"a compound derived from an angeloyl-substituted ingenane, which has activity"
"[a] Euphorbia species"	"a species from the plant genus Euphorbia"

“inhibiting proliferative activity of neoplastic cells”	“selectively decreasing the replication rate of neoplastic cells”
“sap”	“fluid substance in plants”
“pharmaceutically acceptable acidifying agent”	“agent that lowers pH and is suitable for use in a pharmaceutical formulation”
“cancerous skin condition”	“condition of the skin which is or can become cancer”
“across the skin”	“across all layers of the skin”

Given that the court has relied upon material that technically remains under seal, the court is releasing this Report and Recommendation under seal, pending review by the parties. In the unlikely event that the parties believe that certain material in this Report and Recommendation should be redacted, the parties should jointly submit a proposed redacted version by no later than **January 5, 2018**. The court will subsequently issue a publicly available version of its Report and Recommendation.

This Report and Recommendation is filed pursuant to 28 U.S.C. § 636(b)(1)(B), Fed. R. Civ. P. 72(b)(1), and D. Del. LR 72.1. The parties may serve and file specific written objections within fourteen (14) days after being served with a copy of this Report and Recommendation. Fed. R. Civ. P. 72(b)(2). The objections and responses to the objections are limited to ten (10) pages each. The failure of a party to object to legal conclusions may result in the loss of the right to de novo review in the District Court. *See Sincavage v. Barnhart*, 171 F. App'x 924, 925 n.1 (3d Cir. 2006); *Henderson v. Carlson*, 812 F.2d 874, 878-79 (3d Cir. 1987).

The parties are directed to the court's Standing Order For Objections Filed Under Fed. R. Civ. P. 72, dated October 9, 2013, a copy of which is available on the court's website, <http://www.ded.uscourts.gov>.

Dated: December 28, 2017


 Sherry R. Fallon
 UNITED STATES MAGISTRATE JUDGE