

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SUN PHARMACEUTICAL INDUSTRIES, INC. and
SUN PHARMACEUTICAL INDUSTRIES, LTD.
Petitioner

v.

BIOFRONTERA, INC.
Patent Owner

Case No. IPR2026-00396
U.S. Patent No. 12,280,146

DECLARATION OF DAVID W. OSBORNE, PH.D.

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[1Pre] A formulation comprising:

[1A] a nanoemulsion comprising:

[1B] (i) at least one aqueous component;

[1C] (ii) a carrier component comprising:

[1D] (1) at least one lipophilic component,

[1E] (2) at least one surfactant, and

[1F] (3) at least one alcohol; and

[1G] 5-aminolevulinic acid and/or a derivative, a precursor, a metabolite, and/or a pharmaceutically acceptable salt thereof,

[1H] wherein the formulation comprises essentially no propylene glycol and essentially no sorbitol.

[2] The formulation of claim 1, wherein the formulation further comprises less than 1% w/w of a non-cyclic polyol having 2 to 5 carbon atoms.

[3] The formulation of claim 1, wherein the formulation further comprises less than 1% w/w of a non-cyclic polyol having 2 to 12 carbon atoms.

[4] The formulation of claim 1, wherein the at least one alcohol comprises: 3, 4, or 5 carbon atoms; or 1-propanol, 2-propanol, or a mixture thereof.

[5] The formulation of claim 1, comprising the at least one aqueous component in an amount from 50% to 99% (w/w), from 70% to 95% (w/w), from 75% to 95% (w/w), or from 80% to 90% (w/w).

[6] The formulation of claim 4, comprising the at least one lipophilic component in an amount from 0.1% to 30% (w/w), from 0.25% to 15% (w/w), from 0.25% to 10% (w/w), from 2% to 10% (w/w), or 3% to 8% (w/w) based on total weight of the nanoemulsion.

[7] The formulation of claim 1, wherein the formulation comprises no propylene glycol.

[8] The formulation of claim 1, wherein the formulation further comprises less than or equal to 0.99%, 0.95%, 0.9%, 0.8%, 0.7%, 0.6%, 0.5%, 0.4%, 0.3%, 0.2%, or 0.1% w/w of a non-cyclic polyol having 2 to 5 carbon atoms.

[9] The formulation of claim 1, wherein the formulation further comprises essentially no non-cyclic polyol having 2 to 5 carbon atoms.

[10] The formulation of claim 1, wherein the formulation further comprises no non-cyclic polyol having 2 to 5 carbon atoms.

[11] The formulation of claim 1, wherein the formulation further comprises less than or equal to 0.99%, 0.95%, 0.9%, 0.8%, 0.7%, 0.6%, 0.5%, 0.4%, 0.3%, 0.2%, or 0.1% w/w of a non-cyclic polyol having 2 to 12 carbon atoms.

[12] The formulation of claim 1, wherein the formulation further comprises essentially no non-cyclic polyol having 2 to 12 carbon atoms.

[13] The formulation of claim 1, wherein the formulation further comprises no non-cyclic polyol having 2 to 12 carbon atoms.

[14] The formulation of claim 1, wherein the at least one lipophilic component comprises: triglycerides and/or mixtures thereof; or a caprylic triglyceride, a capric triglyceride, or a mixture thereof.

[15] The formulation of claim 1, wherein the at least one surfactant comprises: a phospholipid, a phosphatidylcholine, a lysophospholipid, a ceramide, and/or a mixture thereof; and/or a polyoxyethylene-type surfactant.

[16] The formulation of claim 4, wherein the at least one alcohol is in an amount from 0.1% to 10% (w/w), from 0.5% to 5% (w/w), from 1% to 5% (w/w), or from 1% to 3% based on total weight of the nanoemulsion.

[17] The formulation of claim 1, wherein the formulation further comprises essentially no monosaccharides and disaccharides.

I, David W. Osborne, Ph.D., declare as follows:

I. Introduction

1. My name is David W. Osborne, Ph.D. I submit this declaration as an expert witness in the field of topical formulations on behalf of Petitioner Sun Pharmaceutical Industries, Inc. (“Sun”) to provide expert opinions on the validity of U.S. Patent No. 12,280,146 (the “’146 patent”).

II. Background and Qualifications

2. I am an expert in the field of pharmaceutical development, with specific expertise in physical chemistry, and a particular expertise in formulation and clinical development of pharmaceutically active agents delivered into and across the skin, including via topical dosage forms. The interplay between surface active excipients and the barrier properties of human skin has been the foundation of both my career in pharmaceutical product development and my scientific contributions to chemistry and pharmaceuticals.

3. In 1982, I completed the requirements for a Bachelor of Science degree in Chemistry (ACS Certified) from Missouri State University. In 1985, I earned a Ph.D. in physical chemistry from the University of Missouri-Rolla (renamed Missouri University of Science and Technology in 2008), after completing a dissertation entitled “The Interaction of a Glyceridacid with Lipids of the Stratum Corneum.”

4. I have contributed academically to the field of pharmaceutical development. I was Chairman of the American Chemical Society Division of Colloid and Surface Chemistry in 1992, and Co-Chair of the Surfactants and Association Colloids Symposium Series from 1987 to 1995. I was Adjunct Assistant Professor at the St. Louis College of Pharmacy from 1992 to 1994, and Adjunct Associate Professor of Pharmaceutics at the University of Houston College of Pharmacy from 1993 to 1998. Since 2003, I have been on the Missouri State University Chemistry Department Board of Advisors. In 2011, I became a member of the UMKC School of Pharmacy Research Advisory Council.

5. I have forty years of work experience in the field of pharmaceuticals and have held many positions throughout the industry.

6. From 1985 through 1991, I was a Research Scientist at The Upjohn Company, leading a 3- to 5-person team in pre-formulation, formulation design, clinical supply manufacture and completing relevant sections of Investigational New Drug Applications (“INDs”) and New Drug Applications (“NDAs”) for topical products, transdermal patches, and suppositories.

7. From 1991 through 1993, I was Group Leader, Skin Care for Calgon-Vestal Laboratories (Merck Subsidiary). There I was responsible for developing topical OTC and NDA products that complimented their existing line of wound care and hospital infection control products.

8. In 1993, I became Vice President of Research and Development for ViroTex and was responsible for all aspects (formulation, analytical, non-clinical, clinical, and regulatory) of IND and NDA filing for topical and transmucosal patch (bioerodible) product development. During this time, I developed and patented the 5% Dapsone Topical Gel known as ACZONE® for the treatment of acne.

9. ViroTex was acquired by Atrix Laboratories in 1998, where as Vice President, Pharmaceutical Development, I initially managed topical product development and analytical development for transmucosal patches, parenteral products, and topical products. Between 1999 and 2003, I became responsible for development of transmucosal patches and led the addition of generic dermatology products to the Atrix product pipeline. In 2002, I was promoted to Vice President of the Atrix Dermatology Division.

10. In 2003, I became Vice President for Dow Pharmaceutical Sciences and managed a team of about 25 development scientists that brought to commercialization the topical products METROGEL® 1%, CLOBEX® Spray, DESONATE® Gel, ZIANA® Gel, ACANYA® Gel, and the transmucosal patch product ONSOLIS® (BEMA® fentanyl for cancer pain).

11. I joined TOLMAR in 2008 as Vice President, Product Development assuming responsibility for formulation, analytical, non-clinical, clinical, and

regulatory functions for the development of topical and specialty injectable generic products. I retired from TOLMAR as Chief Scientific Officer in June 2016.

12. I joined Arcutis Inc. in 2017 as Senior Vice President, Product Development. At Arcutis, I led a team responsible for the development of topical roflumilast products. I retired from Arcutis as Chief Technical Officer in 2023.

13. Since August 2016, I have been President of David W. Osborne, Ph.D. Consulting, Inc.

14. As set forth above, I have specific experience in designing and formulating topically applied fluids and semisolids (creams, gels, and ointments). This was my primary function while employed at The Upjohn Company beginning in the summer of 1985, and remained my primary function through my retirement from Arcutis in 2023.

15. During the past 40 years, and under my leadership, I have been responsible for compiling over 30 New Drug Applications (NDAs), Abbreviated New Drug Applications (ANDAs), or Over the Counter launches (OTC), for topical, mucosal, or parenteral pharmaceutical products, all of which have been developed, approved, and commercialized.

16. I have also taught many professional courses regarding dermatological product development throughout my career. During May 4-5, 1993, in Atlanta, Georgia, and June 3-4, 1993, in Basel, Switzerland, I taught a professional two-day

short course with Dr. Umesh Banakar (Saint Louis College of Pharmacy), entitled “Dermatological Product Development & Drug Delivery.” I taught a professional two-day short course entitled “Dermatological Product Development for Managers” on April 20-21, 2006 (Springfield, Missouri), April 24-25, 2008 (Springfield, Missouri), May 14-15, 2009 (Buffalo, New York), and May 6-7, 2010 (Vienna, Virginia). I taught a professional two-day short course entitled “Dermatological Product Development: Current Issues for Topical Products” in Petaluma, California, on October 9-10, 2014, April 13-14, 2016, May 3-4, 2017, and April 18-19, 2018. I also taught a professional one-day short course entitled “Dermatological Product Development Formulation Bootcamp” in Denver, Colorado, on November 13, 2016.

17. As part of my duties over the years, I have had occasion to work with or study over 30 active moieties, and over 50 pharmaceutical excipients contained in FDA-approved products, including at least 10 distinct classes of polymeric viscosity-building agents such as emulsifiers and gelling agents used in topical drug dosage forms.

18. During my many years of developing new drugs and formulations, I had become listed as the inventor on over 100 issued patents and published applications covering pharmaceutical products, including “Azithromycin for Treatment of Skin Disorders,” “Azithromycin for the treatment of nodular acne,”

“Topical Acne Vulgaris Medication with a Sunscreen,” and “Compositions and Methods for Topical Application of Therapeutic Agents.”

19. I have been the co-editor of two published books regarding topical drug product development and drug delivery formulations. I have almost sixty publications, including articles relating to pharmaceutical formulations, topical pharmaceuticals and dermatology, and particle size, including the articles “Understanding microemulsions and nanoemulsions in (trans)dermal delivery,” “Characterization of a Liquid Crystal Stabilized Pharmaceutical Oil-in-Water Emulsion Optimized of Skin Delivery,” and “Microemulsions as Topical Drug Delivery Vehicles: In-Vitro Transdermal Delivery Studies of a Model Hydrophilic Drug.” I have also published in-vitro skin permeation results in peer reviewed journals and have provided the experimental results published as examples of issued patents. My reviews of skin permeation testing results of skin penetration enhancers have often been cited in the technical literature, notably the 1997 Pharmaceutical Technology article “A listing of Skin Penetration Enhancers Cited in the Technical Literature.”

20. My achievements have caused me to become recognized and respected by other professionals in the industry, have allowed me to sit on various committees and boards, and I have won and obtained several awards and grants.

21. I am, or have been, the chairman of several organizations, such as Q3 Working group, the AAPS Dermatopharmaceutics Focus Group, the American Chemical Society Division of Colloid and Surface Science, and of the COLL Division Symposium at the Boston ACS Meeting in 1990. Additionally, I sit, and have sat, on the board for, or am a member of, various other committees, such as the American Chemical Society, American Academy of Dermatology, CSU Advisory Board, UMKC School of Pharmacy Research Advisory Council, and the Missouri State University Chemistry Department Board of Advisors. I am also the Founding North American Editor of the Elsevier Journal, Colloids & Surfaces.

22. I have sat on several graduate committees at the University of Houston, College of Pharmacy, and the Rush University Medical Center, Clinical Pharmacology.

23. I have also received the Outstanding Young Alumni Award from the Southwest Missouri State University.

24. The Small Business Innovation Research Program (SBIR) has awarded me four grants for use in the field of topical pharmacology, totaling over \$1 Million dollars.

25. I am being compensated at my customary rate of \$500 per hour for my work on this case. My compensation is not contingent on the outcome of this case.

26. My *curriculum vitae*, which includes a list of my publications, patents, awards and recognitions, education, and experience, is attached as Appendix A.

27. In view of my experiences and expertise outlined above and provided in my *curriculum vitae*, I am an expert in the field of topical pharmaceutical compositions and formulations. For this reason, I believe that I am qualified to provide an opinion as to what a person of ordinary skill in the art at the time of the invention (“POSA”) would have understood, known, or concluded as of the effective filing date of the ’146 patent, April 6, 2023.

III. Materials Considered

28. I understand that the ’146 patent has a filing date of December 8, 2023, claiming priority to International Patent Application No. PCT/EP2023/059291 filed April 6, 2023. EX1001 (’146 patent), Cover.

29. Therefore, I assume that the earliest possible priority date of the ’146 patent is April 6, 2023. I have considered issues from the perspective of a person of ordinary skill in the art as described in Section VIII below [Level Of Ordinary Skill In The Art] as of April 6, 2023.

30. I have reviewed the following documents in preparing this declaration. U.S. 5,520,905 (EX1004) (“Uhlmann”), published May 28, 1996 and U.S. 2003/0198654 (EX1005) (“Palazzolo”), published October 23, 2003. I understand that these are prior art to the ’146 patent.

31. I have also reviewed all of the exhibits cited in this declaration, including the following:

Exhibit No.	DESCRIPTION
1001	U.S. Patent No. 12,280,146 (“’146 Patent”)
1003	File History of the ’146 Patent
1004	U.S. Patent No. 5,520,905 (“Uhlmann”)
1005	U.S. 2003/0198654 (“Palazzolo”)
1006	U.S. 2021/0393497 (“Alderson”)
1007	Hill, “Preservation of cosmetics and toiletries,” <i>Handbook of Biocide and Preservative Use</i> 1995, Chapter 13. (“Hill”)
1008	U.S. Patent No. 6,858,200 (“Fowler”)
1009	Jaworska et al., “The influence of glicerides oil phase on O/W nanoemulsion formation by pic method,” <i>Periodic Polytechnica Chemical Engineering</i> 2014, 58(Sup), 43-48. (“Jaworska”)
1010	Fiume et al., “Safety Assessment of Monoglyceryl Monoesters as Used in Cosmetics,” <i>International Journal of Toxicology</i> 2020, Vol. 39 (Supplement 3), 93S-126S. (“Fiume 2020”)
1011	Kale et al., “Emulsion Micro Emulsion and Nano Emulsion: A Review,” <i>Sys Rev Pharm</i> 2017, 8(1):39-47. (“Kale”)
1012	Bailey et al., “Polyoxyalkylenes,” <i>Ullmann’s Encyclopedia of Industrial Chemistry</i> 2012. (“Bailey”)
1013	Nelson et al., “Carbohydrates And Glycobiology,” <i>Lehninger Principles of Biochemistry Eighth Edition</i> 2021, Chapter 7. (“Nelson”)
1014	Bunke et al., “Degradation Mechanism and Stability of 5-Aminolevulinic Acid,” <i>Journal of Pharmaceutical Sciences</i> 2000, Vol. 89 No. 10, 1335-1341. (“Bunke”)

Exhibit No.	DESCRIPTION
1015	McCarron et al., “Stability of 5-Aminolevulinic Acid in Novel Non-Aqueous Gel and Patch-Type Systems Intended for Topical Application,” <i>Journal of Pharmaceutical Sciences</i> 2005, Vol. 94 No. 8, 1756-1771. (“McCarron”)
1016	Fiume et al., “Final Report on the Safety Assessment of Sodium Cetearyl Sulfate and Related Alkyl Sulfates as Used in Cosmetics,” <i>International Journal of Toxicology</i> 2010, Vol. 29(Supplement 2), 115S-132S. (“Fiume 2010”)
1017	Vaidya et al., “Comparative study between silicone and fatty surfactant,” <i>World Journal of Pharmaceutical Sciences</i> 2015, 3(3): 532-541. (“Vaidya”)
1018	Araujo et al., “Development of microemulsions to topically deliver 5-aminolevulinic acid in photodynamic therapy,” <i>European Journal of Pharmaceutics and Biopharmaceutics</i> 2010, Vol. 75, 48-55. (“Araujo”)
1019	U.S. 2015/0238457 (“Stensrud”)
1020	Singh et al., “Nanoemulsion: Concepts, development and applications in drug delivery,” <i>Journal of Controlled Release</i> 2017, Vol. 252, 28-49. (“Singh”)

32. The opinions that I express in this declaration are based on the information and evidence currently available to me. I have relied on the above materials, as well as my education, knowledge, and experience that I have acquired over forty years as a practicing pharmaceutical researcher and developer.

IV. Summary of Opinions

33. It is my opinion that claims 1–17 of the ’146 patent are anticipated or obvious in view of the Grounds identified below:

Ground	References	Statutory Ground	Challenged Claims
IA	Uhlmann Example 5 (Anticipation)	35 U.S.C. §102	1, 4-7, 14-17
IB	Uhlmann Example 5 (Obviousness)	35 U.S.C. §103	2, 3, 8-13
IC	Uhlmann Example 5 with Palazzolo (Obviousness)	35 U.S.C. §103	5
IIA	Uhlmann Example 3 (Anticipation)	35 U.S.C. §102	1, 4-7, 14-17
IIB	Uhlmann Example 3 (Obviousness)	35 U.S.C. §103	2, 3, 8-13, 16
IIC	Uhlmann Example 3 with Palazzolo (Obviousness)	35 U.S.C. §103	5

V. Relevant Law

34. I am not an attorney. For the purposes of this declaration, I have been informed about certain aspects of the law that are relevant to my opinions. My understanding of the law is as follows:

A. Person of Ordinary Skill in the Art

35. I have been informed and understand that a patent should be analyzed from the perspective of a person of ordinary skill in the art (“POSA”), which is a hypothetical individual. I have been advised to assume that a POSA would have been familiar with the prior art that was publicly accessible at the time of the priority date of the patent. Here, the ’146 patent has a priority date of April 6, 2023.

36. I have also been informed that several factors are considered when determining the level of a POSA, including: (1) the sophistication of the technology; (2) the types of problems encountered and challenges faced in the field; (3) solutions to those problems that were known as of the patent’s priority date; (4) the educational background of professionals working in the field, including the named inventor; (5) the types of testing discussed in the patent and the skills required to perform such testing; and (6) the overall state of the technology at the relevant time.

37. I have also been informed that a POSA is a person of ordinary creativity. A POSA is not an automaton and would be capable of considering and combining teachings from multiple prior art references.

B. Claim Construction

38. I have been informed that claim construction is a matter of law and that the final claim construction will ultimately be determined by the Board. For the

purposes of my analysis in this proceeding and with respect to the prior art, I have been informed that IPRs are currently reviewed under “the *Phillips* standard.”

39. I have been informed that under the *Phillips* standard, claim terms are given their plain and ordinary meaning as understood by a person of ordinary skill in the art at the time of the invention in light of the claim language and the patent specification.

40. I have been informed that embodiments described in the specification are generally encompassed by the claims.

41. I have been informed that the patentee can serve as their own lexicographer. As such, if a claim term is provided with a specific definition in the specification, then I should interpret that claim term in light of the particular definition provided by the patentee.

C. Anticipation

42. I have been informed and understand a patent claim is considered “anticipated” by the prior art when a single prior art reference discloses each and every limitation of the claims either expressly or inherently, and that the wording in a prior art reference does not need to match the claim. I understand that a reference is anticipatory if a POSA, after reviewing this single reference, would have been able to make and use the described technology in the manner claimed.

43. I further understand that a claim limitation that covers a range can be anticipated by a prior art reference that teaches a specific value or a smaller range within that claimed range. I further understand that a description of a single embodiment of broadly claimed subject matter can be sufficient to anticipate a claim.

D. Obviousness

44. I have been informed and understand that a patent claim can be considered to have been obvious if one or more prior art references, either individually or in combination, teach or suggest the claimed subject matter.

45. I have been informed and further understand that a patent claim is considered obvious to a POSA when, in view of one or more prior art references, the differences between the claimed subject matter and the prior art would have been obvious to a POSA as of the patent's priority date. Accordingly, I understand that the challenged claims should be evaluated from the perspective of a POSA. For example, I understand that a claim may be unpatentable for obviousness where a POSA would have been motivated to combine the teachings of two or more prior art references to arrive at the claimed subject matter and would have had a reasonable expectation of success in doing so.

46. I understand that, in an *inter partes* review, the Patent Trial and Appeal Board (the "Board") evaluates obviousness under a preponderance of the evidence

standard, meaning that a claim is determined to be unpatentable for obviousness if it is more likely obvious than not.

47. I understand that the Supreme Court has held that a combination of known elements according to known methods that yields no more than predictable results is likely to be obvious. I further understand that obviousness may be found, for example, where:

- there is some teaching, suggestion, or motivation in the prior art that would have led a POSA to combine prior art reference teachings or modify the prior art to arrive at the claims;
- the modification is a combination of prior art elements according to known methods yields predictable results;
- the combination of prior art is a simple substitution of one known element for another to obtain predictable results;
- the combination of prior art elements is an application of a known technique to a known device (or method) ready for improvement to yield predictable results;
- the changed element(s) represent one of a finite number of identified, predictable solutions, and a POSA would have a reasonable expectation of success that such modification would work.

48. I understand that an obviousness analysis must not rely on impermissible hindsight derived from the patent at issue. Accordingly, the claims and description of the challenged patent cannot be used as a roadmap for selecting or combining prior art references.

49. I further understand that a claim limitation reciting a range may be rendered obvious by one or more prior art references that disclose a range overlapping the claimed range, where the claimed range is not shown to be critical, such as through demonstrating unexpectedly superior results.

50. I further understand that a prior art range that encompasses or overlaps a claimed range may render the claimed range obvious where the prior art does not teach away from the claimed range and the claimed range does not demonstrate unexpectedly superior results.

51. I further understand that disclosure of a point mathematically close to the endpoint of a claimed range may render obvious that claimed range, where the difference between the disclosed point and the claimed range is negligible, if the endpoint of the claimed range has not been shown to be critical or if there are no unexpected results relating to the claimed range.

VI. Technology Background

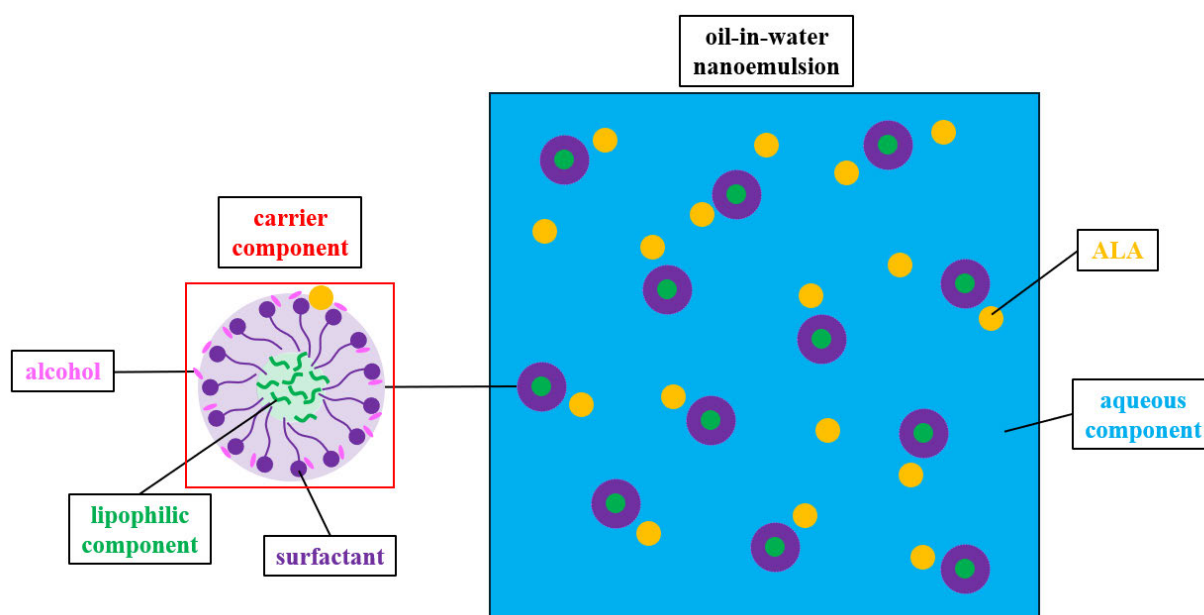
52. Drugs intended for administration through the skin are frequently formulated for topical use. In my experience and understanding of the art, such

topical formulations often rely on dispersion systems known as nanoemulsions to transport active agents—including 5-aminolevulinic acid (“ALA”)—to targeted tissue locations. This approach is well documented in the prior art. *See, e.g.*, EX1018 (Araujo), Abstract, 4-7; EX1019 (Stensrud), [0024], Examples 1-5; EX1020 (Singh), Table 1.

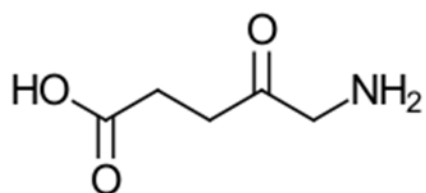
53. In general, nanoemulsions are understood to include three primary components: (1) aqueous components; (2) lipophilic components; and (3) surfactants, which interact with and stabilize the aqueous and lipophilic components so as to produce kinetically stable oil-in-water (“O/W”) dispersions or sometimes thermodynamically stable O/W dispersions (also called microemulsions). *See, e.g.*, EX1020 (Singh), 2, 4-5, Fig. 1. As is well known in the art, surfactants characteristically include both hydrophobic portions and hydrophilic portions. The hydrophobic portions associate with the lipophilic components, while the hydrophilic portions interact with the aqueous components. *See, e.g.*, EX1011 (Kale), 1-3; EX1020 (Singh), 4-5, Fig. 1.

54. As a result of these interactions, the components form small lipophilic or hydrophobic droplets dispersed within a surrounding aqueous matrix. These droplets are often referred to as the “carrier component” because such droplets can “carry” an active agent to the region of interest. In certain applications, the active agent (for example, ALA) is hydrophilic. Under those circumstances, the active

agent is present both within the aqueous component and within the carrier component, such as in proximity to the hydrophilic portions of the surfactants, as illustrated below. *See, e.g.*, EX1018 (Araujo), 1-2; EX1011 (Kale), 1-3, 6; EX1020 (Singh), 4, 18.



55. ALA is a widely recognized active agent and has been incorporated into numerous different types of formulations. These include, for example, formulations used for cancer therapies, acne treatments, as well as cosmetic applications. *See, e.g.*, EX1018 (Araujo), 1-2; EX1019 (Stensrud), [0003]; EX1020 (Singh), 18, Table 1. ALA possesses the chemical structure depicted below, in which one terminus includes a carboxylic acid group (-COOH) and the opposite terminus includes an amino group (-NH₂).



ALA

56. A recognized challenge associated with incorporating ALA into topical formulations is that ALA can degrade over time. By way of example, when ALA is present in aqueous solutions, it has a tendency to dimerize, forming pyrazine-2,5-dipropionic acid. *See, e.g.*, EX1015 (McCarron), 1-2, Fig. 1; EX1014 (Bunke), Fig. 1. In addition, because carboxylic acids are electrophilic, ALA is susceptible to ester formation when nucleophiles, such as diols or polyols, are present. *See, e.g.*, EX1015 (McCarron), 1, 5-15.

57. Consistent with this chemistry, degradation of ALA has been reported in formulations that include glycerol or propylene glycol. *See, e.g.*, EX1014 (Bunke 2000), 6; EX1015 (McCarron), 1, 5-15; EX1019 (Stensrud), Example 2, Example 3. ALA is also known to participate in esterification reactions in the presence of diols and polyols, including glycerol and propylene glycol. *See, e.g.*, EX1015 (McCarron), 7-8, 12, 14; EX1014 (Bunke), 6.

58. For these reasons, nanoemulsions intended for topical delivery of ALA are frequently designed without propylene glycol in order to mitigate ALA degradation. *See, e.g.*, EX1018 (Araujo), 1, 4-7; EX1019 (Stensrud), Examples 1-5.

VII. Overview of the '146 Patent

A. Summary of the '146 Patent

59. I have reviewed the '146 patent. *See* EX1001.

60. The '146 patent describes a topical formulation comprising an oil-in-water nanoemulsion. EX1001, 1:13-16 (“The present invention relates to a composition for topical use comprising an oil in water nanoemulsion and an active ingredient, wherein the composition is essentially free of propylene glycol.”), 12:58-60 (“As used herein, a “nanovesicle emulsion” or a “nanoemulsion” is a dispersion of oil in water (oil-in-water dispersion, oil-in-water emulsion, O/W emulsion).”). As described in the '146 patent, the oil-in-water nanoemulsion contains an aqueous component (for example, a phosphate buffer) together with a hydrophobic carrier component. The hydrophobic carrier component is described as including surfactants (for example, soy lecithin and Polysorbate 80), a lipophilic component (for example, caprylic/capric triglycerides), and an alcohol (for example, isopropyl alcohol). EX1001, Example 1, Tables 2, 3.

61. ALA is employed as the active ingredient in the formulation. EX1001, Example 3, Table 7, 19:8-28. The '146 patent further explains that propylene glycol and sorbitol are intentionally omitted from the topical formulation because those materials were acknowledged to undergo nucleophilic reactions that lead to the formation of undesirable esters with carboxylic acid-containing active agents,

including ALA. EX1001, 1:66-2:6 (“However, cases have been reported in which patients with atopic dermatitis show allergic reactions to propylene glycol and it is known to be irritating to the eyes. Furthermore, it is a diol and may undergo unwanted side reactions, due to its nucleophilic nature. Such reactions are known for example with sorbitol or glycerol in the presence of cetirizine, which is well known as an anti-allergic compound.”), 4:62-5:21 (“Without wishing to be bound by theory, active agents comprising a carboxylic acid group may undergo nucleophilic reactions to form undesired products, such as esters, with propylene glycol. ...”).

B. Summary of the Prosecution History

62. I have reviewed the file history of the '146 patent, which I summarize below. *See* EX1003.

63. The application for the '146 patent was filed on December 8, 2023 by Biofrontera Bioscience GmbH (the “Applicant”). EX1003, 1, 78-79. The application for the '146 patent claimed priority to International Patent Application No. PCT/EP2023/059291, which was filed on April 6, 2023. EX1003, 4, 76.

64. The Applicant elected to proceed with originally filed claim 19, amended the claim, and added new claims 21-26. EX1003, 104, 109-110, 98-99.

65. In an Office Action dated May 1, 2024, claims 19 and 21-26 were rejected by the Examiner as obvious in view of U.S. Patent Publication No.

2009/0324727. EX1003, 148-152. In addition, claims 19 and 21-26 were rejected by the Examiner as obvious over claims 1-20 of Application No. 18/533,521 when considered in combination with U.S. 2009/0324727. EX1003, 154-155.

66. In reply to the Examiner's rejection, the Applicant amended claim 19 to require a formulation comprising "essentially no propylene glycol." EX1003, 158-161, 165-167. The Applicant further asserted that formulations comprising "essentially no propylene glycol" exhibited unexpected results. EX1003, 158-160. In the same response, the Applicant introduced new claims 27-36. EX1003, 166-167.

67. In an Office Action dated September 6, 2024, claim 21 was rejected by the Examiner pursuant to 35 U.S.C. § 112(d) on the basis that the claim failed to further limit the subject matter of the claim from which it depends. EX1003, 175-178. Claims 19, 21-25, and 27-36 were rejected by the Examiner as obvious over U.S. Patent No. 6,559,183. EX1003, 178-180. Claim 26 was rejected by the Examiner as obvious over Schmid in view of U.S. Patent No. 5,152,923. EX1003, 180-181. Claims 19 and 21-36 were also rejected as obvious over claims 1-21 of Application No. 18/533,521. EX1003, 183.

68. In response, the Applicant cancelled claim 21, made amendments to claims 19, 24, and 34, and added new claims 37-39. EX1003, 188-192, 195-198. The

amendment to claim 19 additionally required “essentially no sorbitol.” EX1003, 188-190, 195.

69. An Examiner interview was held on December 6, 2024. EX1003, 221. The Applicant agreed to the Examiner’s recommendations, cancelled claims 38-39, and secured allowance of claims 19 and 22-37. EX1003, 221, 230-236.

70. The ’146 patent subsequently issued on April 22, 2025. EX1001, Cover; EX1003, 330-333.

VIII. Level Of Ordinary Skill In The Art

71. As I noted above in Paragraph 35, I have been informed by counsel that that a patent and the prior art should be analyzed from the perspective of a POSA.

72. A POSA as of the earliest claimed priority date of the ’146 patent (*i.e.*, April 6, 2023) would have had a PhD in physical chemistry, organic chemistry, pharmaceutical chemistry, pharmaceuticals, chemical engineering, or a related field, and a minimum of two to three years of experience in the field of pharmaceutical formulations. A higher level of education or specific skill might make up for less experience, and vice versa.

73. I met and/or exceeded these requirements of a POSA as of April 6, 2023, for at least the reasons provided above in Section II [Background and Qualifications].

IX. Claim Construction

74. I have been asked to determine if any particular claim terms should be construed so the Board can understand how the prior art references read on the challenged claims. As such, I have reviewed the claims, specification, and file history of the '146 patent.

75. Based on my review of the claims, specification, and file history of the '146 patent, I conclude that the term “nanoemulsion” should be construed, as explained below.

A. “nanoemulsion”

76. The term “nanoemulsion” is used in claims 1-17. The '146 patent defines this term as follows: “[a]s used herein, a ‘nanovesicle emulsion’ or a ‘nanoemulsion’ is a dispersion of oil in water (oil-in-water dispersion, oil-in-water emulsion, O/W emulsion).” EX1001, 12:58-60.

77. As I explained above in Paragraph 41, I understand that the patentee may act as his own lexicographer. In this case, the patentee acted as his own lexicographer and provided an explicit definition of the term “nanoemulsion.” Therefore, the term “nanoemulsion” should mean “a dispersion of oil in water.”

78. I understand that the Patent Owner previously argued that “nanoemulsion” should be construed as “a dispersion of oil in water characterized by a mean particle or nanovesicle size of less than 500 nm and a narrow nanovesicle

size distribution.” PGR2026-00021, Paper 9 (Patent Owner Preliminary Response),

8. I disagree with Patent Owner’s proposed construction.

79. First, as I explained above in Paragraph 53, the terms “nanoemulsion” and “microemulsion” are often used interchangeably in the field of pharmaceutical formulations and encompass similarly sized dispersions. Born of colloidal chemistry, the idea of a microemulsion was introduced in the 1940s whereas the term nanoemulsion was coined four decades later, in the 1980s. With a burst of interest in the term “nano” in the 1980s, some drug delivery scientists rebranded their microemulsion work as nanoemulsions. In parallel, advances in emulsion technologies provided a variety of low- or high-energy processing options for developing nanoemulsions which have since been defined and redefined by many. There is little congruity on the proposed size range for nanoemulsions—for example, some nanoemulsions have an average nanovesicle size of 0.7 nm, while others can have an average nanovesicle size of 2000 nm.

80. The additional requirement of a “narrow nanovesicle size distribution” would not allow a POSA to understand the size distributions claimed. A POSA would have understood that the acceptable nanovesicle size distribution in nanoemulsions varies widely, and a POSA would not have an understanding of what qualifies as a “narrow” size distribution. The polydispersity index, which measures the uniformity of nanovesicles, ranges from 0.0 to 1.0. It would be unclear to a POSA

whether a “narrow nanovesicle size distribution” encompasses, for example, only polydispersity indices less than 0.1, only polydispersity indices less than 0.4, or only polydispersity indices less than 0.8, or some other number.

81. For the above reasons, I believe that patentee’s explicit definition “nanoemulsion” as “a dispersion of oil in water” is the correct construction in light of the lexicographic definition provided by the ’146 patent as it specifies that the nanoemulsion to be that of only a dispersion of oil in water while excluding a dispersion of water in oil.

X. PRIMARY PRIOR ART REFERENCE RELIED UPON

A. Overview of Uhlmann (EX1004)

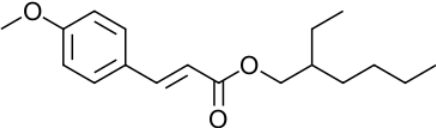
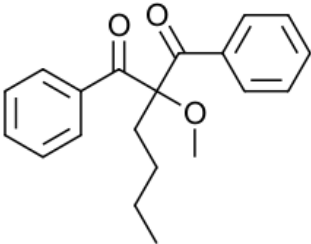
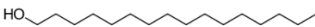
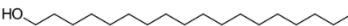
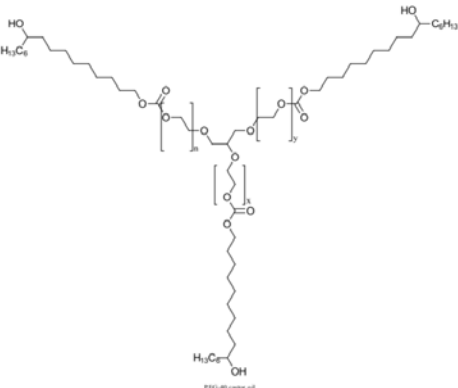
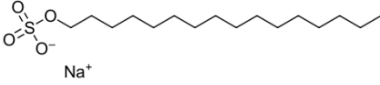
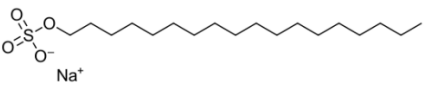
82. Uhlmann is entitled “Cosmetic or dermatological preparation comprising delta-aminolevulinic acid content as an active ingredient” and was published on May 28, 1996. EX1004, Cover. The reference describes “dermatological preparations” containing “ δ -aminolevulinic acid” that are intended to be “used in the treatment of skin...as part of a dermatological...treatment.” EX1004, 5:11-17. Among the disclosed embodiments, Uhlmann sets forth two oil-in-water (O/W) emulsion formulations that include δ -aminolevulinic acid, which are provided in Examples 3 and 5. EX1004, Example 3, Example 5.

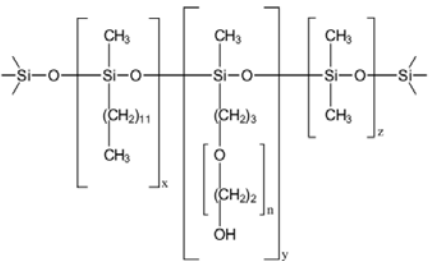
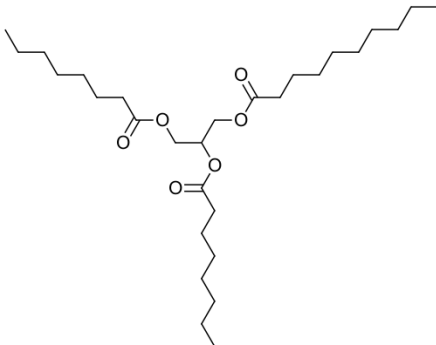
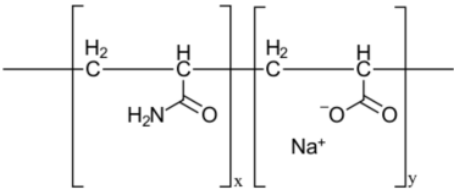
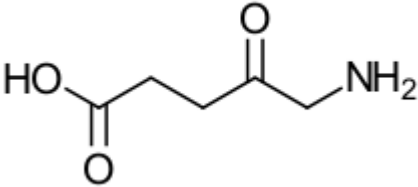
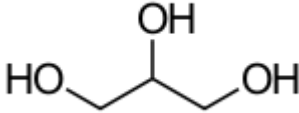
83. In Example 3, Uhlmann describes an oil-in-water emulsion formulation identified as a “Sun Milk O/W.”

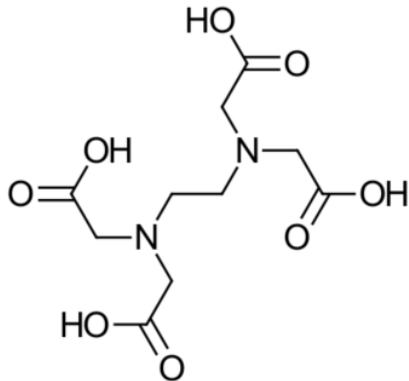
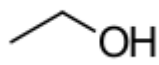
<u>Example 3</u>	
Sun Milk O/W	Percentage by weight
Octylmethoxycinnamate	5.0
Butylmethoxydibenzoylmethane	1.0
Cetearylalcohol + PEG-40 castor oil +	2.5
Sodiumcetearylsulphate	
Glyceryllanolate	1.0
Laurylmethicon copolyol	0.5
Mineral oil (DAB 9)	5.0
Caprylic/capric triglyceride	5.0
Acrylamide/sodiumacrylate copolymer	0.3
Cyclomethicone	2.0
TiO ₂	1.0
δ -aminolevulinic acid	1.0
Glycerine	3.0
EDTA solution (14%)	0.5
Ethanol	5.0
Perfume, preservative	q.s.
Water, fully demineralised	make up to 100.0

EX1004, Example 3 (annotated). As set forth in Example 3, the disclosed O/W emulsion includes a “[discontinuous] lipid phase in an outer aqueous (continuous) phase” and uses δ -aminolevulinic acid as the active ingredient. EX1004, 6:39-48, 4:31-39, Example 3. In this formulation, the carrier component comprises a *lipophilic component* (for example, one or more of *caprylic/capric triglyceride*), a *surfactant* (for example, one or more of *PEG-40 castor oil*, *sodium cetearyl sulphate*, and *lauryl methicone copolyol*), and an *alcohol* (for example, one or more of *cetearyl alcohol*, *glycerine*, and *ethanol*). EX1004, Example 3. The *aqueous component* of this formulation consists of *water*, which is present up to 100.0% of the formulation, and the formulation excludes both propylene glycol and sorbitol. EX1004, Example 3.

84. I have identified the chemical structures of these individual components
in Example 3 below:

Component	Percentage (w/w)	Structure
Octylmethoxycinnamate	5.0	
Butylmethoxydibenzoylme- thane	1.0	
<i>Cetearyl alcohol + PEG-40 castor oil + sodium cetearyl sulphate</i>	2.5	cetyl alcohol  stearyl alcohol  cetearyl alcohol  PEG-40 castor oil  Na⁺  Na⁺ sodium cetearyl sulphate
Glyceryl lanolate	1.0	No discrete structure

<i>Lauryl methicone copolyol</i>	0.5	
Mineral oil (DAB 9)	5.0	No discrete structure
<i>Caprylic/capric triglyceride</i>	5.0	 capric/caprylic triglyceride
Acrylamide/sodium acrylate copolymer	0.3	
Cyclomethicone	2.0	No discrete structure
TiO ₂	1.0	TiO ₂
<i>δ-aminolevulinic acid</i>	1.0	
<i>Glycerine</i>	3.0	

EDTA solution (14%)	0.5	
<i>Ethanol</i>	5.0	
Perfume, preservative	q.s.	No discrete structure
<i>Water, fully demineralised</i>	Make up to 100.0	<i>H₂O</i>

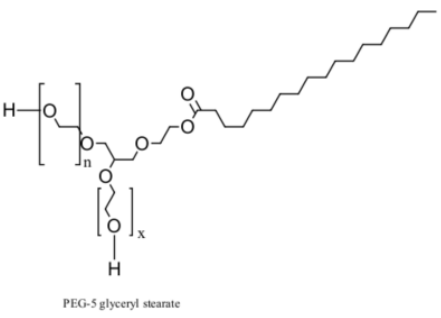
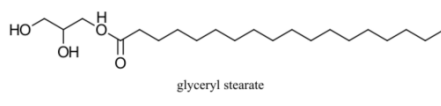
85. In Example 5, Uhlmann describes an oil-in-water emulsion formulation identified as a “Day-car[e] skin cream O/W.”

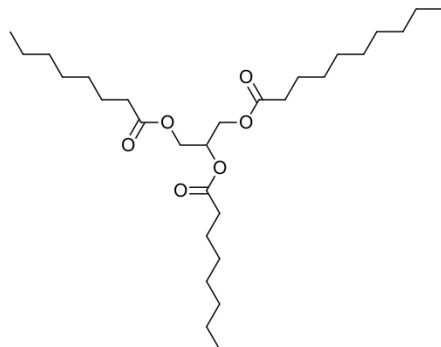
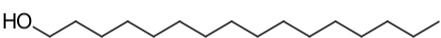
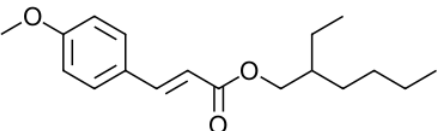
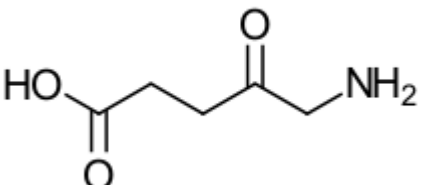
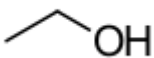
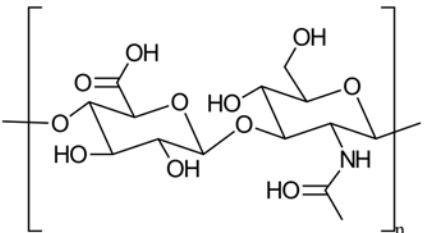
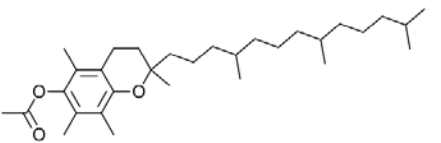
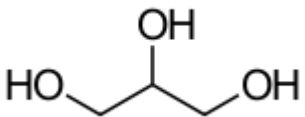
Example 5

Day-car skin cream O/W	Percentage by weight
PEG-5 Glycerylstearate	2.00
Glycerylstearate	3.00
Cyclomethicone	3.00
Caprylic/capric triglyceride	3.00
Cetylalcohol	3.00
Octylmethoxycinnamate	2.50
δ-aminolevulinic acid	5.00
Ethanol	1.00
Hyaluronic acid	0.05
Tocopherylacetate	0.50
Glycerine	4.00
Perfume, preservatives	q.s.
Water, fully demineralised	make up to 100.00

EX1004, Example 5 (annotated). As set forth in Example 5, the disclosed O/W emulsion includes a “[discontinuous] lipid phase in an outer aqueous (continuous) phase” and uses *δ-aminolevulinic acid* as the active ingredient. EX1004, 6:39-48, 4:31-39, Example 5. In this formulation, the carrier component comprises a *lipophilic component* (for example, one or more of *caprylic/capric triglyceride*), a *surfactant* (for example, one or more of *PEG-5 glyceryl stearate* and *glyceryl stearate*), and an *alcohol* (for example, one or more of *cetyl alcohol*, *ethanol*, and *glycerine*). EX1004, Example 5. The *aqueous component* of this formulation consists of *water*, which makes up the remainder of the formulation, and the formulation excludes both propylene glycol and sorbitol. EX1004, Example 5.

86. I have identified the chemical structures of these individual components in Example 5 below:

Component	Percentage (w/w)	Structure
<i>PEG-5 glyceryl stearate</i>	2.00	 PEG-5 glyceryl stearate
<i>Glyceryl stearate</i>	3.00	 glyceryl stearate

Cyclomethicone	3.00	No discrete structure
<i>Caprylic/capric triglyceride</i>	3.00	 capric/caprylic triglyceride
<i>Cetyl alcohol</i>	3.00	
Octylmethoxycinnamate	2.50	
<i>δ-aminolevulinic acid</i>	5.00	
<i>Ethanol</i>	1.00	
Hyaluronic acid	0.05	
Tocopherylacetate	0.50	
<i>Glycerine</i>	4.00	
Perfume, preservative	q.s.	No discrete structure

<i>Water, fully demineralised</i>	Make up to 100.00	<i>H₂O</i>
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XI. Grounds for Challenge

A. Ground IA: Uhlmann Anticipates Claims 1, 4-7, And 14-17 (Example 5 Formulation)

87. Claims 1, 4-7, and 14-17 are all anticipated by Example 5 of Uhlmann for at least the following reasons.

1. Independent Claim 1

i. [1Pre] A formulation comprising:

88. Uhlmann Example 5 discloses the preamble [1Pre].

89. I understand that the preamble may not limit the claims. Regardless, Uhlmann discloses a formulation. In particular, Uhlmann describes “cosmetic or dermatological preparations” that “use a conventional formulation base.” EX1004, 5:11-17 (“*Cosmetic or dermatological preparations according to the invention may actually use a conventional formulation base* and be used in the treatment of skin and/or hair as a part of a dermatological or cosmetic treatment. They should have a δ -aminolevulinic acid content of 0.1% to 10% by weight, but in particular 0.1% to 6% by weight as a percentage of the total weight.”), Title (“Cosmetic or dermatological preparation comprising delta-aminolevulinic acid content as an active ingredient”). In Example 5, Uhlmann provides a “Day-car[e] skin cream O/W” formulation. EX1004, Example 5.

ii. [1A] (a) a nanoemulsion comprising:

90. Uhlmann discloses [1A].

91. As I explained in Section IX.A [Claim Construction], the '146 patent expressly provides the lexicographic definition that “[a]s used herein, a ... ‘nanoemulsion’ is a dispersion of oil in water (oil-in-water dispersion, oil-in-water emulsion, O/W emulsion).” EX1001, 12:58-60.

92. Uhlmann describes a “Day-car[e] skin cream O/W” formulation in Example 5. EX1004, Example 5, 5:39-40 (“an emulsion of ... the oil-in-water type (O/W)”). Uhlmann further explains that “[e]mulsions according to the invention” include a “sun protection cream,” like the “[d]ay-car[e] skin cream” of Example 5. EX1004, 6:8-13 (“Emulsions according to the invention, e.g. in the form of a sun protection cream ...”), 5:35-42 (“Cosmetic preparations according to the invention for protecting the skin against UV radiation may come in different forms, as is generally the case for this type of preparation. They may come as ... an emulsion of ... the oil-in-water type (O/W)...”), 6:39-48 (“Hydrodispersions represent *dispersions of a liquid, half solid or solid inner (discontinuous) lipid phase in an outer aqueous (continuous) phase*. Unlike *O/W emulsions which are characterised by a similar phase arrangement*, hydrodispersions are predominantly free of emulsifiers. Hydrodispersions represent meta stable systems—as do emulsions—and tend to be converted into a state of two connected but discrete phases. In

emulsions, the selection of a suitable emulsif[i]er prevents phase separation.”). On that basis, Uhlmann discloses [1A].

iii. [1B] (i) **at least one aqueous component;**

93. Uhlmann discloses [1B].

94. Uhlmann states that “solvents which may be used” for “[e]mulsions according to the invention,” including the “Day-car[e] skin cream O/W” described in Example 5, can be “*water* or *aqueous solutions*.” EX1004, 5:53-6:13 (“Where the cosmetic or dermatological preparation is a solution or lotion, *solvents which may be used are: Water or aqueous solutions*; ... Emulsions according to the invention, e.g. in the form of a *sun protection cream*, a sun protection lotion or a sun protection milk are useful and may contain the fats, oils, waxes and other fatty compounds mentioned, *in addition to water* and the usual type of emulsifier used for this type of formulation.”). Consistent with that disclosure, Example 5 identifies *water* as the solvent:

Example 5

Day-car skin cream O/W	Percentage by weight
PEG-5 Glycerylstearate	2.00
Glycerylstearate	3.00
Cyclomethicone	3.00
Caprylic/capric triglyceride	3.00
Cetylalcohol	3.00
Octylmethoxycinnamate	2.50
δ -aminolevulinic acid	5.00
Ethanol	1.00
Hyaluronic acid	0.05
Tocopherylacetate	0.50
Glycerine	4.00
Perfume, preservatives	q.s.
Water, fully demineralised	make up to 100.00

EX1004, Example 5 (annotated).

95. The '146 patent expressly states that “[i]n preferred embodiments of the formulations described in the present invention, the *aqueous component comprises an aqueous phase or forms an aqueous phase*. Preferably, the active agent is dissolved in the aqueous phase.” EX1001, 6:6-9. In the formulation in Example 5 of Uhlmann, *water* is the solvent, and therefore constitutes the *aqueous phase* of the nanoemulsion, satisfying the claimed *at least one aqueous component* of the nanoemulsion. Therefore, Uhlmann discloses [1B].

96. Additionally, *water* constitutes the majority component of the formulation in Example 5, further demonstrating that the formulation in Example 5 is an oil-in-water dispersion and meets the claimed “nanoemulsion” of [1A]. *Water*

“make[s] up to 100.00” “[p]ercent[] by weight” of the “Day-car[e] skin cream O/W” formulation. EX1004, Example 5, 8:23-26 (“All the given quantities, ratios and percentages relate to the weight and the overall volume and/or total weight of the preparations unless otherwise stated.”).

97. Apart from *water*, the identified ingredients together total 27.05% (w/w) of the formulation, with an additional quantity of “perfume, preservative” indicated as “q.s.” EX1004, Example 5, 8:23-26. The notation “q.s.” stands for “quantum sufficit” or “quantum satis.” It was well-known that “q.s.” means “the amount which is enough” and has the “standard pharmaceutical meaning of ‘as much as is sufficient,’” as determined by the supplier of that ingredient. *See, e.g.*, EX1006 (Alderson), [0045].

98. It was also well-known that “perfume” and “preservative” were used only in limited amounts in these types of formulations. For example, the amount of “perfume” or fragrance in topical formulations was generally in the range of 0.01% (w/w) to 5.0% (w/w). *See, e.g.*, EX1005 (Palazzolo), [0011] (“Any of a wide variety of fragrances can be utilized ... with a range from about 0.01% by weight to about 5.0% by weight or more of the cosmetic composition.”). The amount of “preservative” in topical formulations was generally in the range of 0.01% (w/w) to 2% (w/w). *See, e.g.*, EX1005 (Palazzolo), [0010] (“The preservative is preferably in

a range from about 0.01% by weight to about 2.0% by weight of the cosmetic composition...”); *see also* EX1007 (Hill), Appendix A, Appendix B.

99. If no “perfume” or “preservative” were present, the **water** content in Example 5 would be approximately 72.95% (w/w). If “perfume” and “preservative” were present at their maximum typical levels of about 5% (w/w) and 2% (w/w), respectively, the **water** content in Example 5 would be approximately 65.95% (w/w).

iv. [1C] (ii) a carrier component comprising:

100. Uhlmann discloses [1C].

101. As explained in Section XI.A.1.ii [1A], Uhlmann discloses a “Day-car[e] skin cream O/W” emulsion in Example 5.

102. As I explained in Paragraph 91, “O/W emulsions” are defined as “dispersions of a liquid, half solid or solid inner (discontinuous) lipid phase in an outer aqueous (continuous) phase” that contain “emulsifiers” to “prevent phase separation.” EX1004, 6:39-48. On that basis, the lipid phase of the O/W emulsion, which is identified as the “discontinuous” phase that includes emulsifiers, satisfies the claimed “**carrier component**.”

103. The ’146 patent expressly explains that “[i]n oil in water nanoemulsion formulations, there are two different phases, which may need to be stabilized and compliant with patients: one is the hydrophobic carrier component, which is usually

the carrier and needs to stabilize and release the API and the other one the aqueous component.” EX1001, 3:47-52. Therefore, Uhlmann discloses [1C].

v. [1D] (1) **at least one lipophilic component,**

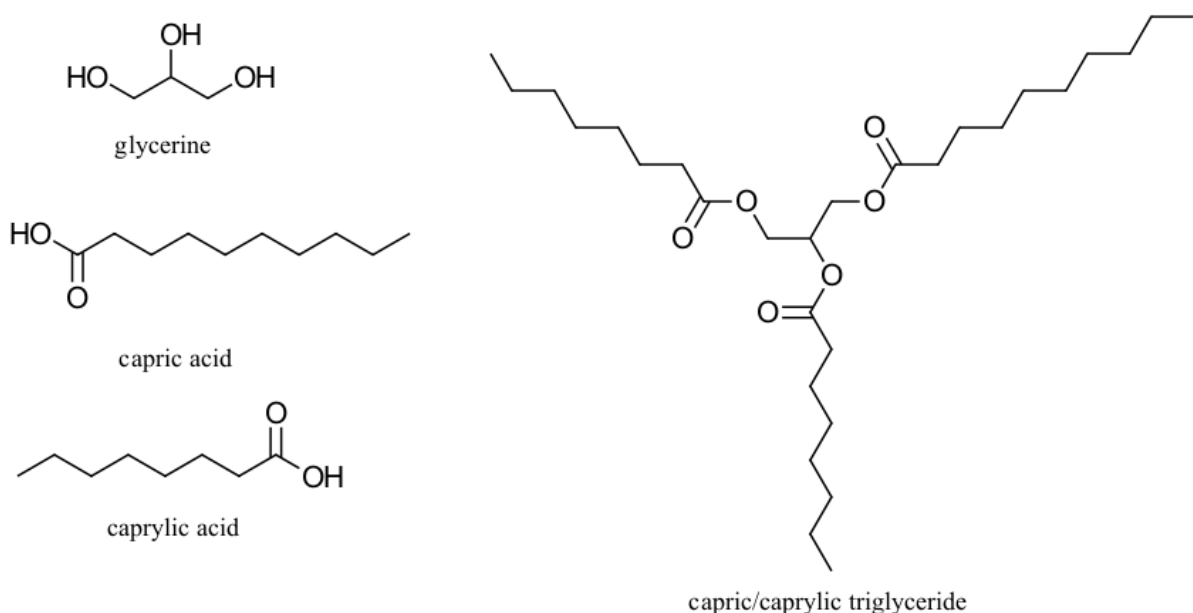
104. Uhlmann discloses [1D].

105. Uhlmann states that “[o]ils such as *triglycerides of capri[c] or caprylic acid*” may be included in “[e]mulsions according to the invention,” including the “Day-car[e] skin cream O/W” described in Example 5. EX1004, 5:53-6:13. Accordingly, in Example 5, the *caprylic/capric triglyceride* satisfies the claimed “*at least one lipophilic component.*”

<u>Example 5</u>	
Day-car skin cream O/W	Percentage by weight
PEG-5 Glycerylstearate	2.00
Glycerylstearate	3.00
Cyclomethicone	3.00
Caprylic/capric triglyceride	3.00
Cetylalcohol	3.00
Octylmethoxycinnamate	2.50
δ -aminolevulinic acid	5.00
Ethanol	1.00
Hyaluronic acid	0.05
Tocopherylacetate	0.50
Glycerine	4.00
Perfume, preservatives	q.s.
Water, fully demineralised	make up to 100.00

EX1004, Example 5 (annotated). As shown in the structure below, *caprylic/capric triglyceride* has caprylic and capric acid “tail” groups and a glycerine backbone. See,

e.g., EX1009 (Jaworska), 1. The hydrophobic “tail” groups made up of long hydrocarbon chains allow the *caprylic/capric triglyceride* to be part of the “discontinuous” lipid phase, or “carrier component,” in the O/W emulsion. See Section XI.A.1.iv [1C].



106. The '146 patent explains that “[p]referably, the *at least one lipophilic component* is a *lipid*” and “[s]uitable *lipids* according to the present invention are physiologically acceptable *lipids* such as ceramide, mono-, di- and triacylglycerin (*triglycerides*).” EX1001, 15:12-16. The '146 patent further explains that “[i]n particular, the *at least one lipophilic component* is a *triglyceride*, preferably a triglyceride comprising a C₈₋₁₀ fatty acid, or a mixture thereof. More particular, the *at least one lipophilic component is a caprylic and/or capric triglyceride and/or a mixture thereof.*” EX1001, 15:16-25; see also EX1001, 15:9-11.

107. Consistent with that disclosure, the working examples in the '146 patent identify “*caprylic/capric triglycerides*” as the *at least one lipophilic component* in the nanoemulsions BF200, BF215, and BF220. EX1001, Example 1, Tables 2, 3 (labeling “*caprylic/capric triglycerides*” as the “*lipid core*” of the “carrier component”); *see also* EX1001, 20:40-21:37 (exemplary “nanovesicles” and “nanoemulsions” comprising “*caprylic/capric triglycerides*”). Therefore, the *caprylic/capric triglyceride* in Example 5 of Uhlmann meets the claimed *at least one lipophilic component*. Accordingly, Uhlmann discloses [1D].

vi. [1E] (2) *at least one surfactant*, and

108. Uhlmann discloses [1E].

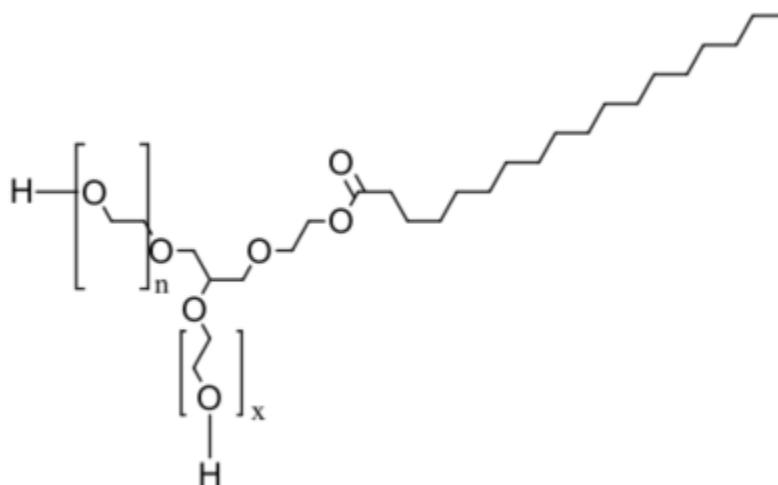
109. Uhlmann states that “the usual type of *emulsifier* used for this type of formulation” may be included in “[e]mulsions according to the invention,” including the “Day-car[e] skin cream O/W” described in Example 5. EX1004, 6:8-13; *see also* EX1004, 6:46-48 (“In emulsions, the selection of a suitable *emulsifier* prevents phase separation.”). Accordingly, in Example 5, one or more of *PEG-5 glyceryl stearate* and *glyceryl stearate* satisfies the claimed “*at least one surfactant*.”

Example 5

Day-car skin cream O/W	Percentage by weight
PEG-5 Glycerylstearate	2.00
Glycerylstearate	3.00
Cyclomethicone	3.00
Caprylic/capric triglyceride	3.00
Cetylalcohol	3.00
Octylmethoxycinnamate	2.50
δ -aminolevulinic acid	5.00
Ethanol	1.00
Hyaluronic acid	0.05
Tocopherylacetate	0.50
Glycerine	4.00
Perfume, preservatives	q.s.
Water, fully demineralised	make up to 100.00

EX1004, Example 5 (annotated).

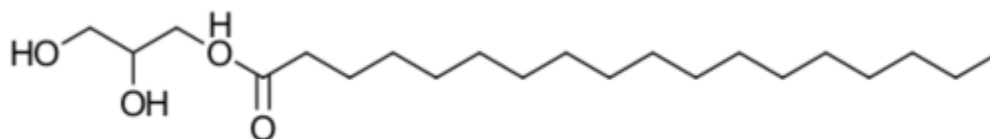
110. As shown in the structure below, *PEG-5 glyceryl stearate* is a polyoxyethylene ester of glyceryl stearate. As shown below, *PEG-5 glyceryl stearate*, has a glyceryl stearate with two polyoxyethylene, or poly(ethylene glycol) (“PEG”), units (with the two polyoxyethylene groups combining to an average of 5 PEG-repeats).



PEG-5 glyceryl stearate

PEG-5 glyceryl stearate is a polyoxyethylene-type *surfactant*. See, e.g., EX1008 (Fowler), 4:1-8 (“...preferred *emulsifiers* are ... *PEG-5 glyceryl stearate* ...”).

111. As shown in the structure below, *glyceryl stearate* is an ester of glycerin in stearic acid.



glyceryl stearate

Glyceryl stearate is a non-ionic *surfactant*. See, e.g., EX1010 (Fiume 2020), Table 2 (“*Glyceryl Stearate*...The monoester of glycerin and stearic acid...*surfactant-emulsifying* agent...”).

112. *PEG-5 glyceryl stearate* and *glyceryl stearate* each have a hydrophilic head group (comprising esters and/or hydroxy groups) and a hydrophobic tail group

(comprising hydrocarbon chains) and function as the *emulsifiers* of the “discontinuous” lipid phase, or the “carrier component,” in the O/W emulsion. See Section XI.A.1.iv [1C].

113. The terms “*emulsifier*” and “*surfactant*” are interchangeable. In fact, the ’146 patent expressly treats the terms “*surfactant*” and “*emulsifier*” as interchangeable. EX1001, 15:43-58 (“*Surfactants*, also referred [to] as surface active agents or *emulsifiers*, are well-known in the art and include any agent linking oil and water in the composition to form an emulsion. They lower the surface tension of two liquids and are amphiphilic. *In emulsions they are referred as emulsifiers* and coat the droplets preventing coalescing. ...”), 1:24-33 (“Emulsions or micro emulsions can be oil in water, water in oil or middle phased dispersions, often dispersed with *surfactants as emulsifiers*. ...”).

114. The ’146 patent further states that the *surfactant* may be “any suitable *surfactant* known to the skilled person,” including “nonionic *surfactant[s]*” and “any polyoxyethylene-type *surfactant*.” EX1001, 15:40-16:36. As I explained above in Paragraphs 110-112, *PEG-5 glyceryl stearate* is a polyoxyethylene-type *surfactant* and the *glyceryl stearate* is a nonionic *surfactant*. Therefore, Example 5 of Uhlmann discloses [1E].

vii. [1F] (3) at least one alcohol; and

115. Uhlmann discloses [1F].

116. Uhlmann states that “[a]lcohols, diols or polyols with a low C number” may be included in “[e]mulsions according to the invention,” including the “Day-car[e] skin cream O/W” described in Example 5. EX1004, 5:53-6:13. Accordingly, in Example 5, the one or more of *cetyl alcohol*, *glycerine*, and *ethanol* satisfies the claimed “at least one alcohol.”

Example 5

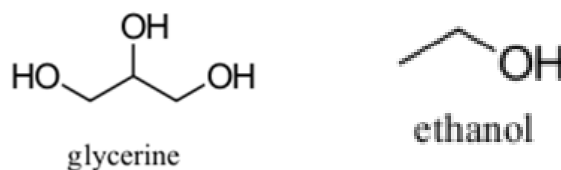
Day-car skin cream O/W	Percentage by weight
PEG-5 Glycerylstearate	2.00
Glycerylstearate	3.00
Cyclomethicone	3.00
Caprylic/capric triglyceride	3.00
Cetylalcohol	3.00
Octylmethoxycinnamate	2.50
δ -aminolevulinic acid	5.00
Ethanol	1.00
Hyaluronic acid	0.05
Tocopherylacetate	0.50
Glycerine	4.00
Perfume, preservatives	q.s.
Water, fully demineralised	make up to 100.00

EX1004, Example 5 (annotated). In Example 5, *cetyl alcohol*, *glycerine*, and *ethanol* are each *alcohols*.

117. As shown in the structure below, *cetyl alcohol* has a hydrophobic “tail” group made up of a hydrocarbon chain that is part of the “discontinuous” lipid phase, or the “carrier component,” in the O/W emulsion. See Section XI.A.1.iv [1C].



118. As shown in the structures below, *glycerine* and *ethanol* each have hydroxy groups that may associate with the hydrophilic head groups of the *surfactants*. See, e.g., EX1011 (Kale), 2 (“The major components of micro emulsion system are: 1) Oil phase 2) Surfactant (Primary surfactant) 3) Co-surfactant (Secondary surfactant) 4) Co-Solvent”), 3 (“... if co-surfactants are added then with minimum concentration of surfactants different curvatures of interfacial film can be formed to generate stable micro emulsion composition. Co surfactants raises the fluidity of the interface due to presence of fluidizing groups like unsaturated bonds, then demolishes liquid crystalline or gel structure and alters the HLB value in such way to cause spontaneous formation of micro emulsion. Example: Short chain alcohols like ethanol to butanol[.] Short chain glycols like propylene glycol[.] Medium chain alcohols like amines or acids”), Fig. 3.



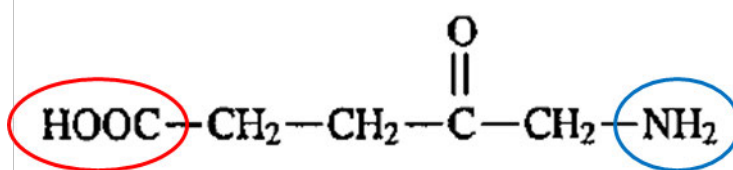
119. As I explained above in Sections XI.A.1.vi [1E] and XI.A.1.iv [1C], the *surfactants* are part of the “discontinuous” lipid phase, or the “carrier component.”

Because *cetyl alcohol*, *glycerine*, and *ethanol* interact with the *surfactants*, each *alcohol* meets the claimed “*at least one alcohol*.” Therefore, Uhlmann discloses [1F].

viii. [1G] (b) **5-aminolevulinic acid** and/or a derivative, a precursor, a metabolite, and/or a pharmaceutically acceptable salt thereof,

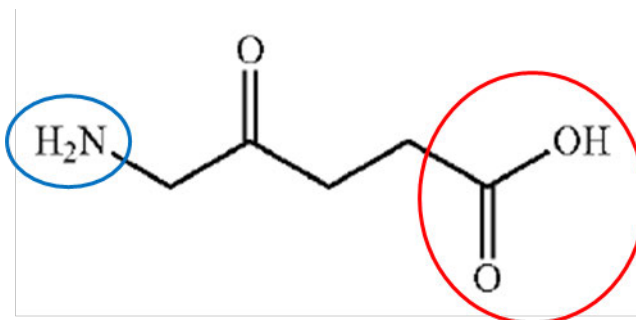
120. Uhlmann discloses [1G].

121. Uhlmann states that the “[c]osmetic or dermatological preparations according to the invention” “should have a *δ-aminolevulinic acid* content of 0.1% to 10% by weight, but in particular 0.1% to 6% by weight as a percentage of the total weight.” EX1004, 5:11-17. Uhlmann provides the structure of *δ-aminolevulinic acid*, which is “also called δ-ALA, 5-amino-4-oxopentanoic acid, δ-amino-γ-keto-valeric acid:”



EX1004, 2:28-37 (annotated). In the structure above, I have highlighted the carboxylic acid in red and the amino group in blue.

122. *δ-aminolevulinic acid* is *5-aminolevulinic acid*. In fact, the '146 patent confirms that *δ-aminolevulinic acid* is *5-aminolevulinic acid*. The '146 patent provides the following structure of *5-aminolevulinic acid*:



EX1001, 19:17-28 (annotated). In the structure above, I have highlighted the carboxylic acid in red and the amino group in blue. As shown in the structures of *δ-aminolevulinic acid* and *5-aminolevulinic acid*, they are identical molecules.

123. Accordingly, in Example 5, the “*δ-aminolevulinic acid*” satisfies the claimed “*5-aminolevulinic acid*.”

Example 5

Day-car skin cream O/W	Percentage by weight
PEG-5 Glycerylstearate	2.00
Glycerylstearate	3.00
Cyclomethicone	3.00
Caprylic/capric triglyceride	3.00
Cetylalcohol	3.00
Octylmethoxycinnamate	2.50
<i>δ-aminolevulinic acid</i>	5.00
Ethanol	1.00
Hyaluronic acid	0.05
Tocopherylacetate	0.50
Glycerine	4.00
Perfume, preservatives	q.s.
Water, fully demineralised	make up to 100.00

EX1004, Example 5 (annotated). Therefore, Uhlmann discloses [1G].

ix. [1H] wherein the formulation comprises essentially no propylene glycol and essentially no sorbitol.

124. Uhlmann discloses [1H].

125. In Example 5, the “Day-car[e] skin cream O/W” emulsion contains no propylene glycol and no sorbitol.

Example 5

Day-car skin cream O/W	Percentage by weight
PEG-5 Glycerylstearate	2.00
Glycerylstearate	3.00
Cyclomethicone	3.00
Caprylic/capric triglyceride	3.00
Cetylalcohol	3.00
Octylmethoxycinnamate	2.50
δ -aminolevulinic acid	5.00
Ethanol	1.00
Hyaluronic acid	0.05
Tocopherylacetate	0.50
Glycerine	4.00
Perfume, preservatives	q.s.
Water, fully demineralised	make up to 100.00

EX1004, Example 5 (annotated). The formulation described in Example 5 is a complete formulation where water “makes up to 100.00” percent by weight of the formulation. EX1004, Example 5, 8:23-26 (“All the given quantities, ratios and percentages relate to the weight and the overall volume and/or total weight of the preparations unless otherwise stated.”). A POSA would have readily recognized that, because Example 5 details a complete formulation, there would be no other ingredients added to the formulation. Therefore, a POSA would have readily

recognized that Example 5 details a formulation free of propylene glycol and sorbitol.

126. The '146 patent explains that ““comprises essentially no compound X”” “specif[ies] that the formulation is either free of compound X or comprises less than 0.1% (w/w)” of compound X “based on the total weight of the formulation.” EX1001, 6:50-59 (“As used herein, the expressions “essentially free of compound X”, “does essentially not comprise compound X”, or “comprises essentially no compound X” with respect to a formulation are interchangeable. In particular, these expressions specify that the formulation is either free of compound X or comprises less than 0.1% (w/w), less than 0.08% (w/w), less than 0.07% (w/w), less than 0.06% (w/w), less than 0.05% (w/w), less than 0.04% (w/w), less than 0.03% (w/w), less than 0.02% (w/w), or less than 0.01% (w/w) of compound X based on the total weight of the formulation.”). Uhlmann discloses [1H] because the formulation in Example 5 is free of propylene glycol and sorbitol, and therefore has less than 0.1% (w/w) of propylene glycol and sorbitol.

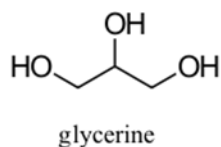
2. Dependent Claims 4 And 16

- i. [4] The formulation of claim 1, wherein the at least one alcohol comprises: 3, 4, or 5 carbon atoms; or 1-propanol, 2-propanol, or a mixture thereof.**

127. Uhlmann discloses [4].

128. As I explained above in Section XI.A.1.vii [1F], Example 5 contains *glycerine* as one of the *at least one alcohol* in the carrier component of the “Day-car[e] skin cream O/W” emulsion. EX1004, Example 5.

129. As shown in the structure below, *glycerine* has 3 carbon atoms.



Therefore, *glycerine* meets the claimed “wherein the *at least one alcohol* comprises: 3 ... carbon atoms” and Uhlmann discloses [4].

- ii. [16] The formulation of claim 4, wherein the *at least one alcohol* is in an amount from 0.1% to 10% (w/w), from 0.5% to 5% (w/w), from 1% to 5% (w/w), or from 1% to 3% based on total weight of the nanoemulsion.

130. Uhlmann discloses [16].

131. As I explained above in Section XI.A.1.vii [1F], Example 5 contains *glycerine* as one of the *at least one alcohol* in the carrier component of the “Day-car[e] skin cream O/W” emulsion.

132. *Glycerine* is 4.00% (w/w) of the formulation in Example 5, which is within the claimed “0.1 to 10% (w/w).” EX1004, Example 5, 8:23-26 (“All the given quantities, ratios and percentages relate to the weight and the overall volume and/or total weight of the preparations unless otherwise stated.”).

133. Even if [16] requires all of the ingredients identified in [1F] that meet the *at least one alcohol* in the carrier component to meet the claimed “0.1% to 10% (w/w)” of the formulation, Uhlmann still discloses [16]. As I explained above in Section XI.A.1.vii [1F], Example 5 further contains *ethanol* and *cetyl alcohol* that meet the claimed “*at least one alcohol*” in the carrier component. *Ethanol* is 1.00% (w/w) of the formulation and *cetyl alcohol* is 3.00% (w/w) of the formulation. When combined, the total amount of the “*at least one alcohol*” in the carrier component is 8.00% (w/w) (4.00% (w/w) *glycerine* + 1.00% (w/w) *ethanol* + 3.00% (w/w) *cetyl alcohol*). The total amount of the *at least one alcohol* in the carrier component is within the claimed “0.1 to 10% (w/w)” of the formulation. EX1004, Example 5, 8:23-26 (“All the given quantities, ratios and percentages relate to the weight and the overall volume and/or total weight of the preparations unless otherwise stated.”).

134. As I explained in Paragraph 43, I understand that disclosure of a single point within a claimed range may anticipate that claimed range. Therefore, Example 5 discloses [16].

3. Dependent Claim 5

- i. [5] The formulation of claim 1, comprising the **at least one aqueous component** in an amount from 50% to 99% (w/w), from 70% to 95% (w/w), from 75% to 95% (w/w), or from 80% to 90% (w/w).

135. Uhlmann discloses [5].

136. As I explained in Section XI.A.1.iii [1B], Example 5 contains *water* and meets the claimed *at least one aqueous component*. EX1004, Example 5.

137. *Water* “make[s] up to 100.00” “[p]ercent[] by weight” of the “Day-car[e] skin cream O/W” formulation. EX1004, Example 5, 8:23-26 (“All the given quantities, ratios and percentages relate to the weight and the overall volume and/or total weight of the preparations unless otherwise stated.”).

138. As I explained above in Section XI.A.1.iii [1B], the other identified ingredients together total 27.05% (w/w) of the formulation, with an additional quantity of “perfume, preservative” indicated as “q.s.” EX1004, Example 5, 8:23-26. The notation “q.s.” stands for “quantum sufficit” or “quantum satis.” It was well-known that “q.s.” means “the amount which is enough” and has the “standard pharmaceutical meaning of ‘as much as is sufficient,’” as determined by the supplier of that ingredient. *See, e.g.*, EX1006 (Alderson), [0045].

139. It was also well-known that “perfume” and “preservative” were used only in limited amounts in these types of formulations. For example, the amount of “perfume” or fragrance in topical formulations was generally in the range of 0.01% (w/w) to 5.0% (w/w). *See, e.g.*, EX1005 (Palazzolo), [0011] (“Any of a wide variety of fragrances can be utilized ... with a range from about 0.01% by weight to about 5.0% by weight or more of the cosmetic composition.”). The amount of “preservative” in topical formulations was generally in the range of 0.01% (w/w) to

2% (w/w). *See, e.g.*, EX1005 (Palazzolo), [0010] (“The preservative is preferably in a range from about 0.01% by weight to about 2.0% by weight of the cosmetic composition...”); *see also* EX1007 (Hill), Appendix A, Appendix B.

140. If no “perfume” or “preservative” were present, *the water content in Example 5 would be approximately 72.95% (w/w)*. If “perfume” and “preservative” were present at their maximum typical levels of about 5% (w/w) and 2% (w/w), respectively, *the water content in Example 5 would be approximately 65.95% (w/w)*. Therefore, the *water* content in Example 5 ranges from about 65.95% (w/w) to 72.95% (w/w), which falls within the claimed “50% to 99% (w/w).”

141. As I explained in Paragraph 43, I understand that disclosure of a single point within a claimed range may anticipate that claimed range. Therefore, Example 5 discloses [5].

4. Dependent Claim 6

- i. [6] The formulation of claim 4, comprising the *at least one lipophilic component* in an amount from 0.1% to 30% (w/w), from 0.25% to 15% (w/w), from 0.25% to 10% (w/w), from 2% to 10% (w/w), or 3% to 8% (w/w) based on total weight of the nanoemulsion.

142. Uhlmann discloses [6].

143. As I explained above in Section XI.A.1.v [1D], the *caprylic/capric triglyceride* in Example 5 is one of the components of the *at least one lipophilic component*.

144. *Caprylic/capric triglyceride* is 3.00% (w/w) of the formulation in Example 5, which is within the claimed “0.1 to 30% (w/w).” EX1004, Example 5, 8:23-26 (“All the given quantities, ratios and percentages relate to the weight and the overall volume and/or total weight of the preparations unless otherwise stated.”).

145. As I explained in Paragraph 43, I understand that disclosure of a single point within a claimed range may anticipate that claimed range. Therefore, Example 5 discloses [6].

5. Dependent Claim 7

- i. [7] The formulation of claim 1, wherein the formulation comprises no propylene glycol.

146. Uhlmann discloses [7].

147. As I explained in Section XI.A.1.ix [1H], the “Day-car[e] skin cream O/W” formulation in Example 5 does not contain propylene glycol.

6. Dependent Claim 14

- i. [14] The formulation of claim 1, wherein the *at least one lipophilic component* comprises: triglycerides and/or mixtures thereof; or a *caprylic triglyceride, a capric triglyceride, or a mixture thereof*.

148. Uhlmann discloses [14].

149. As I explained above in Section XI.A.1.v [1D], the *caprylic/capric triglyceride* in Example 5 is one of the components of the *at least one lipophilic component*.

150. The *caprylic/capric triglyceride* in Example 5 meets the claimed “*caprylic triglyceride, a capric triglyceride, or a mixture thereof*.” Therefore, Uhlmann discloses [14].

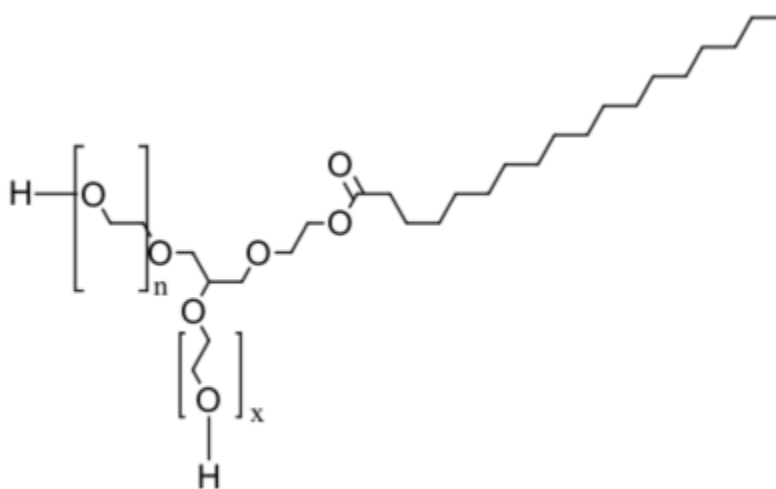
7. Dependent Claim 15

- i. [15] The formulation of claim 1, wherein the **at least one surfactant** comprises: a phospholipid, a phosphatidylcholine, a lysophospholipid, a ceramide, and/or a mixture thereof; and/or a **polyoxyethylene-type surfactant**.

151. Uhlmann discloses [15].

152. As I explained in Section XI.A.1.vi [1E], Uhlmann discloses *PEG-5 glyceryl stearate* as one of the **at least one surfactant** in Example 5.

153. *PEG-5 glyceryl stearate* has the chemical structure shown below.



PEG-5 glyceryl stearate

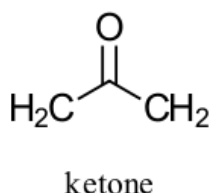
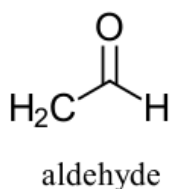
PEG-5 glyceryl stearate is a *polyoxyethylene-type surfactant*. Typically, shorter-length polyoxyethylenes are referred to as poly(ethylene glycols), or “PEGs.” See, e.g., EX1012 (Bailey), 1 (“Polyoxyethylenes of less than ca. 20 000 number-average molecular mass are usually referred to as poly(ethylene glycols).”).

8. Dependent Claim 17

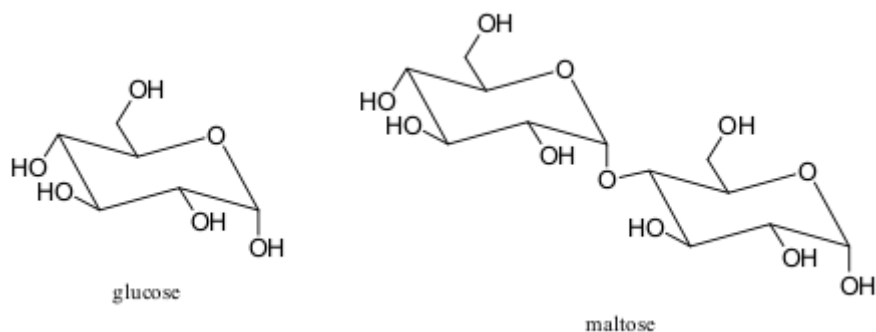
- i. [17] The formulation of claim 1, wherein the formulation further comprises essentially no monosaccharides and disaccharides.

154. Uhlmann discloses [17].

155. Monosaccharides are simple sugars that consist of a single aldehyde or ketone with multiple (at least two) hydroxyl groups. Below are structures of representative aldehydes and ketones.



Disaccharides are sugars composed of two monosaccharides. The structures of exemplary monosaccharides and disaccharides are shown below. Glucose is a common monosaccharide. Maltose, made up of two glucose molecules, is a common disaccharide.



See, e.g., EX1013 (Nelson), 229-230, 233, 237.

156. In Example 5 of Uhlmann, the “Day-car[e] skin cream O/W” formulation contains no monosaccharides and no disaccharides.

Example 5

Day-car skin cream O/W	Percentage by weight
PEG-5 Glycerylstearate	2.00
Glycerylstearate	3.00
Cyclomethicone	3.00
Caprylic/capric triglyceride	3.00
Cetylalcohol	3.00
Octylmethoxycinnamate	2.50
δ -aminolevulinic acid	5.00
Ethanol	1.00
Hyaluronic acid	0.05
Tocopherylacetate	0.50
Glycerine	4.00
Perfume, preservatives	q.s.
Water, fully demineralised	make up to 100.00

EX1004, Example 5 (annotated). The formulation described in Example 5 is a complete formulation where water “makes up to 100.00” percent by weight of the formulation. EX1004, Example 5, 8:23-26 (“All the given quantities, ratios and

percentages relate to the weight and the overall volume and/or total weight of the preparations unless otherwise stated.”). A POSA would have readily recognized that, because Example 5 details a complete formulation, there would be no other ingredients added to the formulation. Therefore, a POSA would have readily recognized that Example 5 details a formulation free of monosaccharides and disaccharides.

157. The '146 patent explains that ““comprises essentially no compound X”” “specif[ies] that the formulation is either free of compound X or comprises less than 0.1% (w/w)” of compound X “based on the total weight of the formulation.” EX1001, 6:50-59 (“As used herein, the expressions “essentially free of compound X”, “does essentially not comprise compound X”, or “comprises essentially no compound X” with respect to a formulation are interchangeable. In particular, these expressions specify that the formulation is either free of compound X or comprises less than 0.1% (w/w), less than 0.08% (w/w), less than 0.07% (w/w), less than 0.06% (w/w), less than 0.05% (w/w), less than 0.04% (w/w), less than 0.03% (w/w), less than 0.02% (w/w), or less than 0.01% (w/w) of compound X based on the total weight of the formulation.”). Uhlmann discloses [17] because the formulation in Example 5 is free of monosaccharides and disaccharides, and therefore has less than 0.1% (w/w) of monosaccharides and disaccharides.

B. Ground IB: Uhlmann Renders Obvious Dependent Claims 2, 3, And 8-13 (Modified Example 5 Formulation)

158. Claims 2, 3, and 8-13 are all rendered obvious by Example 5 of Uhlmann for at least the following reasons.

1. Dependent Claims 2, 3, 8-13

i. [2] The formulation of claim 1, wherein the formulation further comprises less than 1% w/w of a non-cyclic polyol having 2 to 5 carbon atoms.

[3] The formulation of claim 1, wherein the formulation further comprises less than 1% w/w of a non-cyclic polyol having 2 to 12 carbon atoms.

[8] The formulation of claim 1, wherein the formulation further comprises less than or equal to 0.99%, 0.95%, 0.9%, 0.8%, 0.7%, 0.6%, 0.5%, 0.4%, 0.3%, 0.2%, or 0.1% w/w of a non-cyclic polyol having 2 to 5 carbon atoms.

[9] The formulation of claim 1, wherein the formulation further comprises essentially no non-cyclic polyol having 2 to 5 carbon atoms.

[10] The formulation of claim 1, wherein the formulation further comprises no non-cyclic polyol having 2 to 5 carbon atoms.

[11] The formulation of claim 1, wherein the formulation further comprises less than or equal to 0.99%, 0.95%, 0.9%, 0.8%, 0.7%, 0.6%, 0.5%, 0.4%, 0.3%, 0.2%, or 0.1% w/w of a non-cyclic polyol having 2 to 12 carbon atoms.

[12] The formulation of claim 1, wherein the formulation further comprises essentially no non-cyclic polyol having 2 to 12 carbon atoms.

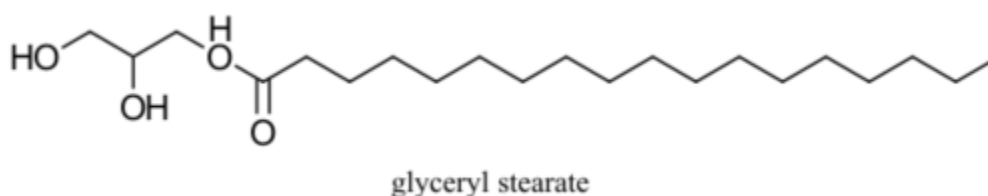
[13] The formulation of claim 1, wherein the formulation further comprises no non-cyclic polyol having 2 to 12 carbon atoms.

159. Uhlmann renders obvious [2], [3], and [8]-[13].

160. The only component in Example 5 of Uhlmann that is a “non-cyclic polyol” having “2 to 5 carbon atoms” or “2 to 12 carbon atoms” is *glycerine*. However, as I explain below, a POSA would have found it obvious to replace *glycerine* with a different alcohol, such as *isopropanol*. *Isopropanol* is not a non-cyclic polyol.

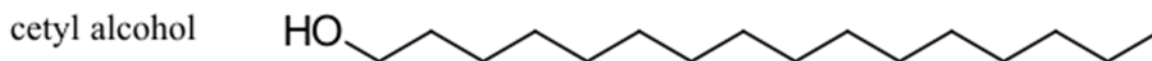
161. None of the other components in Example 5 meet the claimed “non-cyclic polyol” having “2 to 5 carbon atoms” or “2 to 12 carbon atoms.”

162. The formulation in Example 5 contains *glyceryl stearate*, which is a non-cyclic polyol. EX1004, Example 5. However, as shown in the structure below, *glyceryl stearate* has 21 carbon atoms and therefore does not meet the claimed “non-cyclic polyol” having “2 to 5 carbon atoms” or “2 to 12 carbon atoms.”



163. The other alcohols (*i.e.*, hydroxy (-OH) group containing compounds) in Example 5 are not non-cyclic polyols. As I explained in Section XI.A.1.vii [1F], the “Day-car[e] skin cream O/W” formulation in Example 5 includes *cetyl alcohol*, *ethanol*, and *glycerine*. However, *cetyl alcohol* and *ethanol* are not non-cyclic

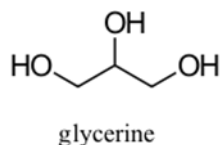
polyols. As shown in the structure below, *cetyl alcohol* contains only one alcohol group and is therefore not a polyol. *Cetyl alcohol* contains 16 carbon atoms.



As shown in the structure below, *ethanol* also contains only one alcohol group and is therefore not a polyol. *Ethanol* contains 2 carbon atoms.

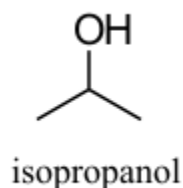


164. As I explained above in Paragraphs 160-161, *glycerine* (also known as *glycerol*) is the only “non-cyclic polyol” having “2 to 5 carbon atoms” or “2 to 12 carbon atoms” in the formulation in Example 5 of Uhlmann. As shown in the structure below, *glycerine* is a non-cyclic polyol having 3 carbon atoms.



165. Nevertheless, a POSA would have found it obvious to replace *glycerine* with a different alcohol, such as *isopropanol*. Uhlmann explains that “[a]lcohols, diols or polyols with a low C number and their ethers, preferably *ethanol*,

isopropanol, propylene glycol, *glycerine*, ethylene glycol, ethylene glycol monoethylether, ethylene glycol monobutylether, propylene glycol monomethylether, propylene glycol monoethyl ether, propylene glycol monobutylether, diethylene glycol monomethylether, diethylene glycol monoethylether and analogous products” may be used in “[e]mulsions according to the invention.” EX1004, 5:53-6:13. Based on this disclosure, a POSA would have understood that polyols and alcohols are interchangeable in Uhlmann’s disclosed emulsions, including the “Day-car[e] skin cream O/W” formulation in Example 5. As shown in the structure below, *isopropanol* is not a non-cyclic polyol because it contains only one alcohol group. *Isopropanol* has 3 carbon atoms.



166. In view of Uhlmann’s disclosure that polyols and alcohols, such as *glycerine* and *isopropanol*, respectively, are suitable alternatives that are interchangeable with one another, a POSA would have found it trivial to replace *glycerine* with *isopropanol*. I have annotated Example 5 to show *isopropanol* in the “Day-car[e] skin cream O/W” formulation below.

Example 5

Day-car skin cream O/W	Percentage by weight
PEG-5 Glycerylstearate	2.00
Glycerylstearate	3.00
Cyclomethicone	3.00
Caprylic/capric triglyceride	3.00
Cetylalcohol	3.00
Octylmethoxycinnamate	2.50
δ -aminolevulinic acid	5.00
Ethanol	1.00
Hyaluronic acid	0.05
Tocopherylacetate	0.50
Isopropanol	4.00
Perfume, preservatives	q.s.
Water, fully demineralised	make up to 100.00

EX1004, Example 5 (annotated). A POSA would have found it obvious to try replacing the *glycerine* with *isopropanol* with a reasonable expectation of success because Uhlmann discloses that both are preferred *alcohols* (with *glycerine* being a polyol) suitable for use with the disclosed topical formulations.

167. In addition, a POSA would have been motivated to remove *glycerine* from the formulation containing *δ -aminolevulinic acid* because *glycerine*, also called *glycerol*, was known to cause degradation of *δ -aminolevulinic acid*. For example, a 2000 study found that, while “*ALA* is sufficiently soluble in *glycerol* (~10%), DMSO (~10%), and propylene glycol (~5%),” “the immediate yellow appearance of these solutions when *ALA* is dissolved may be considered to indicate *ALA* degradation.” EX1014 (Bunke), 6 (“One possible approach to prepare stable

and clinically useful *ALA* solutions consists of using nonaqueous, water-miscible solvents for *ALA*. *ALA* is sufficiently soluble in *glycerol* (~10%), DMSO (~10%), and propylene glycol (~5%). However, the immediate yellow appearance of these solutions when *ALA* is dissolved may be considered to indicate *ALA* degradation. Thus, this approach was not further pursued.”). As another example, a 2005 study found that esterification reactions between *ALA* and *glycerine* occurred readily. EX1015 (McCarron), 1 (“...an esterification reaction involving *ALA* and ... *glycerol*...”), 5-15, Fig. 7. A POSA would have recognized that one of the well-known suitable components to replace *glycerine* was *isopropanol*, as explained by Uhlmann. EX1004, 5:53-6:13. Therefore, a POSA would have been motivated to replace *glycerine* with *isopropanol* and would have had a reasonable expectation of success in doing so. This replacement is nothing more than simple substitution of one known element (*i.e.*, *glycerine*) for another (*i.e.*, *isopropanol*) to obtain predictable results (*i.e.*, a stable topical formulation).

168. The resulting formulation in Example 5 replaces *glycerine* with *isopropanol*. This modified formulation does not contain any “non-cyclic polyol” having “2 to 5 carbon atoms” or “2 to 12 carbon atoms.” Therefore, the modified Example 5 of Uhlmann meets the claimed “less than 1% w/w,” ([2], [3]) “less than or equal to 0.99% ...w/w,” ([8], [11]) “essentially no,” ([9], [12]) and “no” ([10],

[13]) non-cyclic polyol having 2-5 or 2-12 carbon atoms. Accordingly, Uhlmann Example 5 renders obvious [2], [3], and [8]-[13].

169. The '146 patent explains that ““comprises essentially no compound X” “specif[ies] that the formulation is either free of compound X or comprises less than 0.1% (w/w)” of compound X “based on the total weight of the formulation.” EX1001, 6:50-59 (“As used herein, the expressions “essentially free of compound X”, “does essentially not comprise compound X”, or “comprises essentially no compound X” with respect to a formulation are interchangeable. In particular, these expressions specify that the formulation is either free of compound X or comprises less than 0.1% (w/w), less than 0.08% (w/w), less than 0.07% (w/w), less than 0.06% (w/w), less than 0.05% (w/w), less than 0.04% (w/w), less than 0.03% (w/w), less than 0.02% (w/w), or less than 0.01% (w/w) of compound X based on the total weight of the formulation.”). Uhlmann renders obvious [9] and [12] because the modified formulation in Example 5 is free of, and therefore has less than 0.1% (w/w) of, a “non-cyclic polyol” having “2 to 5 carbon atoms” or “2 to 12 carbon atoms.”

C. Ground IC: Uhlmann in View of Palazzolo Renders Obvious Claim 5 (Example 5 Formulation)

170. Claim 5 is rendered obvious by Example 5 of Uhlmann in view of Palazzolo for at least the following reasons.

1. Dependent Claim 5

- i. [5] The formulation of claim 1, comprising the **at least one aqueous component** in an amount from 50% to 99% (w/w), from 70% to 95% (w/w), from 75% to 95% (w/w), or from 80% to 90% (w/w).

171. As I explained above in Section XI.A.3 [Ground IA, [5]], Uhlmann discloses [5]. In the alternative, Uhlmann in combination with Palazzolo renders obvious [5].

172. **Water** “make[s] up to 100.00” “[p]ercent[] by weight” of the “Day-car[e] skin cream O/W” formulation in Example 5 of Uhlmann. EX1004, Example 5, 8:23-26 (“All the given quantities, ratios and percentages relate to the weight and the overall volume and/or total weight of the preparations unless otherwise stated.”).

173. As I explained above in Section XI.A.1.iii [Ground IA, [1B]], the other identified ingredients together total 27.05% (w/w) of the formulation, with an additional quantity of “perfume, preservative” indicated as “q.s.” EX1004, Example 5, 8:23-26. The notation “q.s.” stands for “quantum sufficit” or “quantum satis.” It was well-known that “q.s.” means “the amount which is enough” and has the “standard pharmaceutical meaning of ‘as much as is sufficient,’” as determined by the supplier of that ingredient. *See, e.g.*, EX1006 (Alderson), [0045].

174. Palazzolo teaches that “perfume” and “preservative” were used only in limited amounts in these types of formulations. For example, the amount of

“perfume” or fragrance in topical formulations was generally in the range of 0.01% (w/w) to 5.0% (w/w). *See, e.g.*, EX1005 (Palazzolo), [0011] (“Any of a wide variety of fragrances can be utilized ... with a range from about 0.01% by weight to about 5.0% by weight or more of the cosmetic composition.”). The amount of “preservative” in topical formulations was generally in the range of 0.01% (w/w) to 2% (w/w). *See, e.g.*, EX1005 (Palazzolo), [0010] (“The preservative is preferably in a range from about 0.01% by weight to about 2.0% by weight of the cosmetic composition...”); *see also* EX1007 (Hill), Appendix A, Appendix B.

175. A POSA would have been able to combine the teachings of Example 5 of Uhlmann with Palazzolo with a reasonable expectation of success because Palazzolo teaches that ***typical amounts*** of such “perfume” and “preservative” ranges from 0.01% (w/w) to 5% (w/w) and 0.01% (w/w) to 2% (w/w), respectively. EX1005 (Palazzolo), [0010]-[0011]. And, Uhlmann Example 5 teaches to use the sufficient quantity of “perfume” and “preservative” in the “Day-car[e] skin cream O/W” formulation. Therefore, it would have been a trivial combination to put in the typical amounts of “perfume” and “preservative” to achieve the predictable result of a formulation that smells nicer and/or lasts longer.

176. If no “perfume” or “preservative” were present, ***the water content in Example 5 of Uhlmann would be approximately 72.95% (w/w)***. If the “perfume” and “preservative” were present at their maximum typical levels disclosed by

Palazzolo of about 5% (w/w) and 2% (w/w), respectively, *the water content in Example 5 of Uhlmann would be approximately 65.95% (w/w)*. Therefore, the *water* content in Example 5 ranges from about 65.95% (w/w) to 72.95% (w/w), which falls within the claimed “50% to 99% (w/w).”

177. As I explained in Paragraph 49, I understand that disclosure of a single point within a claimed range may render obvious that claimed range. Therefore, Uhlmann Example 5 in combination with Palazzolo renders obvious [5].

D. Ground IIA: Uhlmann Anticipates Claims 1, 4-7, And 14-17 (Example 3 Formulation)

178. Claims 1, 4-7, and 14-17 are all anticipated by Example 3 of Uhlmann for at least the following reasons.

1. Independent Claim 1

i. [1Pre] A formulation comprising:

179. Uhlmann Example 3 discloses the preamble [1Pre].

180. I understand that the preamble may not limit the claims. Regardless, Uhlmann discloses a formulation. In particular, Uhlmann describes “cosmetic or dermatological preparations” that “use a conventional formulation base.” EX1004, 5:11-17 (“*Cosmetic or dermatological preparations according to the invention may actually use a conventional formulation base* and be used in the treatment of skin and/or hair as a part of a dermatological or cosmetic treatment. They should have a

δ -aminolevulinic acid content of 0.1% to 10% by weight, but in particular 0.1% to 6% by weight as a percentage of the total weight.”), Title (“Cosmetic or dermatological preparation comprising delta-aminolevulinic acid content as an active ingredient”). In Example 3, Uhlmann provides a “Sun Milk O/W” formulation. EX1004, Example 3.

ii. [1A] (a) a nanoemulsion comprising:

181. Uhlmann discloses [1A].

182. As I explained in Section IX.A [Claim Construction], the ’146 patent expressly provides the lexicographic definition that “[a]s used herein, a ... ‘nanoemulsion’ is a dispersion of oil in water (oil-in-water dispersion, oil-in-water emulsion, O/W emulsion).” EX1001, 12:58-60.

183. Uhlmann describes a “Sun Milk O/W” formulation in Example 3. EX1004, Example 3, 5:39-40 (“an emulsion of ... the oil-in-water type (O/W)”). Uhlmann further explains that “[e]mulsions according to the invention” include a “sun protection milk,” like the “Sun Milk O/W” of Example 3. EX1004, 6:8-13 (“Emulsions according to the invention, e.g. in the form of ... a sun protection milk ...”), 5:35-42 (“Cosmetic preparations according to the invention for protecting the skin against UV radiation may come in different forms, as is generally the case for this type of preparation. They may come as ... an emulsion of ... the oil-in-water type (O/W)”), 6:39-48 (“Hydrodispersions represent *dispersions of a liquid, half*

solid or solid inner (discontinuous) lipid phase in an outer aqueous (continuous) phase. Unlike *O/W emulsions which are characterised by a similar phase arrangement*, hydrodispersions are predominantly free of emulsifiers. Hydrodispersions represent meta stable systems—as do emulsions—and tend to be converted into a state of two connected but discrete phases. In emulsions, the selection of a suitable emulsifier prevents phase separation.”). On that basis, Uhlmann discloses [1A].

iii. [1B] (i) **at least one aqueous component;**

184. Uhlmann discloses [1B].

185. Uhlmann states that “solvents which may be used” for “[e]mulsions according to the invention,” including the “Sun Milk O/W” described in Example 3, can be “**water** or **aqueous solutions**.” EX1004, 5:53-6:13 (“Where the cosmetic or dermatological preparation is a solution or lotion, *solvents which may be used are: **Water or aqueous solutions***; ... Emulsions according to the invention, e.g. in the form of a sun protection cream, a sun protection lotion or *a sun protection milk* are useful and may contain the fats, oils, waxes and other fatty compounds mentioned, *in addition to **water*** and the usual type of emulsifier used for this type of formulation.”). Consistent with that disclosure, Example 3 identifies **water** as the solvent.

<u>Example 3</u>	
Sun Milk O/W	Percentage by weight
Octylmethoxycinnamate	5.0
Butylmethoxydibenzoylmethane	1.0
Cetearylalcohol + PEG-40 castor oil + Sodiumcetearylsulphate	2.5
Glyceryllanolate	1.0
Laurylmethicon copolyol	0.5
Mineral oil (DAB 9)	5.0
Caprylic/capric triglyceride	5.0
Acrylamide/sodiumacrylate copolymer	0.3
Cyclomethicone	2.0
TiO ₂	1.0
δ-aminolevulinic acid	1.0
Glycerine	3.0
EDTA solution (14%)	0.5
Ethanol	5.0
Perfume, preservative	q.s.
Water, fully demineralised	make up to 100.0

EX1004, Example 3 (annotated).

186. The '146 patent expressly states that “[i]n preferred embodiments of the formulations described in the present invention, the *aqueous component comprises an aqueous phase or forms an aqueous phase*. Preferably, the active agent is dissolved in the aqueous phase.” EX1001, 6:6-9. In the formulation in Example 3 of Uhlmann, *water* is the solvent, and therefore constitutes the *aqueous phase* of the nanoemulsion, satisfying the claimed *at least one aqueous component* of the nanoemulsion. Therefore, Uhlmann discloses [1B].

187. Additionally, *water* constitutes the majority component of the formulation in Example 3, further demonstrating that the formulation in Example 3 is an oil-in-water dispersion and meets the claimed “nanoemulsion” of [1A]. *Water*

“make[s] up to 100.0” “[p]ercent[] by weight” of the “Sun Milk O/W” formulation. EX1004, Example 3, 8:23-26 (“All the given quantities, ratios and percentages relate to the weight and the overall volume and/or total weight of the preparations unless otherwise stated.”).

188. Apart from *water*, the identified ingredients together total 32.8% (w/w) of the formulation, with an additional quantity of “perfume, preservative” indicated as “q.s.” EX1004, Example 3, 8:23-26. The notation “q.s.” stands for “quantum sufficit” or “quantum satis.” It was well-known that “q.s.” means “the amount which is enough” and has the “standard pharmaceutical meaning of ‘as much as is sufficient,’” as determined by the supplier of that ingredient. *See, e.g.*, EX1006 (Alderson), [0045].

189. It was also well-known that “perfume” and “preservative” were used only in limited amounts in these types of formulations. For example, the amount of “perfume” or fragrance in topical formulations was generally in the range of 0.01% (w/w) to 5.0% (w/w). *See, e.g.*, EX1005 (Palazzolo), [0011] (“Any of a wide variety of fragrances can be utilized ... with a range from about 0.01% by weight to about 5.0% by weight or more of the cosmetic composition.”). The amount of “preservative” in topical formulations was generally in the range of 0.01% (w/w) to 2% (w/w). *See, e.g.*, EX1005 (Palazzolo), [0010] (“The preservative is preferably in

a range from about 0.01% by weight to about 2.0% by weight of the cosmetic composition...”); *see also* EX1007 (Hill), Appendix A, Appendix B.

190. If no “perfume” or “preservative” were present, the **water** content in Example 3 would be approximately 67.2% (w/w). If “perfume” and “preservative” were present at their maximum typical levels of about 5% (w/w) and 2% (w/w), respectively, the **water** content in Example 3 would be approximately 60.2% (w/w).

iv. [1C] (ii) a carrier component comprising:

191. Uhlmann discloses [1C].

192. As explained in Section XI.D.1.ii [1A], Uhlmann discloses a “Sun Milk O/W” emulsion in Example 3.

193. As I explained in Paragraph 182, “O/W emulsions” are defined as “dispersions of a liquid, half solid or solid inner (discontinuous) lipid phase in an outer aqueous (continuous) phase” that contain “emulsifiers” to “prevent phase separation.” EX1004, 6:39-48. On that basis, the lipid phase of the O/W emulsion, which is identified as the “discontinuous” phase that includes emulsifiers, satisfies the claimed “**carrier component**.”

194. The ’146 patent expressly explains that “[i]n oil in water nanoemulsion formulations, there are two different phases, which may need to be stabilized and compliant with patients: one is the hydrophobic carrier component, which is usually

the carrier and needs to stabilize and release the API and the other one the aqueous component.” EX1001, 3:47-52. Therefore, Uhlmann discloses [1C].

v. [1D] (1) **at least one lipophilic component,**

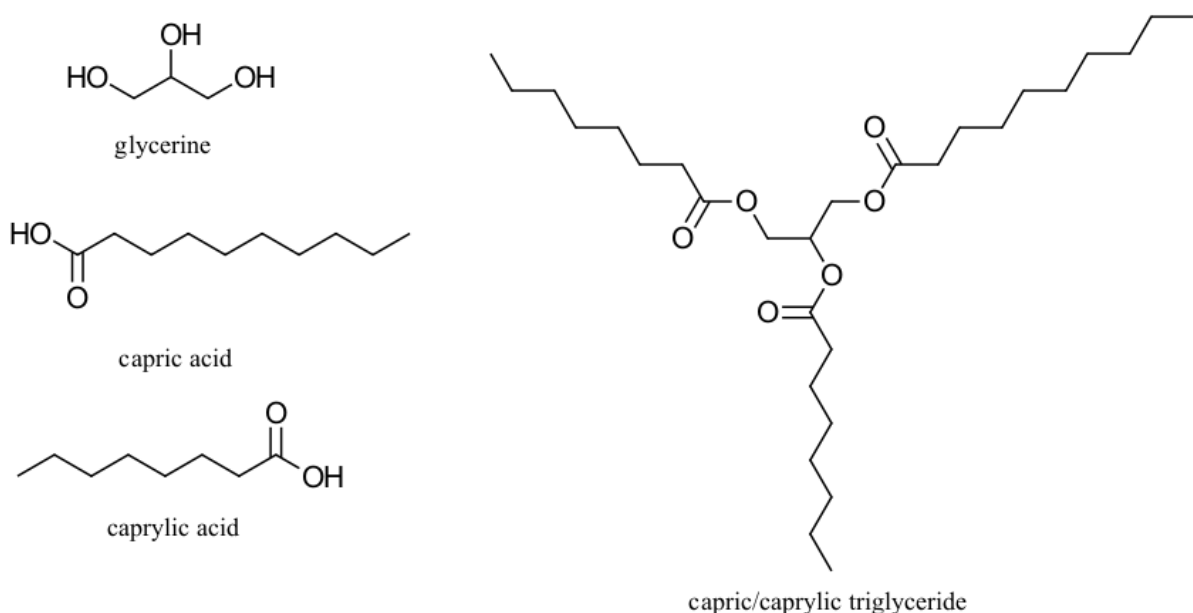
195. Uhlmann discloses [1D].

196. Uhlmann states that “[o]ils such as *triglycerides of capri[c] or caprylic acid*” may be included in “[e]mulsions according to the invention,” including the “Sun Milk O/W” described in Example 3. EX1004, 5:53-6:13. Accordingly, in Example 3, the *caprylic/capric triglyceride* satisfies the claimed “**at least one lipophilic component.**”

Example 3	
Sun Milk O/W	Percentage by weight
Octylmethoxycinnamate	5.0
Butylmethoxydibenzoylmethane	1.0
Cetearylalcohol + PEG-40 castor oil +	2.5
Sodiumcetearylsulphate	
Glyceryllanolate	1.0
Laurylmethicon copolyol	0.5
Mineral oil (DAB 9)	5.0
Caprylic/capric triglyceride	5.0
Acrylamide/sodiumacrylate copolymer	0.3
Cyclomethicone	2.0
TiO ₂	1.0
δ-aminolevulinic acid	1.0
Glycerine	3.0
EDTA solution (14%)	0.5
Ethanol	5.0
Perfume, preservative	q.s.
Water, fully demineralised	make up to 100.0

EX1004, Example 3 (annotated). As shown in the structure below, *caprylic/capric triglyceride* has caprylic and capric acid “tail” groups and a glycerine backbone. See,

e.g., EX1009 (Jaworska), 1. The hydrophobic “tail” groups made up of long hydrocarbon chains allow the *caprylic/capric triglyceride* to be part of the “discontinuous” lipid phase, or “carrier component,” in the O/W emulsion. See Section XI.D.1.iv [1C].



197. The '146 patent explains that “[p]referably, the *at least one lipophilic component* is a *lipid*” and “[s]uitable *lipids* according to the present invention are physiologically acceptable *lipids* such as ceramide, mono-, di- and triacylglycerin (*triglycerides*).” EX1001, 15:12-16. The '146 patent further explains that “[i]n particular, the *at least one lipophilic component* is a *triglyceride*, preferably a triglyceride comprising a C₈₋₁₀ fatty acid, or a mixture thereof. More particular, the *at least one lipophilic component is a caprylic and/or capric triglyceride and/or a mixture thereof.*” EX1001, 15:16-25; see also EX1001, 15:9-11.

198. Consistent with that disclosure, the working examples in the '146 patent identify “*caprylic/capric triglycerides*” as the *at least one lipophilic component* in the nanoemulsions BF200, BF215, and BF220. EX1001, Example 1, Tables 2, 3 (labeling “*caprylic/capric triglycerides*” as the “*lipid core*” of the “carrier component”); *see also* EX1001, 20:40-21:37 (exemplary “nanovesicles” and “nanoemulsions” comprising “*caprylic/capric triglycerides*”). Therefore, the *caprylic/capric triglyceride* in Example 3 of Uhlmann meets the claimed *at least one lipophilic component*. Accordingly, Uhlmann discloses [1D].

vi. [1E] (2) at least one surfactant, and

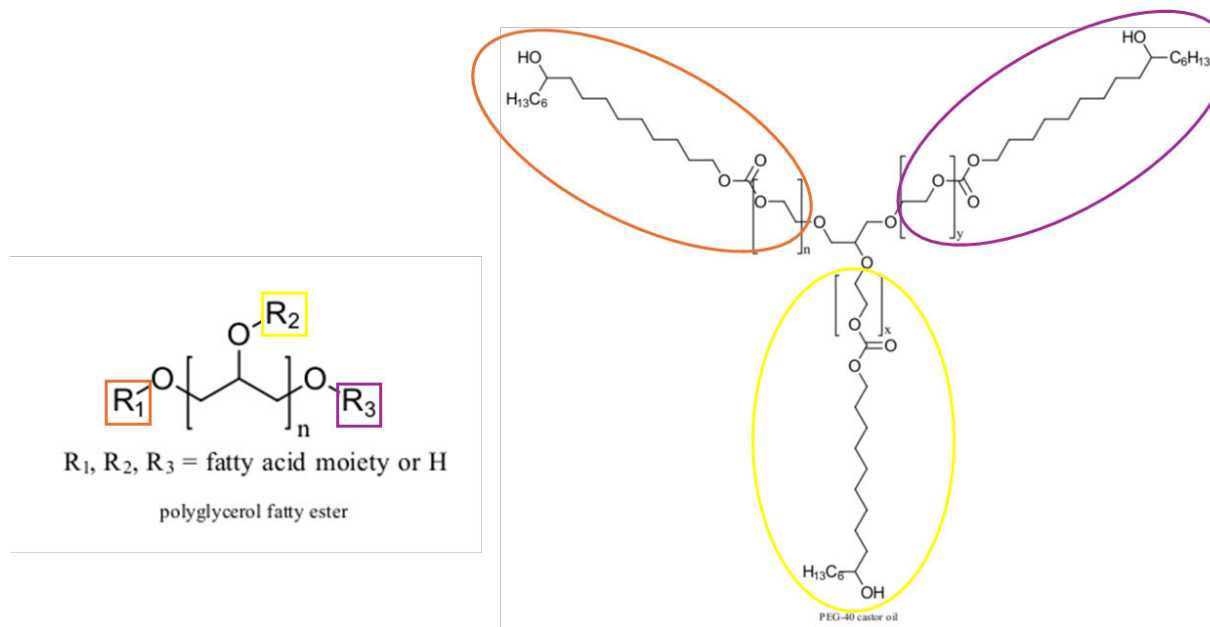
199. Uhlmann discloses [1E].

200. Uhlmann states that “the usual type of *emulsifier* used for this type of formulation” may be included in “[e]mulsions according to the invention,” including the “Sun Milk O/W” described in Example 3. EX1004, 6:8-13; *see also* EX1004, 6:46-48 (“In emulsions, the selection of a suitable *emulsifier* prevents phase separation.”). Accordingly, in Example 3, the one or more of *PEG-40 castor oil*, *sodium cetearyl sulphate*, and *lauryl methicone copolyol* satisfies the claimed “*at least one surfactant*.”

<u>Example 3</u>	
Sun Milk O/W	Percentage by weight
Octylmethoxycinnamate	5.0
Butylmethoxydibenzoylmethane	1.0
Cetearylalcohol + PEG-40 castor oil +	2.5
Sodiumcetearylsulphate	
Glyceryllanolate	1.0
Laurylmethicon copolyol	0.5
Mineral oil (DAB 9)	5.0
Caprylic/capric triglyceride	5.0
Acrylamide/sodiumacrylate copolymer	0.3
Cyclomethicone	2.0
TiO ₂	1.0
δ-aminolevulinic acid	1.0
Glycerine	3.0
EDTA solution (14%)	0.5
Ethanol	5.0
Perfume, preservative	q.s.
Water, fully demineralised	make up to 100.0

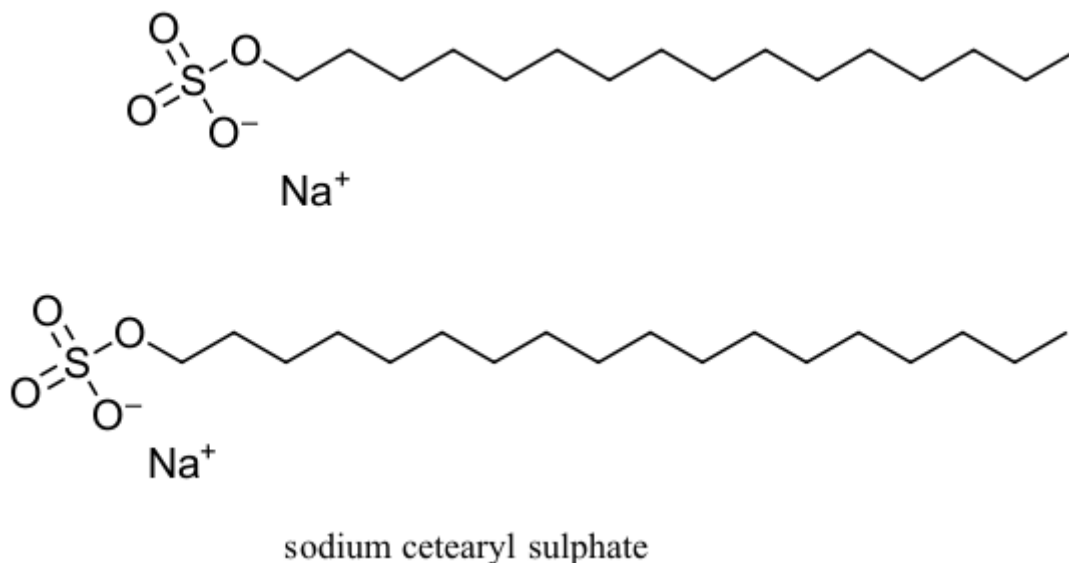
EX1004, Example 3 (annotated).

201. As shown in the structure below, *PEG-40 castor oil* is a polyoxyethylene ester, or polyglycerol fatty ester, of castor oil fatty acids. As shown below, polyglycerol fatty esters have a glycerine backbone with three “R” groups: R₁ (orange), R₂ (yellow), and R₃ (magenta). In *PEG-40 castor oil*, each of the “R” groups comprises a number of polyoxyethylene, or poly(ethylene glycol) (“PEG”), units (with an average of 40). Each of the “R” groups further comprises a castor oil fatty acid.



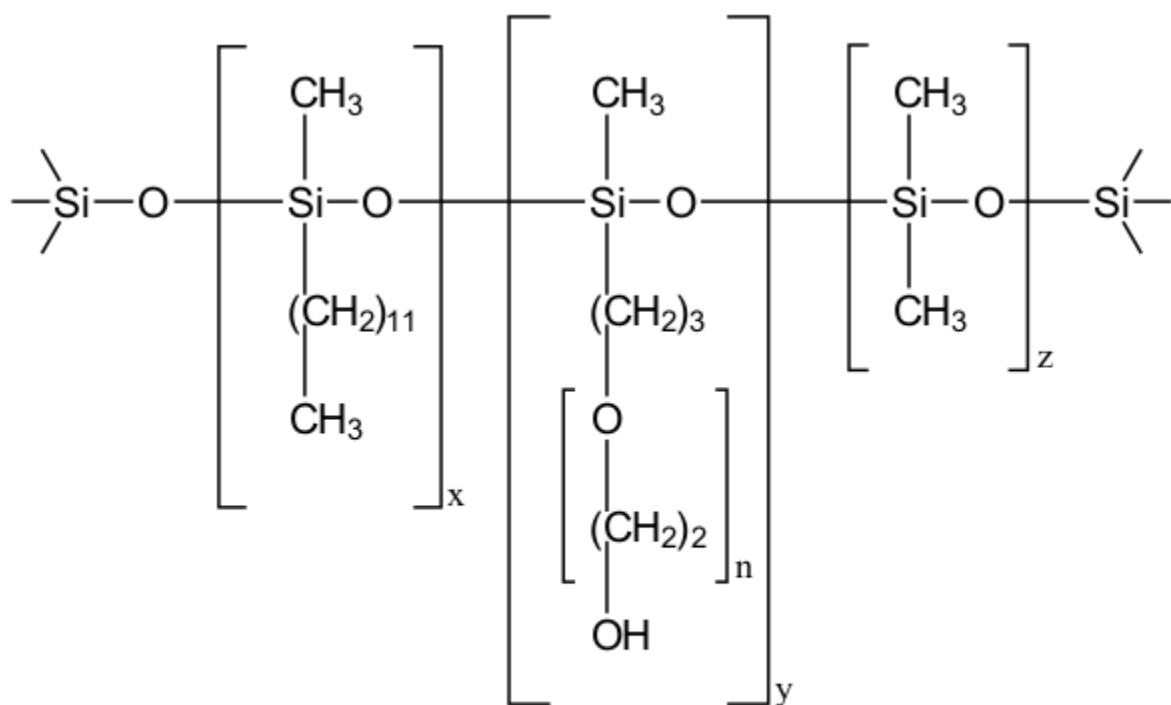
PEG-40 castor oil is a polyglycerol fatty ester *surfactant*. See, e.g., EX1011 (Kale), 3 (“Examples of non-ionic[] *surfactants* [include] ... *polyoxyl 40 hydrogenated castor oil* ...”).

202. As shown in the structure below, *sodium cetearyl sulphate* is a mixture of sodium cetyl sulfate and sodium stearyl sulfate.



Sodium cetearyl sulphate is an anionic alkylsulfate *surfactant*. See, e.g., EX1016 (Fiume 2010), 1 (“*Sodium cetearyl sulfate* is a *surfactant*...”).

203. As shown in the structure below, *lauryl methicone copolyol* comprises a methicone backbone with copolyol side chains.



lauryl methicone copolyol

Lauryl methicone copolyol is a *surfactant*. See, e.g., EX1017 (Vaidya), 3 (“*Dimethicone copolyol surfactants* ...”).

204. *PEG-40 castor oil*, *sodium cetearyl sulphate*, and *laurylmethicone copolyol* each have a hydrophilic head group (comprising esters and/or hydroxy groups) and a hydrophobic tail group (comprising hydrocarbon chains) and function as the *emulsifiers* of the “discontinuous” lipid phase, or the “carrier component,” in the O/W emulsion. See Section XI.D.1.iv [1C].

205. The terms “*emulsifier*” and “*surfactant*” are interchangeable. In fact, the ’146 patent expressly treats the terms “*surfactant*” and “*emulsifier*” as

interchangeable. EX1001, 15:43-58 (“*Surfactants*, also referred [to] as surface active agents or *emulsifiers*, are well-known in the art and include any agent linking oil and water in the composition to form an emulsion. They lower the surface tension of two liquids and are amphiphilic. *In emulsions they are referred as emulsifiers* and coat the droplets preventing coalescing. ...”), 1:24-33 (“Emulsions or micro emulsions can be oil in water, water in oil or middle phased dispersions, often dispersed with *surfactants as emulsifiers*. ...”).

206. The '146 patent further states that the *surfactant* may be “any suitable *surfactant* known to the skilled person,” including “anionic *surfactants*” such as “alkylsulfates” and “any polyoxyethylene-type *surfactant*,” such as a “polyglycerol fatty ester.” EX1001, 15:40-16:36. As I explained above in Paragraphs 201-202, *PEG-40 castor oil* is a polyglycerol fatty ester *surfactant* and *sodium cetearyl sulphate* is an anionic alkylsulfate *surfactant*. Therefore, Example 3 of Uhlmann discloses [1E].

vii. [1F] (3) at least one alcohol; and

207. Uhlmann discloses [1F].

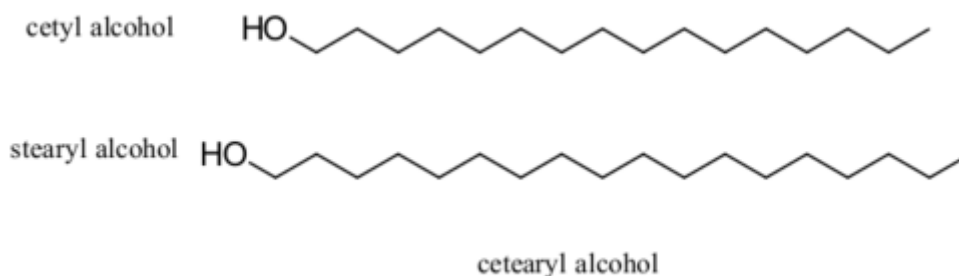
208. Uhlmann states that “*[a]lcohols, diols or polyols with a low C number*” may be included in “[e]mulsions according to the invention,” including the “Sun Milk O/W” described in Example 3. EX1001, 5:53-6:13. Accordingly, in Example

3, the one or more of *cetearyl alcohol*, *glycerine*, and *ethanol* satisfies the claimed “*at least one alcohol*.”

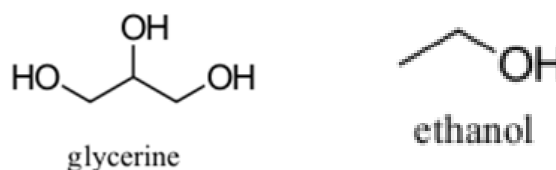
Example 3	
Sun Milk O/W	Percentage by weight
Octylmethoxycinnamate	5.0
Butylmethoxydibenzoylmethane	1.0
Cetearylalcohol + PEG-40 castor oil + Sodiumcetearylsulphate	2.5
Glyceryllanolate	1.0
Laurylmethicon copolyol	0.5
Mineral oil (DAB 9)	5.0
Caprylic/capric triglyceride	5.0
Acrylamide/sodiumacrylate copolymer	0.3
Cyclomethicone	2.0
TiO ₂	1.0
δ-aminolevulinic acid	1.0
Glycerine	3.0
EDTA solution (14%)	0.5
Ethanol	5.0
Perfume, preservative	q.s.
Water, fully demineralised	make up to 100.0

EX1004, Example 3 (annotated). In Example 3, *cetearyl alcohol*, *glycerine*, and *ethanol* are each *alcohols*.

209. As shown in the structure below, *cetearyl alcohol* has hydrophobic “tail” groups made up of hydrocarbon chains that are part of the “discontinuous” lipid phase, or the “carrier component,” in the O/W emulsion. See Section XI.D.1.iv [1C]. *Cetearyl alcohol* is a mixture of cetyl alcohol and stearyl alcohol.



210. As shown in the structures below, *glycerine* and *ethanol* each have hydroxy groups that may associate with the hydrophilic head groups of the *surfactants*. See, e.g., EX1011 (Kale), 2 (“The major components of micro emulsion system are: 1) Oil phase 2) Surfactant (Primary surfactant) 3) Co-surfactant (Secondary surfactant) 4) Co-Solvent”), 3 (“... if co-surfactants are added then with minimum concentration of surfactants different curvatures of interfacial film can be formed to generate stable micro emulsion composition. Co surfactants raises the fluidity of the interface due to presence of fluidizing groups like unsaturated bonds, then demolishes liquid crystalline or gel structure and alters the HLB value in such way to cause spontaneous formation of micro emulsion. Example: Short chain alcohols like ethanol to butanol[.] Short chain glycols like propylene glycol[.] Medium chain alcohols like amines or acids”), Fig. 3.

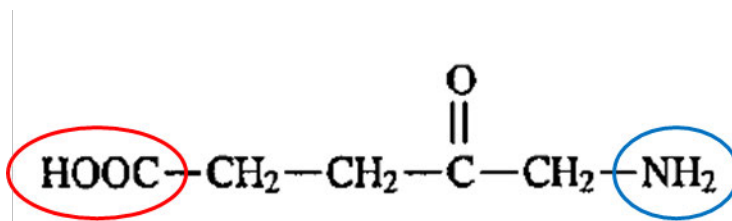


211. As I explained above in Sections XI.D.1.vi [1E] and XI.D.1.iv [1C], the *surfactants* are part of the “discontinuous” lipid phase, or the “carrier component.” Because *cetearyl alcohol*, *glycerine*, and *ethanol* interact with the *surfactants*, each *alcohol* meets the claimed “*at least one alcohol*.” Therefore, Uhlmann discloses [1F].

viii. [1G] (b) **5-aminolevulinic acid** and/or a derivative, a precursor, a metabolite, and/or a pharmaceutically acceptable salt thereof,

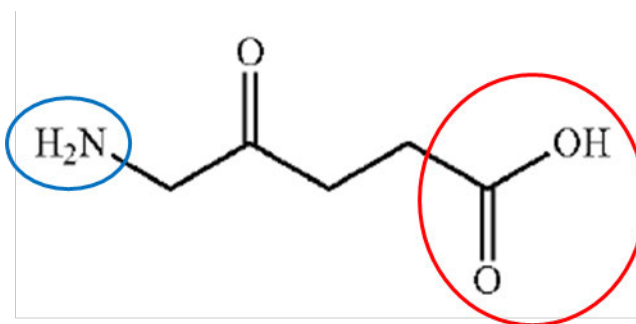
212. Uhlmann discloses [1G].

213. Uhlmann states that the “[c]osmetic or dermatological preparations according to the invention” “should have a *δ-aminolevulinic acid* content of 0.1% to 10% by weight, but in particular 0.1% to 6% by weight as a percentage of the total weight.” EX1004, 5:11-17. Uhlmann provides the structure of *δ-aminolevulinic acid*, which is “also called δ-ALA, 5-amino-4-oxopentanoic acid, δ-amino-γ-keto-valeric acid:”



EX1004, 2:28-34 (annotated). In the structure above, I have highlighted the carboxylic acid in red and the amino group in blue.

214. *δ-aminolevulinic acid* is *5-aminolevulinic acid*. In fact, the '146 patent confirms that *δ-aminolevulinic acid* is *5-aminolevulinic acid*. The '146 patent provides the following structure of *5-aminolevulinic acid*:



EX1001, 19:17-28 (annotated). In the structure above, I have highlighted the carboxylic acid in red and the amino group in blue. As shown in the structures of *δ-aminolevulinic acid* and *5-aminolevulinic acid*, they are identical molecules.

215. Accordingly, in Example 3, the “*δ-aminolevulinic acid*” satisfies the claimed “*5-aminolevulinic acid*.”

<u>Example 3</u>	
Sun Milk O/W	Percentage by weight
Octylmethoxycinnamate	5.0
Butylmethoxydibenzoylmethane	1.0
Cetearylalcohol + PEG-40 castor oil + Sodiumcetearylsulphate	2.5
Glyceryllanolate	1.0
Laurylmethicon copolyol	0.5
Mineral oil (DAB 9)	5.0
Caprylic/capric triglyceride	5.0
Acrylamide/sodiumacrylate copolymer	0.3
Cyclomethicone	2.0
TiO ₂	1.0
δ-aminolevulinic acid	1.0
Glycerine	3.0
EDTA solution (14%)	0.5
Ethanol	5.0
Perfume, preservative	q.s.
Water, fully demineralised	make up to 100.0

EX1004, Example 3 (annotated). Therefore, Uhlmann discloses [1G].

ix. [1H] wherein the formulation comprises essentially no propylene glycol and essentially no sorbitol.

216. Uhlmann discloses [1H].

217. In Example 3, the “Sun Milk O/W” emulsion contains no propylene glycol and no sorbitol.

<u>Example 3</u>	
Sun Milk O/W	Percentage by weight
Octylmethoxycinnamate	5.0
Butylmethoxydibenzoylmethane	1.0
Cetearylalcohol + PEG-40 castor oil + Sodiumcetearylsulphate	2.5
Glyceryllanolate	1.0
Laurylmethicon copolyol	0.5
Mineral oil (DAB 9)	5.0
Caprylic/capric triglyceride	5.0
Acrylamide/sodiumacrylate copolymer	0.3
Cyclomethicone	2.0
TiO ₂	1.0
δ-aminolevulinic acid	1.0
Glycerine	3.0
EDTA solution (14%)	0.5
Ethanol	5.0
Perfume, preservative	q.s.
Water, fully demineralised	make up to 100.0

EX1004, Example 3 (annotated). The formulation described in Example 3 is a complete formulation where water “makes up to 100.0” percent by weight of the formulation. EX1004, Example 3, 8:23-26 (“All the given quantities, ratios and percentages relate to the weight and the overall volume and/or total weight of the preparations unless otherwise stated.”). A POSA would have readily recognized that, because Example 3 details a complete formulation, there would be no other ingredients added to the formulation. Therefore, a POSA would have readily recognized that Example 3 details a formulation free of propylene glycol and sorbitol.

218. The '146 patent explains that “‘comprises essentially no compound X’” “specif[ies] that the formulation is either free of compound X or comprises less than

0.1% (w/w)” of compound X “based on the total weight of the formulation.” EX1001, 6:50-59 (“As used herein, the expressions “essentially free of compound X”, “does essentially not comprise compound X”, or “comprises essentially no compound X” with respect to a formulation are interchangeable. In particular, these expressions specify that the formulation is either free of compound X or comprises less than 0.1% (w/w), less than 0.08% (w/w), less than 0.07% (w/w), less than 0.06% (w/w), less than 0.05% (w/w), less than 0.04% (w/w), less than 0.03% (w/w), less than 0.02% (w/w), or less than 0.01% (w/w) of compound X based on the total weight of the formulation.”). Uhlmann discloses [1H] because the formulation in Example 3 is free of propylene glycol and sorbitol, and therefore has less than 0.1% (w/w) of propylene glycol and sorbitol.

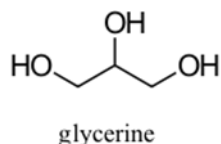
2. Dependent Claims 4 And 16

- i. [4] The formulation of claim 1, wherein the **at least one alcohol** comprises: 3, 4, or 5 carbon atoms; or 1-propanol, 2-propanol, or a mixture thereof.

219. Uhlmann discloses [4].

220. As I explained above in Section XI.D.1.vii [1F], Example 3 contains **glycerine** as one of the **at least one alcohol** in the carrier component of the “Sun Milk O/W” emulsion. EX1004, Example 3.

221. As shown in the structure below, **glycerine** has 3 carbon atoms.



Therefore, *glycerine* meets the claimed “wherein the *at least one alcohol* comprises: 3 ... carbon atoms” and Uhlmann discloses [4].

- ii. [16] The formulation of claim 4, wherein the *at least one alcohol* is in an amount from 0.1% to 10% (w/w), from 0.5% to 5% (w/w), from 1% to 5% (w/w), or from 1% to 3% based on total weight of the nanoemulsion.

222. Uhlmann discloses [16].

223. As I explained above in Section XI.D.1.vii [1F], Example 3 contains *glycerine* as one of the *at least one alcohol* in the carrier component of the “Sun Milk O/W” emulsion.

224. *Glycerine* is 3.0% (w/w) of the formulation in Example 3, which is within the claimed “0.1 to 10% (w/w).” EX1004, Example 3, 8:23-26 (“All the given quantities, ratios and percentages relate to the weight and the overall volume and/or total weight of the preparations unless otherwise stated.”).

225. As I explained in Paragraph 43, I understand that disclosure of a single point within a claimed range may anticipate that claimed range. Therefore, Example 3 discloses [16].

3. Dependent Claim 5

- i. [5] The formulation of claim 1, comprising the **at least one aqueous component** in an amount from 50% to 99% (w/w), from 70% to 95% (w/w), from 75% to 95% (w/w), or from 80% to 90% (w/w).

226. Uhlmann discloses [5].

227. As I explained in Section XI.D.1.iii [1B], Example 3 contains **water** and meets the claimed **at least one aqueous component**. EX1004, Example 3.

228. **Water** “make[s] up to 100.0” “[p]ercent[] by weight” of the “Sun Milk O/W” formulation. EX1004, Example 3, 8:23-26 (“All the given quantities, ratios and percentages relate to the weight and the overall volume and/or total weight of the preparations unless otherwise stated.”).

229. As I explained above in Section XI.D.1.iii [1B], the other identified ingredients together total 32.8% (w/w) of the formulation, with an additional quantity of “perfume, preservative” indicated as “q.s.” EX1004, Example 3, 8:23-26. The notation “q.s.” stands for “quantum sufficit” or “quantum satis.” It was well-known that “q.s.” means “the amount which is enough” and has the “standard pharmaceutical meaning of ‘as much as is sufficient,’” as determined by the supplier of that ingredient. *See, e.g.,* EX1006 (Alderson), [0045].

230. It was also well-known that “perfume” and “preservative” were used only in limited amounts in these types of formulations. For example, the amount of

“perfume” or fragrance in topical formulations was generally in the range of 0.01% (w/w) to 5.0% (w/w). *See, e.g.*, EX1005 (Palazzolo), [0011] (“Any of a wide variety of fragrances can be utilized ... with a range from about 0.01% by weight to about 5.0% by weight or more of the cosmetic composition.”). The amount of “preservative” in topical formulations was generally in the range of 0.01% (w/w) to 2% (w/w). *See, e.g.*, EX1005 (Palazzolo), [0010] (“The preservative is preferably in a range from about 0.01% by weight to about 2.0% by weight of the cosmetic composition...”); *see also* EX1007 (Hill), Appendix A, Appendix B.

231. If no “perfume” or “preservative” were present, *the water content in Example 3 would be approximately 67.2% (w/w)*. If “perfume” and “preservative” were present at their maximum typical levels of about 5% (w/w) and 2% (w/w), respectively, *the water content in Example 3 would be approximately 60.2% (w/w)*. Therefore, the *water* content in Example 3 ranges from about 60.2% (w/w) to 67.2% (w/w), which falls within the claimed “50% to 99% (w/w).”

232. As I explained in Paragraph 43, I understand that disclosure of a single point within a claimed range may anticipate that claimed range. Therefore, Example 3 discloses [5].

4. Dependent Claim 6

- i. [6] The formulation of claim 4, comprising the **at least one lipophilic component** in an amount from 0.1% to 30% (w/w), from 0.25% to 15% (w/w), from 0.25% to 10% (w/w), from 2% to 10% (w/w), or 3% to 8% (w/w) based on total weight of the nanoemulsion.

233. Uhlmann discloses [6].

234. As I explained above in Section XI.D.1.v [1D], the *caprylic/capric triglyceride* in Example 3 is one of the components of the **at least one lipophilic component**.

235. *Caprylic/capric triglyceride* is 5.0% (w/w) of the formulation in Example 3, which is within the claimed “0.1 to 30% (w/w).” EX1004, Example 3, 8:23-26 (“All the given quantities, ratios and percentages relate to the weight and the overall volume and/or total weight of the preparations unless otherwise stated.”).

236. As I explained in Paragraph 43, I understand that disclosure of a single point within a claimed range may anticipate that claimed range. Therefore, Example 3 discloses [6].

5. Dependent Claim 7

- i. [7] The formulation of claim 1, wherein the formulation comprises no propylene glycol.

237. Uhlmann discloses [7].

238. As I explained in Section XI.D.1.ix [1H], the “Sun Milk O/W” formulation in Example 3 does not contain propylene glycol.

6. Dependent Claim 14

- i. [14] The formulation of claim 1, wherein the **at least one lipophilic component** comprises: triglycerides and/or mixtures thereof; or a **caprylic triglyceride, a capric triglyceride, or a mixture thereof**.

239. Uhlmann discloses [14].

240. As I explained above in Section XI.D.1.v [1D], the **caprylic/capric triglyceride** in Example 3 is one of the components of the **at least one lipophilic component**.

241. The **caprylic/capric triglyceride** in Example 3 meets the claimed “**caprylic triglyceride, a capric triglyceride, or a mixture thereof**.” Therefore, Uhlmann discloses [14].

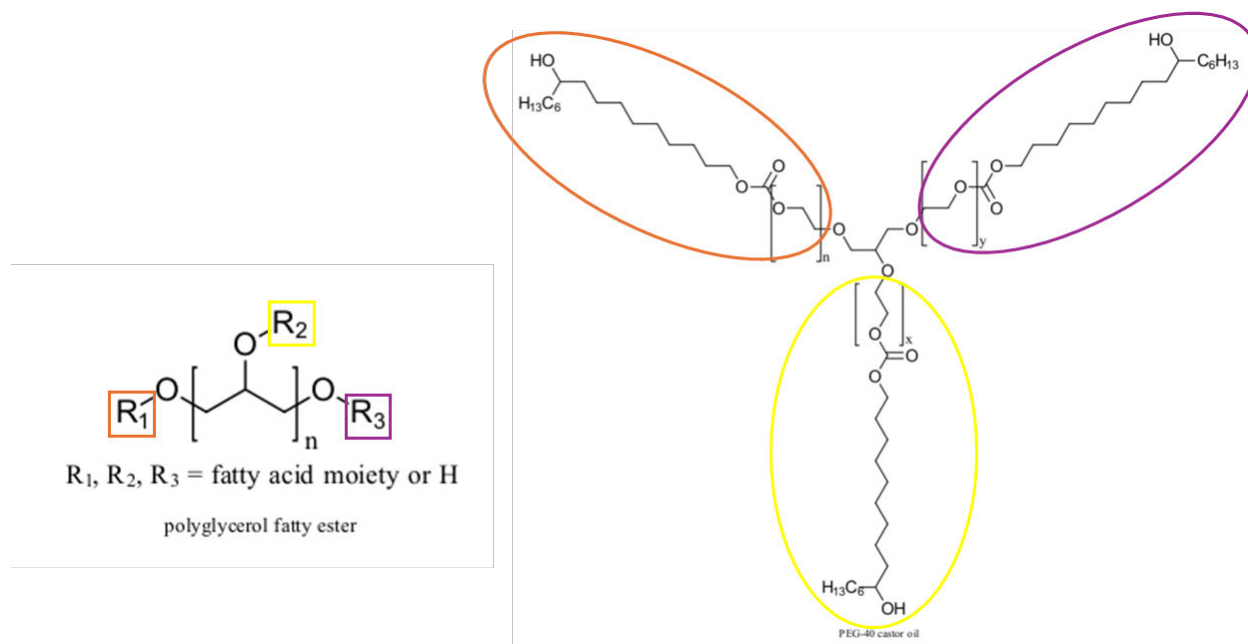
7. Dependent Claim 15

- i. [15] The formulation of claim 1, wherein the **at least one surfactant** comprises: a phospholipid, a phosphatidylcholine, a lysophospholipid, a ceramide, and/or a mixture thereof; and/or a **polyoxyethylene-type surfactant**.

242. Uhlmann discloses [15].

243. As I explained in Section XI.D.1.vi [1E], Uhlmann discloses **PEG-40 castor oil** as one of the **at least one surfactant** in Example 3.

244. **PEG-40 castor oil** has the chemical structure shown below.



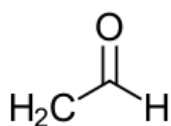
PEG-40 castor oil is a *polyoxyethylene-type surfactant*. Typically, shorter-length polyoxyethylenes are referred to as poly(ethylene glycols), or “PEGs.” *See, e.g.,* EX1012 (Bailey), 1 (“Polyoxyethylenes of less than ca. 20 000 number-average molecular mass are usually referred to as poly(ethylene glycols).”).

8. Dependent Claim 17

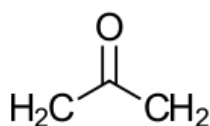
- i. [17] The formulation of claim 1, wherein the formulation further comprises essentially no monosaccharides and disaccharides.

245. Uhlmann discloses [17].

246. Monosaccharides are simple sugars that consist of a single aldehyde or ketone with multiple (at least two) hydroxyl groups. Below are structures of representative aldehydes and ketones.

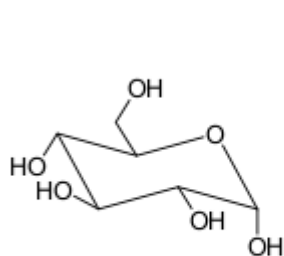


aldehyde

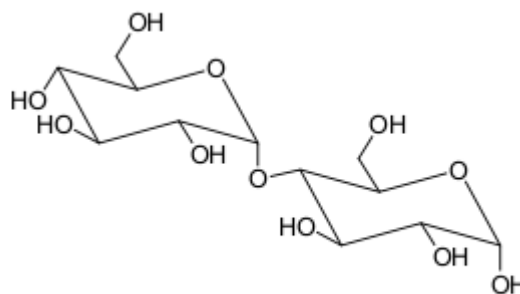


ketone

Disaccharides are sugars composed of two monosaccharides. The structures of exemplary monosaccharides and disaccharides are shown below. Glucose is a common monosaccharide. Maltose, made up of two glucose molecules, is a common disaccharide.



glucose



maltose

See, e.g., EX1013 (Nelson), 229-230, 233, 237.

247. In Example 3 of Uhlmann, the “Sun Milk O/W” formulation contains no monosaccharides and no disaccharides.

<u>Example 3</u>	
Sun Milk O/W	Percentage by weight
Octylmethoxycinnamate	5.0
Butylmethoxydibenzoylmethane	1.0
Cetearylalcohol + PEG-40 castor oil +	2.5
Sodiumcetearylsulphate	
Glyceryllanolate	1.0
Laurylmethicon copolyol	0.5
Mineral oil (DAB 9)	5.0
Caprylic/capric triglyceride	5.0
Acrylamide/sodiumacrylate copolymer	0.3
Cyclomethicone	2.0
TiO ₂	1.0
δ-aminolevulinic acid	1.0
Glycerine	3.0
EDTA solution (14%)	0.5
Ethanol	5.0
Perfume, preservative	q.s.
Water, fully demineralised	make up to 100.0

EX1004, Example 3 (annotated). The formulation described in Example 3 is a complete formulation where water “makes up to 100.0” percent by weight of the formulation. EX1004, Example 3, 8:23-26 (“All the given quantities, ratios and percentages relate to the weight and the overall volume and/or total weight of the preparations unless otherwise stated.”). A POSA would have readily recognized that, because Example 3 details a complete formulation, there would be no other ingredients added to the formulation. Therefore, a POSA would have readily recognized that Example 3 details a formulation free of monosaccharides and disaccharides.

248. The '146 patent explains that “‘comprises essentially no compound X’” “specif[ies] that the formulation is either free of compound X or comprises less than

0.1% (w/w)” of compound X “based on the total weight of the formulation.” EX1001, 6:50-59 (“As used herein, the expressions “essentially free of compound X”, “does essentially not comprise compound X”, or “comprises essentially no compound X” with respect to a formulation are interchangeable. In particular, these expressions specify that the formulation is either free of compound X or comprises less than 0.1% (w/w), less than 0.08% (w/w), less than 0.07% (w/w), less than 0.06% (w/w), less than 0.05% (w/w), less than 0.04% (w/w), less than 0.03% (w/w), less than 0.02% (w/w), or less than 0.01% (w/w) of compound X based on the total weight of the formulation.”). Uhlmann discloses [17] because the formulation in Example 3 is free of monosaccharides and disaccharides, and therefore has less than 0.1% (w/w) of monosaccharides and disaccharides.

E. Ground IIB: Uhlmann Renders Obvious Dependent Claims 2, 3, 8-13, And 16 (Modified Example 3 Formulation)

249. Claims 2, 3, 8-13, and 16 are all rendered obvious by Example 3 of Uhlmann for at least the following reasons.

1. Dependent Claims 2, 3, 8-13

i. [2] The formulation of claim 1, wherein the formulation further comprises less than 1% w/w of a non-cyclic polyol having 2 to 5 carbon atoms.

[3] The formulation of claim 1, wherein the formulation further comprises less than 1% w/w of a non-cyclic polyol having 2 to 12 carbon atoms.

[8] The formulation of claim 1, wherein the formulation further comprises less than or equal to 0.99%, 0.95%, 0.9%, 0.8%, 0.7%, 0.6%, 0.5%, 0.4%, 0.3%, 0.2%, or 0.1% w/w of a non-cyclic polyol having 2 to 5 carbon atoms.

[9] The formulation of claim 1, wherein the formulation further comprises essentially no non-cyclic polyol having 2 to 5 carbon atoms.

[10] The formulation of claim 1, wherein the formulation further comprises no non-cyclic polyol having 2 to 5 carbon atoms.

[11] The formulation of claim 1, wherein the formulation further comprises less than or equal to 0.99%, 0.95%, 0.9%, 0.8%, 0.7%, 0.6%, 0.5%, 0.4%, 0.3%, 0.2%, or 0.1% w/w of a non-cyclic polyol having 2 to 12 carbon atoms.

[12] The formulation of claim 1, wherein the formulation further comprises essentially no non-cyclic polyol having 2 to 12 carbon atoms.

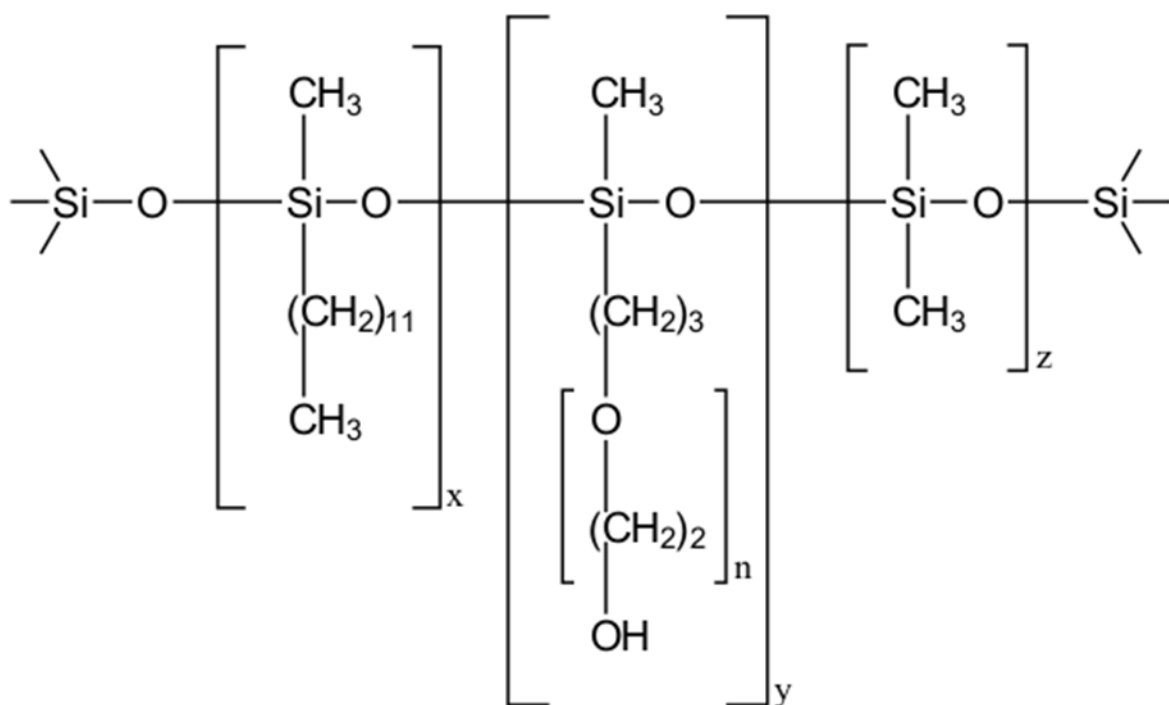
[13] The formulation of claim 1, wherein the formulation further comprises no non-cyclic polyol having 2 to 12 carbon atoms.

250. Uhlmann renders obvious [2], [3], and [8]-[13].

251. The only component in Example 3 of Uhlmann that is a “non-cyclic polyol” having “2 to 5 carbon atoms” or “2 to 12 carbon atoms” is *glycerine*. However, as I explain below, a POSA would have found it obvious to replace *glycerine* with a different alcohol, such as *isopropanol*. *Isopropanol* is not a non-cyclic polyol.

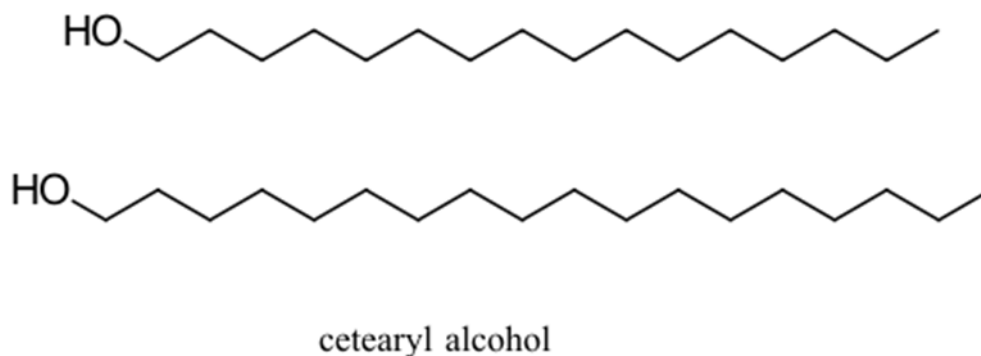
252. None of the other components in Example 3 meet the claimed “non-cyclic polyol” having “2 to 5 carbon atoms” or “2 to 12 carbon atoms.”

253. The formulation in Example 3 contains *lauryl methicone copolyol*, which is a non-cyclic polyol. EX1004, Example 3. However, as shown in the structure below, *lauryl methicone copolyol* has at least 25 carbon atoms and therefore does not meet the claimed “non-cyclic polyol” having “2 to 5 carbon atoms” or “2 to 12 carbon atoms.”



lauryl methicone copolyol

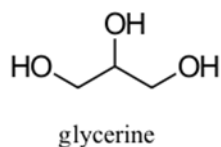
254. The other alcohols (*i.e.*, hydroxy (-OH) group containing compounds) in Example 3 are not non-cyclic polyols. As I explained in Section XI.D.1.vii [1F], the “Sun Milk O/W” formulation in Example 3 includes *cetearyl alcohol*, *ethanol*, and *glycerine*. However, *cetearyl alcohol* and *ethanol* are not non-cyclic polyols. As shown in the structure below, *cetearyl alcohol* contains only one alcohol group per molecule and is therefore not a polyol. *Cetearyl alcohol* is a mixture of cetyl alcohol, which contains 16 carbon atoms, and stearyl alcohol, which contains 18 carbon atoms.



As shown in the structure below, *ethanol* also contains only one alcohol group and is therefore not a polyol. *Ethanol* contains 2 carbon atoms.

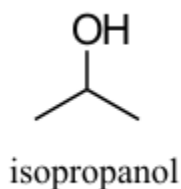


255. As I explained above in Paragraphs 251-252, *glycerine* (also known as *glycerol*) is the only “non-cyclic polyol” having “2 to 5 carbon atoms” or “2 to 12 carbon atoms” in the formulation in Example 3 of Uhlmann. As shown in the structure below, *glycerine* is a non-cyclic polyol having 3 carbon atoms.



256. Nevertheless, a POSA would have found it obvious to replace *glycerine* with a different alcohol, such as *isopropanol*. Uhlmann explains that “[a]lcohols,

diols or polyols with a low C number and their ethers, preferably *ethanol*, *isopropanol*, propylene glycol, *glycerine*, ethylene glycol, ethylene glycol monoethylether, ethylene glycol monobutylether, propylene glycol monomethylether, propylene glycol monoethyl ether, propylene glycol monobutylether, diethylene glycol monomethylether, diethylene glycol monoethylether and analogous products” may be used in “[e]mulsions according to the invention.” EX1004, 5:53-6:13. Based on this disclosure, a POSA would have understood that polyols and alcohols are interchangeable in Uhlmann’s disclosed emulsions, including the “Sun Milk O/W” formulation in Example 3. As shown in the structure below, *isopropanol* is not a non-cyclic polyol because it contains only one alcohol group. *Isopropanol* has 3 carbon atoms.



257. In view of Uhlmann’s disclosure that polyols and alcohols, such as *glycerine* and *isopropanol*, respectively, are suitable alternatives that are interchangeable with one another, a POSA would have found it trivial to replace *glycerine* with *isopropanol*. I have annotated Example 3 to show *isopropanol* in the “Sun Milk O/W” formulation below.

<u>Example 3</u>	
Sun Milk O/W	Percentage by weight
Octylmethoxycinnamate	5.0
Butylmethoxydibenzoylmethane	1.0
Cetearylalcohol + PEG-40 castor oil +	2.5
Sodiumcetearylsulphate	
Glyceryllanolate	1.0
Laurylmethicon copolyol	0.5
Mineral oil (DAB 9)	5.0
Caprylic/capric triglyceride	5.0
Acrylamide/sodiumacrylate copolymer	0.3
Cyclomethicone	2.0
TiO ₂	1.0
δ-aminolevulinic acid	1.0
Isopropanol	3.0
EDTA solution (14%)	0.5
Ethanol	5.0
Perfume, preservative	q.s.
Water, fully demineralised	make up to 100.0

EX1004, Example 3 (annotated). A POSA would have found it obvious to try replacing the *glycerine* with *isopropanol* with a reasonable expectation of success because Uhlmann discloses that both are preferred *alcohols* (with *glycerine* being a polyol) suitable for use with the disclosed topical formulations.

258. In addition, a POSA would have been motivated to remove *glycerine* from the formulation containing *δ-aminolevulinic acid* because *glycerine*, also called *glycerol*, was known to cause degradation of *δ-aminolevulinic acid*. For example, a 2000 study found that, while “*ALA* is sufficiently soluble in *glycerol* (~10%), DMSO (~10%), and propylene glycol (~5%),” “the immediate yellow appearance of these solutions when *ALA* is dissolved may be considered to indicate *ALA* degradation.” EX1014 (Bunke), 6 (“One possible approach to prepare stable

and clinically useful *ALA* solutions consists of using nonaqueous, water-miscible solvents for *ALA*. *ALA* is sufficiently soluble in *glycerol* (~10%), DMSO (~10%), and propylene glycol (~5%). However, the immediate yellow appearance of these solutions when *ALA* is dissolved may be considered to indicate *ALA* degradation. Thus, this approach was not further pursued.”). As another example, a 2005 study found that esterification reactions between *ALA* and *glycerine* occurred readily. EX1015 (McCarron), 1 (“...an esterification reaction involving *ALA* and ... *glycerol*...”), 5-15, Fig. 7. A POSA would have recognized that one of the well-known suitable components to replace *glycerine* was *isopropanol*, as explained by Uhlmann. EX1004, 5:53-6:13. Therefore, a POSA would have been motivated to replace *glycerine* with *isopropanol* and would have had a reasonable expectation of success in doing so. This replacement is nothing more than simple substitution of one known element (*i.e.*, *glycerine*) for another (*i.e.*, *isopropanol*) to obtain predictable results (*i.e.*, a stable topical formulation).

259. The resulting formulation in Example 3 replaces *glycerine* with *isopropanol*. This modified formulation does not contain any “non-cyclic polyol” having “2 to 5 carbon atoms” or “2 to 12 carbon atoms.” Therefore, the modified Example 3 of Uhlmann meets the claimed “less than 1% w/w,” ([2], [3]) “less than or equal to 0.99% ...w/w,” ([8], [11]) “essentially no,” ([9], [12]) and “no” ([10],

[13]) non-cyclic polyol having 2-5 or 2-12 carbon atoms. Accordingly, Uhlmann Example 3 renders obvious [2], [3], and [8]-[13].

260. The '146 patent explains that “comprises essentially no compound X” “specif[ies] that the formulation is either free of compound X or comprises less than 0.1% (w/w)” of compound X “based on the total weight of the formulation.” EX1001, 6:50-59 (“As used herein, the expressions “essentially free of compound X”, “does essentially not comprise compound X”, or “comprises essentially no compound X” with respect to a formulation are interchangeable. In particular, these expressions specify that the formulation is either free of compound X or comprises less than 0.1% (w/w), less than 0.08% (w/w), less than 0.07% (w/w), less than 0.06% (w/w), less than 0.05% (w/w), less than 0.04% (w/w), less than 0.03% (w/w), less than 0.02% (w/w), or less than 0.01% (w/w) of compound X based on the total weight of the formulation.”). Uhlmann renders obvious [9] and [12] because the modified formulation in Example 3 is free of, and therefore has less than 0.1% (w/w) of, a “non-cyclic polyol” having “2 to 5 carbon atoms” or “2 to 12 carbon atoms.”

2. Dependent Claim 16

- i. [16] The formulation of claim 4, wherein the **at least one alcohol** is in an amount from 0.1% to 10% (w/w), from 0.5% to 5% (w/w), from 1% to 5% (w/w), or from 1% to 3% based on total weight of the nanoemulsion.

261. As I explained above in Section XI.D.2.ii [Ground IIA, [16]], Uhlmann discloses [16]. In the alternative, Uhlmann Example 3 renders obvious [16]. As I explained above in Sections XI.D.1.vii [Ground IIA, [1F]] and XI.D.2.ii [Ground IIA, [16]], **glycerine** is 3.0% (w/w) of the formulation in Example 3, which is within the claimed “0.1 to 10% (w/w).” EX1004, Example 3, 8:23-26 (“All the given quantities, ratios and percentages relate to the weight and the overall volume and/or total weight of the preparations unless otherwise stated.”).

262. Even if [16] requires all of the compounds identified in claim 1 that meet the **at least one alcohol** in the carrier component to meet the claimed “0.1 to 10% (w/w)” of the formulation, Uhlmann Example 3 still renders obvious [16]. As I explained above in Section XI.D.1.vii [Ground IIA, [1F]], Example 3 further contains **ethanol** and **cetearyl alcohol** that meet the claimed “**at least one alcohol**” in the carrier component. **Ethanol** is 5.0% (w/w) of the formulation. EX1004, Example 3, 8:23-26 (“All the given quantities, ratios and percentages relate to the weight and the overall volume and/or total weight of the preparations unless otherwise stated.”). **Cetearyl alcohol** cannot exceed 2.5% (w/w) of the formulation,

because the combination of *cetearyl alcohol*, *PEG-40 castor oil*, and *sodium cetearyl sulphate* is 2.5% (w/w) of the formulation. EX1004, Example 3, 8:23-26 (“All the given quantities, ratios and percentages relate to the weight and the overall volume and/or total weight of the preparations unless otherwise stated.”). Therefore, a POSA would recognize the amount of *cetearyl alcohol* in the formulation is likely less than 2.5% (w/w).

263. Even if there were zero *PEG-40 castor oil* and *sodium cetearyl sulphate* in the formulation, the combined amount of *ethanol*, *glycerine*, and *cetearyl alcohol* would not exceed 10.5% (w/w). A POSA would have readily understood that the endpoints of the claimed “0.1 to 10% (w/w)” are not critical and there are no unexpected results relating to the claimed range. The difference between the 10.5% (w/w) disclosed in Uhlmann Example 3 and the claimed “0.1 to 10% (w/w)” is negligible.

264. As I explained in Paragraph 51, I understand that disclosure of a point mathematically close to the endpoint of a claimed range, where the difference between the disclosed point and the claimed range is negligible, may render obvious that claimed range if the endpoint of the claimed range has not been shown to be critical or if there are no unexpected results relating to the claimed range. Therefore, Uhlmann Example 3 renders obvious [16].

F. Ground IIC: Uhlmann in View of Palazzolo Renders Obvious Claim 5 (Example 3 Formulation)

265. Claim 5 is rendered obvious by Example 3 of Uhlmann in view of Palazzolo for at least the following reasons.

1. Dependent Claim 5

- i. [5] The formulation of claim 1, comprising the **at least one aqueous component** in an amount from 50% to 99% (w/w), from 70% to 95% (w/w), from 75% to 95% (w/w), or from 80% to 90% (w/w).

266. As I explained above in Section XI.D.3 [Ground IIA, [5]], Uhlmann discloses [5]. In the alternative, Uhlmann in combination with Palazzolo renders obvious [5].

267. **Water** “make[s] up to 100.0” “[p]ercent[] by weight” of the “Sun Milk O/W” formulation in Example 3 of Uhlmann. EX1004, Example 3, 8:23-26 (“All the given quantities, ratios and percentages relate to the weight and the overall volume and/or total weight of the preparations unless otherwise stated.”).

268. As I explained above in Section XI.D.1.iii [Ground IIA, [1B]], the other identified ingredients together total 32.8% (w/w) of the formulation, with an additional quantity of “perfume, preservative” indicated as “q.s.” EX1004, Example 3, 8:23-26. The notation “q.s.” stands for “quantum sufficit” or “quantum satis.” It was well-known that “q.s.” means “the amount which is enough” and has the

“standard pharmaceutical meaning of ‘as much as is sufficient,’” as determined by the supplier of that ingredient. *See, e.g.*, EX1006 (Alderson), [0045].

269. Palazzolo teaches that “perfume” and “preservative” were used only in limited amounts in these types of formulations. For example, the amount of “perfume” or fragrance in topical formulations was generally in the range of 0.01% (w/w) to 5.0% (w/w). *See, e.g.*, EX1005 (Palazzolo), [0011] (“Any of a wide variety of fragrances can be utilized ... with a range from about 0.01% by weight to about 5.0% by weight or more of the cosmetic composition.”). The amount of “preservative” in topical formulations was generally in the range of 0.01% (w/w) to 2% (w/w). *See, e.g.*, EX1005 (Palazzolo), [0010] (“The preservative is preferably in a range from about 0.01% by weight to about 2.0% by weight of the cosmetic composition...”); *see also* EX1007 (Hill), Appendix A, Appendix B.

270. A POSA would have been able to combine the teachings of Example 3 of Uhlmann with Palazzolo with a reasonable expectation of success because Palazzolo teaches that ***typical amounts*** of such “perfume” and “preservative” ranges from 0.01% (w/w) to 5% (w/w) and 0.01% (w/w) to 2% (w/w), respectively. EX1005 (Palazzolo), [0010]-[0011]. And, Uhlmann Example 3 teaches to use the sufficient quantity of “perfume” and “preservative” in the “Day-car[e] skin cream O/W” formulation. Therefore, it would have been a trivial combination to put in the

typical amounts of “perfume” and “preservative” to achieve the predictable result of a formulation that smells nicer and/or lasts longer.

271. If no “perfume” or “preservative” were present, *the water content in Example 3 of Uhlmann would be approximately 67.2% (w/w)*. If the “perfume” and “preservative” were present at their maximum typical levels disclosed by Palazzolo of about 5% (w/w) and 2% (w/w), respectively, *the water content in Example 3 of Uhlmann would be approximately 60.2% (w/w)*. Therefore, the water content in Example 3 ranges from about 60.2% (w/w) to 67.2% (w/w), which falls within the claimed “50% to 99% (w/w).”

272. As I explained in Paragraph 49, I understand that disclosure of a single point within a claimed range may render obvious that claimed range. Therefore, Uhlmann Example 3 in combination with Palazzolo renders obvious [5].

XII. Conclusion

273. In my opinion, the challenged claims 1–17 of the ’146 patent are unpatentable.

XIII. Availability for Cross-Examination

274. In signing this declaration, I recognize that the declaration will be filed as evidence in a case before the Patent Trial and Appeal Board of the United States Patent and Trademark Office. I also recognize that I may be subject to cross

examination in the case. If cross examination is required of me, I will appear for cross examination during the time allotted for cross examination.

XIV. Right to Supplement

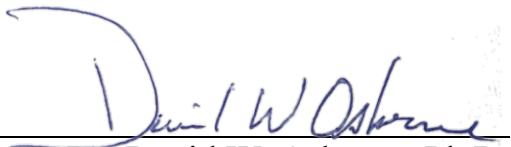
275. I reserve the right to supplement my opinions in the future to respond to any arguments that the Patent Owner may raise and to take into account new information as it becomes available to me.

XV. Jurat

276. 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 §1001 of Title 18 of the United States Code.

July 8, 2026

Date



Dr. David W. Osborne, Ph.D.

APPENDIX A

DAVID W. OSBORNE, Ph.D.

david.wade.osborne@gmail.com
970-691-3452

EDUCATION and TRAINING

- 2005 **Professional Degree in Chemistry (Honorary)**
University of Missouri-Rolla, Rolla, Missouri
- 1985 **Ph.D. in Physical Chemistry**
University of Missouri-Rolla, Rolla, Missouri
Research Advisor: Professor Stig E. Friberg
Dissertation: The interaction of a glyceridacid with lipids of the stratum corneum
- 1982 **Bachelor of Science in Chemistry (ACS Certified), Math Minor**
Southwest Missouri State University, Springfield, Missouri

PROFESSIONAL EXPERIENCE

2016-Present **DAVID W. OSBORNE PHD CONSULTING INC**

- 2016-Present **President**
Colorado S-Corporation formed in late August of 2016 providing consulting and educational services in pharmaceutical product development including intellectual property and serving as a fact/expert witness in Paragraph 4 litigations.
- Retained Consulting
Arcutis Biotherapeutics 2024-Present
Sudo Biosciences 2024-Present
Palvella Therapeutics 2025-Present
Concerto Biosciences 2025-Present
RenPharm 2025-Present
- Scientific Advisory Boards
Iolyx Therapeutics 2019-Present
Stratum Bio 2024-Present
ProPedix 2024-Present
- Fact/Expert Witness
Galderma Laboratories, L.P., et al. v. TOLMAR Inc.; N.D. Texas Case No. 09-CV-00400
- Galderma Laboratories, L.P., et al. v. TOLMAR, Inc. (Dist. Del. C.A. No. 10-45 (LPS) consolidated*
- LEO Pharma A/S v. TOLMAR Inc. (Dist. Del. C.A. No. 10-cv-269) (consolidated)*

Fougera Pharmaceuticals Inc. and Jagotec AG v. TOLMAR, Inc. (Dist. N.J. C.A. No. 10-2635 (KSH) (PS)

Anacor Pharmaceuticals, Inc. v. Valeant Pharmaceuticals International Inc. (JAMS Arbitration Reference No. 1100072088 order number 12)

Technical Expert for the Proprietor at the oral proceedings before the EU OPPOSITION DIVISION (July 23, 2015 at the European Patent Office, Munich Germany) in the Opposition of EP 2158900 B1 (Proprietor: TOLMAR Therapeutics, Inc.) in the name of: Generics [UK] Limited (trading as Mylan) and the subsequent February 14, 2019 Appeal no. T006/16-3.3.07.

BioDelivery Sciences International, Inc. and Arius Two, Inc. v. Actavis Laboratories UT, Inc. and Actavis, Inc. (Dist. Del. C.A. No. 1:16-cv-00175).

UCB, Inc et.al. v. Zydus Worldwide DMCC, et.al. Case No. 16-1023 (SLR).

Almirall, LLC v. Amneal Pharmaceuticals LLC, District of Delaware Case No. 1:19-cv-00658-LPS.

Amneal Pharmaceuticals LLC & Amneal Pharmaceuticals of New York, LLC v. Almirall, LLC, IPR2019-00207.

Conflict of Interest Companies—SolGel, Padagis and Quoin Pharmaceuticals.

2017-2023

ARCUTIS Biotherapeutics Inc

2018-2023

Chief Technical Officer

Developed 0.3% roflumilast cream for the treatment of psoriasis, 0.15% and 0.05% roflumilast cream for the treatment of atopic dermatitis, 0.3% roflumilast foam for the treatment of scalp psoriasis and seborrheic dermatitis, 0.3% ivarmacitinib (SHR0302) cream for the treatment of hand eczema and vitiligo, and 3% ivarmacitinib suspension for the treatment of alopecia areata. Arcutis had a successful IPO in January 2020.

2017-2018

Senior Vice President, Product Development

Venture capital (Frazier Healthcare) funded start-up virtual company developing topical dermatological products. First Arcutis employee with full time employment beginning on April 11, 2017.

2008-2016	TOLMAR Inc. (Retired in June 2016—TOLMAR had about 650 total employees with 105 employees reporting to the CSO) <i>Combined annual sales of developed products exceeded \$1.2 billion in 2015—The last full year of data prior to retiring from Tolmar in June 2016.</i>
2014-2016	Chief Scientific Officer Responsible for managing Formulation & Process Development, Analytical Development, Polymer Development, Clinical Development, and Tech Services. In addition to continuing development of generic topical and specialty injectable products, TOLMAR developed a pipeline of proprietary dermatology products and in-licensed a specialty injectable technology (one active advanced into the clinic prior to 2017). Worked closely with TOLMAR and external patent attorneys concerning intellectual property. Implemented a QbD adoption campaign.
2008-2014	Vice President, Product Development Responsible for managing the Formulations Development, Analytical Development, Clinical Development, and Regulatory groups within TOLMAR. Between October 2008 and March 2010, this team filed five First-to-File topical ANDAs requiring clinical endpoint bioequivalence studies. All five First-to-File ANDAs successfully navigated litigation, were approved and launched. In addition to generic topical dermatology products (ANDAs filed: 2 in 2009, 3 in 2009, 1 in 2010, 1 in 2011, 1 in 2012, 6 in 2013, 1 in 2014, 2 in 2015, and 2 in 2016), generic specialty injectable product development was added as a second product development focus in 2010.
2003-2008	Dow Pharmaceutical Sciences Vice President, Product Development Managed Formulations & Product Development (FPD), Clinical Labeling, Skin Biology Laboratory, and the Internal Development Program (IDP) at Dow. FPD developed dermatological products from pre-formulation through scale-up and commercial manufacturing for Dow clients. Clinical Labeling provided randomization, labeling and product kits for clinical studies. The Skin Biology Laboratory completed in-vitro skin and membrane permeation studies to guide formulation selection. IDP selected development opportunities, established defensible intellectual property, and coordinated initial development of products that were then out licensed to marketing partners (Valeant acquired DPSI and the IDP pipeline in 2008 for \$285 million).

1993-2003

Atrix Laboratories, ViroTex Corporation

(ViroTex was acquired by Atrix on November 30, 1998)

2002 – 2003

Vice President, Dermatology Division, Atrix

- Responsible for establishing Atrix as a leading developer of generic and proprietary topical formulations and forward integrating this business unit to become a specialty pharmaceutical company focused on Dermatology.

Operational duties included:

- Selection and Management of generic product development with an ever-increasing number of annual ANDA filings (2 in 2001, 5 in 2002, and 7 in 2003). Marketing partner for this program was Geneva (Sandoz/Novartis).
- Directed all proprietary dermatology product development including being chairman of the Joint Development Management Committee between Atrix and Fujisawa that directed the development of 5% Aczone Topical Gel. The dapsone development program had a 2003 budget of \$18 Million.
- Directed all business development activities related to dermatology products and provide a strategy for the creation of a specialty pharmaceutical company focused on Dermatology.
- Managed both proprietary and generic analytical methods development and validation groups for all Atrix products
- **Responsible for overseeing worldwide patenting of all dermatology related Atrix intellectual property.**

1998 – 2002

Vice President, Pharmaceutical Development, Atrix

- Transition of ViroTex technologies into Atrix following the November 30, 1998 acquisition. Managed product and analytical development groups for all products. Managed approximately 20-25% of Atrix Employees for this period of time

Operational duties included:

- Oversight of patent applications
- Product development from formulation selection to commercial scale-up
- Lead analytical methods development and validation of Eligard 1-month (NDA approved January 2002), 3-month (NDA approved April 2002), 4-month (NDA approved February 2003) and 6-month (NDA approved December 2004) products.

- **Project Team Leader for Dapsone Topical Gel**

Laboratory responsibilities included:

- New dermatological and mucosal product development
- Novel delivery system evaluation
- Transfer of Atrigel products from Drug Delivery to Process Development

1993 – 1998

Vice President, Research & Development, ViroTex

(3rd Employee, ~ 22 employees in R&D when acquired)

- Designed and equipped a product development laboratory, quality control laboratory, virology/microbiology laboratory and a GMP manufacturing area.

Operational duties included:

- Oversight of patent applications, contract manufacture of both OTC and Rx products, contract toxicology testing, animal pharmacology/efficacy testing, human clinical trials.

Laboratory responsibilities included:

- New product research, topical drug delivery research, analytical methods development, product stability testing, quality control release of raw materials, and antiviral mechanism of action studies.

1991 – 1993

**Calgon Vestal Laboratories, Subsidiary of MERCK & CO.
(Product Development ~45 employees)**

Group Leader, Skin Care

Development of:

- Routine and high-risk handwashing products for preventing the spread of infection.
- Development of skin conditioning products for maintaining healthy, normal and aging skin in hospitals and nursing homes.
- Development of topically applied products to treat diseased skin or relieve skin discomfort.
- Development efforts included evaluation of potential actives/products for licensing, formulation design including stability and efficacy testing, manufacture of GLP and GMP supplies for use in toxicological evaluations, and support of clinical studies.

1985-1991

THE UPJOHN COMPANY (~7,000 employees)

1988 – 1991

Research Scientist, Drug Delivery R&D-Specialty Products

- Areas of specialization included: topicals, transdermal delivery systems (patches), and suppositories.
- Typical activities included: pre-formulation characterization, bulk drug stability, formulation design, final formulation stability, Phase I, II and III clinical supply manufacture, GLP pathology/toxicology supply manufacture and preparation of the corresponding sections of the IND and NDA.

1985 – 1988

Research Scientist, Pharmaceutical Manufacturing Technical Services--Group was reorganized into Drug Development R&D in January 1988

- Areas of specialization included: topicals
- Responsible for scale-up, manufacturing phase-in and marketed product support including validation of packaging and raw material changes.

COMMERCIALIZED PRODUCTS

Inventor/Developer

PrimaHex Foam (Approved "NDA" marketed by CV Ltd)
Viractin Gel (OTC marketed by Combe Inc)
Orajel Ultra (OTC marketed by Del Laboratories)
Eucalyptamint 2000 (OTC marketed by Heratige)
Aczone (5% Gel Approved NDA marketed by Allergan)
Onsolis (BEMA-Fentanyl NDA marketed by Meda Pharmaceuticals)
Zoryve (0.3% Cream Approved NDA marketed by Arcutis)
Zoryve (0.3% Foam Approved NDA marketed by Arcutis)
Zoryve (0.15% Cream Approved NDA marketed by Arcutis)

Named Inventor on Orange Book listed patent

Bunavail (BEMA-Buprenorphine and Naloxone) US 6,159,498 and 7,579,019
Belbuca (BEMA-Buprenorphine) US 6,159,498 and 7,579,019

Developer

Cleocin Vaginal Ovules (Approved NDA marketed by Pfizer)
Viractin Cream (OTC marketed by Combe Inc)
Aloe Vestal Antifungal Ointment (OTC marketed by ConvaTec)
Eligard 1 month (Approved NDA marketed by TPI, Astellas, and others)
Eligard 3 month (Approved NDA marketed by TPI, Astellas, and others)
Eligard 4 month (Approved NDA marketed by TPI, Astellas, and others)
Eligard 6 month (Approved NDA marketed by TPI, Astellas, and others)
MetroGel 1% (Approved NDA marketed by Galderma)
Clobex Spray (Approved NDA marketed by Galderma)
Desonate Gel (Approved NDA marketed by Bayer AG)
Acanya Gel (NDA marketed by Arcutis/Valeant)
Orajel Protective Mouth Sore Discs (OTC marketed by Del Laboratories)
Jublia Topical Solution 10% Efinaconazole (NDA marketed by Valeant)

Developer ANDA

Erythromycin Benzoyl Peroxide Gel (AB rated generic to **ERYTHROMYCIN** Sandoz)
Fluticasone Cream (AB rated generic to **CUTIVATE** Sandoz)
Lidocaine/Prilocaine Cream (AB rated generic to **EMLA** Impax)
Mometasone Ointment 0.1% (AB rated generic to **ELOCON** Impax)
Betamethasone Dipropionate Cream (AB rated generic to **DIPROLENE AF** Impax)
Ketoconazole Shampoo 2% (AB rated generic to **NIZORAL** Sandoz)
Metronidazole Topical Gel 1% (AB rated generic to **METROGEL 1%** Impax)
Metronidazole Vaginal Gel (AB rated to **METROGEL-VAGINAL** Sandoz)
Mometasone Cream (AB rated generic to **ELOCON** Impax)
Mometasone Lotion (AB rated generic to **ELOCON** Impax)
Clindamycin Benzoyl Peroxide Gel (AB rated generic to **BENZACLIN** Mylan)
5% Imiquimod Cream (AB rated generic to **ALDARA** Impax)
Calcipotriene Cream (AB rated generic to **DOVONEX** Sandoz)
Diclofenac Gel, 3% (AB rated generic to **SOLOLON** Impax)
Calcipotriene 0.005% and BMDP Ointment (AB rated generic to **TACLONEX** Sandoz)
Adapalene Gel, 0.03% (AB rated generic to **DIFFERIN** Sandoz)
Clindamycin Benzoyl Peroxide Gel (AB rated generic to **DUAC** Impax)
Naftifine Cream 2% (AB rated generic to **NAFTIN** Impax)

Clindamycin Benzoyl Peroxide Gel (AB rated generic to **ACANYA** Impax)
Acyclovir Ointment 5% (AB rated generic to **ZOVIRAX** Impax)
Azeleic Acid Gel 15% (AB rated generic to **FINACEA** Impax)

PROFESSIONAL SOCIETIES

American Chemical Society
American Academy of Dermatology
American Association of Pharmaceutical Scientists (inactive)
The Society for Investigative Dermatology (inactive)
Skin Pharmacology Society (inactive)

PROFESSIONAL ACTIVITIES AND HONORS

6 Sept 2024	NASDAQ Bell Ringing Ceremony for Arcutis Biotherapeutics
2018-present	Member, Board of Trustees for the Missouri State University Foundation
2016-2019	Chair, Q3 Working Group
2015-2016	Colorado State University Advisory Board Member for developing a Professional Science Master's degree in Biodata Analytics in the Department of Biochemistry and Molecular Biology
2011-2015	Member of the UMKC School of Pharmacy Research Advisory Council
2005	Chair AAPS Dermatopharmaceutics Focus Group
2004	Faculty for the "Society for Investigative Dermatology Basics of Skin: Pharmaceutics and Pharmacology" Course.
2003-present	Founding Member of the Missouri State University Chemistry Department Board of Advisors
2002	Outstanding Young Alumni Award, Southwest Missouri State University.
1995	Organizer of the COLL Division Symposium "Surfactants and Association Colloids: Symposium in Honor of Stig Friberg", Anaheim ACS Meeting.
1993-1998	Adjunct Associate Professor of Pharmaceutics, University of Houston, College of Pharmacy.
1992-1995	Founding North American Editor of the Elsevier Journal Colloids & Surfaces B: Biointerfaces Editor of Volumes 1-4.
1992-1994	Adjunct Assistant Professor of Pharmaceutics, Saint Louis College of Pharmacy.
1992	Co-Organizer of the 66 th Colloid and Surface Science Symposium symposia on "Surfactants: Isotropic Solutions and Liquid Crystals."

1992	Chairman of the American Chemical Society Division of Colloid and Surface Science
1991	Chairman Elect of the American Chemical Society Division of Colloid and Surface Science.
1990	Vice Chairman of the American Chemical Society Division of Colloid and Surface Science.
1990	Co-Chairman of the COLL Division Symposium "Surfactants and Association Colloids: Zwitterionic Surfactants," Boston ACS Meeting.
1987	Co-Organizer of the 61 st Colloid and Surface Science Symposium symposia on "Topical Drug Delivery Formulations."
1986-1989	National Meeting Secretary (Program Chairman) for the American Chemical Society Division of Colloid and Surface Science.
1986-1989	Coordinator and Host of the First (1986), Second (1987), Third (1988) and Fourth (1989) Kalamazoo Section of the ACS Undergraduate Symposium.
1983-1985	Coordinator and Host of the First (1984) and Second (1985) South Central Missouri Section of the ACS Undergraduate Symposium.

PATENTS

48 Issued US Patents

12,257,242	Inhibition of Crystal Growth of Roflumilast. Inventor: David W. Osborne. Assignee Arcutis Biotherapeutics, Inc.
12,220,409	Roflumilast Formulations with an Improved Pharmacokinetic Profile. Inventor: David W. Osborne. Assignee Arcutis Biotherapeutics, Inc.
12,144,802	Pharmaceutical Compositions of Roflumilast and Solvents Capable of Dissolving High Amounts of the Drug. David W. Osborne, Babak N. Tofig, Frank Watanabe. Assignee Arcutis Biotherapeutics, Inc.
12,083,122	Laureth-4 Containing Topical Formulations. David W. Osborne. Assignee Arcutis Biotherapeutics, Inc.
12,053,481	Compositions and Methods for Deep Dermal Drug Delivery. David W. Osborne, Babak N. Tofig. Assignee Arcutis Biotherapeutics, Inc.
12,042,487	Method for Reducing Side Effects from Administering Phosphodiesterase-4 Inhibitors. David W. Osborne. Assignee Arcutis Biotherapeutics, Inc.

12,016,848	Roflumilast Formulations with an Improved Pharmacokinetic Profile. Inventor: David W. Osborne. Assignee Arcutis Biotherapeutics, Inc.
12,011,437	Roflumilast Formulations with an Improved Pharmacokinetic Profile. Inventor: David W. Osborne. Assignee Arcutis Biotherapeutics, Inc.
12,005,051	Topical Roflumilast Formulation Having Improved Delivery and Plasma Half Life. Inventor: David W. Osborne. Assignee Arcutis Biotherapeutics, Inc.
11,992,480	Method for Reducing side effects From Administration of Phosphodiesterase-4 inhibitors. Inventors: David W. Osborne, Howard Welgus. Assignee Arcutis Biotherapeutics, Inc.
11,819,496	Topical Roflumilast Formulation Having Improved Delivery and Plasma Half-Life. Inventor: David W. Osborne. Assignee Arcutis Biotherapeutics, Inc.
11,793,796	Means for Inhibiting Crystal Growth. Inventor: David W. Osborne. Assignee Arcutis Biotherapeutics, Inc.
11,730,740	Laureth-4 Containing Topical Formulations. Inventor: David W. Osborne. Assignee Arcutis Biotherapeutics, Inc.
11,707,454	Topical Roflumilast Formulation Having Antifungal Properties. Inventors: David R. Berk, Patrick E. Burnett, Saori Kato, David W. Osborne. Assignee Arcutis Biotherapeutics, Inc.
11,628,177	Compositions and Methods for Deep Dermal Drug Delivery. Inventors: David W. Osborne, Babak N. Tofig. Assignee Arcutis Biotherapeutics, Inc.
11,534,493	Pharmaceutical Compositions of Roflumilast in Aqueous Blends of Water-miscible, Pharmaceutically Acceptable Solvents. Inventor: David W. Osborne. Assignee Arcutis Biotherapeutics, Inc.
11,129,818	Topical Roflumilast Formulation Having Improved Delivery and Plasma Half Life. Inventors: David W. Osborne, Bhaskar Chaudhuri, Archie W. Thurston, Jr. Assignee Arcutis Biotherapeutics, Inc.
10,940,142	Inhibition of Crystal Growth of Roflumilast. Inventor: David W. Osborne. Assignee: Arcutis Biotherapeutics, Inc.

10,441,530	Skin Penetration Enhancing Systems for Polar Drugs. Inventors: Pramod P. Sarpotdar, Arturo J. Angel, Inigo Saenz De Tegada Gorman, Pedro Cuevas Sanchez, David W. Osborne. Assignee: AmDerma Pharmaceuticals.
10,172,841	Inhibition of Crystal Growth of Roflumilast. Inventor: David W. Osborne. Assignee: Arcutis Biotherapeutics, Inc.
10,111,956	Corticosteroid Compositions. Inventors: Robert W. Lathrop, David W. Osborne. Assignee: TOLMAR.
10,105,354	Inhibition of Crystal Growth of Roflumilast. Inventor: David W. Osborne. Assignee: Arcutis Biotherapeutics, Inc.
9,907,788	Inhibition of Crystal Growth of Roflumilast. Inventor: David W. Osborne. Assignee: Arcutis Biotherapeutics, Inc.
9,895,359	Inhibition of Crystal Growth of Roflumilast. Inventor: David W. Osborne. Assignee: Arcutis Biotherapeutics, Inc.
9,884,050	Inhibition of Crystal Growth of Roflumilast. Inventor: David W. Osborne. Assignee: Arcutis Biotherapeutics, Inc.
8,143,227	Azithromycin for Treatment of Skin Disorders. Inventors: Gordon J. Dow, Bhaskar Chaudhuri, David W. Osborne, Barry Calvarese. Assignee: Dow Pharmaceutical Sciences.
8,124,123	Controlled Release Azithromycin Solid Dosage Forms. Inventors: Radhakrishnan Pillai, Pramod Sarpotdar, David W. Osborne, Gordon J. Dow. Assignee: Valient.
7,704,959	Azithromycin for the treatment of nodular acne. Inventors: David W. Osborne, Gordon J. Dow, Bhaskar Chaudhuri, Barry Calvarese. Assignee: Valient.
7,579,019	Pharmaceutical Carrier Device Suitable for Delivery of Pharmaceutical Compounds to Mucosal Surfaces. Inventors: Gilles H. Tapolsky, David W. Osborne. Assignee: Arius Two Inc.
7,399,462	Protectant for UV-induced skin damage. Inventor: David W. Osborne. Assignee: QLT, USA.
7,326,408	Topical Acne Vulgaris Medication with a Sunscreen. Inventors: Arturo Angel, David W. Osborne, Gordon J. Dow. Assignee: Dow Pharmaceutical Sciences.

7,252,816	Topical Acne Vulgaris Medication with a Sunscreen. Inventors: Arturo Angle, David W. Osborne, Gordon J. Dow. Assignee: Dow Pharmaceutical Sciences.
6,620,435	Compositions for Topical Application of Therapeutic Agents. Inventor: David W. Osborne. Assignee: ViroTex Corporation.
6,432,415	Pharmaceutical Gel and Aerosol Formulations and Methods to Administer the Same to Skin and Mucosal Surfaces. Inventors: David W. Osborne, Russell J. Mumper. Assignee: Atrix Laboratories.
6,355,657	System for Percutaneous Delivery of Opioid Analgesics. Inventor: David W. Osborne. Assignee: Atrix Laboratories
6,290,984	Pharmaceutical Preparation Applicable to Mucosal Surfaces and Body Tissues. Inventors: Gilles H. Tapolsky and David W. Osborne. Assignee: ViroTex Corporation.
6,159,498	Bioerodible Film for Delivery of Pharmaceutical Compounds of Mucosal Surfaces. Inventors: Gilles H. Tapolsky, David W. Osborne. Assignee: ViroTex Corporation
6,103,266	Pharmaceutical Gel Preparation Applicable to Mucosal Surfaces and Body Tissues. Inventors: Gilles H. Tapolsky, David W. Osborne. Assignee: ViroTex Corporation
6,060,085	Compositions and Methods for Topical Application of Therapeutic Agents. Inventor: David W. Osborne. Assignee: ViroTex Corporation
5,955,097	Pharmaceutical Preparation Applicable to Mucosal Surfaces and Body Tissues. Inventors: Gilles H. Tapolsky, David W. Osborne. Assignee: ViroTex Corporation.
5,906,808	Process of Preparing a Topical Antimicrobial Cleanser. Inventors: David W. Osborne, Fred Kirchner. Assignee: Calgon Vestal, Inc.
5,905,092	Topical Antibiotic Composition Providing Optimal Moisture Environment for Rapid Wound Healing that Reduces Skin Contraction. Inventors: David W. Osborne, Meidong Yang. Assignee: ViroTex Corporation
5,863,560	Composition and Methods for Topical Application of Therapeutic Agents. Inventor: David W. Osborne, Assignee: ViroTex Corporation

5,800,832	Bioerodible Film for Delivery of Pharmaceutical Compounds to Mucosal Surfaces. Inventors: Gilles H. Tapolsky, David W. Osborne, Assignee: ViroTex Corporation.
5,776,430	Topical Antimicrobial Cleanser Containing Chlorhexidine Gluconate and Alcohol. Inventors: David W. Osborne, Fred Kirchner, Assignee: Calgon Vestal, Inc.
5,762,917	Method and Composition for Cleansing Wounds with Minimal Cytotoxicity for Minimal Scarring. Inventor: David W. Osborne, Assignee: ViroTex Corporation.
5,631,301	Topical Antibiotic Composition Providing Optimal Moisture Environment. Inventor: David W. Osborne, Assignee: ViroTex Corporation.
DO350601	Vaginal Drug Delivery Insert. Inventor: David W. Osborne, Charles R. Whitman. Assignee: The Upjohn Company

PUBLISHED PATENT APPLICATIONS

20100304426	Analytical Methods for Measuring Synthetic Progesterone. Inventors: David Osborne, Paul Winkler. Filed May 26, 2010.
20090182004	Imiquimod Formulation. Inventors: Gareth Winckle, David W. Osborne. Filed January 14, 2009.
20080268021	Adhesive bioerodible ocular drug delivery system. Inventors: Stephen L. Warren, David W. Osborne, Richard Holl. Filed June 24, 2008.
20070207107	Silicone based emulsions for topical drug delivery. Inventors: Gareth Winkle, David W. Osborne, Gordon J. Dow, Assignee: Not Disclosed. Filed January 30, 2007.
20060204526	Emulsive composition containing Dapsone. Inventors: Robert W. Lathrop, David W. Osborne. Assignee: Atrix Laboratories. Filed February 13, 2006. (11/352,935)

FEDERAL GRANT SUPPORT

SBIR Grant No. R44 AI058358-02 (NIAID). Topical Use of TEAC to Treat Cutaneous Viral Infection. \$915,160 grant awarded August 2005.

SBIR Grant No. R43 AI63706-01 (NIAID). P-113: A Novel Peptide Therapy for Vaginal Candidiasis. \$86,650 grant awarded March 2005.

SBIR Grant No. R43 AR43531-01AI (NIAMS). 1% Dapsone Topical Gel for Dermatitis Herpetiformis. \$99,844 grant awarded April 1997.

SBIR Grant No. R43 AI38158-01 (NIAID). Optimized Dermal Delivery of Tetracaine for HSV-2 Lesions. \$99,970 grant awarded October 1995.

GRADUATE COMMITTEE MEMBER

Missouri State University, Graduate College

Melinda Sutton, MSci, Chemistry Characterization of Lamellar Liquid Crystal Emulsifiers in Topical Creams Containing a Novel Solvent. April 2021.

Rush University Medical Center, Clinical Pharmacology

Kathleen C. Heneghan, PhD Topical Loperamide for Pain Reduction.
June 2015.

University of Houston, College of Pharmacy

Adwoa O. Nornoo, PhD Microemulsion formulations of Paclitaxel.
August, 1998.

Robert O. Kumi, PhD Formulation Development, Preclinical Pharmacokinetics and Efficacy of Liposomes Incorporating Annamycin, a Lipophilic Analog of Doxorubicin.
November 1997.

Dong Liang, PhD Liposomal Formulation of Cefazolin.
June 1995.

PUBLICATIONS [Citations July 2023]

1. "Solubilization of Calcium Dodecyl Sulfate in a Micellar Solution and in Lamellar Liquid Crystal," S.E. Friberg and D.W. Osborne, *Colloids and Surfaces*, 12, 357-365 (1984). [10]
2. "X-Ray Diffraction Study of Human Stratum Corneum," S.E. Friberg, D.W. Osborne and T.L. Tombridge, *J. Society Cosmetic Chemists*, 36, 349-354 (1985). [7]
3. "Cooperative Education – A New Perspective," David Osborne, *ACS Co-Op Newsletter*, 6(1), 5 (1985). [0]

4. "Diacid – A Non-Traditional Hydrotrope," S.E. Friberg, D.W. Osborne and T.D. Flaim, Symposium Proceedings, XVI Congress of the Spanish Committee on Surfactants, Barcelona, Spain, 1985. [0]
5. "Small Angle X-ray Diffraction Patterns of Stratum Corneum and a Model Structure For Its Lipids," S.E. Friberg and D.W. Osborne, *Journal of Dispersion Science and Technology*, 6(4), 485-495 (1985). [117]
6. "Viscosities of Solutions of Lithium Chloride in Water-Dimethyl Sulfoxide Mixtures at 25, 35 and 45 C," D.W. Osborne and James F. O'Brien, *J. Chemical Engineering Data* 31, 317-320 (1986). [2]
7. "A Lamellar Liquid Crystal As An In Situ Surface Balance II. The Conformation of 2-(alkoxyloxy)-1[(alkoxyloxy)methyl] – heptyl-7-(4-heptyl-5, 6dicarboxyl-2-cyclohexene-2-yl)heptanoate," S.E. Friberg and D.W. Osborne, *Colloid and Polymer Sci.* 264, 182-184 (1986). [4]
8. "The Mechanism of Hydrotrope Action of a Dicarboxylic Acid," S.E. Friberg, S.B. Rananavare and D.W. Osborne, *J. Colloid Interface Sci.*, 109, 487-492 (1986). [37]
9. "Interactions of a Model Skin Surface Lipid with a Modified Triglyceride," S.E. Friberg and D.W. Osborne, *J. American Oil Chemical Society*, 63, 123-126 (1986). [15]
10. "Computational Methods for Predicting Skin Permeability," D.W. Osborne, *Pharmaceutical Manufacturing*, 3(4), 41-48 (1986). [13]
11. "The Structure of Stratum Corneum Lipids and its Cosmetical Implications," S.E. Friberg, D.W. Osborne and L. Goldsmith, Symposium Proceedings I.F.S.C.C. 14th Congress – Barcelona, Spain, 208 (1986). [0]
12. "Interaction of a Model Epidermal Lipid with a Vegetable Oil Adduct," S.E. Friberg and D.W. Osborne, *J. Disp. Sci. Tech.*, 8(3), 249-258 (1987). [7]
13. "Role of Stratum Corneum Lipids as Moisture Retaining Agent," D.W. Osborne and S.E. Friberg, *Journal of Dispersion Science and Technology*, 8(2), 173-179 (1987). [34]
14. "Evaluation of the Usefulness of Cloud Point Elevation to Predict Transdermal Delivery Enhancers," D.W. Osborne. *Drug Development and Industrial Pharmacy*, 13(3), 391-403 (1987). [0]
15. "Hard Water and Skin Irritation," D.W. Osborne, *J. Amer. Acad. Dermatol.*, 16(6), 1263-1264 (1987). [5]
16. "Automation of Surfactant Phase Behavior Determination by Laboratory Robotics," C.V. Pesheck, K.J. O'Neill and D.W. Osborne, *J. Colloid Interface Sci.* 119, 289-290 (1987). [5]
17. "A Small-Angle Neutron-Scattering Study of a Non-Aqueous Three Component Microemulsion," S.B. Rananavare, A.J.I. Ward, D.W. Osborne, S.E. Friberg and H. Kaiser, *J. Phys. Chem.*, 92, 5181-5183 (1988). [5]

18. "The Penetration of 2-(alkoxyloxy)-1[(alkoxyloxy)methyl]-ethyl-7-(4-heptyl-5, 6-dicarboxyl-2-cyclohexene-2-yl) heptanoate into Human Stratum Corneum," S.E. Friberg, L.B. Goldsmith, D.W. Osborne and R. Brown, *J.Soc.Cosmet.Chem.*, 39, 283-290 (1988). [2]
19. "Alcohol-free Microemulsions," D.W. Osborne, C.A. Middleton and R.L. Rogers, *J.Disp.Sci.Tech.*, 9, 415-423 (1988). [46]
20. "The Effect of the Monosodium Salt of a C₂₁ Dicarboxylic Acid Hydrotrope on Biosurfactant Bilayers: Transdermal Delivery Considerations," D.W. Osborne, *Colloids & Surfaces*, 30, 13-23 (1988). [12]
21. "Microemulsions as Topical Drug Delivery Vehicles. I. Characterization of a Model System," D.W. Osborne, A.J.I. Ward and K.J. O'Neill, *Drug Development and Industrial Pharmacy*, 14, (9), 1203-1219 (1988). [72]
22. "Laboratory Robotics for the Personal Care Industry: Phase Behavior Studies," D.W. Osborne, C.V. Pesheck, K.J. O'Neill, A.J.I. Ward and M. El-Nokaly. *Cosmetics and Toiletries*, 103 (November), 53-62 (1988). [0]
23. "The Skin Softening Properties of Maleated Soybean Oil," D.W. Osborne, *Cosmetics & Toiletries*, 103 (August), 57-70 (1988). [6]
24. "Phase Studies of Zwitterionic Surfactants: Alkyl Sulphobetaines," P.G. Faulkner, A.J.I. Ward and D.W. Osborne, *Langmuir* 5(4), 924-926 (1989). [12]
25. "Theoretical Considerations of Transdermal Drug Delivery," D.W. Osborne, *Drug News & Perspectives*, 2(6), 329, (1989). [0]
26. "Influence of Skin Surface Lipids on Topical Formulations," D.W. Osborne and D.A. Hatzenbuehler, in Topical Drug Delivery Formulations, D.W. Osborne and A.H. Amann eds., Marcel Dekker, New York, 69-86 (1990). [23]
27. "Computational Methods that Aid Topical Drug Design," D.W. Osborne, in Topical Drug Delivery Formulations, D.W. Osborne and A.H. Amann eds., Marcel Dekker, New York, 109-126 (1990). [0]
28. "Surfactant Association Colloids as Topical Drug Delivery Vehicles," D.W. Osborne and A.J.I. Ward, in Topical Drug Delivery Formulations, D.W. Osborne and A.H. Amann eds., Marcel Dekker, New York, 349-379 (1990). [19]
29. "The Use of Phase Behavior and Laboratory Robotics For The Optimization of Pharmaceutical Topical Formulations," D.W. Osborne, Topical Drug Delivery Formulations, D.W. Osborne and A.H. Amann eds., Marcel Dekker, New York, 143-195 (1990). [1]
30. "Stratum Corneum Structure and Transport Properties," S.E. Friberg, I. Kayali, M. Margosiak, D.W. Osborne and A.J.I. Ward, in Topical Drug Delivery Formulations, D.W. Osborne and A.H. Amann eds., Marcel Dekker, New York, 29-45 (1990). [16]

31. "Microemulsions as Topical Drug Delivery Vehicles: In-Vitro Transdermal Delivery Studies of a Model Hydrophilic Drug," D.W. Osborne, A.J.I. Ward, and K.J. O'Neill. *J. Pharm. Pharmacol.* 43, 451-454 (1991). [197]
32. "Use of a Lamellar Liquid Crystal as a Matrix to Follow Free Radical Initiated Lipid Peroxidation," D.W. Osborne, O.C. Donoghue, J.M. Braugher, A.J.I. Ward. *Langmuir*, 7, 323-326 (1991). [0]
33. "Evaluation of Cefmetazole Rectal Suppository Formulations," E. Novak, D.W. Osborne, L.E. Matheson, E.L. Parrott, J.L. Lach, W.B. Morrison, *Drug Dev. Ind. Pharm.* 17(3), 373-389 (1991). [2]
34. "Dioctyl Sodium Sulfosuccinate-Sorbitan Monolaurate Microemulsions," D.W. Osborne, C.V. Pesheck, R.J. Chipman, in Microemulsions and Emulsions In Foods, M. ElNokaly, and D. Cornell eds., ACS Symposium Series 448, American Chemical Society, Washington DC, 62-79 (1991). [4]
35. "Symposium on Zwitterionic Surfactants: Preface," D.W. Osborne, A.J.I. Ward, *Langmuir*, 7, 840-841 (1991). [2]
36. "Phase Behavior Characterization of Propylene Glycol, White Petrolatum, Surfactant Ointments," D.W. Osborne, *Drug Development and Industrial Pharmacy*, 18, 1883-1894 (1992). [3]
37. "A Computational Method for Predicting Optimization of Prodrugs or Analogs for Percutaneous Delivery," D.W. Osborne, W.J. Lambert, in Prodrugs for Dermal Delivery, K.B. Sloan ed., Marcel Dekker, New York, 163-178 (1992). [4]
38. "Hydrotrophy and Skin Penetration Enhancement," A.J.I. Ward and D.W. Osborne, in Pharmaceutical Skin Penetration Enhancement, J. Hadgraft and K.A. Walters eds., Marcel Dekker, New York, 365-388 (1993). [0]
39. "Phase Behavior Characterization of Ointments Containing Lanolin or a Lanolin Substitute," D.W. Osborne, *Drug Development and Industrial Pharmacy*, 19, 1283-1302 (1993). [7]
40. "Preformulation characterization of Topical Ibuprofen Piconol", C.V. Pesheck, D.W. Osborne, *Drug Dev. Ind. Pharm.* 19, 1889-1902 (1993). [0]
41. "Lyotropic Liquid Crystals as Topical Drug Delivery Vehicles", D.W. Osborne, A.J.I. Ward, *Int'l J. of Pharm Advances* 1 (1), 38-45 (1995). [0]
42. "Skin Penetration Enhancers Cited in the Technical Literature" D.W. Osborne, J.J. Henke, *Pharmaceutical Technology* 21 (11), 58-66 (1997). [42]
43. "A Double-Blind, Placebo-Controlled Study of Topical Tetracaine in the Treatment of Herpes Labialis" L. H. Kaminester, R. Pariser, R. J. Pariser, D. M. Pariser, J. S. Weiss, J. S. Shavin, L. Landsman, H. G. Haines, D. W. Osborne. *J. Amer. Acad. Dermatol.* 41 (6), 996-1001 (1999). [30]

44. "Parenteral microemulsion of paclitaxel: Formulation, pharmacokinetics and cytotoxicity in cancer cell line" A.O. Nornoo, D.W. Osborne, J.R. Chen, D.S.-L. Chow. *Proc. Control. Rel. Soc.* 26, 1080-1081 (1999). **[0]**
45. "Pharmacokinetic Profiles in Rats after Intravenous, Oral or Dermal Administration of Dapsone" D. R. Helton, D. W. Osborne, S. K. Pierson, M. H. Buonarati, R. A. Bethem. *Drug Metabolism and Disposition* 28 (8), 925-929 (2000). **[24]**
46. "Cremophor-free intravenous microemulsions for paclitaxel. I: Formulation, cytotoxicity and hemolysis" A.O. Nornoo, D.W. Osborne, D.S.-L. Chow *Int. J. Pharma.* 349(1-2), 108-116 (2008). **[130]**
47. "Review of Changes in Topical Drug Product Classification." D.W. Osborne, *Pharm. Tech.* 32 (10), 66-74 (2008). **[10]**
48. "Gel Formulation Containing Mixed surfactant and Lipids Associating with Carboplatin" K.A. Woll, E.J. Schuchardt, C.R. Willis, C.D. Ortengren, N. Hendricks, M. Johnson, E. Gaidamauskas, B. Baruah, A.C. Sostarecz, D.R. Worley, D.W. Osborne, D.C. Crans *Chemistry & Biodiversity* 8(12),2195-2210 (2011). **[4]**
49. "Diethylene glycol monoethyl ether: an emerging solvent in topical dermatology products" D.W. Osborne, *J. Cosmet. Dermatol.* 10, 324-329 (2011). **[67]**
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51. "Impact of Quality by Design on Topical Product Excipient Suppliers Part II. Reasonable Expectations" D.W. Osborne, *Pharmaceutical Technology*, 40(11), 30-33 (2016). **[0]**
52. "Formulating Topical Products Containing Live Microorganisms as the Active Ingredient" J. Carbol, P.I. Tan, Y. Varma and D.W. Osborne, *Pharmaceutical Technology* 42(3), 32-36 (2018). **[10]**
53. "Skin Penetration and Permeation Properties of TRANSCUTOL® - Neat or Diluted Mixtures" D.W. Osborne and J. Musakhanian, *AAPS Pharm SciTech.* 19(8):3512-3533 (2018) DOI: 10.1208/s12249-018-1196-8 **[120]**
54. "Characterization of a Liquid Crystal Stabilized Pharmaceutical Oil-in-Water Emulsion Optimized of Skin Delivery" M.J. Sutton, D.W. Osborne, K. Dahl, V. Bax, and G.A. Schick, *Journal of Cosmetics, Dermatological Sciences and Applications*, 8(4):207-217 (2018) DOI: 10.4236/jcdsa.2018.84022. **[7]**
55. "Determination of Particle Size and Microstructure in Topical Pharmaceuticals" D.W. Osborne, K. Dahl and H. Parikh in The Role of Microstructure in Topical Drug Product Development, Nigel Langley, Bozena Michniak-Kohn and David W. Osborne, eds., Springer International Publishing AG, AAPS Advances in Pharmaceutical Sciences Series, Volume 36, pages 89-106 (2019). **[5]**
56. "Quality Assessment of API in Semisolid Topical Drug Products" K. Wu, Y-L. Hsieh, T Yeon and D.W. Osborne in The Role of Microstructure in Topical Drug Product

Development, Nigel Langley, Bozena Michniak-Kohn and David W. Osborne, eds., Springer International Publishing AG, AAPS Advances in Pharmaceutical Sciences Series, Volume 36, pages 109-154 (2019). [8]

57. "Roflumilast Cream Improves Signs and Symptoms of Plaque Psoriasis: Results from a Phase 1/2a Randomized, Controlled Study" K.A. Papp, M. Gooderham, M. Droege, C. Merritt, D.W. Osborne, D.R. Berk, A. Thurston, V.H. Smith and H. Welgus, J. Drugs Dermatol 19(8):734-740 (2020) DOI: 10.36849/JDD.2020.5370. [13]
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66. "Understanding microemulsions and nanoemulsions in (trans)dermal delivery" Jasmine Musakhanian and David W. Osborne. AAPS PharmSciTech 26:31 (2025) doi: 10.1208/s12249-024-02997-2.

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The Role of Microstructure in Topical Drug Product Development, Nigel Langley, Bozena Michniak-Kohn and David W. Osborne, eds., Springer International Publishing AG, AAPS Advances in Pharmaceutical Sciences Series, Volume 36 (2019). DOI 10.1007/978-3-030-17355-5.

Topical Drug Delivery Formulations, D.W. Osborne and A.H. Amman eds., Marcel Dekker, New York, NY (1990).

The Pharmaceutical Applications of Dimethyl Sulfoxide, Nigel Langley, Orn Almarsson, David W Osborne, eds., Springer Nature target publication date 2026.

PODCAST GUEST

Dr. Ted Lain ***Skin Care Confidential*** Episode 18: Dr. David Osborne, Dermatology's Master Formulator. September 19, 2023.

Dr. Alan Friedman ***JDD Podcast*** Formulation Foundations: A Peak Behind the Development Curtain. October 4, 2024

SHORT COURSES AND RECENT PRESENTATIONS

2 Day Short Course (with Dr. Umesh Banakar) – “Dermatological Product Development & Drug Delivery” Atlanta, GA, May 4-5, 1993, and Basel, Switzerland, June 3-4, 1993.

2 Day Short Course (with Dr. Umesh Banakar) – “Transdermal Drug Product Development” Basel, Switzerland October 27-28, 1994 and October 12-13, 1995.

2 Day Short Course – “Dermatological Product Development for Managers” Springfield MO, April 20-21, 2006

2 Day Short Course – “Dermatological Product Development for Managers” Springfield MO, April 24-25, 2008.

2 Day Short Course – “Dermatological Product Development Course” Buffalo NY (CPL-Niagara), May 14-15, 2009.

2 Day Short Course – “Dermatological Product Development Course” Vienna VA, May 6-7, 2010.

2 Day Short Course – “Dermatological Product Development: Current Issues for Topical Products” Petaluma CA, October 9-10, 2014.

2 Day Short Course – “Dermatological Product Development: Current Issues for Topical Products” Petaluma CA, April 13-14, 2016.

1 Day Short Course – “Dermatological Product Development Formulation Bootcamp” Denver CO, November 13, 2016.

2 Day Short Course – “Dermatological Product Development: Current Issues for Topical Products” Petaluma CA, May 3-4, 2017.

2 Day Short Course – “Dermatological Product Development: Current Issues for Topical Products” Petaluma CA, April 18-19, 2018.

1 Day Workshop – “Arcutis Formulation Workshop and Ad Board” Largo FL, Psoriasis KOLs February 26, 2022.

1 Day Workshop – “Arcutis Formulation Workshop and Ad Board” Largo FL, Contact Dermatitis KOLs April 30, 2022.

1 Day Workshop – “Arcutis Formulation Workshop and Ad Board” Largo FL, Canadian KOLs December 10, 2022.

1 Day Workshop – “Dermatological Product Development” CPL Limited, Mississauga, Ontario Canada February 6-7, 2025.