UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SUN PHARMACEUTICAL INDUSTRIES, INC.
Petitioner

v.

BIOFRONTERA BIOSCIENCE GMBH
Patent Owner

Case No. PGR2026-00021
U.S. Patent No. 12,280,146

PETITION FOR *POST GRANT* REVIEW OF U.S. PATENT NO. 12,280,146

CHALLENGING CLAIMS 1–17
UNDER 35 U.S.C. § 321 AND 37 C.F.R. § 42.204

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PETITIONER'S TABLE OF EXHIBITS

Exhibit No.	DESCRIPTION
1001	U.S. Patent No. 12,280,146 ("'146 Patent")
1002	Declaration of Dr. David Osborne, Ph.D.
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," *Handbook of Biocide and Preservative Use* 1995, Chapter 13. ("Hill")
1008	U.S. Patent No. 6,858,200
1009	Jaworska et al., "The influence of glicerides oil phase on O/W nanoemulsion formation by pic method," *Periodic Polytechnica Chemical Engineering* 2014, 58(Sup), 43-48.
1010	Fiume et al., "Safety Assessment of Monoglyceryl Monoesters as Used in Cosmetics," *International Journal of Toxicology* 2020, Vol. 39 (Supplement 3), 93S-126S.
1011	Kale et al., "Emulsion Micro Emulsion and Nano Emulsion: A Review," *Sys Rev Pharm* 2017, 8(1):39-47.
1012	Bailey et al., "Polyoxyalkylenes," *Ullmann's Encyclopedia of Industrial Chemistry* 2012.
1013	Nelson et al., "Carbohydrates And Glycobiology," *Lehninger Principles of Biochemistry Eighth Edition* 2021, Chapter 7.
1014	Bunke et al., "Degradation Mechanism and Stability of 5-Aminolevulinic Acid," *Journal of Pharmaceutical Sciences* 2000, Vol. 89 No. 10, 1335-1341.
1015	McCarron et al., "Stability of 5-Aminolevulinic Acid in Novel Non-Aqueous Gel and Patch-Type Systems Intended for Topical Application," *Journal of Pharmaceutical Sciences* 2005, Vol. 94 No. 8, 1756-1771.
1016	Fiume et al., "Final Report on the Safety Assessment of Sodium Cetearyl Sulfate and Related Alkyl Sulfates as Used in Cosmetics," *International Journal of Toxicology* 2010, Vol. 29(Supplement 2), 115S-132S.
1017	Vaidya et al., "Comparative study between silicone and fatty surfactant," *World Journal of Pharmaceutical Sciences* 2015, 3(3): 532-541.

Exhibit No.	DESCRIPTION
1018	Araujo et al., "Development of microemulsions to topically deliver 5-aminolevulinic acid in photodynamic therapy," *European Journal of Pharmaceutics and Biopharmaceutics* 2010, Vol. 75, 48-55.
1019	U.S. 2015/0238457
1020	Singh et al, "Nanoemulsion: Concepts, development and applications in drug delivery," *Journal of Controlled Release* 2017, Vol. 252, 28-49.

Throughout the Petition, all annotations, coloring, and emphases have been added unless indicated otherwise.

LISTING OF CLAIMS

[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. INTRODUCTION

Sun Pharmaceutical Industries, Inc. ("Sun"), the "Petitioner," respectfully requests post-grant review ("PGR") and cancellation of claims 1–17 in U.S. Patent No. 12,280,146 ("'146 Patent") (EX1001).

II. MANDATORY NOTICES

A. Real Party-In-Interest (37 C.F.R. § 42.8(b)(1))

Petitioner identifies itself as a real party-in-interest.

B. Related Matters (37 C.F.R. § 42.8(b)(2))

Petitioner is not aware of any other judicial or administrative matter that would affect, or be affected by, a decision in this instant PGR.

C. Lead And Back-up Counsel (37 C.F.R. § 42.8(b)(3))

Petitioner is filing a Power of Attorney appointing the practitioners associated with Customer Number 132,593. Petitioner designates the following lead and back-up counsel:

Lead Counsel	First Back-up Counsel
Yung-Hoon Ha (Reg. No. 56,368) Desmarais LLP 230 Park Ave New York, NY 10169 Telephone: (212) 351-3400 Email: yha@desmaraisllp.com	Bridget Belcher (Reg. No. 82,861) Desmarais LLP 101 California Street San Francisco, CA 94111 Telephone: (415) 490-2554 Email: bbelcher@desmaraisllp.com

D. Service Information (37 C.F.R. § 42.8(b)(4))

Post and hand delivery: Desmarais LLP

230 Park Ave, New York, NY 10169

Telephone: 212-351-3400

Email: SunPharmaPGRService@desmaraisllp.com

Please address all correspondence to counsel identified above. Petitioner consents to electronic service by email at:

SunPharmaPGRService@desmaraisllp.com

III. FEES

Petitioner is concurrently electronically submitting the required fees for this Petition. The Board is authorized to charge Desmarais LLP's deposit account, No. 50-6822, for any fee deficiency.

IV. CERTIFICATION OF GROUNDS FOR STANDING (37 C.F.R. § 42.204(a))

Petitioner certifies that the '146 Patent is available for post grant review and that Petitioner is not barred or estopped from requesting post grant review.

V. OVERVIEW OF CHALLENGE AND RELIEF REQUESTED

Under 37 C.F.R. §§ 42.22(a)(1) and 42.204(b)(1)-(2), Petitioner requests post grant review and cancellation of Claims 1–17 of the '146 Patent.

A. Identification of Prior Art

For purposes of this PGR only, Petitioner assumes that the priority date of the '146 Patent is April 6, 2023. *See* Section VII. This Petition applies AIA provisions

of 35 U.S.C. §§ 102 and 103. The following references are pertinent to the grounds of unpatentability:

Pat. Pub. No.	Publication/ Priority Date	Prior Art Under At Least (35 U.S.C.)
U.S. 5,520,905 ("Uhlmann") (EX1004)	May 28, 1996 / June 16, 1994	102(a)(1) and 102(a)(2)
U.S. 2003/0198654 ("Palazzolo")	October 23, 2003 / April 22, 2002	102(a)(1) and 102(a)(2)

B. Statutory Grounds of Unpatentability

Petitioner requests cancellation of Claims 1–17 of the '146 Patent under 35 U.S.C. §§ 102 and 103 based on the following Grounds.

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

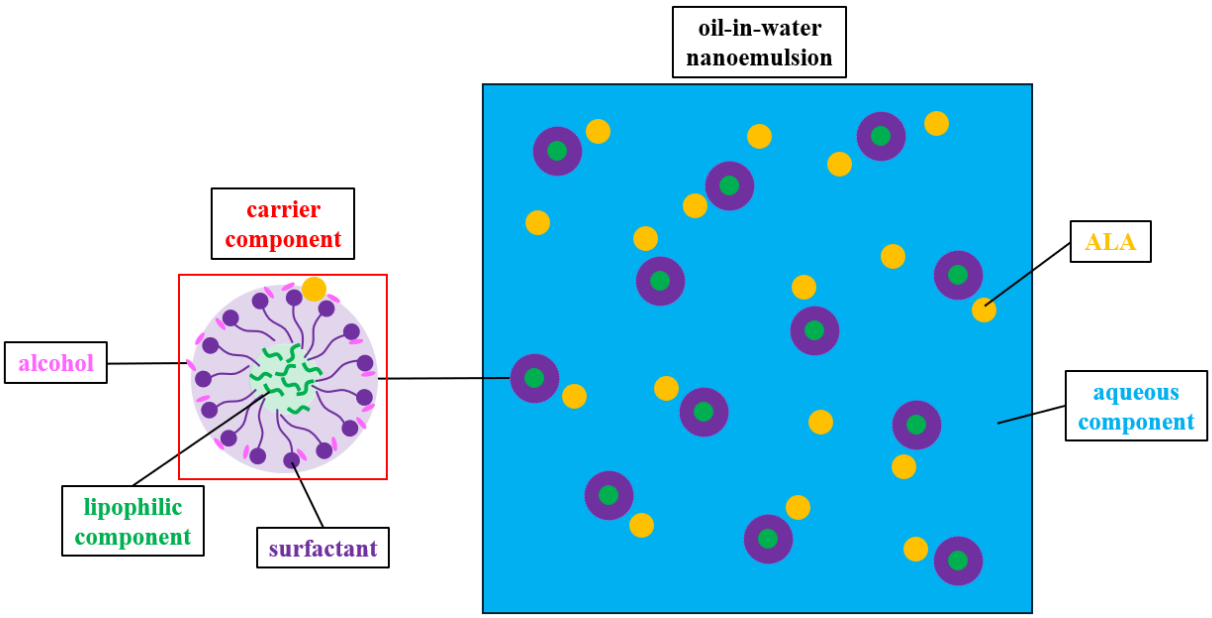
This Petition demonstrates that there is a reasonable likelihood that Petitioner would prevail with respect to at least one of the Challenged Claims. 35 U.S.C. § 314(a).

VI. TECHNOLOGY BACKGROUND

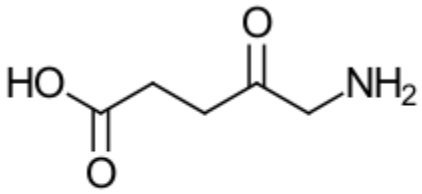
Many drugs are applied to the skin as topical formulations. Topical formulations often utilize dispersions called nanoemulsions to deliver the active agents, such as 5-aminolevulinic acid ("ALA"), to the regions of interest. *See, e.g.,*

EX1018, Abstract, 4-7; EX1019, [0024], Examples 1-5; EX1020, Table 1; EX1002, ¶52.

Nanoemulsions typically contain three components: (1) aqueous components, (2) lipophilic components, and (3) surfactants that bridge and stabilize the aqueous and lipophilic components to form kinetically stable oil-in-water ("O/W") dispersions. *See, e.g.,* EX1020, 2, 4-5, Fig. 1; EX1002, ¶53. Surfactants typically have both hydrophobic and hydrophilic portions. The lipophilic components interact with the hydrophobic portions of the surfactants and the aqueous components interact with the hydrophilic portions of the surfactants. *See, e.g.,* EX1011, 1-3; EX1020, 4-5, Fig. 1; EX1002, ¶53. What often results are small lipophilic/hydrophobic droplets (often called the "carrier component" because the droplets can "carry" the active agent to the region of interest) surrounded by a matrix of aqueous components. In some cases, as illustrated below, the active agent (*e.g.,* ALA) is hydrophilic, which results in the active agent being found in both the aqueous component and the carrier component (*e.g.,* near the hydrophilic portions of the surfactants). *See, e.g.,* EX1018, 1-2; EX1011, 1-3, 6; EX1020, 4, 18; EX1002, ¶54.



ALA is a well-known active agent that has been utilized in a wide range of formulations, including formulations for cancer treatment, acne treatment, and cosmetic applications. *See, e.g.,* EX1018, 1-2; EX1019, [0003]; EX1020, 18, Table 1. ALA has the chemical structure shown below, where one end has a carboxylic acid group (-COOH) and the other end has an amino group (-NH_2). EX1002, ¶55.



ALA

One known issue with ALA in topical formulations is the potential degradation of ALA over time. For example, in aqueous solutions, ALA is prone to dimerization to pyrazine-2,5-dipropionic acid. *See, e.g.,* EX1015, 1-2, Fig. 1; EX1014, Fig. 1.

Additionally, due to the electrophilic nature of carboxylic acids, ALA is prone to ester formation in the presence of nucleophiles such as diols and polyols. *See, e.g.,* EX1015, 1, 5-15. For example, degradation of ALA is observed in the presence of glycerol and propylene glycol. *See, e.g.,* EX1014, 6; EX1015, 1, 5-15; EX1019, Example 2, Example 3. And ALA is known to undergo an esterification reaction in the presence of diols and polyols, including glycerol and propylene glycol. *See, e.g.,* EX1015, 7-8, 12, 14; EX1014, 6. EX1002, ¶¶56-57. To prevent the degradation of ALA, nanoemulsions for use in topical formulations of ALA are often formulated without propylene glycol. *See, e.g.,* EX1018, 1, 4-7; EX1019, Examples 1-5; EX1002, ¶58.

VII. OVERVIEW OF THE '146 PATENT

A. Purported Invention

The '146 Patent is directed to a topical formulation comprising an oil-in-water nanoemulsion. EX1001, 1:13-16, 12:58-60. The '146 Patent describes an oil-in-water nanoemulsion comprising an aqueous component (*e.g.,* phosphate buffer) and a hydrophobic carrier component that includes surfactants (*e.g.,* soy lecithin and Polysorbate 80), a lipophilic component (*e.g.,* caprylic/capric triglycerides), and an alcohol (*e.g.,* isopropyl alcohol). EX1001, Example 1, Tables 2, 3. ALA is used as the active ingredient. EX1001, Example 3, Table 7, 19:8-28. Propylene glycol and sorbitol are excluded from the topical formulation because they were admittedly

known to undergo nucleophilic reactions to form undesired esters with carboxylic acid-containing active agents, including ALA. EX1001, 1:66-2:6; *see also id.* 4:62-5:21; EX1002, ¶¶59-61.

B. Prosecution History

The '146 Patent issued from U.S. Patent Application No. 18/533,497, filed on December 8, 2023 by Biofrontera Bioscience GmbH (the "Applicant"). EX1003, 1, 78-79. The '146 Patent claims priority to International Patent Application No. PCT/EP2023/059291, filed on April 6, 2023. EX1003, 4, 76.

In response to a restriction requirement, the Applicant elected and amended originally filed claim 19 and added new claims 21-26. EX1003, 104, 109-110, 98-99.

In a first Non-Final Rejection, the Examiner rejected claims 19 and 21-26 as obvious over U.S. Patent Publication No. 2009/0324727 ("Roca"). EX1003, 148-152. The Examiner further rejected claims 19 and 21-26 as unpatentable over claims 1-20 of co-pending Application No. 18/533,521 in view of Roca. EX1003, 154-155.

In response, the Applicant amended claim 19 to require a formulation comprising "essentially no propylene glycol." EX1003, 158-161, 165-167. The Applicant also argued unexpected results regarding formulations comprising "essentially no propylene glycol." EX1003, 158-160. The Applicant added new claims 27-36. EX1003, 166-167.

In a Final Rejection, the Examiner rejected claim 21 under 35 U.S.C. § 112(d) for failing to limit the subject matter of the claim from which it depends. EX1003, 175-178. The Examiner also rejected claims 19, 21-25, and 27-36 as obvious over U.S. Patent No. 6,559,183 ("Schmid") and claim 26 as obvious over Schmid in view of U.S. Patent No. 5,152,923 ("Weber"). EX1003, 178-181. The Examiner further rejected claims 19 and 21-36 as unpatentable over claims 1-21 of co-pending Application No. 18/533,521. EX1003, 183.

In response, the Applicant cancelled claim 21, amended claims 19, 24, and 34, and added new claims 37-39. EX1003, 188-192, 195-198. The Applicant amended claim 19 to further require "essentially no sorbitol." EX1003, 188-190, 195.

Following an Examiner interview dated December 6, 2024, the Applicant accepted the Examiner's recommendations to cancel claims 38-39 and obtained allowance of claims 19 and 22-37. EX1003, 221, 230-236.

The '146 Patent issued on April 22, 2025. EX1001, Cover; EX1003, 330-333; EX1002, ¶¶62-70.

VIII. LEVEL OF ORDINARY SKILL IN THE ART

A person of ordinary skill in the art (POSA) would have had, as of the earliest claimed priority date of April 6, 2023, a PhD in physical chemistry, organic chemistry, pharmaceutical chemistry, pharmaceutics, 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. EX1002, ¶¶71-73.

IX. CLAIM CONSTRUCTION

The claims should be construed "in accordance with the ordinary and customary meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent." 37 C.F.R. § 42.100(b); *see also Phillips v. AWH Corp.*, 415 F.3d 1303

(Fed. Cir. 2005) (*en banc*). The Patent Owner can act as his own lexicographer. *See In re Paulsen,* 30 F.3d 1475, 1480 (Fed. Cir. 1994). Moreover, the Board "need[s] only construe terms 'that are in controversy, and only to the extent necessary to resolve the controversy.'" *Nidec Motor Corp. v. Zhongshan Broad Ocean Motor, Co.,* 868 F.3d 1013, 1017 (Fed. Cir. 2017).[1] Patent Owner has acted as his own lexicographer for the following term in the '146 Patent.

A. "nanoemulsion"

Claims 1-17 recite "nanoemulsion." The term "nanoemulsion" should be construed as "a dispersion of oil in water" because the '146 Patent states that "[a]s

[1] Petitioner reserves the right to raise other/additional claim construction arguments in any other/parallel proceedings.

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; EX1002, ¶¶76-77.

X. PRIMARY PRIOR ART REFERENCE RELIED UPON

A. Overview of Uhlmann

Uhlmann is titled "[c]osmetic or dermatological preparation comprising delta-aminolevulinic acid content as an active ingredient" and published on May 28, 1996. EX1004, Title, [45]. Uhlmann discloses "dermatological preparations" of "δ-aminolevulinic acid" to be "used in the treatment of skin…as part of a dermatological…treatment." EX1004, 5:11-17. Specifically, Uhlmann discloses two oil-in-water (O/W) emulsion formulations containing δ-aminolevulinic acid in Examples 3 and 5. EX1004, Examples 3, 5; EX1002, ¶78.

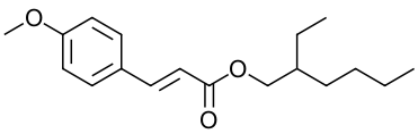
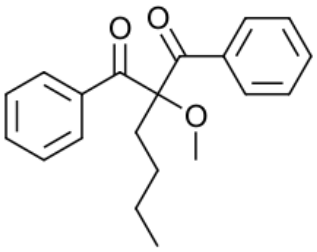
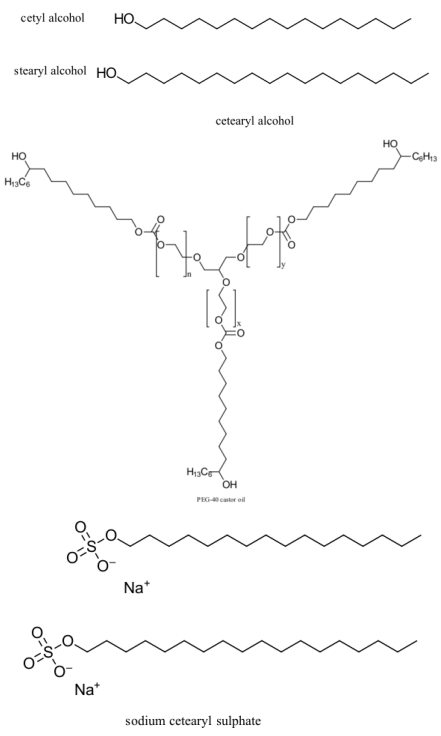
In Example 3, Uhlmann discloses a "Sun Milk O/W" emulsion formulation.

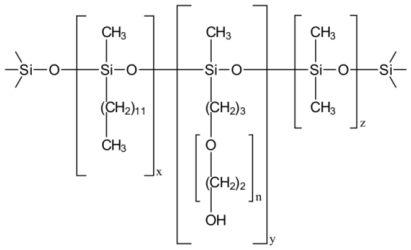
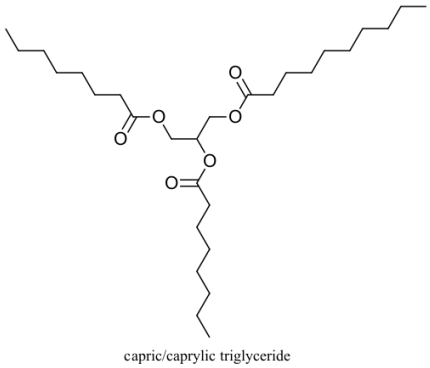
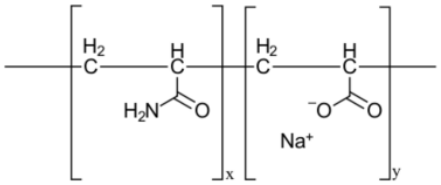
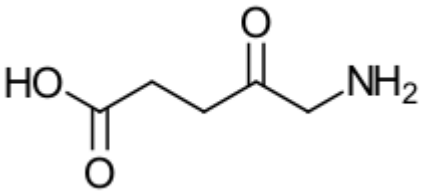
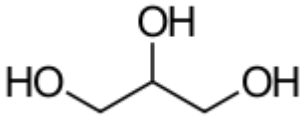
Example 3

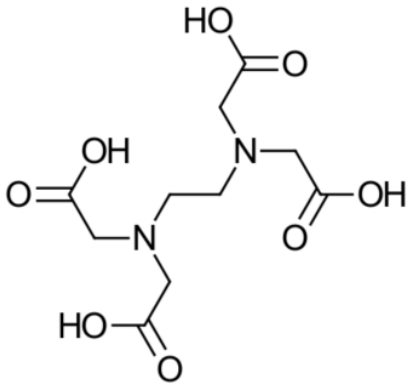
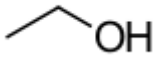
Sun Milk O/W	Percentage by weight
Octylmethoxycinnamate	5.0
Butylmethoxydibenzoylmethane	1.0
Cetearylalcohol + PEG-40 castor oil + Sodiumcetearylsulphate	2.5
Glyceryllanolate	1.0
Laurylmethicon copolyol	0.5
Mineral oil (DAB 9)	5.0
Caprylic/capric triglyceride	5.0
Acrylamide/sodiumacrylate copolymer	0.3
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. The O/W emulsion in Example 3 comprises a "[]discontinuous[] lipid phase in an outer (continuous) aqueous phase" and contains ***δ-aminolevulinic acid*** as the active ingredient. EX1004, 6:39-48, 4:31-39, Example 3. The carrier component is made up of a ***lipophilic component*** (*e.g.*, one or more of ***caprylic/capric triglyceride***), a ***surfactant*** (*e.g.*, one or more of ***PEG-40 castor oil***, ***sodium cetearyl sulphate***, and ***lauryl methicone copolyol***), and an ***alcohol*** (*e.g.*, one or more of ***cetearyl alcohol***, ***glycerine***, and ***ethanol***). EX1004, Example 3. ***Water*** makes up to 100.0% of the formulation as the ***aqueous component*** and the formulation does ***not*** include any propylene glycol or sorbitol. EX1004, Example 3; EX1002, ¶789

The chemical structures of these individual components in Example 3 are identified below (EX1002, ¶80):

Component	Percentage (w/w)	Structure
Octylmethoxycinnamate	5.0	
Butylmethoxydibenzoylmethane	1.0	
Cetearyl alcohol* + *PEG-40 castor oil* + *sodium cetearyl sulphate	2.5	
Glyceryl lanolate	1.0	No discrete structure

Lauryl methicone copolyol	0.5	
Mineral oil (DAB 9)	5.0	No discrete structure
Caprylic/capric triglyceride	5.0	
Acrylamide/sodium acrylate copolymer	0.3	
Cyclomethicone	2.0	No discrete structure
TiO_2	1.0	TiO_2
δ-aminolevulinic acid	1.0	
Glycerine	3.0	

EDTA solution (14%)	0.5	
Ethanol	5.0	
Perfume, preservative	q.s.	No discrete structure
Water, fully demineralised	Make up to 100.0	*H_2O*

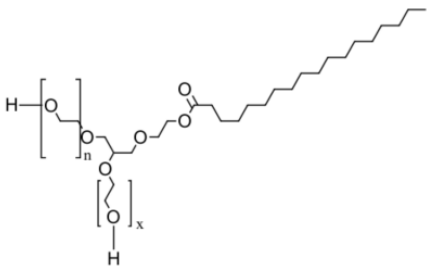
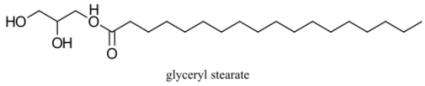
In Example 5, Uhlmann discloses a "Day-car[e] skin cream O/W" emulsion formulation.

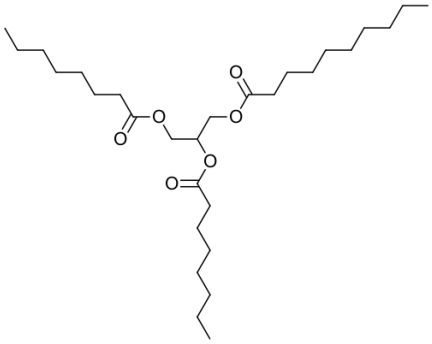
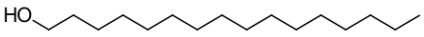
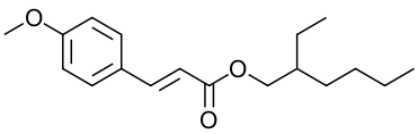
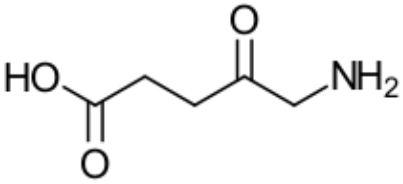
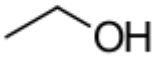
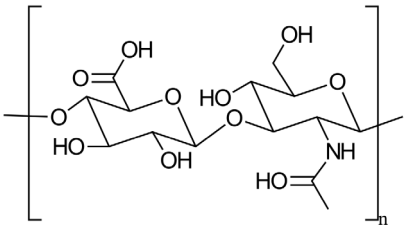
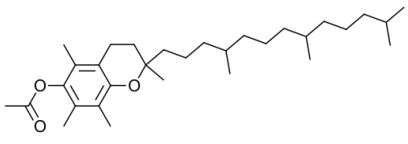
Example 5

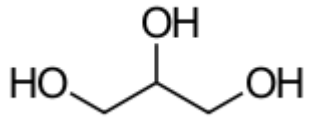
Day-car skin cream O/W	Percentage by weight
PEG-5 Glycerylstearate	2.00
Glycerylstearate	3.00
Cyclomethicone	3.00
Caprylic/capric triglyceride	3.00
Cetylalcohol	3.00
Octylmethoxycinnamate	2.50
δ-aminolevulinic acid	5.00
Ethanol	1.00
Hyaluronic acid	0.05
Tocopherylacetate	0.50
Glycerine	4.00
Perfume,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

EX1004, Example 5. The O/W emulsion in Example 5 comprises a "[]discontinuous[] lipid phase in an outer (continuous) aqueous phase" and contains ***δ-aminolevulinic acid*** as the active ingredient. EX1004, 6:39-48, 4:31-39, Example 5. The carrier component is made up of a ***lipophilic component*** (*e.g.*, one or more of ***caprylic/capric triglyceride***), a ***surfactant*** (*e.g.*, one or more of ***PEG-5 glyceryl stearate*** and ***glyceryl stearate***), and an ***alcohol*** (*e.g.*, one or more of ***cetyl alcohol***, ***ethanol***, and ***glycerine***). EX1004, Example 5. ***Water*** makes up to 100.00% of the formulation as the ***aqueous component*** and the formulation does not include any propylene glycol or sorbitol. EX1004, Example 5; EX1002, ¶81.

The chemical structure of these individual components in Example 5 are identified below (EX1002, ¶82):

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

Cyclomethicone	3.00	No discrete structure
Caprylic/capric triglyceride	3.00	 capric/caprylic triglyceride
Cetyl alcohol	3.00	
Octylmethoxycinnamate	2.50	
δ-aminolevulinic acid	5.00	
Ethanol	1.00	
Hyaluronic acid	0.05	
Tocopherylacetate	0.50	

Glycerine	4.00	
Perfume, preservative	q.s.	No discrete structure
Water, fully demineralised	Make up to 100.00	***H_2O***

XI. GROUNDS

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

1. Independent Claim 1

a) [1Pre] A formulation comprising:

To the extent limiting, Uhlmann discloses [1Pre]. Uhlmann discloses "cosmetic or dermatological preparations" that "use a conventional formulation base." EX1004, 5:11-17, Title. For example, Uhlmann discloses a "Day-car[e] skin cream O/W" formulation in Example 5. EX1004, Example 5; EX1002, ¶¶84-85.

b) [1A] (a) a nanoemulsion comprising:

At the outset, as discussed in Section IX.A, the '146 Patent states 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. Under this lexicographic definition, Uhlmann discloses [1A]. EX1002, ¶¶86-87.

Uhlmann discloses a "Day-car[e] skin cream ***O/W***" formulation in Example 5. EX1004, Example 5; *see also id.*, 5:39-40 (explaining "an emulsion of … the oil-in-water type (O/W)"). Uhlmann explains that the "[d]ay-car[e] skin cream" in

Example 5 is an "***[e]mulsion***[] according to the invention." EX1004, 6:8-13; *see also id.*, 5:35-42, 6:39-48. Accordingly, Uhlmann discloses [1A]. EX1002, ¶88.

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

Uhlmann discloses [1B]. Uhlmann explains that suitable solvents for "***[e]mulsions*** according to the invention"—such as the "Day-car[e] skin cream O/W" in Example 5—may be "***water*** or ***aqueous solutions***." EX1004, 5:53-6:13. In Example 5, the solvent is ***water***:

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. Because ***water*** is the solvent, the ***water*** forms the ***aqueous phase*** and meets the ***at least one aqueous component*** of the nanoemulsion in Example 5. EX1002, ¶¶89-90. Indeed, the '146 Patent itself explains that the ***aqueous component*** "comprises an ***aqueous phase*** or ***forms an aqueous phase***." EX1001, 6:6-9; EX1002, ¶91.

In Example 5, ***water*** is the majority component of the formulation, which further confirms that the formulation in Example 5 is an oil-in-water dispersion, meeting the claimed "nanoemulsion" recited in [1A]. ***Water*** "make[s] up to 100.00" "[p]ercent[] by weight" of the "Day-car[e] skin cream O/W" formulation. The other components of the formulation make up 27.05% (w/w) plus an amount of "perfume, preservative" which is marked as "q.s." EX1004, Example 5, 8:23-26. It was well-known that "q.s." means a "sufficient quantity" of the ingredient specified by the supplier of that ingredient. *See, e.g.,* EX1006, [0045]. And typical amounts of "perfume" and "preservative" in such formulations range from 0.01-5.0% (w/w) and 0.01-2% (w/w), respectively. *See, e.g.,* EX1005, [0010]-[0011]; *see also* EX1007, Appendix A, Appendix B. Hence, the amount of ***water*** in Example 5 is about ***72.95% (w/w)*** (assuming no "perfume, preservative") to about ***65.95% (w/w)*** (assuming maximum typical amounts of "perfume" and "preservative" of about 5% (w/w) and 2% (w/w), respectively). EX1002, ¶¶92-95

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

Uhlmann discloses [1C]. Uhlmann discloses a "Day-car[e] skin cream O/W" emulsion. *See* Section XI.A.1.b) [1A]. "O/W emulsions" are "dispersions of a liquid, half solid or solid inner (discontinuous) lipid phase in an outer aqueous (continuous) phase" that contain "emulsifiers." *See, e.g.,* EX1004, 6:39-48.

Accordingly, the "discontinuous" lipid phase that contain emulsifiers of the O/W emulsion meets the claimed "**carrier component**." EX1002, ¶¶96-98.

Indeed, the '146 Patent itself explains that the two phases in an O/W emulsion are the hydrophobic carrier component and the aqueous component. EX1001, 3:47-52 ("[i]n oil in water nanoemulsion formulations, there are two different phases…: one is the ***hydrophobic carrier component***…and the other one the aqueous component."). EX1002, ¶99.

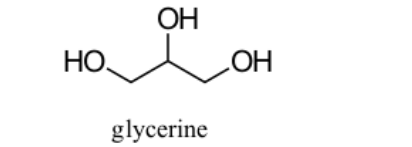
e) [1D] (1) at least one lipophilic component,

Uhlmann discloses [1D]. Uhlmann explains that "[e]mulsions according to the invention"—such as the "Day-car[e] skin cream O/W" in Example 5—may contain "***[o]ils*** such as ***triglycerides of capri[c] or caprylic acid***." EX1004, 5:53-6:13. In Example 5, at least ***caprylic/capric triglyceride*** meets the "***at least one lipophilic component***:"

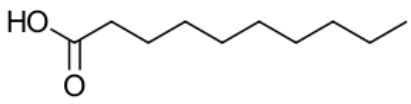
Example 5

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

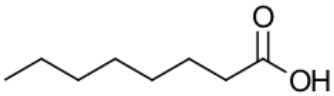
EX1004, Example 5. ***Caprylic/capric triglyceride*** has a glycerine backbone with capric acid and caprylic acid pendant groups:



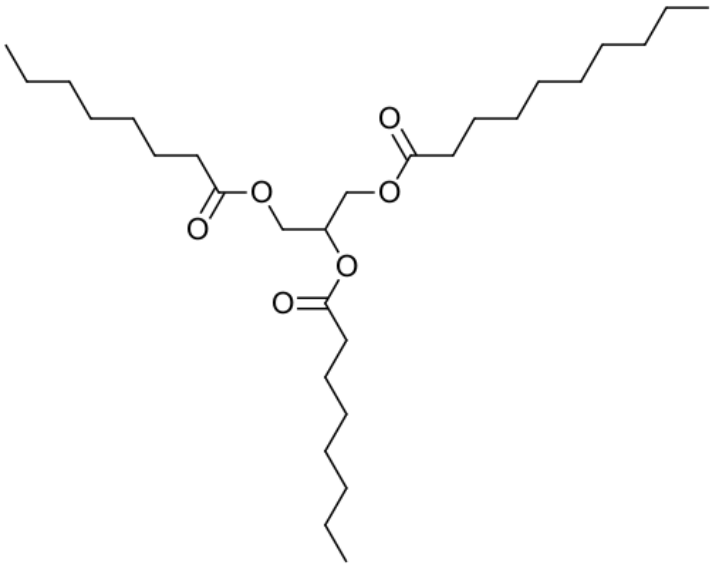
glycerine



capric acid



caprylic acid



capric/caprylic triglyceride

See, e.g., EX1009, 1; EX1002, ¶¶100-101.

The ***caprylic/capric triglyceride*** has hydrophobic tail groups that are part of the "discontinuous" lipid phase in the O/W emulsion. *See* Section XI.A.1.d) [1C]; EX1002, ¶101.

Indeed, the '146 Patent itself explains that the ***lipophilic component*** may include "a ***lipid***" and is preferentially "a ***caprylic and/or capric triglyceride and/or a mixture thereof***." EX1001, 15:9-25. In the working examples of the '146 Patent, the ***at least one lipophilic component*** of the nanoemulsions BF200, BF215, and BF220 is "***caprylic/capric triglycerides***." EX1001, Example 1, Tables 2, 3 (labeling "***caprylic/capric triglycerides***" as the "***lipid core***" of the "carrier component"); *see also id.*, 20:40-21:37; EX1002, ¶¶102-103.

In Example 5 of Uhlmann, the ***caprylic/capric triglyceride*** meets the ***at least one lipophilic component***. Accordingly, Uhlmann discloses [1D]. EX1002, ¶¶100-103.

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

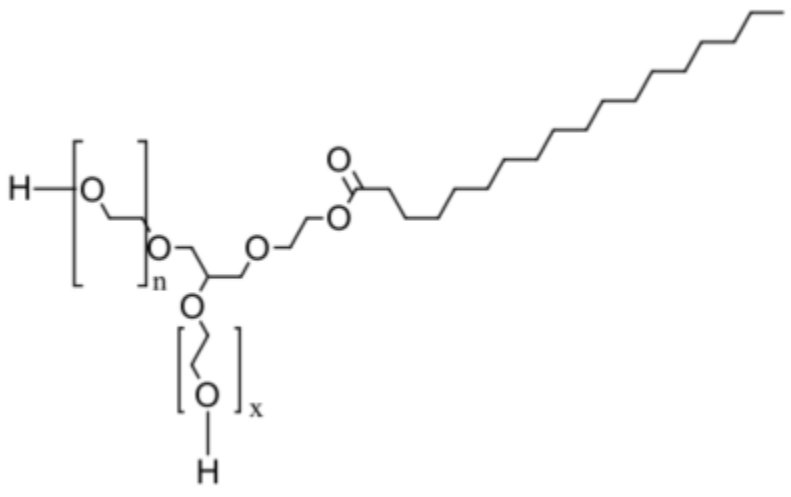
Uhlmann discloses [1E]. Uhlmann explains that "[e]mulsions according to the invention"—such as the "Day-car[e] skin cream O/W" in Example 5—may contain "the usual type of ***emulsifier*** used for this type of formulation" to "prevent[] phase separation." EX1004, 6:8-13, 6:46-48. In Example 5, one or more of ***PEG-5 glyceryl stearate*** and ***glyceryl stearate*** meets the "***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; EX1002, ¶¶104-105.

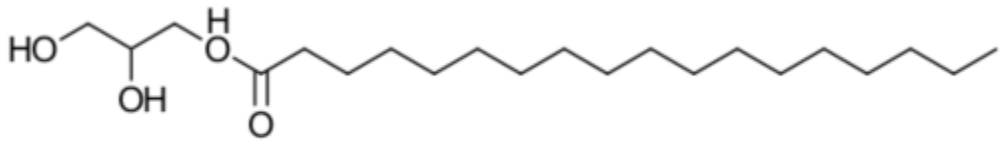
PEG-5 glyceryl stearate is a polyoxyethylene ester of glyceryl stearate and is a polyoxyethylene-type ***surfactant***.



PEG-5 glyceryl stearate

See, e.g., EX1008, 4:1-8 ("…preferred emulsifiers are … PEG-5 glyceryl stearate …"); EX1002, ¶106.

Glyceryl stearate is a non-ionic ***surfactant*** that is an ester of glycerin in stearic acid.



glyceryl stearate

See, e.g., EX1010, Table 2 ("Glyceryl Stearate…The monoester of glycerin and stearic acid…surfactant-emulsifying agent…"); EX1002, ¶107.

PEG-5 glyceryl stearate and ***glyceryl stearate*** each have a hydrophilic head group and a hydrophobic tail group and function as the emulsifiers of the "discontinuous" lipid phase in the O/W emulsion and meets the claimed "carrier component." *See* Section XI.A.1.d) [1C]; EX1002, ¶108.

Indeed, the '146 Patent itself uses "***surfactant***" and "***emulsifier***" interchangeably. 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***. …"). And, the '146 Patent explains 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; EX1002, ¶¶109-110.

In Example 5 of Uhlmann, the ***PEG-5 glyceryl stearate*** is a polyoxyethylene-type ***surfactant*** and the ***glyceryl stearate*** is a nonionic ***surfactant***. Accordingly, Uhlmann discloses [1E]. EX1002, ¶110.

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

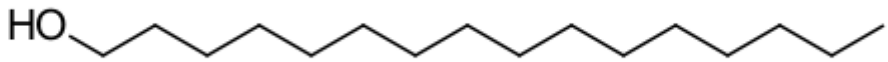
Uhlmann discloses [1F]. Uhlmann explains that "[e]mulsions according to the invention"—such as the "Day-car[e] skin cream O/W" in Example 5—may contain "***[a]lcohols, diols or polyols with a low C number***." EX1004, 5:53-6:13. In Example 5, one or more of ***cetyl alcohol***, ***glycerine***, and ***ethanol*** meets the "***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

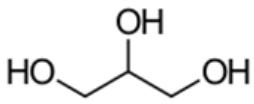
EX1004, Example 5. Each of ***cetyl alcohol***, ***glycerine***, and ***ethanol*** are ***alcohols***. EX1002, ¶¶111-112.

Cetyl alcohol has the following structure.

cetyl alcohol 

Cetyl alcohol has a hydrophobic tail group that is part of the "discontinuous" lipid phase in the O/W emulsion. *See* Section XI.A.1.d) [1C]; EX1002, ¶113.

Glycerine and ***ethanol*** have the following structures.



glycerine

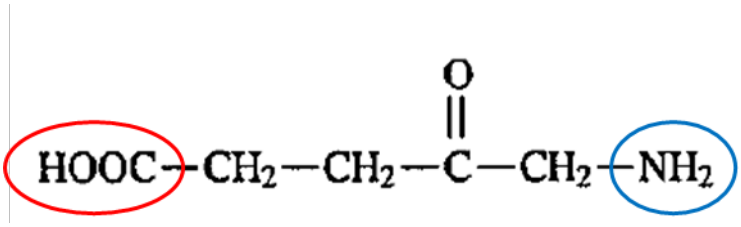


ethanol

Glycerine and ***ethanol*** each have hydroxy (-OH) groups that may be associated with the hydrophilic head groups of the ***surfactants*** contained in the "discontinuous" lipid phase. *See, e.g.,* EX1011, 2, 3, Fig. 3; *see also* Sections XI.A.1.d) [1C], XI.A.1.f) [1E]. Accordingly, Uhlmann discloses [1F]. EX1002, ¶¶114-115.

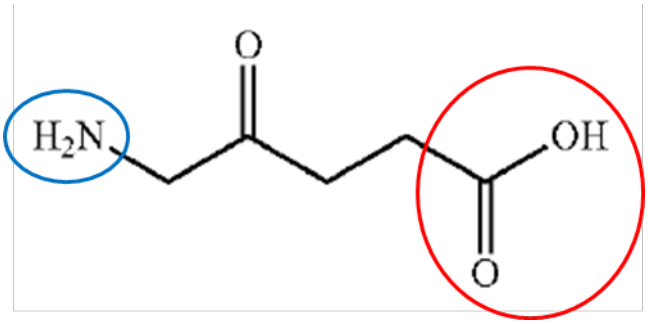
h) [1G] (b) 5-aminolevulinic acid and/or a derivative, a precursor, a metabolite, and/or a pharmaceutically acceptable salt thereof,

Uhlmann discloses [1G]. Uhlmann discloses O/W emulsions with "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 explains that "***δ-aminolevulinic acid*** (also called δ-ALA, 5-amino-4-oxopentanoic acid, δ-amino-γ-keto-valeric acid) has the following structure:"



EX1004, 2:28-37 (annotated). ***δ-aminolevulinic acid*** is ***5-aminolevulinic acid***. EX1002, ¶¶116-118.

Indeed, the '146 Patent itself provides the structure of ***5-aminolevulinic acid*** as being identical to ***δ-aminolevulinic acid***, where the corresponding carboxylic and amino groups have been highlighted for ease of reference.



EX1001, 19:17-28 (annotated); EX1002, ¶118.

The "Day-car[e] skin cream O/W" emulsion in Example 5 comprises ***δ-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
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. Accordingly, Uhlmann discloses [1G]. EX1002, ¶119.

i) [1H] wherein the formulation comprises essentially no[2] propylene glycol and essentially no sorbitol.

The "Day-car[e] skin cream O/W" formulation of Example 5 does not contain any propylene glycol or 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. Example 5 details a complete formulation that "make[s] up to 100.00" "[p]ercent[] by weight" with water, which excludes the possibility of an

[2] The '146 Patent explains that "the expression[] … 'comprises essentially no compound X' …specif[ies] that the formulation is either free of compound X or comprises less than 0.1% (w/w) … based on the total weight of the formulation." EX1001, 6:50-59; EX1002, ¶122. The expression "comprises essentially no…" is similarly recited in limitations [1H], [9], [12], and [17].

additional unnamed ingredient. EX1004, Example 5, 8:23-26; EX1002, ¶¶120-121. *See, e.g., United Services Automobile Association v. PNC Bank N.A.*, No. 2023-2244, 2025 WL 706080, at *3 (Fed. Cir. Mar. 5, 2025) ("In determining what a prior art reference discloses, we look to what a skilled artisan would understand from reading the reference, which includes the internal context within the reference.") (citing *Almirall, LLC v. Amneal Pharmaceuticals LLC*, 28 F.4th 265 (Fed. Cir. Mar. 14, 2022) ("[I]t was reasonable for the Board to find that, in the context of [a prior art reference], a skilled artisan would recognize that the reference discloses a complete formulation—excluding the possibility of an additional active ingredient.")); *see also Amneal Pharmaceuticals LLC v. Almirall, LLC*, IPR2019-00207, Paper 58, 41 (PTAB May 29, 2020), ("It is not Garrett's mere silence as to the presence of adapalene, but its disclosure of complete dapsone formulations to treat acne in its absence that suggests that adapalene is not included in Garrett's formulations. … Thus, a skilled artisan would have understood based on Garrett's disclosure that no adapalene was included or otherwise required for any of the dapsone formulations."). Accordingly, Uhlmann discloses a formulation that is free of propylene glycol and sorbitol or at least contains less than 0.1% (w/w) of propylene glycol and sorbitol based on the total weight of the formulation. EX1002, ¶¶122.

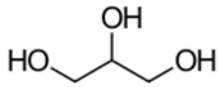
2. Dependent Claims 4 And 16

a) [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.

[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.

Uhlmann discloses [4] and [16]. As explained in Section XI.A.1.g) [1F], Uhlmann discloses ***glycerine*** as one of the ***at least one alcohol*** in the carrier component. EX1004, Example 5; EX1002, ¶¶123-124, 126-127.

For [4], ***glycerine*** has ***3 carbon atoms***:



glycerine

EX1002, ¶125.

As for [16], ***glycerine is 4.00% (w/w)*** of the formulation, which is within the claimed "0.1% to 10% (w/w)." EX1004, Example 5, 8:23-26; EX1002, ¶128.

To the extent [16] requires all of the compounds identified in claim 1 as the claimed "***at least one alcohol***" to meet the claimed "0.1% to 10% (w/w)," Example 5 still anticipates [16]. ***Ethanol*** is 1.00% (w/w) of the formulation and ***cetyl alcohol*** is 3.00% (w/w) of the formulation. Hence, ***the combined amount of ethanol, glycerine, and cetyl alcohol is 8.00% (w/w)***, which is also 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."); EX1002, ¶129. *See Ineos USA LLC v. Berry Plastics Corp.*, 783 F.3d 865, 869 (Fed. Cir. 2015) ("When a patent claims a range, as in this case, that range is anticipated by a prior art reference if the reference discloses a point within the range.") (*citing Titanium Metals Corp. v. Banner*, 778 F.2d 775, 782 (Fed. Cir. 1985); *see also In re Geisler*, 116 F.3d 1465, 1469-71 (Fed. Cir. 1997). Accordingly, Uhlmann discloses [4] and [16]. EX1002, 123-130.

3. Dependent Claim 5

a) [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).

Uhlmann discloses [5]. As explained in Section XI.A.1.c) [1B], Uhlmann discloses ***water*** in Example 5 and meets the claimed ***at least one aqueous component***. EX1004, Example 5. ***Water*** "make[s] up to 100.00" "[p]ercent[] by weight" of the "Day-car[e] skin cream O/W" formulation. EX1004, Example 5. The other components of the formulation make up 27.05% (w/w) plus an amount of "perfume, preservative" which is marked as "q.s." EX1004, Example 5, 8:23-26. As explained above in Section XI.A.1.c) [1B], it was well-known that "q.s." means a "sufficient quantity" of the ingredient specified by the supplier of that ingredient.

See, e.g., EX1006, [0045]. And typical amounts of "perfume" and "preservative" in such formulations range from 0.01-5.0% (w/w) and 0.01-2% (w/w), respectively. *See, e.g.,* EX1005, [0010]-[0011]; *see also* EX1007, Appendix A, Appendix B. Hence, the amount of ***water*** in Example 5 is about ***72.95% (w/w)*** (assuming no "perfume, preservative") to about ***65.95% (w/w)*** (assuming maximum typical amounts of "perfume" and "preservative" of about 5% (w/w) and 2% (w/w), respectively). EX1002, ¶¶131-137. Example 5 discloses (Ground IA), or at a minimum renders obvious (Ground IC), [5].[3] EX1002, ¶¶131-137, 167-173. *See Ineos v. Berry Plastics*, 865, 869 ("When a patent claims a range, as in this case, that range is anticipated by a prior art reference if the reference discloses a point within

[3] To the extent Patent Owner argues that Uhlmann alone does not teach or render obvious [5], Petitioner submits an alternative Ground IC based on the combination of Uhlmann and Palazzolo. A POSA would have been able to combine the teachings of Uhlmann with Palazzolo with a reasonable expectation of success because Palazzolo merely 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, [0010]-[0011]. It would have been a trivial combination to put in the typical amounts of "perfume, preservative" to achieve the predictable result of a formulation that smells nicer and/or lasts longer. EX1002, ¶¶167-173.

the range.") (*citing Titanium Metals v. Banner*, 775, 782; *see also In re Geisler*, 1465, 1469-71 (Fed. Cir. 1997).

4. Dependent Claim 6

a) [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.

Uhlmann discloses [6]. As explained above in Section XI.A.1.e) [1D], Uhlmann discloses ***caprylic/capric triglyceride*** as one of the components of the ***at least one lipophilic component*** in Example 5. Uhlmann discloses ***caprylic/capric triglyceride as 3.00% (w/w)*** of the nanoemulsion, which is within the claimed "0.1% to 30% (w/w)." EX1004, Example 5, 8:23-26; EX1002, ¶¶138-141. *See Ineos v. Berry Plastics*, 865, 869 ("When a patent claims a range, as in this case, that range is anticipated by a prior art reference if the reference discloses a point within the range.") (*citing Titanium Metals v. Banner*, 775, 782; *see also In re Geisler*, 1465, 1469-71 (Fed. Cir. 1997).

5. Dependent Claim 7

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

Uhlmann discloses [7]. As explained in Section XI.A.1.i) [1H], Uhlmann discloses a "Day-car[e] skin cream O/W" formulation that does not contain propylene glycol. EX1002, ¶¶142-143.

6. Dependent Claim 14

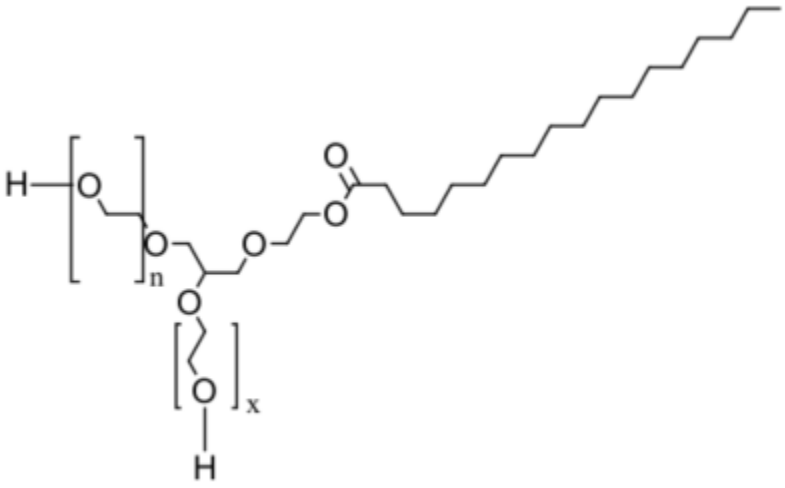
a) [14] The formulation of claim 1, wherein the at least one lipophilic component comprises: triglycerides and/or mixtures thereof; or a caprylic triglyceride, a capric triglyceride, or a mixture thereof.

Uhlmann discloses [14]. As explained in Section XI.A.1.e) [1D], Uhlmann discloses ***caprylic/capric triglyceride*** that meets the "***at least one lipophilic component***." EX1002, ¶¶144-146.

7. Dependent Claim 15

a) [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.

Uhlmann discloses [15]. As explained in Section XI.A.1.f) [1E], Uhlmann discloses ***PEG-5 glyceryl stearate*** as one of the ***at least one surfactant***. ***PEG-5 glyceryl stearate*** has the following chemical structure and is a ***polyoxyethylene-type surfactant***. *See, e.g.,* EX1012, 1 ("Polyoxyethylenes of less than ca. 20 000 number-average molecular mass are usually referred to as poly(ethylene glycols)."). EX1002, ¶¶147-149.

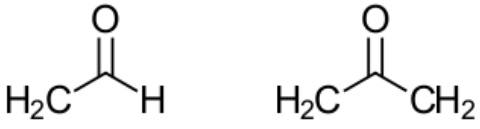


PEG-5 glyceryl stearate

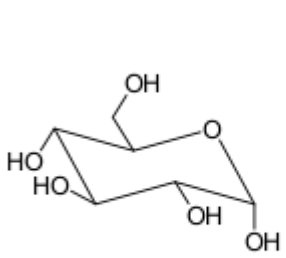
8. Dependent Claim 17

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

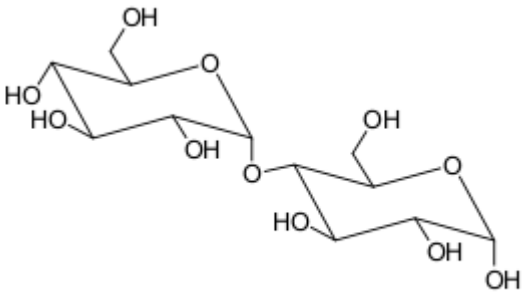
A monosaccharide is a simple sugar that consists of a single aldehyde or ketone with at least two hydroxyl groups. A disaccharide is a sugar composed of two monosaccharides. EX1013, 229-230, 233, 237. Shown below are an exemplary aldehyde and ketone, and an exemplary monosaccharide (glucose) and disaccharide (maltose, made up of two glucose molecules). EX1002, ¶151.



aldehyde ketone



glucose



maltose

The "Day-car[e] skin cream O/W" formulation of Example 5 does not contain any monosaccharides or 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. Example 5 details a complete formulation that "make[s] up to 100.00" "[p]ercent[] by weight" with water, which excludes the possibility of an additional unnamed ingredient. EX1002, ¶152. *See, e.g., United Services v. PNC Bank*, *3 ("In determining what a prior art reference discloses, we look to what a skilled artisan would understand from reading the reference, which includes the

internal context within the reference.") (citing *Almirall v. Amneal*, 265, 273 ("[I]t was reasonable for the Board to find that, in the context of [a prior art reference], a skilled artisan would recognize that the reference discloses a complete formulation—excluding the possibility of an additional active ingredient.")); *see also Amneal v. Almirall*, Paper 58, 41 ("It is not Garrett's mere silence as to the presence of adapalene, but its disclosure of complete dapsone formulations to treat acne in its absence that suggests that adapalene is not included in Garrett's formulations. … Thus, a skilled artisan would have understood based on Garrett's disclosure that no adapalene was included or otherwise required for any of the dapsone formulations.").

None of the named components in the formulation of Example 5 is a monosaccharide or dissacharide. Accordingly, Uhlmann discloses a formulation that is free of monosaccharides and dissacharides or at least less than 0.1% (w/w) of the formulation. *See* n.2; EX1002, ¶¶150-153.

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

1. Dependent Claims 2, 3, And 8-13

a) **[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.

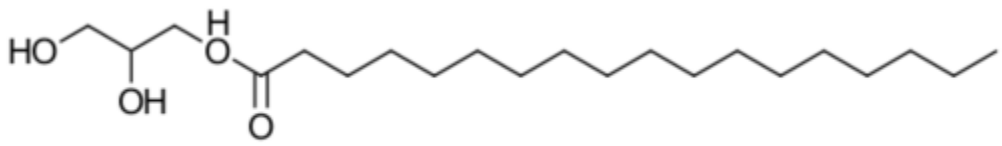
[11] The formulation of claim 1, wherein the formulation further comprises less than or equal to 0.99%, 0.95%, 0.9%, 0.8%, 0.7%, 0.6%, 0.5%, 0.4%, 0.3%, 0.2%, or 0.1% w/w of a non-cyclic polyol having 2 to 12 carbon atoms.

[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.

Uhlmann renders obvious [2], [3], and [8]-[13]. The only component in Example 5 that meets the claimed "non-cyclic polyol having 2 to 5 carbon atoms" or "2 to 12 carbon atoms" is ***glycerine***. As more fully explained below, it would have been obvious to replace ***glycerine*** with another ***alcohol***, such as ***isopropanol***, which is ***not*** a non-cyclic polyol. EX1002, ¶¶155-157.

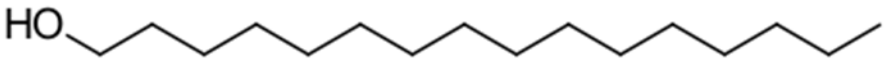
At the outset, the other components in the formulation of Example 5 that include hydroxy (-OH) groups do not meet the claimed "non-cyclic polyol having 2 to 5 carbon atoms" or "2 to 12 carbon atoms." *First*, one of the polyols contained in the formulation of Example 5 is ***glyceryl stearate***. But ***glyceryl stearate*** is ***not*** a "non-cyclic polyol ***having 2 to 5 carbon atoms***" or "***having 2 to 12 carbon atoms***." As shown in the structure below, ***glyceryl stearate*** is a non-cyclic polyol containing 21 carbon atoms. EX1002, ¶¶157-158.



glyceryl stearate

Second, remaining components that may even remotely resemble a "polyol" are the named alcohols because they contain a hydroxy (-OH) group. As explained in Section XI.A.1.g) [1F], the formulation in Example 5 includes one or more of ***cetyl alcohol***, ***ethanol***, and ***glycerine***. ***Cetyl alcohol*** is ***not*** a non-cyclic ***polyol***,

because it contains only a ***single alcohol*** group, as shown in the following chemical structure. EX1002, ¶¶157, 159.

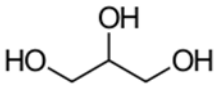
cetyl alcohol 

Ethanol is similarly ***not*** a non-cyclic ***polyol***, because it contains only a ***single alcohol*** group, as shown in the following chemical structure. EX1002, ¶¶157, 159.



ethanol

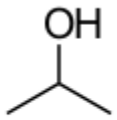
The only component in the formulation of Example 5 that is a "non-cyclic polyol having 2 to 5 carbon atoms" or "2 to 12 carbon atoms" is *glycerine*, which is a non-cyclic polyol having 3 carbon atoms. EX1002, ¶¶156-157, 160.



glycerine

However, a POSITA would have found it obvious to replace *glycerine* with an *alcohol*, such as *isopropanol*, because Uhlmann explains that both *polyols* (such as *glycerine*) and *alcohols* (such as *isopropanol*) are interchangeable with one another. EX1004, 5:53-6:13 ("***Alcohols, diols or polyols with a low C number*** and their ethers, ***preferably*** … *isopropanol*, … *glycerine*, …."). As shown below,

isopropanol contains only a ***single alcohol group*** and, hence, is ***not*** a non-cyclic ***polyol***. EX1002, ¶161.



isopropanol

Based on Uhlmann's disclosure that ***glycerine*** and ***isopropanol*** are suitable alternatives with one another, a POSA would have found it trivial to replace ***glycerine*** with ***isopropanol***, as shown 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); EX1002, ¶162. 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/polyols suitable for use with the disclosed topical formulations. EX1002, ¶162.

Further, 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***. *See, e.g.,* EX1014, 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."); EX1015, 1, 5-15, Fig. 7. And, one of the well-known substitutable components to replace ***glycerine*** would have been ***isopropanol***, as taught by Uhlmann. EX1004, 5:53-6:13. A POSA would have been motivated to replace ***glycerine*** with ***isopropanol*** and would have had a reasonable expectation of success in doing so because it 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). EX1002, ¶163.

The resulting "Day-car[e] skin cream O/W" formulation, which replaces ***glycerine*** with ***isopropanol***, comprises ***zero*** non-cyclic polyol having 2-5 or 2-12 carbon atoms, and meets the claimed "less than 1% w/w," "less than or equal to

0.99% …w/w," "essentially no," and "no" non-cyclic polyol having 2-5 or 2-12 carbon atoms. *See* n.2; EX1002, ¶¶164-165. *See also Ineos v. Berry Plastics*, 865, 869 (citing *Titanium Metals v. Banner*, 775, 782; *see also In re Geisler*, 1465, 1469-71.

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

1. Independent Claim 1

a) [1Pre] A formulation comprising:

To the extent limiting, Uhlmann discloses [1Pre]. Uhlmann discloses "cosmetic or dermatological preparations" that "use a conventional formulation base." EX1004, 5:11-17, Title. For example, Uhlmann discloses a "Sun Milk O/W" formulation in Example 3. EX1004, Example 3; EX1002, ¶¶175-176.

b) [1A] (a) a nanoemulsion comprising:

At the outset, as discussed in Section IX.A [Claim Construction], the '146 Patent states 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. Under this lexicographic definition, Uhlmann discloses [1A]. EX1002, ¶¶177-178.

Uhlmann discloses a "Sun Milk ***O/W***" formulation in Example 3. EX1004, Example 3; *see also id.*, 5:39-40 (explaining "an emulsion of … the oil-in-water type (O/W)"). Uhlmann explains that the "sun protection milk" in Example 3 is an

"***[e]mulsion***[] according to the invention." EX1004, 6:8-13; *see also id.*, 5:35-42, 6:39-48. Accordingly, Uhlmann discloses [1A]. EX1002, ¶179.

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

Uhlmann discloses [1B]. Uhlmann explains that suitable solvents for "***[e]mulsions*** according to the invention"—such as the "Sun Milk O/W" in Example 3—may be "***water*** or ***aqueous solutions***." EX1004, 5:53-6:13. In Example 3, the solvent is ***water***:

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; EX1002, ¶¶180-181. Because ***water*** is the solvent, the ***water*** forms the ***aqueous phase*** and meets the ***at least one aqueous component*** of the nanoemulsion in Example 3. Indeed, the '146 Patent itself explains that the ***aqueous***

component "comprises an ***aqueous phase*** or ***forms an aqueous phase***." EX1001, 6:6-9. EX1002, ¶182.

In Example 3, ***water*** is the majority component of the formulation, which further confirms that the formulation in Example 3 is an oil-in-water dispersion, meeting the claimed "nanoemulsion" recited in [1A]. ***Water*** "make[s] up to 100.0" "[p]ercent[] by weight" of the "Sun Milk O/W" formulation. The other components of the formulation make up 32.8% (w/w) plus an amount of "perfume, preservative" which is marked as "q.s." EX1004, Example 3, 8:23-26. It was well-known that "q.s." means a "sufficient quantity" of the ingredient specified by the supplier of that ingredient. *See, e.g.,* EX1006, [0045]. And typical amounts of "perfume" and "preservative" in such formulations range from 0.01-5.0% (w/w) and 0.01-2% (w/w), respectively. *See, e.g.,* EX1005, [0010]-[0011]; *see also* EX1007, Appendix A, Appendix B. Hence, the amount of ***water*** in Example 3 is about ***67.2% (w/w)*** (assuming no "perfume, preservative") to about ***60.2% (w/w)*** (assuming maximum typical amounts of "perfume" and "preservative" of about 5% (w/w) and 2% (w/w), respectively). EX1002, ¶¶183-186.

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

Uhlmann discloses [1C]. Uhlmann discloses a "Sun Milk O/W" emulsion. *See* Section XI.C.1.b) [1A]. "O/W emulsions" are "dispersions of a liquid, half solid or solid inner (discontinuous) lipid phase in an outer aqueous (continuous) phase"

that contain "emulsifiers." *See, e.g.,* EX1004, 6:39-48. Accordingly, the "discontinuous" lipid phase that contains emulsifiers of the O/W emulsion meets the claimed "**carrier component**." EX1002, ¶¶187-189.

Indeed, the '146 Patent itself explains that the two phases in an O/W emulsion are the hydrophobic carrier component and the aqueous component. EX1001, 3:47-52 ("[i]n oil in water nanoemulsion formulations, there are two different phases…: one is the ***hydrophobic carrier component***…and the other one the aqueous component."); EX1002, ¶190.

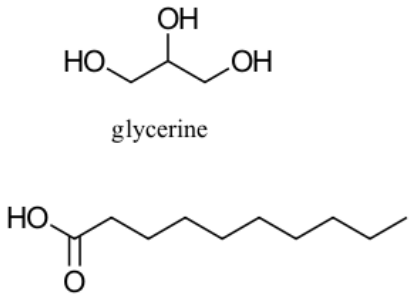
e) [1D] (1) at least one lipophilic component,

Uhlmann discloses [1D]. Uhlmann explains that "[e]mulsions according to the invention"—such as the "Sun Milk O/W" in Example 3—may contain "***[o]ils*** such as ***triglycerides of capri[c] or caprylic acid***." EX1004, 5:53-6:13. In Example 3, at least ***caprylic/capric triglyceride*** meets the "***at least one lipophilic component***:"

Example 3

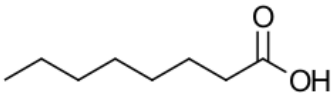
Sun Milk O/W	Percentage by weight
Octylmethoxycinnamate	5.0
Butylmethoxydibenzoylmethane	1.0
Cetearylalcohol + PEG-40 castor oil + Sodiumcetearylsulphate	2.5
Glyceryllanolate	1.0
Laurylmethicon copolyol	0.5
Mineral oil (DAB 9)	5.0
Caprylic/capric triglyceride	5.0
Acrylamide/sodiumacrylate copolymer	0.3
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. ***Caprylic/capric triglyceride*** has a glycerine backbone with capric acid and caprylic acid pendant groups:

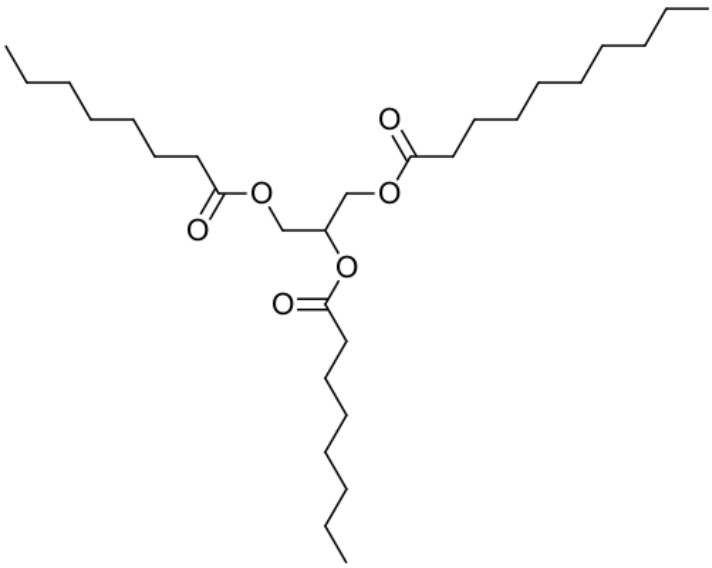


glycerine

capric acid



caprylic acid



capric/caprylic triglyceride

See, e.g., EX1009, 1; EX1002, ¶¶191-192.

The ***caprylic/capric triglyceride*** has hydrophobic tail groups that are part of the "discontinuous" lipid phase in the O/W emulsion. *See* Section XI.C.1.d) [1C]; EX1002, ¶192.

Indeed, the '146 Patent itself explains that the ***lipophilic component*** may include "a ***lipid***" and is preferentially "a ***caprylic and/or capric triglyceride and/or a mixture thereof***." EX1001, 15:9-25. In the working examples of the '146 Patent, the ***at least one lipophilic component*** of the nanoemulsions BF200, BF215, and BF220 is "***caprylic/capric triglycerides***." EX1001, Example 1, Tables 2, 3 (labeling "***caprylic/capric triglycerides***" as the "***lipid core***" of the "carrier component"); *see also id.*, 20:40-21:37; EX1002, ¶¶193-194.

In Example 3 of Uhlmann, the ***caprylic/capric triglyceride*** meets the ***at least one lipophilic component***. Accordingly, Uhlmann discloses [1D]. EX1002, ¶194.

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

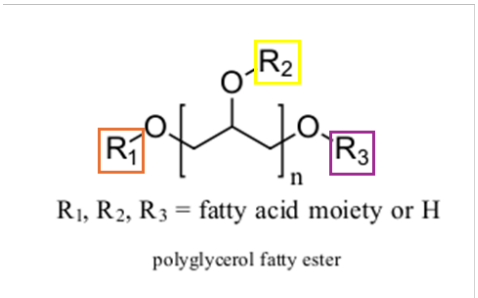
Uhlmann discloses [1E]. Uhlmann explains that "[e]mulsions according to the invention"—such as the "Sun Milk O/W" in Example 3—may contain "the usual type of ***emulsifier*** used for this type of formulation" to "prevent[] phase separation." EX1004, 6:8-13, 6:46-48. In Example 3, one or more of ***PEG-40 castor oil***, ***sodium cetearyl sulphate***, and ***lauryl methicone copolyol*** meets the "***at least one surfactant***:"

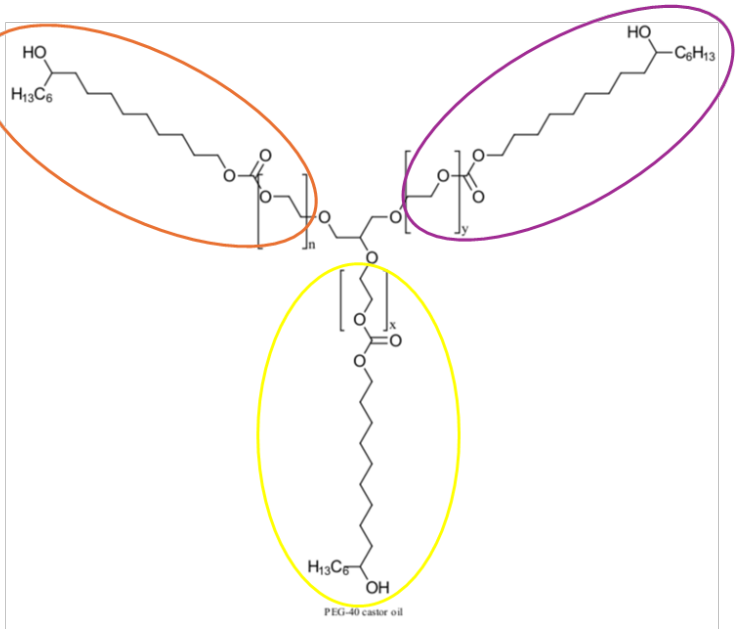
Example 3

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; EX1002, ¶¶195-196.

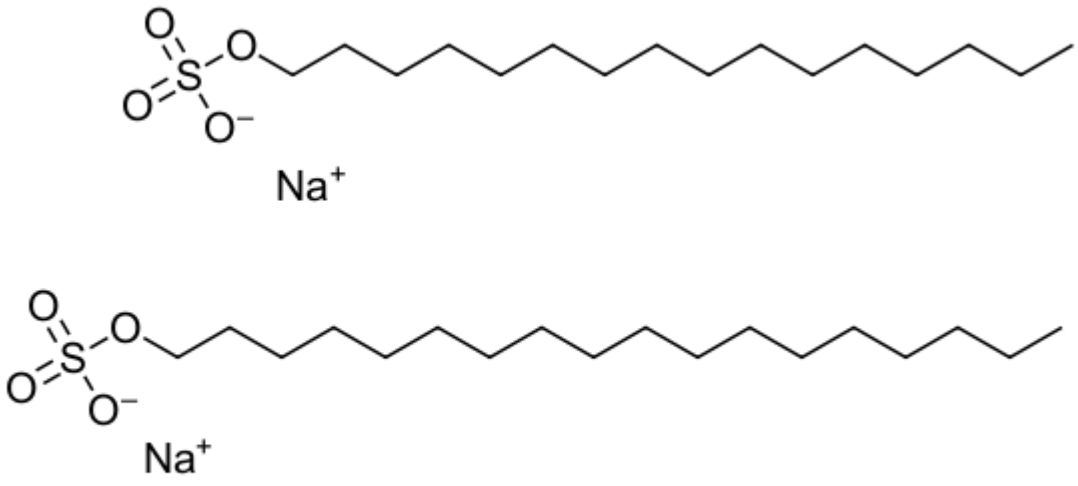
PEG-40 castor oil is a polyoxyethylene ester of castor oil fatty acids and is a polyglycerol fatty ester ***surfactant***:





See, e.g., EX1011, 3 ("Examples of non-ionic[ ]surfactants [include] … polyoxyl 40 hydrogenated castor oil …"); EX1002, ¶197.

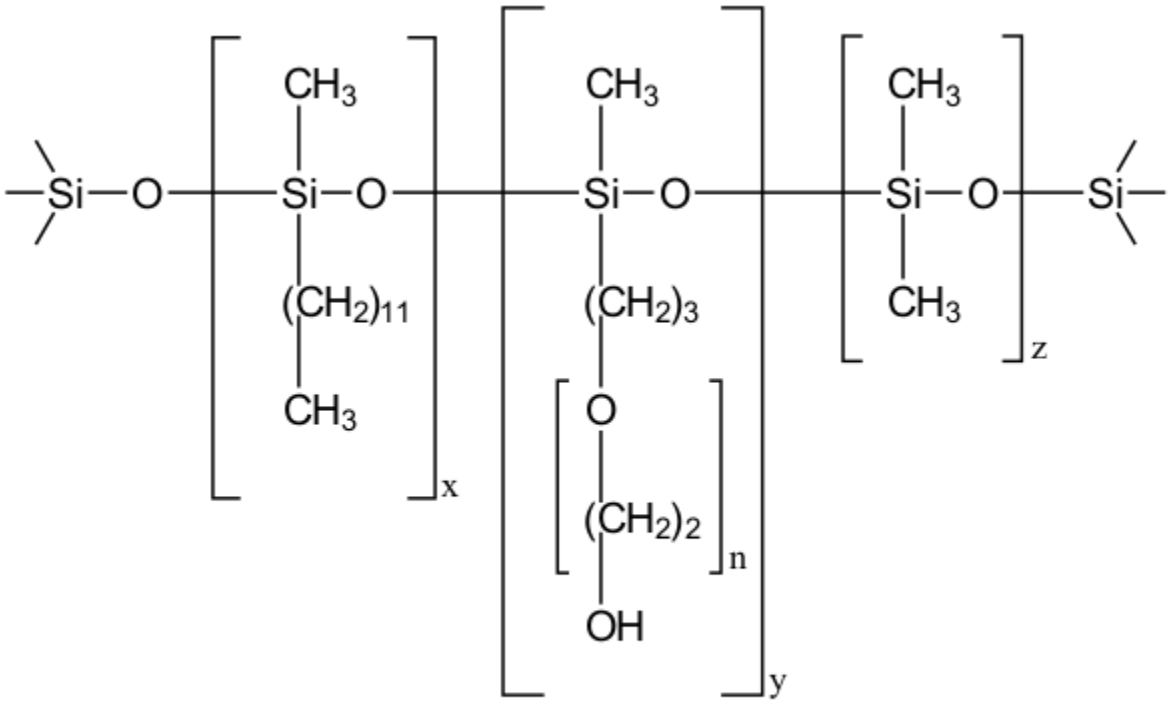
Sodium cetearyl sulphate is an anionic alkylsulfate ***surfactant***:



sodium cetearyl sulphate

See, e.g., EX1016, 1 ("Sodium cetearyl sulfate is a surfactant…"); EX1002, ¶198.

Lauryl methicone copolyol is a ***surfactant***:



lauryl methicone copolyol

See, e.g., EX1017, 3 ("Dimethicone copolyol surfactants …"); EX1002, ¶199.

PEG-40 castor oil, ***sodium cetearyl sulphate***, and ***laurylmethicone copolyol*** each have a hydrophilic head group and a hydrophobic tail group and function as the ***emulsifiers*** of the "discontinuous" lipid phase in the O/W emulsion and meets the claimed "carrier component." *See* Section XI.C.1.d) [1C]; EX1002, ¶200.

Indeed, the '146 Patent itself uses "***surfactant***" and "***emulsifier***" interchangeably. 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***. …"). And, the '146 Patent explains 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; EX1002, ¶¶201-202.

In Example 3 of Uhlmann, the ***PEG-40 castor oil*** is a polyglycerol fatty ester ***surfactant*** and the ***sodium cetearyl sulphate*** is an anionic alkylsulfate ***surfactant***. Accordingly, Uhlmann discloses [1E]. EX1002, ¶202.

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

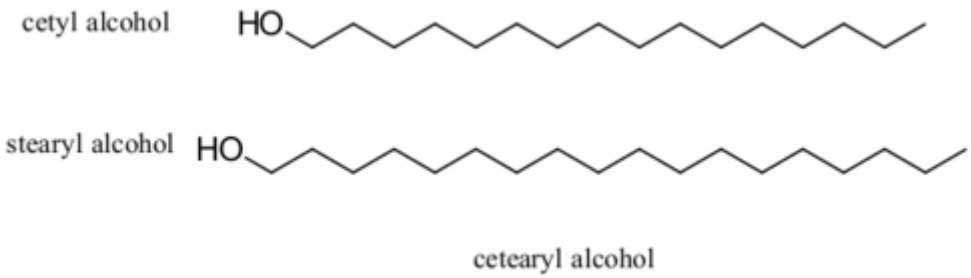
Uhlmann discloses [1F]. Uhlmann explains that "[e]mulsions according to the invention"—such as the "Sun Milk O/W" in Example 3—may contain "***[a]lcohols, diols or polyols with a low C number***." EX1004, 5:53-6:13. In Example 3, one or more of ***cetearyl alcohol***, ***glycerine***, and ***ethanol*** meets the "***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. Each of ***cetearyl alcohol***, ***glycerine***, and ***ethanol*** are alcohols. EX1002, ¶¶203-204.

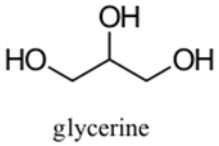
Cetearyl alcohol is a mixture of cetyl alcohol and stearyl alcohol:



cetearyl alcohol

Cetearyl alcohol has hydrophobic tail groups that are part of the "discontinuous" lipid phase in the O/W emulsion. *See* Section XI.C.1.d) [1C]; EX1002, ¶205.

Glycerine and ***ethanol*** have the following structures:



glycerine

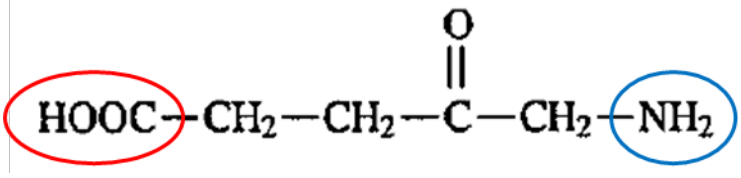


ethanol

Glycerine and ***ethanol*** each have hydroxy (-OH) groups that may be associated with the hydrophilic head groups of the ***surfactants*** contained in the "discontinuous" lipid phase. *See, e.g.,* EX1011, 2, 3, Fig. 3; *see also* Sections XI.C.1.d) [1C], XI.C.1.f) [1E]. Accordingly, Uhlmann discloses [1F]. EX1002, ¶¶206-207.

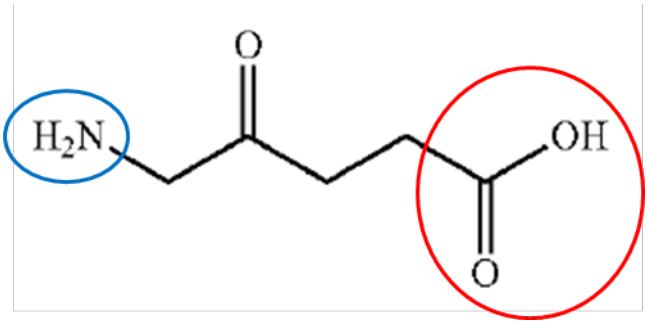
h) [1G] (b) 5-aminolevulinic acid and/or a derivative, a precursor, a metabolite, and/or a pharmaceutically acceptable salt thereof,

Uhlmann discloses [1G]. Uhlmann discloses O/W emulsions with "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 explains that "***δ-aminolevulinic acid*** (also called δ-ALA, 5-amino-4-oxopentanoic acid, δ-amino-γ-keto-valeric acid) has the following structure:"



EX1004, 2:28-34 (annotated). ***δ-aminolevulinic acid*** is ***5-aminolevulinic acid***. EX1002, ¶¶208-210.

Indeed, the '146 Patent itself provides the structure of ***5-aminolevulinic acid*** as being identical, where the corresponding carboxylic and amino groups have been highlighted for ease of reference:



EX1001, 19:17-28 (annotated); EX1002, ¶210.

The "Sun Milk O/W" emulsion in Example 3 comprises ***δ-aminolevulinic acid***:

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. Accordingly, Uhlmann discloses [1G]. EX1002, ¶211.

i) [1H] wherein the formulation comprises essentially no[4] propylene glycol and essentially no sorbitol.

The "Sun Milk O/W" formulation of Example 3 does not contain any propylene glycol or sorbitol:

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

[4] The '146 Patent explains that "the expression[] … 'comprises essentially no compound X' …specif[ies] that the formulation is either free of compound X or comprises less than 0.1% (w/w) … based on the total weight of the formulation." EX1001, 6:50-59. EX1002, ¶214. The expression "comprises essentially no…" is similarly recited in limitations [1H], [9], [12], and [17].

EX1004, Example 3. Example 3 details a complete formulation that "make[s] up to 100.0" "[p]ercent[] by weight" with water, which excludes the possibility of an additional unnamed ingredient. EX1004, Example 3, 8:23-26; EX1002, ¶¶212-213. *See, e.g., United Services Automobile Association v. PNC Bank N.A.*, No. 2023-2244, 2025 WL 706080, at *3 (Fed. Cir. Mar. 5, 2025) ("In determining what a prior art reference discloses, we look to what a skilled artisan would understand from reading the reference, which includes the internal context within the reference.") (citing *Almirall, LLC v. Amneal Pharmaceuticals LLC*, 28 F.4th 265 (Fed. Cir. Mar. 14, 2022) ("[I]t was reasonable for the Board to find that, in the context of [a prior art reference], a skilled artisan would recognize that the reference discloses a complete formulation—excluding the possibility of an additional active ingredient.")); *see also Amneal Pharmaceuticals LLC v. Almirall, LLC*, IPR2019-00207 (PTAB May 29, 2020), Paper 58, 41 ("It is not Garrett's mere silence as to the presence of adapalene, but its disclosure of complete dapsone formulations to treat acne in its absence that suggests that adapalene is not included in Garrett's formulations. … Thus, a skilled artisan would have understood based on Garrett's disclosure that no adapalene was included or otherwise required for any of the dapsone formulations."). Accordingly, Uhlmann discloses a formulation that is free of propylene glycol and sorbitol or at least contains less than 0.1% (w/w) of

propylene glycol and sorbitol based on the total weight of the formulation. EX1002, ¶214.

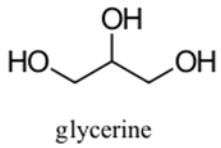
2. Dependent Claims 4 And 16

a) [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.

[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.

Uhlmann discloses [4] and [16]. As explained in Section XI.C.1.g) [1F], Uhlmann discloses ***glycerine*** as one of the ***at least one alcohol*** in the carrier component. EX1004, Example 3; EX1002, ¶¶215-216, 218-219

For [4], ***glycerine*** has 3 carbon atoms:



glycerine

EX1002, ¶217.

As for [16], ***glycerine*** is 3.0% (w/w) of the formulation, is within the claimed "0.1% to 10% (w/w)." EX1004, Example 3, 8:23-26; EX1002, ¶¶220-221.

3. Dependent Claim 5

a) [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).

Uhlmann discloses [5]. As explained in Section XI.C.1.c) [1B], Uhlmann discloses ***water*** in Example 3 and meets the claimed ***at least one aqueous component***. EX1004, Example 3. ***Water*** "make[s] up to 100.0" "[p]ercent[] by weight" of the "Sun Milk O/W" formulation. EX1004, Example 3. The other components of the formulation make up 32.8% (w/w) plus an amount of "perfume, preservative" which is marked as "q.s." EX1004, Example 3, 8:23-26. As explained above in Section XI.C.1.c) [1B], it was well-known that "q.s." means a "sufficient quantity" of the ingredient specified by the supplier of that ingredient. *See, e.g.,* EX1006, [0045]. And typical amounts of "perfume" and "preservative" in such formulations range from 0.01-5.0% (w/w) and 0.01-2% (w/w), respectively. *See, e.g.,* EX1005, [0010]-[0011]; *see also* EX1007, Appendix A, Appendix B. Hence, the amount of ***water*** in Example 3 is about ***67.2% (w/w)*** (assuming no "perfume, preservative") to about ***60.2% (w/w)*** (assuming maximum typical amounts of "perfume" and "preservative" of about 5% (w/w) and 2% (w/w), respectively). EX1002, ¶¶222-228. Example 3 discloses (Ground IIA), or at a minimum renders

obvious (Ground IIC), [5].[5] EX1002, ¶¶222-228, 262-268. *See Ineos v. Berry Plastics*, 865, 869 ("When a patent claims a range, as in this case, that range is anticipated by a prior art reference if the reference discloses a point within the range.") (*citing Titanium Metals v. Banner*, 775, 782; *see also In re Geisler*, 1465, 1469-71 (Fed. Cir. 1997).

[5] To the extent Patent Owner argues that Uhlmann alone does not teach or render obvious [5], Petitioner submits an alternative Ground IIC based on the combination of Uhlmann and Palazzolo. A POSA would have been able to combine the teachings of Uhlmann with Palazzolo with a reasonable expectation of success because Palazzolo merely 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, [0010]-[0011]. It would have been a trivial combination to put in the typical amounts of "perfume, preservative" to achieve the predictable result of a formulation that smells nice and/or lasts longer. EX1002, ¶¶262-268.

4. Dependent Claim 6

a) [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.

Uhlmann discloses [6]. As explained above in Section XI.C.1.e) [1D], Uhlmann discloses ***caprylic/capric triglyceride*** as one of the components of the ***at least one lipophilic component*** in Example 3. Uhlmann discloses ***caprylic/capric triglyceride as 5.0% (w/w)*** of the nanoemulsion, which is within the claimed "0.1% to 30% (w/w)." EX1004, Example 3, 8:23-26; EX1002, ¶¶229-232. *See Ineos v. Berry Plastics*, 865, 869 ("When a patent claims a range, as in this case, that range is anticipated by a prior art reference if the reference discloses a point within the range.") (*citing Titanium Metals v. Banner*, 775, 782; *see also In re Geisler*, 1465, 1469-71 (Fed. Cir. 1997).

5. Dependent Claim 7

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

Uhlmann discloses [7]. As explained in Section XI.C.1.i) [1H], Uhlmann discloses a "Sun Milk O/W" formulation that does not contain propylene glycol. EX1002, ¶¶233-234.

6. Dependent Claim 14

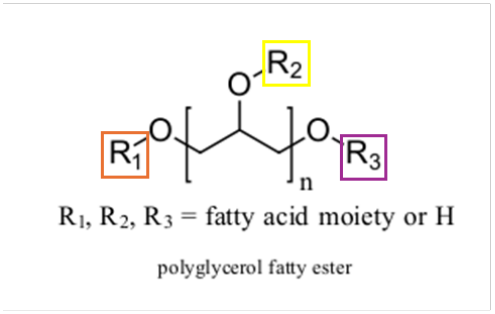
a) [14] The formulation of claim 1, wherein the at least one lipophilic component comprises: triglycerides and/or mixtures thereof; or a caprylic triglyceride, a capric triglyceride, or a mixture thereof.

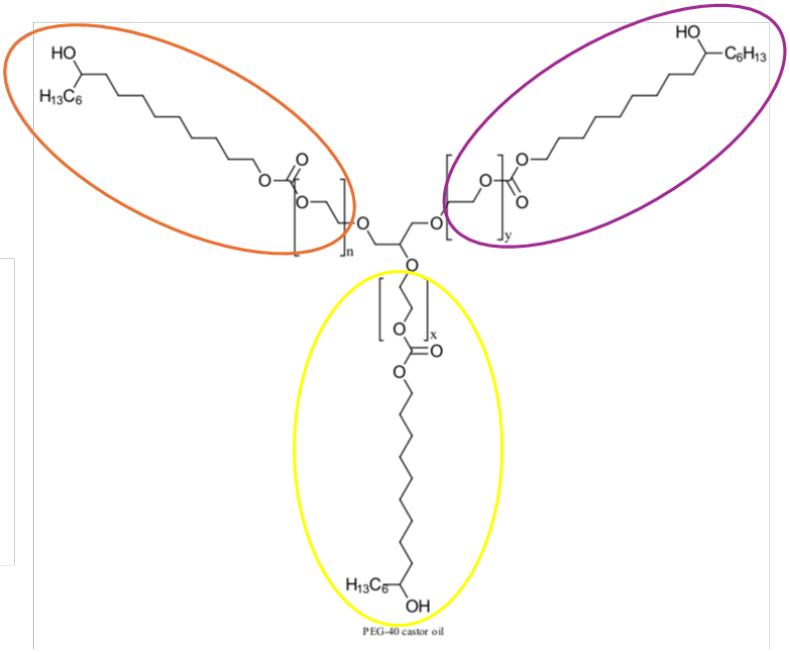
Uhlmann discloses [14]. As explained in Section XI.C.1.e) [1D], Uhlmann discloses ***caprylic/capric triglyceride*** that meets the "***at least one lipophilic component***." EX1002, ¶¶234-236.

7. Dependent Claim 15

a) [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.

Uhlmann discloses [15]. As explained in Section XI.C.1.f) [1E], Uhlmann discloses ***PEG-40 castor oil*** as one of the components of the ***at least one surfactant***. ***PEG-40 castor oil*** has the following chemical structure and is a polyoxyethylene-type surfactant. *See, e.g.,* EX1012, 1 ("Polyoxyethylenes of less than ca. 20 000 number-average molecular mass are usually referred to as poly(ethylene glycols)."); EX1002, ¶¶238-240.

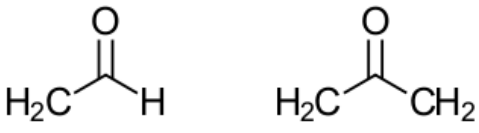


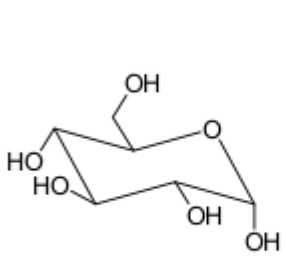


8. Dependent Claim 17

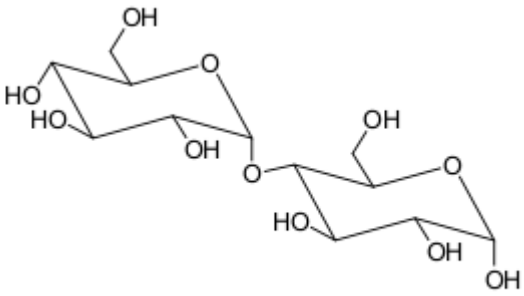
a) [17] The formulation of claim 1, wherein the formulation further comprises essentially no monosaccharides and disaccharides.

A monosaccharide is a simple sugar that consists of a single aldehyde or ketone with at least two hydroxyl groups. A disaccharide is a sugar composed of two monosaccharides. *See, e.g.,* EX1013, 229-230, 233, 237. Shown below are an exemplary aldehyde and ketone, and an exemplary monosaccharide (glucose) and disaccharide (maltose, made up of two glucose molecules). EX1002, ¶242.





glucose



maltose

The "Sun Milk O/W" formulation of Example 3 does not contain any monosaccharides or disaccharides:

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. Example 3 details a complete formulation that "make[s] up to 100.0" "[p]ercent[] by weight" with water, which excludes the possibility of an additional unnamed ingredient. EX1004, Example 3, 8:23-26; EX1002, ¶243. *See, e.g., United Services v. PNC Bank*, *3 ("In determining what a prior art reference

discloses, we look to what a skilled artisan would understand from reading the reference, which includes the internal context within the reference.") (citing *Almirall v. Amneal*, 265, 273 ("[I]t was reasonable for the Board to find that, in the context of [a prior art reference], a skilled artisan would recognize that the reference discloses a complete formulation—excluding the possibility of an additional active ingredient.")); *see also Amneal v. Almirall*, Paper 58, 41 ("It is not Garrett's mere silence as to the presence of adapalene, but its disclosure of complete dapsone formulations to treat acne in its absence that suggests that adapalene is not included in Garrett's formulations. … Thus, a skilled artisan would have understood based on Garrett's disclosure that no adapalene was included or otherwise required for any of the dapsone formulations.").

None of the named components in the formulation of Example 3 is a monosaccharide or dissacharide. Accordingly, Uhlmann discloses a formulation that is free of monosaccharides and dissacharides or at least less than 0.1% (w/w) of the formulation. *See* n.4; EX1002, ¶¶241-244.

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

1. Dependent Claims 2, 3, And 8-13

a) **[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.

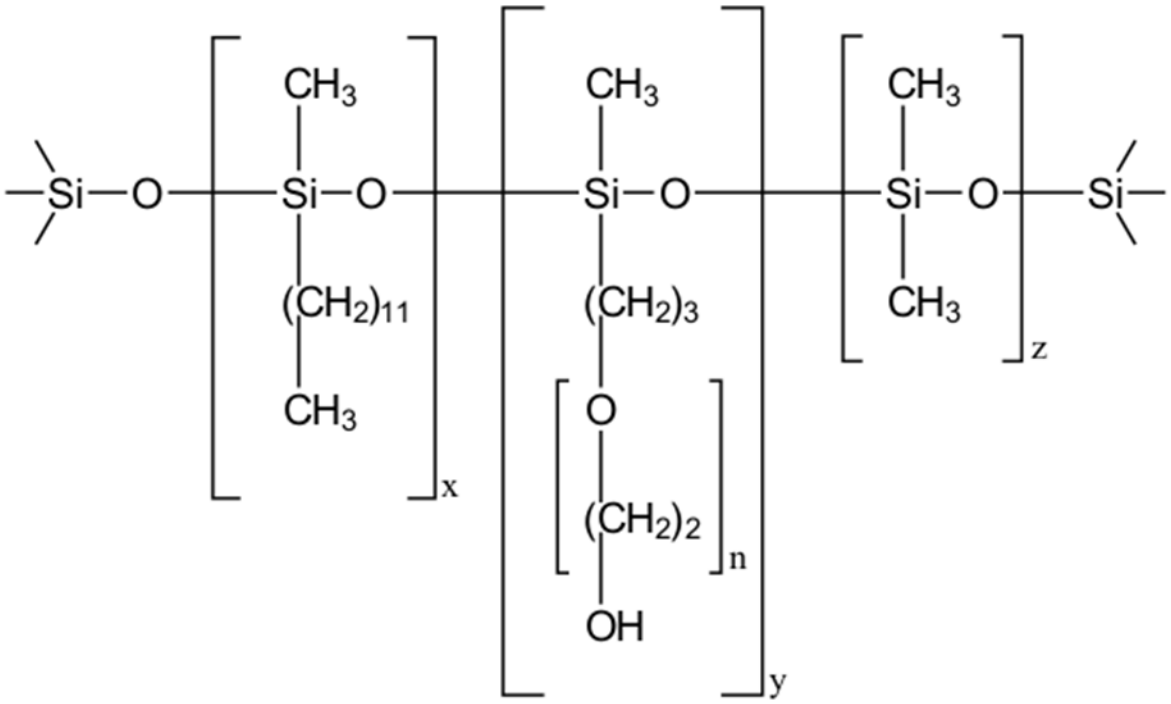
[11] The formulation of claim 1, wherein the formulation further comprises less than or equal to 0.99%, 0.95%, 0.9%, 0.8%, 0.7%, 0.6%, 0.5%, 0.4%, 0.3%, 0.2%, or 0.1% w/w of a non-cyclic polyol having 2 to 12 carbon atoms.

[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.

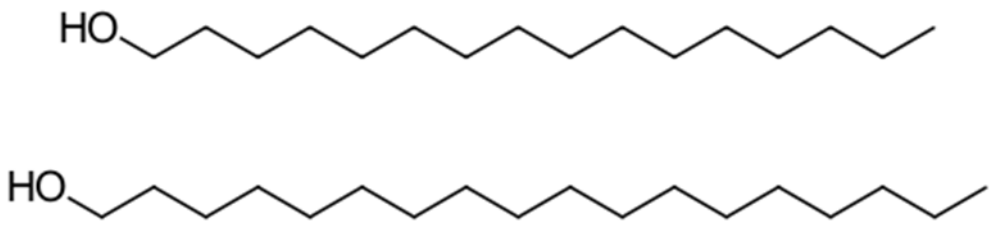
Uhlmann renders obvious [2], [3], and [8]-[13]. The only component in Example 3 that meets the claimed "non-cylic polyol having 2 to 5 carbon atoms" or "2 to 12 carbon atoms" is ***glycerine***. As more fully explained below, it would have been obvious to replace ***glycerine*** with another ***alcohol***, such as ***isopropanol***, which is ***not*** a non-cyclic polyol. EX1002, ¶¶246-248.

However, the Petition ***first*** explains why the other components that include hydroxy (-OH) groups do not meet the claimed "non-cyclic polyol having 2 to 5 carbon atoms" or "2 to 12 carbon atoms." One of the polyols contained in the formulation of Example 3 is ***lauryl methicone copolyol***. EX1004, Example 3. But ***lauryl methicone copolyol*** has 25 carbon atoms and does not meet the claimed "non-cyclic polyol ***having 2 to 5 carbon atoms***" or "***having 2 to 12 carbon atoms***." As shown in the structure below, ***lauryl methicone copolyol*** has at least 25 carbon atoms. EX1002, ¶¶248-249.



lauryl methicone copolyol

As for any remaining components that may even remotely resemble a "polyol" because it contains an alcohol (-OH) group, as explained in Section XI.C.1.g) [1F], the formulation in Example 3 includes one or more of ***cetearyl alcohol***, ***ethanol***, and ***glycerine***. ***Cetearyl alcohol*** is ***not*** a non-cyclic ***polyol***, because each molecule in the mixture contains only a ***single alcohol*** group, as shown in the following chemical structure. EX1002, ¶¶248, 250.



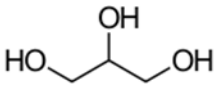
cetearyl alcohol

Ethanol is similarly ***not*** a non-cyclic ***polyol***, because it contains only a ***single alcohol*** group, as shown in the following chemical structure. EX1002, ¶¶248, 250.



ethanol

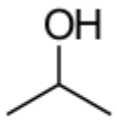
The only component in the formulation of Example 3 that is a "non-cyclic polyol having 2 to 5 carbon atoms" or "2 to 12 carbon atoms" is ***glycerine***, which is a non-cyclic polyol having 3 carbon atoms. EX1002, ¶¶247-248, 251.



glycerine

However, a POSITA would have found it obvious to replace ***glycerine*** with an ***alcohol***, such as ***isopropanol***, because Uhlmann explains that both ***polyols***, such as ***glycerine***, and ***alcohols***, such as ***isopropanol***, are interchangeable with one

another. EX1004, 5:53-6:13 ("***Alcohols*, *diols or polyols* *with a low C number*** and their ethers, ***preferably*** … ***isopropanol***, … ***glycerine***, …."). As shown below, ***isopropanol*** is ***not*** a non-cyclic ***polyol*** because it contains only a ***single alcohol group***. EX1002, ¶252.



isopropanol

Based on Uhlmann's disclosure that ***glycerine*** and ***isopropanol*** are suitable alternatives with one another, a POSA would have found it trivial to replace ***glycerine*** with ***isopropanol***, as shown below:

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
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); EX1002, ¶253. 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/polyols suitable for use with the disclosed topical formulations. EX1002, ¶253.

Further, 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***. *See, e.g.,* EX1014, 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."); EX1015, 1, 5-15, Fig. 7. And, one of the well-known substitutable components to replace ***glycerine*** would have been ***isopropanol***, as taught by Uhlmann. EX1004, 5:53-6:13. A POSA would have been motivated to replace ***glycerine*** with ***isopropanol*** and had a reasonable expectation of success in doing so because it is nothing more than simple substitution of one known element (*i.e.*, ***isopropanol***) for another (*i.e.,* ***glycerine***) to obtain predictable results (*i.e.,* a stable topical formulation). EX1002, ¶254.

The resulting "Sun Milk O/W" formulation, which replaces ***glycerine*** with ***isopropanol***, comprises ***zero*** non-cyclic polyol having 2-5 or 2-12 carbon atoms, encompassing the claimed "less than 1% w/w," "less than or equal to 0.99% …w/w," "essentially no," and "no" non-cyclic polyol having 2-5 or 2-12 carbon atoms. *See* n.4; EX1002, ¶¶255-256. *See also Ineos v. Berry Plastics*, 865, 869 (citing *Titanium Metals v. Banner*, 775, 782; *see also In re Geisler*, 1465, 1469-71.

2. Dependent Claim 16

a) [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.

To the extent [16] requires all of the compounds identified in claim 1 as the claimed "***at least one alcohol***" to meet the claimed "0.1% to 10% (w/w)," Example 3 still renders obvious [16]. ***Ethanol*** is 5.0% (w/w) of the formulation and ***cetearyl alcohol*** does not exceed 2.5% (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."). Accordingly, 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). EX1002, ¶¶258-259. *See In re Aller*, 220 F.2d 454, 456 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C

and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%); *K-Swiss Inc. v. Glide N Lock GmbH,* 567 Fed. App'x 906 (Fed. Cir. 2014)(reversing the Board's decision, in an appeal of an inter partes reexamination proceeding, that certain claims were not prima facie obvious due to non-overlapping ranges); *In re Brandt,* 886 F.3d 1171, 1177 (Fed. Cir. 2018) (finding claimed range to be obvious because the claimed range of "less than 6 pounds per cubic feet" and the prior art range of "between 6 lbs./ft^3 and 25 lbs./ft^3" were so mathematically close that the difference between the claimed ranges was virtually negligible absent any showing of unexpected results or criticality.). There is no criticality to the claimed "0.1% to 10% (w/w)." Accordingly, Uhlmann Example 3 renders obvious [16]. EX1002, ¶¶259-260.

XII. Conclusion

Petitioner respectfully requests that the Director and Board institute post grant review, hold the Challenged Claims unpatentable, and cancel the Challenged Claims.

Dated: January 16, 2026

Respectfully submitted,

/Yung-Hoon Ha/

Yung-Hoon Ha (Reg. No. 56,368)
DESMARAIS LLP
230 Park Avenue
New York, NY 10169
Telephone: 212-351-3400
Facsimile: 212-351-3401

Counsel for Petitioner
Sun Pharmaceutical Industries, Inc.

CERTIFICATION UNDER 37 C.F.R. § 42.24(d)

I hereby certify that this Petition for *Post-Grant* Review of U.S. Patent No. 12,280,146 has, excluding the portions exempted under 37 C.F.R. § 42.24(a), 10,139 words as counted by the word-processing system used to prepare this document, in compliance with 37 C.F.R. § 42.24(d).

Dated: January 16, 2026

Respectfully submitted,

/Yung-Hoon Ha/
Yung-Hoon Ha (Reg. No. 56,368)
DESMARAIS LLP
230 Park Avenue
New York, NY 10169
Telephone: 212-351-3400
Facsimile: 212-351-3401

Counsel for Petitioner
Sun Pharmaceutical Industries, Inc.

CERTIFICATE OF SERVICE

Under 37 C.F.R. §§ 42.6(e) and 42.105, the undersigned certifies that on January 16, 2026, complete copies of the foregoing and any accompanying exhibits were caused to be served by sending them via Federal Express Priority Overnight shipping, which is at least as fast and reliable as U.S. Priority Mail Express, to the correspondence address of record for U.S. Patent No. 12,280,146 as indicated in Patent Center:

12779 - Lathrop GPM LLP
28 State Street, 7th Floor
Boston, MA
UNITED STATES

Dated: January 16, 2026

Respectfully submitted,

/Yung-Hoon Ha/
Yung-Hoon Ha (Reg. No. 56,368)
DESMARAIS LLP
230 Park Avenue
New York, NY 10169
Telephone: 212-351-3400
Facsimile: 212-351-3401

Counsel for Petitioner
Sun Pharmaceutical Industries, Inc.