

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent of: Kirk E. Apt et al.
U.S. Patent No.: 8,207,363 B2 Attorney Docket No.: 55973-0002IP1
Issue Date: June 26, 2012
Appl. Serial No.: 12/407,687
Filing Date: March 19, 2009
Title: THRAUSTOCHYTRIDS, FATTY ACID COMPOSITIONS, AND
METHODS OF MAKING AND USES THEREOF

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**PETITION FOR *INTER PARTES* REVIEW OF UNITED STATES PATENT
NO. 8,207,363 B2 PURSUANT TO 35 U.S.C. §§ 311–319, 37 C.F.R. § 42**

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EXHIBITS

MARA-1001	U.S. Patent No. 8,207,363 B2 to Apt et al. (“the ’363 patent”)
MARA-1002	Excerpts from the Prosecution History of the ’363 Patent (“the Prosecution History”)
MARA-1003	Declaration of Dr. Jonathan Curtis
MARA-1004	Curriculum Vitae of Dr. Jonathan Curtis
MARA-1005	RESERVED
MARA-1006	RESERVED
MARA-1007	WO 2008/129358 to Radianingtyas et al. (“Radianingtyas”)
MARA-1008	WO 97/37032 to Bijl et al. (“Bijl”)
MARA-1009	Peter D. Nichols et al., <i>New Australian Single Cell and Crop Plant Sources of Health-Enhancing Long-Chain Omega-3 Oils</i> , Australasian Biotechnology 13(5):26–28 (Oct./Nov. 2003) (“Nichols-I”)
MARA-1010	<i>Single Cell Oils</i> , Z. Cohen and C. Ratledge (Eds.), AOCS Press, Champaign, Illinois, USA (2005)
MARA-1011	RESERVED
MARA-1012	RESERVED
MARA-1013	RESERVED
MARA-1014	RESERVED
MARA-1015	U.S. Pat. App. Pub. No. 2004/0161831 to Komazawa et al. (“Komazawa”)
MARA-1016	RESERVED

MARA-1017	RESERVED
MARA-1018	RESERVED
MARA-1019	U.S. Patent No. 5,130,242 to Barclay (“Barclay”)
MARA-1020	Peter D. Nichols et al., <i>Omega-3 oils down under—An update</i> , Inform 15(6):383–385 (June 2004) (“Nichols-II”)
MARA-1021	RESERVED
MARA-1022	<i>Long-Chain Omega-3 Specialty Oils</i> , H. Breivik (Ed.), The Oily Press, Bridgewater, UK (2007)
MARA-1023	<i>Fennema’s Food Chemistry</i> , S. Damodaran and K.L. Parkin (Eds.), CRC Press, Boca Raton, Florida, USA (5th ed. 2017)
MARA-1024	<i>Food Lipids</i> , C.C. Akoh and D.B. Min (Eds.), Marcel Dekker, New York, New York, USA (2nd ed. 2002)
MARA-1025	Adam M. Burja et al., <i>Isolation and characterization of polyunsaturated fatty acid producing Thraustochytrium species: screening of strains and optimization of omega-3 production</i> , Applied Microbiology and Biotechnology 72:1161–1169 (2006)
MARA-1026	RESERVED
MARA-1027	Edwin N. Frankel, <i>Lipid Oxidation</i> , The Oily Press, Cambridge, UK (2nd ed. 2005)
MARA-1028	RESERVED
MARA-1029	RESERVED
MARA-1030	WO 2009/040676 to Kralovec et al. (“Kralovec”)
MARA-1031	RESERVED

- MARA-1032 Thomas Eric Lewis, *Characterisation and application of Australian thraustochytrids*, Doctoral Thesis, University of Tasmania (June 2001)
- MARA-1033 Seshagiri Raghukumar, *Thraustochytrid Marine Protists: Production of PUFAs and Other Emerging Technologies*, Marine Biotechnology 10:631–640 (2008)
- MARA-1034 U.S. Pat. App. Pub. No. 2003/0161864 to Tanaka et al. (“Tanaka”)
- MARA-1035 W.M.N. Ratnayake et al., *Preparation of Omega-3 PUFA Concentrates from Fish Oils via Urea Complexation*, Fat Science Technology 90(10):381–386 (1988)
- MARA-1036 Fereidoon Shahidi and Priyatharini Ambigaipalan, *Omega-3 Polyunsaturated Fatty Acids and Their Health Benefits*, Annual Review of Food Science and Technology 9:345–381 (2018)
- MARA-1037 RESERVED
- MARA-1038 Owen P. Ward and Ajay Singh, *Omega-3/6 Fatty Acids: Alternative Sources of Production*, Process Biochemistry 40:3627–3652 (2005)
- MARA-1039 Anthony P. Bimbo, *Marine Oils*, AOCS Lipid Library, <https://lipidlibrary.aocs.org/edible-oil-processing/marine-oils> (last accessed August 21, 2023)
- MARA-1040 King Wai Fan and Feng Chen, *Chapter 11. Production of High-Value Products by Marine Microalgae Thraustochytrids, in Bioprocessing for Value-Added Products from Renewable Resources: New Technologies and Applications* 293-323, S.-T. Yang (Ed.), Elsevier B.V., Amsterdam, The Netherlands (2007) (“Fan”)
- MARA-1041 Eneko Ganuza Taberna, *Heterotrophic cultivation of microalgae as a source of docosahexaenoic acid for aquaculture*, Doctoral Thesis, University of Las Palmas de Gran Canaria (2008) (“Taberna”)

- MARA-1042 Kim Jye Lee-Chang et al., *Docosahexaenoic Acid Is Naturally Concentrated at the sn-2 Position in Triacylglycerols of the Australian Thraustochytrid Aurantiochytrium sp. Strain TC 20*, Marine Drugs 19:382 (2021)
- MARA-1043 Excerpts from the Prosecution History of U.S. Patent Application No. 16/935,818, filed on July 22, 2020 (“the ’818 application”), which is a child of the ’363 patent
- MARA-1044 U.S. Pat. App. Pub. No. 2003/0060509 to Elswyk (“Elswyk”)
- MARA-1045 U.S. Provisional App. No. 60/821,084
- MARA-1046 J.J. Myher et al., *Stereospecific Analysis of Triacylglycerols Rich in Long-Chain Polyunsaturated Fatty Acids*, Lipids 31(2):207–215 (1996)

LISTING OF CHALLENGED CLAIMS

Claim	Identifier	Claim Language
1	[1pre]	A microbial oil comprising
	[1a]	a triglyceride fraction of at least 70% by weight,
	[1b]	wherein the docosahexaenoic acid content of the triglyceride fraction is at least 50% by weight,
	[1c]	wherein the docosapentaenoic acid n-6 content of the triglyceride fraction is from 0.5% by weight to 6% by weight,
	[1d]	and wherein the oil comprises 5% by weight or less of heptadecanoic acid.
2	[2]	The microbial oil of claim 1, further comprising an arachidonic acid content of the triglyceride fraction of 1.5% or less by weight.
3	[3pre]	A microbial oil comprising
	[3a]	a triglyceride fraction of at least 70% by weight,
	[3b]	wherein the docosahexaenoic acid content of the triglyceride fraction is at least 40% by weight,
	[3c.1]	wherein the docosapentaenoic acid n-6 content of the triglyceride fraction is from at least 0.5% by weight to 6% by weight,
	[3c.2]	wherein the ratio of docosahexaenoic acid to docosapentaenoic acid n-6 is greater than 6:1,
	[3d]	and wherein the oil comprises 5% by weight or less of heptadecanoic acid.
4	[4pre]	A microbial oil comprising

	[4a]	a triglyceride fraction of at least 70% by weight,
	[4b]	wherein the docosahexaenoic acid content of the triglyceride fraction is at least 60% by weight,
	[4c]	and wherein the oil comprises 5% by weight or less of heptadecanoic acid.
5	[5]	The microbial oil of any one of claims 1 to 4, wherein at least 20% of the triglycerides in the triglyceride fraction contain docosahexaenoic acid at two positions in the triglyceride selected from any two of the sn-1, sn-2, and sn-3 positions.
6	[6]	The microbial oil of any one of claims 1 to 4, wherein at least 5% of the triglycerides in the triglyceride fraction contain docosahexaenoic acid at all three of the sn-1, sn-2, and sn-3 positions in the triglyceride.
7	[7]	A food product, cosmetic, or pharmaceutical composition for animals or humans, comprising the microbial oil of any one of claims 1 to 4.
8	[8]	The food product of claim 7, wherein the food product is an infant formula.
9	[9]	The food product of claim 8, wherein the infant formula can be consumed by premature infants.
10	[10]	The food product of claim 7, wherein the food product is milk, a beverage, a therapeutic drink, a nutritional drink, or a combination thereof.
11	[11]	The food product of claim 7, wherein the food product is an additive for animal or human food.
12	[12]	The food product of claim 7, wherein the food product is a nutritional supplement.
13	[13]	The food product of claim 7, wherein the food product is an animal feed.
14	[14]	The animal feed of claim 13, wherein the animal feed is an aquaculture feed.
15	[15]	The animal feed of claim 13, wherein the animal feed

		is a domestic animal feed, a zoological animal feed, a work animal feed, a livestock feed, or a combination thereof.
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Mara Renewables Corporation (“Petitioner” or “Mara”) petitions for *Inter Partes* Review (“IPR”) under 35 U.S.C. §§311–319 and 37 C.F.R. §42 of claims 1-15 (“the Challenged Claims”) of U.S. Patent No. 8,207,363 B2 (“the ’363 patent”). Compelling evidence presented in this Petition demonstrates at least a reasonable likelihood that Mara will prevail with respect to at least one Challenged Claim.

I. REQUIREMENTS FOR IPR UNDER 37 C.F.R. §42.104

A. Grounds for Standing

Mara certifies that the ’363 patent is available for IPR. Mara has not filed any civil litigation challenging the validity of the ’363 patent nor has any litigation been filed against Mara accusing it of patent infringement. Mara is not barred or estopped from requesting this review challenging the Challenged Claims on the below-identified grounds.

B. Challenge and Relief Requested

Mara requests IPR and cancellation of the Challenged Claims on the grounds below. In support, a declaration from Dr. Jonathan Curtis (MARA-1003) is provided. MARA-1003, ¶¶1-312.

Ground	’363 Patent Claims	Basis for Rejection
Ground 1	1-3	Anticipated (§102) by Radianingtyas
Ground 2	1-15	Obvious (§103) over Radianingtyas and Kralovec
Ground 3	1-15	Obvious (§103) over Bijl and Barclay

Each applied reference pre-dates the filing date of the ’363 patent, i.e.,

March 19, 2009, which is the earliest priority date. While Petitioner does not concede as to whether the '363 patent is entitled to the priority date of March 19, 2009 (the "Critical Date"), Petitioner has applied references that pre-date the Critical Date and qualify as prior art, as shown below. None of the applied references was substantively opined on by the Examiner during prosecution of the '363 patent.¹

Reference		Date Published	Section
Radianingtyas (MARA-1007)	WO 2008/129358	October 30, 2008	§102(a),(e)
Kralovec (MARA-1030)	WO 2009/040676	April 2, 2009	§102(e)
Bijl (MARA-1008)	WO 97/37032	October 9, 1997	§102(b)
Barclay (MARA-1019)	U.S. Pat. No. 5,130,242	July 14, 1992	§102(b)

C. Claim Construction

No formal claim constructions are presently necessary since "claim terms need only be construed to the extent necessary to resolve the controversy."

¹ Radianingtyas (as US 2010/0285105), related family members for Bijl (USPN 6,255,505 and EP 0894142), and Barclay appear on the face of the patent, but none was cited in a rejection or discussed substantively during prosecution of the '363 patent.

Wellman, Inc. v. Eastman Chem. Co., 642 F.3d 1355, 1361 (Fed. Cir. 2011). All claim terms should be given their plain and ordinary meaning. MARA-1003, ¶¶15-16.

II. SUMMARY OF THE '363 PATENT

A. Brief Description

Generally, the '363 patent purportedly provides for compositions derived from thraustochytrids and methods of producing or using thraustochytrids or thraustochytrid-derived compositions. MARA-1001, Abstract, 3:4-6, 5:54-6:10; MARA-1003, ¶¶48-53.

Thraustochytrids of the purported invention, as well as microbial oils derived therefrom, are described as having certain fractions, including a triglyceride (TG) fraction and a total fatty acid (TFA) fraction. MARA-1001, 6:23-31, 11:13-13:23, 5:66-6:5. The TG and/or TFA fraction can include varying amounts of docosapentaenoic acid (DPA n-6 or 22:5 n-6), eicosapentaenoic acid (EPA or 20:5 n-3), heptadecaenoic acid (HDA or 17:0), arachidonic acid (ARA or 20:4 n-6), and/or docosahexaenoic acid (DHA or 22:6 n-3). MARA-1001, 1:34-48, 2:53-61, 3:42-62, 4:4-5.

The '363 patent also describes methods of producing microbial oils by culturing thraustochytrids in varying well-known conditions (e.g., using certain amounts of dissolved oxygen) and then extracting their oils. MARA-1001, 4:21-

39, 6:34-50, 7:20-43, 10:1-11; MARA-1019.

The microbial oils of the invention extend to “any oil derived from a microorganism,” including, e.g., a “crude oil,” a “refined oil,” or an “enriched oil.” MARA-1001, 10:13-23. These oils are included in compositions, e.g., “food products, pharmaceutical compositions, cosmetics, and industrial compositions.” MARA-1001, 14:62-64; MARA-1003, ¶¶48-52.

B. Summary of the Prosecution History of the ’363 Patent

U.S. 8,207,363 issued on June 26, 2012, from U.S. Patent Application No. 12/407,687 (“the ’687 application”), filed on March 19, 2009. *See* MARA-1002²; MARA-1003, ¶¶53-54.

The ’363 patent’s prosecution was brief. After two restriction requirements, the Examiner rejected almost all of the then-pending claims over Elswyk, U.S. Pat. Pub. No. 2003/0060509 alone or in combination with Corley et al., U.S. Pat. No. 6,399,803. MARA-1002, 143. Patentee traversed the rejections, arguing that Elswyk provides an algal oil that fails to meet the “at least 70% triglycerides by weight” limitation for multiple reasons. *Id.*, 103-104.

In a final Office Action, the Examiner, however, maintained the prior

² For this reference, page numbers are provided based on the PDF having a total of 337 pages.

rejections. MARA-1002, 71. During an interview, Patentee advanced an interpretation of Elswyk that “the 70% minimum content (for the algal oil composition) refers to [an oil comprising 70% or more of the desired HUFA, which does not require the desired HUFAs to be present in the triglyceride fraction].” MARA-1002, 59, 67, 103-104. The Examiner allowed the pending claims based on this interpretation of Elswyk and the cancelling of non-elected claims. MARA-1002, 20; MARA-1003, ¶¶54-60.

C. The Effective Priority Date of the Claims of the '363 Patent

Claims 1, 3, and 4 of the '363 patent are independent claims, and claims 2 and 5-15 depend directly or indirectly from claims 1, 3, and/or 4. *See* MARA-1003, ¶¶54, 61-62.

D. Level of Ordinary Skill in the Art

A person having ordinary skill in the art relating to the subject matter of the '363 patent as of March 19, 2009 (a “PHOSITA”) would have had a Master of Science degree in an academic discipline emphasizing chemistry, chemical engineering, or biochemistry, in combination with training or at least two to three years of related work experience with lipid chemistry technologies, including but not limited to lipid extraction technologies. MARA-1003, ¶¶63-64. Alternatively, the person could have also had a Doctorate degree in a relevant academic

discipline with one to two years of related work experience in the same discipline.

Id.

A PHOSITA would have been familiar with microbial oils, a summary of which Dr. Curtis provides in his declaration. *See* MARA-1003, ¶¶35-47, 64. In particular, a PHOSITA would have understood the benefits of polyunsaturated fats (PUFAs), microbial sources for obtaining them, and methods for culturing and extracting oils from those microbial sources. *Id.*, ¶64.

III. THE CHALLENGED CLAIMS ARE UNPATENTABLE

This request shows how the prior art discloses each of the elements of the Challenged Claims, thereby rendering claims 1-15 of the '363 patent unpatentable. As detailed below, this request shows a reasonable likelihood that Mara will prevail with respect to claims 1-15 of the '363 patent. *See* MARA-1003, ¶¶65-312.

A. GROUND 1: Claims 1-3 are anticipated by Radianingtyas

1. Overview of Radianingtyas

Radianingtyas, like the '363 patent, is directed to methods of culturing oil-producing microbes and extracting microbial oils rich in omega-3 and omega-6 fatty acids. MARA-1007, 1:27-2:2; MARA-1001, 1:16-21, 1:49-2:3, 2:18-37, 9:66-14:3. The method of Radianingtyas includes collecting cell biomass, breaking or disrupting that biomass, and then extracting the biomass with solvents. MARA-1007, 32:10-14; MARA-1003, ¶66.

Radianingtyas's resultant oils comprise unsaturated fatty acids with

approximately 96-100 wt.% triglycerides in the neutral lipid fraction, where the percentage of neutral lipids “can be at least 95% by weight of total lipids.”

MARA-1007, 32:20-21, 33:1-2. Constituent fatty acids include DHA, DPA, as well as low levels of heptadecanoic acid (HDA or 17:0 or margaric acid). *Id.*, 11:4-9, 99:22-24, 99:29-32, 100:23-25, Figure on 9/16 (PDF page 123), Table on 11/16 (PDF page 125). As Radianingtyas discloses, naturally-occurring microorganisms can produce microbial oils with “high concentrations of omega-3 fatty acids...and low concentrations of omega-6 fatty acids.” *Id.*, 12:22-25; *see also id.*, 13:7-10, 17:19-20, 40:2-4; MARA-1003, ¶¶67-69.

The method parameters of Radianingtyas can be modified to obtain different yields of DHA. MARA-1007, 27:4-8. Radianingtyas explains that “the composition of the lipid produced by the oil producing microbe can be manipulated based on the growing medium composition the oil producing microbe multipl[i]es in”, such as “[b]y changing both the ratios and types of carbon to nitrogen sources, the chemical composition of salt used and by the addition of certain chemical compounds which impact upon fatty acid production.” *Id.*, 27:13-18. Radianingtyas also explains that fatty acid production antagonists can be employed, “[f]or example, the ratio of omega n-3 and/or n-6 oils to omega n-9 oils can be increased by sumplementing [sic] the medium of an oil producing microbe with a fatty acid production antagonist.” *Id.*, 27:22-28. More specifically,

Radianingtyas teaches that increasing agitation, temperature, or dissolved oxygen during culturing can decrease DHA content, while adding acetate, trace elements, metal, and vitamins to the production medium increases DHA content. *Id.*, 28:14-20, 30:15-17; MARA-1003, ¶70.

As one example, Radianingtyas discloses a specific strain of Thraustochytrids (i.e., a marine microorganism) labeled ONC-T18. *See* MARA-1007, 16:1-20:23, 26:29-27:3, 81:5-92:2; MARA-1003, ¶71. Radianingtyas discloses that “the fatty acid component which ONC-T18 produces under heterotrophic fermentation is almost entirely triglyceride (*at least 95%*) in nature.”³ MARA-1007, 89:24-26. Further, Radianingtyas discloses that microorganisms such as ONC-T18 can produce “a lipid composition comprising from about 25% to about 40% of an omega-3 fatty acid, such as n-3 DHA, (for example, at least 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55% or 60% by weight)...and from about 4% to about 12% of an omega-6 fatty acid, such as n-6 DPA, (for example, at least 4%, 5%, 6%, 7%, 8%, 9%, or 10% by weight).” MARA-1007, 26:29-34, 37:2-3; MARA-1003, ¶¶66-71.

³ All emphasis added herein unless otherwise noted.

2. Analysis

Claim 1

[1pre] A microbial oil comprising

Radianingtyas discloses [1pre]. MARA-1003, ¶¶72-76. Radianingtyas describes “compositions and methods related to oil producing microbes that can produce unsaturated fatty acids which can be purified and used.” MARA-1007, Abstract; *id.*, 12:1-2, 1:27-31, 1:22-26, 40:29-31; MARA-1003, ¶74.

Radianingtyas discloses that “[c]ellular lipids containing the (n-3) DHA, EPA and (n-6) DPA PUFAs can...be extracted from the cellular biomass...to produce a sample of concentrated lipid material.” MARA-1007, 42:10-14; *see also id.*, 32:10-14, 42:10-43:10; MARA-1003, ¶¶75-76.

[1a] a triglyceride fraction of at least 70% by weight,

Radianingtyas discloses [1a]. MARA-1003, ¶¶77-80.

For example, Radianingtyas generally discloses “oil producing microbes of the order Thraustochytriales...having the ability to produce lipids” containing “omega-3 fatty acids” and “omega-6 fatty acids.” MARA-1007, 11:4-9.

Radianingtyas’s compositions include triglycerides representing from “96 to about 100%” of the neutral lipids, which “can be at least 95% by weight of total lipids.” *Id.*, 32:17-33:5; *see also id.*, 89:24-26; MARA-1003, ¶78.

More specifically, Radianingtyas discloses the strain ONC-T18, of which “[a]nalysis of results shows that the fatty acid component which ONC-T18

produces under heterotrophic fermentation *is almost entirely triglyceride (at least 95%)* in nature.” MARA-1007, 89:24-26; MARA-1003, ¶79.

[1b] wherein the docosahexaenoic acid content of the triglyceride fraction is at least 50% by weight,

Radianingtyas discloses [1b]. MARA-1003, ¶¶81-88.

Radianingtyas discloses that microorganism ONC-T18 produces a lipid composition comprising “an omega-3 fatty acid, such as n-3 DHA, (for example, at least...**60% by weight**).” MARA-1007, 26:29-34. Because the majority of Radianingtyas’s microbial oils are made up of triglycerides (e.g., “at least 95%” in the lipid composition), a PHOSITA would have understood that the majority of PUFAs (e.g., at least 60% DHA in the lipid composition) in Radianingtyas must be present in triglyceride form and that such an oil would satisfy [1b]. MARA-1007, 89:24-26; *see also, id.*, 32:17-33:5; MARA-1003, ¶¶82-84. Consistent with this understanding, Komazawa discloses a *Thraustochytrium* strain that contains DHA components ranging from 62% to 84% in triglyceride form. *See, e.g.*, MARA-1015, [0116] (stating that “[t]he DHA component in the triglycerides produced shows characteristic tendency. Namely,...DHA component becomes a high content of 80% or more, when culturing was carried out at pH8.5”); *see, id.*, Fig. 3 (stating “DHA content in triglyceride” in the header and disclosing about 80% DHA in triglyceride form at pH 8.5 and about 58% DHA in triglyceride form at pH 4.5).

Indeed, high DHA content in thraustochytrid oils was contemplated and described by Radianingtyas, in which various thraustochytrid strains contained more than 50% DHA by weight. *See, e.g.*, MARA-1007, 82&tbl.3 (showing the following strains having more than 50% DHA when taking DHA amount (in mg/g) and dividing by total lipid amount (in mg/g): ONC-T02 (60%), ONC-T07 (53%), ONC-T09 (58%), ONC-T10 (54%), ONC-T12 (60%), ONC-T19 (52%), ONC-T25 (59%), ONC-T46 (52%), ONC-T52 (64%), ONC-T67 (55%), and ONC-T68 (55%)); *id.*, 32:2-3, 3:25-28, tbls.7-8, Fig. 10 on 10/16 (page 124) (showing various total lipid, TFA, or lipid content in “mg/g”); MARA-1003, ¶85.

Radianingtyas also teaches that extracted oils can be further purified to increase DHA content. *See* MARA-1007, 8:2-4 (“For example, if a disclosed eukaryotic microorganism, for example, produces 35% DHA, this could be further ‘purified’ such that the final lipid composition was greater than 90% DHA.”); MARA-1003, ¶86.

Based on Radianingtyas, a PHOSITA would have understood that ONC-T18 had additional beneficial properties (e.g., increased amount of total lipid production) and that high DHA-producing thraustochytrid strains were readily available, even under non-optimized screening conditions. MARA-1003, ¶¶85-88.

[1c] wherein the docosapentaenoic acid n-6 content of the triglyceride fraction is from 0.5% by weight to 6% by weight,

Radianingtyas discloses [1c]. MARA-1003, ¶¶89-94.

Radianingtyas discloses that microorganisms “such as ONC-T18....can produce a lipid composition comprising...from about 4% to about 12% of an omega-6 fatty acid, such as n-6 DPA, (for example, **at least 4%**, 5%, 6%, 7%, 8%, 9%, or **10% by weight**).” MARA-1007, 26:29-27:3. A PHOSITA would have understood that because the majority of Radianingtyas’s microbial oils are made up of triglycerides (e.g., “at least 95%” in the lipid composition), the majority of PUFAs (e.g., at least 4% DPA in the lipid composition) in Radianingtyas must be present in triglyceride form, and that such an oil would satisfy [1c]. MARA-1007, 89:24-26; *see also, id.*, 32:17-33:5; MARA-1003, ¶¶90-91.

Radianingtyas discloses that microorganisms “such as ONC-T18....can produce a lipid composition comprising...from about 4% to about 12% of an omega-6 fatty acid.” MARA-1007, 26:29-27:3. As provided in Fig. 11 with ONC-T18, Radianingtyas shows that DPA n-6 (C22:5w6) is present in an amount between 3.88% to 9.43% of the total fatty acid (TFA) content, in which 9 of 13 conditions provided between 0.5% to 6% DPA n-6 of TFA. MARA-1007, Fig. 11 on 12/16 (PDF page 126); MARA-1003, ¶92. “A prior art reference that discloses an overlapping but different range than the claimed range can be anticipatory, even where the prior art range only partially or slightly overlaps with the claimed range.” *Genentech, Inc. v. Hospira, Inc.*, 946 F.3d 1333, 1338 (Fed. Cir. 2020); *see also Ineos USA LLC v. Berry Plastics Corp.*, 783 F.3d 865, 870–71 (Fed. Cir.

2015) (affirming summary judgment of anticipation of patent claims for composition with “0.05 to 0.5% by weight of at least one saturated fatty acid amide” lubricant in view of a prior art reference disclosing the same class of lubricant in an overlapping range of “0.1 to 5 parts by weight,” and where a measurement in “% by weight” was equivalent to one in “parts by weight”). MARA-1003, ¶¶93-94.

[1d] and wherein the oil comprises 5% by weight or less of heptadecanoic acid.

Radianingtyas discloses [1d]. MARA-1003, ¶¶95-100.

Radianingtyas discloses exemplary oils containing low (or even undetectable) amounts of HDA. *See* MARA-1007, 34:4-37:14 (showing HDA (i.e., 17:0) ranging from 0.17% to 2.69% as percentage of total fatty acid); *see also id.*, Fig. 11 on 11/16 (PDF page 125); *see, e.g., id.*, 32:20-25 (“typical composition of fatty acids for ONC-T18, in the neutral lipids” summing to 100% without disclosing HDA). MARA-1003, ¶¶96-98. As discussed in §III.A.2[1c], *supra*, “an overlapping but different range than the claimed range can be anticipatory.” *Genentech*, 946 F.3d 1333, 1338 (Fed. Cir. 2020).

Furthermore, Element [1d] is an optional negative limitation, for which prior art disclosure is not necessary to meet the claim element. “[A] reference need not state a feature’s absence in order to disclose a negative limitation.” *AC Techs., S.A. v. Amazon.com, Inc.*, 912 F.3d 1358, 1367 (Fed. Cir. 2019). In other words,

an oil containing no HDA meets this limitation. Radianingtyas also discloses a microbial oil in which HDA is not disclosed at all, and is either absent or below the limit of detection. *See, e.g.*, MARA-1007, 32:20-25; MARA-1003, ¶¶98-100.

Thus, Radianingtyas anticipates claim 1.

Claim 2

[2] The microbial oil of claim 1, further comprising an arachidonic acid content of the triglyceride fraction of 1.5% or less by weight.

Radianingtyas discloses [2]. MARA-1003, ¶¶101-104.

Radianingtyas discloses exemplary oils that contain 1.5% by weight or less of arachidonic acid (ARA). For instance, in Example 13, Radianingtyas discloses 68 isolates (ONC-T01 to ONC-T68) and states that “[i]n addition to the omega-3 oils produced, approximately 80% of all isolates synthesized the omega-6 PUFAs, ***arachidonic acid (AA)*** or docosapentaenoic acids (DPA), ***at concentrations varying between 1 and 18%*** and 3 and 7% w/w, respectively.” MARA-1007, 96:1-3, 99:8-12&29-32⁴; MARA-1003, ¶102. As discussed in §III.A.2[1c], *supra*, “an overlapping but different range than the claimed range can be anticipatory.”

⁴ While Radianingtyas (MARA-1007) refers to Fig. 11 as describing PUFA content in isolates, this is likely a clerical error and should refer to Fig. 11 of the US priority document (MARA-1045) for Radianingtyas. *See* MARA-1003, ¶102&fn.5.

Genentech, 946 F.3d 1333, 1338 (Fed. Cir. 2020).

Specifically regarding Fig. 11 with ONC-T18, Radianingtyas shows that this strain can produce oils that all consistently contain low amounts of ARA. *See* MARA-1007, Fig. 11 on 11/16 (PDF page 125) (showing ARA (C20:4w6) present in amounts between 0.13% to 0.9% of TFA); 34:4-37:14 (stating ARA ranging from 0.13% to 0.90% of TFA). MARA-1003, ¶103.

Consistent with the analysis in §III.A.2[1d], *supra*, claim 2 also recites an optional negative limitation, in which an oil containing no ARA meets this limitation. Radianingtyas discloses a microbial oil in which ARA is not disclosed at all, and is either absent or below the limit of detection. *See, e.g.*, MARA-1007, 32:20-25 (fatty acids in neutral lipids summing to 100% without disclosing ARA); MARA-1003, ¶104.

Claim 3

[3pre] A microbial oil comprising

See §III.A.2[1pre], *supra*.

[3a] a triglyceride fraction of at least 70% by weight,

See §III.A.2[1a], *supra*.

[3b] wherein the docosaheptaenoic acid content of the triglyceride fraction is at least 40% by weight,

See §III.A.2[1b], *supra*.

[3c.1] wherein the docosapentaenoic acid n-6 content of the triglyceride fraction is from at least 0.5% by weight to 6% by weight,

See §III.A.2[1c], supra.

[3c.2] wherein the ratio of docosahexaenoic acid to docosapentaenoic acid n-6 is greater than 6:1,

Radianingtyas discloses [3c.2]. MARA-1003, ¶¶109-110.

As discussed above, Radianingtyas discloses a microbial oil having at least 55% DHA in triglyceride form and at least 5% DPA in triglyceride form. *See* §III.A.2[1b]-[1c], *supra*; MARA-1003, ¶110. As such, the resultant ratio of DHA to DPA is greater than 6:1 (i.e., a ratio of 11:1 for 55% DHA:5% DPA).

[3d] and wherein the oil comprises 5% by weight or less of heptadecanoic acid.

See §III.A.2[1d], *supra*.

B. GROUND 2: Claims 1-15 are obvious over Radianingtyas in view of Kralovec

1. Overview of Radianingtyas

See §III.A.1, *supra*.

2. Overview of Kralovec

Kralovec describes methods for modifying oil compositions in microbial oils by concentrating polyunsaturated fatty acids. MARA-1030, 1:9-11. Kralovec recognizes that omega-3 fatty acids like DHA have “well established” beneficial effects, such as reduction of “cardiovascular and heart disease risk” and “prevention and/or treatment of inflammation, neurogenerative diseases, and cognitive development.” MARA-1030, 1:16-2:3. Kralovec also acknowledges

that omega-3 fatty acids can be found in microbial oils, which “typically provide the PUFA in a triglyceride form where other undesired, fatty acids...are present along side a desired PUFA in the triglyceride molecule.” *Id.*, 2:4-8. Kralovec is thus directed to modification methods to produce “an oil having higher levels of a PUFA...than the starting oil composition.” *Id.*, 5:24-28; MARA-1003, ¶113.

Kralovec also acknowledges that “[s]everal methods of producing PUFA concentrates from oils, such as marine, microbial, and/or algal oils, are known, for example, selective lipase hydrolysis, PUFA complexation using urea...and a physical removal of unwanted components by fractionation”, in which “[f]ractionation involving molecular distillation is usually conducted on ethyl esters prepared from the starting triglycerides since they are more volatile than corresponding triglycerides”, thus demonstrating exemplary methods that a PHOSITA would have considered for further concentrating PUFA, including DHA, from oils including microbial and algal oils. MARA-1030, 2:9-16; MARA-1003, ¶113.

Kralovec’s method is broadly applicable with “any suitable oil composition that comprises a glyceride,” including microbial and algal oils. MARA-1030, 6:28-7:2. Kralovec’s methods allow the “specific composition of a treated oil” to be “adjusted and/or tailored to have a target ratio of various polyunsaturated fatty acids,” which can allow for “high concentrations of DHA.” *Id.*, 6:9-13; MARA-

1003, ¶114.

Kralovec's method employs three steps: hydrolysis, separation, and esterification. MARA-1003, ¶115. Hydrolysis utilizes lipase enzyme to contact a starting oil, which induces at least partial hydrolysis of the oil. MARA-1030, 9:8-10, 11:15-28. The "hydrolyzed glyceride composition...can then be separated...to separate at least a portion of the free saturated fatty acid from the glyceride." *Id.*, 12:13-16. After, lipase is utilized to attach "desirable polyunsaturated fatty acid components, for example, EPA and/or DHA" to the hydrolyzed glyceride compositions. *Id.*, 13:27-30. Kralovec's method provides compositions containing "triglycerides with higher DHA...contents than the starting triglycerides." *Id.*, 35:20-32; MARA-1003, ¶¶113-117.

3. Combination of Radianingtyas and Kralovec

a) DHA as the preferred PUFA

As discussed above (§III.A.1, *supra*), Radianingtyas teaches methods of culturing oil-producing microbes and extracting microbial oils rich in omega-3 and omega-6 fatty acids. MARA-1007, 1:27-2:2. Significantly, Radianingtyas discloses that these oils, which contain unsaturated fatty acids including DHA, are "capable of being purified as all such compositions are used." *Id.*, 1:25-26, 1:29-30. More specifically, Radianingtyas discloses examples directed to "[o]ptimized production of [DHA] by strain ONC-T18" and "[o]ptimal time for harvesting of

ONC-T18 for maximal DHA production.” *Id.*, 87:6-89:10. In light of

Radianingtyas’s disclosures, it would have been obvious for a PHOSITA to have sought microbial oils having high levels of DHA as the preferred PUFA based on its teachings as well as those of other references available before the Critical Date. *See, e.g.*, MARA-1009, 27 (disclosing certain microbial strain as “particularly attractive” for “contain[ing] very high levels of DHA (61%)”); MARA-1003, ¶¶118-120. A PHOSITA would have been motivated to obtain increased DHA in Radianingtyas’s extracted microbial oil for at least the following reasons.

First, a PHOSITA would have been motivated to increase DHA in Radianingtyas’s extracted microbial oil because there were many recognized health benefits associated with DHA. MARA-1003, ¶121. For example, Radianingtyas teaches that “[t]here is overwhelming scientific evidence that (n-3) highly unsaturated fatty acids such as docosahexaenoic acid (DHA) have a positive effect on cardio-circulatory diseases, chronic inflammations and brain disorders....” MARA-1007, 1:6-8.

Second, moreover, consistent with the teachings in Radianingtyas, Kralovec teaches that DHA is an omega-3 fatty acid, known to be “vital to everyday life and function.” MARA-1030, 1:13-14; MARA-1003, ¶122. For example, “[o]mega-3 fatty acids not only exhibit proven effects on lowering serum triglyceride levels, but they have strong connection to diabetes.” MARA-1030, 18:8-12. Omega-3

fatty acids were also “known for other cardioprotective benefits,” such as “reduc[ing] cardiovascular and heart disease risk.” *Id.*, 1:13-2:3. With regard to DHA, Kralovec teaches that DHA was associated with “a strong insulin permeability enhancement effect” and was “viewed as a potential absorption enhancer for intestinal delivery of insulin.” *Id.*, 18:10-19:2. For example, DHA was understood to “prevent[] certain biochemical processes that originate from insulin deficiency” and “significantly increase fasting insulin levels.” *Id.*, 19:2-6.

Third, a PHOSITA would have been motivated to focus on increasing DHA in Radianingtyas’s oil because DHA would have been an obvious choice selected from a small and finite number of preferred omega-3 fatty acids. *In re Kuhle*, 526 F.2d 553, 555 (C.C.P.A. 1975); MARA-1003, ¶123. For example, Radianingtyas discloses DHA as one of the two desirable n-3 PUFAs: docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). MARA-1007, 1:6-20; MARA-1003, ¶123. Based on these limited desirable choices, a PHOSITA would have expected to be successful in pursuing increased DHA in a microbial oil as contemplated by Radianingtyas (and others). MARA-1007, 1:6-31, 26:29-34, 27:4-12; *see, e.g.*, MARA-1038, 3639 (stating that “[s]tudies with thraustochytrids have established these marine protists as preeminent industrial strains for production of DHA. Initial research, at relatively, low cell densities, (5-20 g/L) established the capacities of *Thraustochytrium* species to accumulate greater than 50% of their

lipids as DHA and to produce > 1 g DHA/L of culture, with productivities of about 0.2 g/(L day).”); MARA-1003, ¶123.

Additionally, a PHOSITA would have expected success in obtaining extracted oils with high DHA levels given that it was already known that certain strains contained high DHA levels, including various thraustochytrid strains in Radianingtyas containing more than 50% DHA by weight. MARA-1007, 82&tbl.3 (showing at least eleven (11) strains having more than 50% DHA and three strains having at least 60% DHA); *see, e.g.*, MARA-1015, [0116], Fig. 3 (disclosing a *Thraustochytrium* strain with a DHA content of about 80% in triglyceride form); *see also, e.g.*, MARA-1009, 27 (stating that “[s]train O is particularly attractive as it contains very high levels of DHA (61%)”); *see also, e.g.*, MARA-1040, 300-301 (stating that “thraustochytrids are one of the most promising sources of DHA” and that “DHA may represent as much as 50% of the total fatty acids in thraustochytrids”); *id.*, 305 (stating that “*Thraustochytrium* spp., in general, contained a larger proportion of DHA, ranging from 38.5%–59.5% of the total fatty acids”); *see also, e.g.*, MARA-1019, tbl.3 (showing that, excluding “PRIOR STRAINS” (a term employed by Barclay), more than twenty (20) strains have more than 50% DHA and 0.5% to 6% DPA (n-6) of total fatty acids, of which three (3) strains have more than 70% DHA); MARA-1003, ¶124.

b) Increased Omega-3 Fatty Acid (DHA) Concentration in Microbial Oils

Radianingtyas teaches suitable starting oils that have not been treated, such as microbial oils from organisms that “can be used in a process for preparing a lipid or fat containing DHA, EPA and DPA.” MARA-1007, 16:31-17:3. As discussed above (§III.B.2, *supra*), Kralovec provides methods for obtaining compositions containing “triglycerides with higher DHA...contents than the starting triglycerides.” MARA-1030, 35:20-32. It would have been obvious for a PHOSITA to combine the teachings of Radianingtyas, directed to microbial oils having high levels of triglycerides (e.g., “at least 95%” in the lipid composition) and DHA (at least 60% by weight in the lipid composition), with a method to increase the concentration of DHA in the microbial oil, such as methods described by Kralovec. MARA-1007, 26:31-34, 32:17-21, 33:1-2, 89:24-26; MARA-1030, 1:9-11; MARA-1003, ¶¶125-126. Specifically, a PHOSITA would have found it obvious to implement Kralovec’s oil modification techniques (or similar) to Radianingtyas’s extracted microbial oil to increase the amount of DHA for at least the following reasons.

First, a PHOSITA would have been motivated to apply Kralovec’s oil modification techniques to Radianingtyas’s extracted microbial oil to increase its DHA content because “purifying and concentrating PUFA’s [sic] in a triglyceride form is generally desired.” MARA-1030, 2:7-8; MARA-1003, ¶127. It would have been well-known that concentrating PUFA is desirable to reduce the

concentration of unwanted components (e.g., saturated fatty acids) in a microbial oil so as to deliver high levels of active PUFA in lower amounts of oil, which is preferable for supplements and food applications. *See, e.g.*, MARA-1030, 2:4-8; MARA-1003, ¶127. Indeed, a higher-purity, DHA-containing oil would be preferable because it results in a consumer needing to take fewer supplements (i.e. capsules) and reduces the “calories ingested from unwanted fatty acids.” MARA-1022, 113; MARA-1035, 381 (“Concentrates keep the intake of calories and other possibly physiologically active fatty acids as low as possible.”); MARA-1003, ¶128.

Second, a PHOSITA would have been motivated to apply Kralovec’s oil modification techniques to Radianingtyas’s extracted microbial oil to increase its DHA content because the produced oils include “‘designer’ glycerides” and “often non-naturally occurring, ratios of polyunsaturated fatty acid ester” that provide “triglycerides [of fatty acids] that have better color and lower levels of trans-isomers” as well as “better sensory properties”, as compared to corresponding ethyl ester forms of fatty acids. MARA-1030, 35:21-36:2; MARA-1003, ¶129. “Such oils can be incorporated into food products, nutraceuticals, pharmaceutical formulations, and microcapsules.” MARA-1030, 35:21-36:2.

Third, a PHOSITA would have been motivated to apply Kralovec’s oil modification techniques to Radianingtyas’s extracted microbial oil because such

combinations reflect nothing more than the use of a known technology (e.g., enzymatic modification) to improve similar oils (e.g., extracted microbial oils) according to known methods (e.g., oil refinement methods) to yield predictable results (e.g., obtain oil with an increased concentration of a desired PUFA, e.g., DHA). *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 417 (2007); MARA-1003, ¶130.

Fourth, a PHOSITA would also have been motivated to apply Kralovec’s oil modification techniques (or similar) to Radianingtyas’s microbial oils because concentrating high DHA oils from thraustochytrids can simplify processing, as compared to complex oils. A complex oil can include, e.g., “fish oil with up to 20 fatty acids (representing a continuous range of saturated, mono-, di-, tri-, and polyenoic fatty acids, and as such, a series of overlapping crystallization temperatures).” MARA-1019, 14:30-33. Instead, a PHOSITA would have sought microbial oils having high levels of the desired PUFA (such as DHA) that are more amenable to further processing to concentrate the PUFA of interest. *See, e.g.*, MARA-1019, 14:18-33 (stating that “[t]he advantage of this process is that it is not necessary to go through the urea complex process or other expensive extraction methods...to remove saturated and mono-unsaturated fatty acids prior to cold crystallization” and that this advantage begins “by starting the purification process with *an oil consisting of a simple fatty acid profile such as that produced by*

Thraustochytrids (3 or 4 saturated or monounsaturated fatty acids with 3 or 4 HUFAs, two groups of fatty acids widely separated in terms of their crystallization temperatures) rather than a complex oil such as fish oil with up to 20 fatty acids (representing a continuous range of saturated, mono-, di-, tri-, and polyenoic fatty acids, and as such, a series of overlapping crystallization temperatures)"). MARA-1003, ¶131.

A PHOSITA would have expected to be successful in applying Kralovec's techniques to increase the concentration of DHA in the microbial oil because Radianingtyas teaches that "[t]he omega-3 and omega-6 PUFAs may be further concentrated by hydrolyzing the lipids and concentrating the highly unsaturated fraction by employing traditional methods." MARA-1007, 42:14-16, 42:19-20 ("The extracted oils can be refined by well-known processes routinely employed to refine vegetable oils (e.g. by chemical or physical refining)"); MARA-1003, ¶132. A PHOSITA would have naturally considered "traditional" or "well-known" methods for hydrolyzing an oil, such as Radianingtyas's oil, and would have looked to methods including hydrolysis, such as in Kralovec's methods or similar, for use in making DHA concentrates, for example. MARA-1003, ¶133. Thus, a PHOSITA would have been motivated to refine Radianingtyas's oils in accordance with Radianingtyas's teachings by looking to Kralovec. *Id.*

Moreover, a PHOSITA would have expected success in using Kralovec's

method techniques for increasing the concentration of the preferred PUFA (i.e., DHA) particularly in the context of an extracted microbial oil given that Radianingtyas and Kralovec teach that their oils can be microbial in origin. MARA-1007, 1:22-31; MARA-1030, 2:28-29, 7:18-21; MARA-1003, ¶134. Both Radianingtyas and Kralovec acknowledge their oils can be derived from *Thraustochytrium* or *Schizochytrium* species. MARA-1007, 11:4-5; MARA-1030, 7:20. Also, both acknowledge their oils contain omega-3 PUFAs, including DHA. MARA-1007, 1:22-31; MARA-1030, 19:7-12. Furthermore, both Radianingtyas and Kralovec acknowledge similar uses for their oils, such as human nutritional uses. Radianingtyas, for example, teaches that its resultant oil is “used as a nutritional supplements[sic] for humans, as a food additive, or as pharmaceutical applications.” MARA-1007, 43:6-8. Kralovec too discloses that its oils “can be incorporated into food products, nutraceuticals, pharmaceutical formulations, and microcapsules.” MARA-1030, 35:31-36:2; MARA-1003, ¶¶118-136.

4. Analysis

Claim 1

[1pre] A microbial oil comprising

Radianingtyas-Kralovec discloses and/or renders obvious [1pre]. MARA-1003, ¶¶137-139.

Radianingtyas discloses [1pre]. *See* §III.A.2[1pre], *supra*. Kralovec also discloses that its methods can be used with microbial oils. *See, e.g.*, MARA-1030,

6:28-7:2; MARA-1003, ¶138.

Additionally, extracted microbial oils were well known to a PHOSITA prior to the Critical Date. For example, other prior art references, such as Barclay, describe an extracted microbial oil, e.g., oils “produced by *Thraustochytrids*” and *Schizochytrium*. See MARA-1019, 1:23-28, 14:23-47; see also MARA-1033, 632, 631, 635; MARA-1003, ¶139.

[1a] a triglyceride fraction of at least 70% by weight,

Radianingtyas-Kralovec discloses and/or renders obvious [1a]. MARA-1003, ¶¶140-143.

Radianingtyas discloses [1a]. See §III.A.2[1a], *supra*. Similarly, Kralovec discloses oils that “have a high TG (triglyceride) content,” for example, “the oil can comprise greater than or equal to about 60%, 65%, **70%, 75%, or 80% TG** by weight of the total composition.” MARA-1030, 37:22-24; see also *id.*, 36, tbl.5; see also *id.*, 40-41, tbl.8.1; see also *id.*, 43, tbl.9.2; see also *id.*, 46, tbl.10.2; MARA-1003, ¶141.

Indeed, triglyceride-rich oils were well known to a PHOSITA prior to the Critical Date. Consistent with the teachings in Radianingtyas and Kralovec, other references also disclosed triglyceride-rich oils. MARA-1008, 2:30-33 (disclosing “a microbial oil...which has a triglyceride content of greater than 90%”); MARA-1034, [0037]-[0038]; MARA-1040, 301; *id.*, 302; MARA-1003, ¶¶142-143.

[1b] wherein the docosahexaenoic acid content of the triglyceride fraction is at least 50% by weight,

Radianingtyas-Kralovec discloses and/or renders obvious [1b]. MARA-1003, ¶¶144-146.

Radianingtyas discloses [1b]. See §III.A.2[1b], *supra*. Radianingtyas discloses that the ONC-T18 strain can produce a lipid composition comprising an omega-3 fatty acid, such as n-3 DHA in an amount of “at least...40%, 45%, 50%, 55% or 60% by weight” and that other strains of thraustochytrids contained more than 50% DHA by weight. MARA-1007, 26:29-34, 82:tbl.3 (showing at least eleven strains having more than 50% DHA and three strains having at least 60% DHA); MARA-1003, ¶144.

Additionally, as discussed above in §III.B.3, a PHOSITA would have understood and/or found obvious to apply Kralovec’s (or similar) methods to the Radianingtyas microbial oil to produce a DHA-enriched microbial oil containing at least 50 wt.% DHA, or higher, such as at least 60 wt.% DHA in triglyceride form. MARA-1003, ¶¶145-146. That in turn discloses or renders obvious [1b]. *Id.*

[1c] wherein the docosapentaenoic acid n-6 content of the triglyceride fraction is from 0.5% by weight to 6% by weight,

Radianingtyas-Kralovec discloses and/or renders obvious [1c]. MARA-1003, ¶147.

Radianingtyas discloses that microorganism ONC-T18 can produce a lipid

composition comprising an omega-6 fatty acid, such as n-6 DPA in an amount of “at least 4%, 5%, 6%, 7%, 8%, 9%, or 10% by weight”, and a PHOSITA would have understood that at least one of these lower DPA oils would contain 0.5% to 6% DPA in triglyceride form. *See* §III.A.2[1c], *supra*; MARA-1007, 26:29-27:3. Additionally, a PHOSITA would have understood and/or found obvious to apply Kralovec’s (or similar) methods to Radianingtyas’s microbial oil to produce an enriched microbial oil containing a desired amount of DPA in triglyceride form. MARA-1003, ¶147.

[1d] and wherein the oil comprises 5% by weight or less of heptadecanoic acid.

Radianingtyas-Kralovec discloses and/or renders obvious [1d]. MARA-1003, ¶¶148-153.

Based on Radianingtyas, it would have been obvious to a PHOSITA that Radianingtyas’s oil has 5% by weight or less of HDA because Radianingtyas discloses production of a wide range of oils with consistently low amounts of HDA. *See* MARA-1007, 34:4-37:14; *see* §III.A.2[1d], *supra*. In some embodiments, HDA is not detectable at all. *See, e.g.*, MARA-1007, 32:20-25; MARA-1003, ¶¶148-149. As described in more detail in §III.A.2[1d], *supra*, “5% by weight or less” includes compositions with 0% (or undetectable) HDA.

Consistent with Radianingtyas, Kralovec similarly describes specific saturated fatty acids and esters that can be removed by hydrolysis, and one such

specific compound includes “margaric acid (C17),” which is a synonym for HDA and 17:0. MARA-1030, 9:1-3; MARA-1003, ¶150. Additionally, Kralovec teaches that in an embodiment using Kralovec’s method for increasing DHA, HDA is present at 0.1% in the product after re-esterification. MARA-1030, 42-43, tbl.9.1; MARA-1003, ¶150.

Moreover, a PHOSITA would have understood and/or found obvious that it was desirable to have any non-DHA component (of which HDA is just one example) present at only low levels in a primarily DHA-containing oil. As motivation, a PHOSITA would have recognized and/or found obvious that high-DHA, low-HDA concentrations would be preferable to DHA from fish oil because of “the low content of the desired fatty acids” in fish oils. MARA-1034, [0005]; MARA-1003, ¶151. A PHOSITA would have therefore wanted to achieve a high-purity, DHA-containing oil free of contaminants or other PUFAs for more efficient supplementation of human and animal food products. Indeed, a higher-purity, DHA-containing oil would be preferable because it results in a consumer needing to take fewer supplements (i.e. capsules) and reduces the “calories ingested from unwanted fatty acids.” MARA-1022, 113; MARA-1035, 381.

Furthermore, HDA is an odd-chain fatty acid (OCFA). As explained by Taberna, “the physiological implications of OCFA nutrition for humans are relatively unknown,” and “15:0 and 17:0 accumulation can decrease the percentage

of other fatty acids including the valuable DHA.” MARA-1041, 82-84. Also, Radianingtyas discloses production of a wide range of oils with consistently low amounts of HDA. *See* MARA-1007, 34:4-37:14. Thus, a PHOSITA would have sought out microbial oils that would contain or maintain low amounts of HDA. MARA-1003, ¶152.

Therefore, Radianingtyas-Kralovec renders obvious claim 1.

Claim 2

[2] The microbial oil of claim 1, further comprising an arachidonic acid content of the triglyceride fraction of 1.5% or less by weight.

Radianingtyas-Kralovec discloses and/or renders obvious [2]. MARA-1003, ¶¶154-157.

As previously discussed, Radianingtyas discloses production of a wide range of oils with consistently low (or undetectable) amounts of ARA. *See* §III.A.2[2], *supra*; *see also* MARA-1007, 34:4-37:14; *see, e.g.*, MARA-1007, 32:20-25. As described in more detail in §III.A.2[1d]-[2], *supra*, “1.5% by weight or less” includes compositions with 0% ARA; MARA-1003, ¶155.

Moreover, a PHOSITA would have understood that it was desirable to have any omega-6 fatty acid (of which ARA is just one example) present at only low levels in a primarily DHA (an omega-3 fatty acid)-containing oil. As motivation, a PHOSITA would recognize that high-DHA, low-omega-6 (of which low ARA is only an example) concentrations would be preferable for ***economical production***

of high purity, DHA-containing oils. MARA-1003, ¶156; *see, e.g.*, MARA-1019, 6:44-50 (stating that “economically desirable characteristics for the production of omega-3 highly unsaturated fatty acids” can include “high content of omega-3 highly unsaturated fatty acids” and “preferably low content of saturated and omega-6 highly unsaturated fatty acids”). In turn, high purity, DHA-containing oils can simplify processing, including those that can be used to form concentrates of such DHA-containing oils. *See, e.g.*, MARA-1019, 14:18-33. A PHOSITA would have therefore wanted to achieve a high-purity, DHA-containing oil free of contaminants or other PUFAs for more efficient and economic processing. Thus, a PHOSITA would have sought out microbial oils containing low amounts of ARA, such as in Radianingtyas or Barclay, for example. MARA-1007, 99: 29-32 (stating that “[i]n addition to the omega-3 oils produced, approximately 80% of all isolates synthesized the omega-6 PUFAs, *arachidonic acid (AA)*...*at concentrations varying between 1 and 18%*”); MARA-1019, 19:46-49 (stating that “[s]trains can also be isolated which have less than 1% (as % of total fatty acids) of the *undesirable C20:4w6* [ARA] and C22:5w6 highly unsaturated fatty acids”); *id.* 10:40-45 (stating that various strains “tend to have high concentrations of three omega-3 highly unsaturated fatty acids: C20:5w3, C22:5w3 and C22:6w3 and *very low concentration of C20:4w6* [ARA].”). MARA-1003, ¶157.

Claim 3

[3pre] A microbial oil comprising

See §III.B.4[1pre], supra.

[3a] a triglyceride fraction of at least 70% by weight,

See §III.B.4[1a], supra.

[3b] wherein the docosahexaenoic acid content of the triglyceride fraction is at least 40% by weight,

See §III.B.4[1b], supra.

[3c.1] wherein the docosapentaenoic acid n-6 content of the triglyceride fraction is from at least 0.5% by weight to 6% by weight,

See §III.B.4[1c], supra.

[3c.2] wherein the ratio of docosahexaenoic acid to docosapentaenoic acid n-6 is greater than 6:1,

Radianingtyas discloses [3c.2]. MARA-1003, ¶¶162-163.

As discussed with respect to Elements [1b] and [1c] in §III.B.4[1b]-[1c], *supra*, Radianingtyas discloses a microbial oil having at least 55% DHA in triglyceride form and at least 5% DPA in triglyceride form. *See* §III.B.4[1b]-[1c], *supra*. Taking such an oil, the resultant ratio of DHA to DPA is greater than 6:1 (i.e., a ratio of 11:1 for 55% DHA:5% DPA).

[3d] and wherein the oil comprises 5% by weight or less of heptadecanoic acid.

See §III.B.4[1d], supra.

Claim 4

[4pre] A microbial oil comprising

See §III.B.4[1pre], *supra*.

[4a] a triglyceride fraction of at least 70% by weight,

See §III.B.4[1a], *supra*.

[4b] wherein the docosahexaenoic acid content of the triglyceride fraction is at least 60% by weight,

Radianingtyas-Kralovec discloses and/or renders obvious [4b]. MARA-1003, ¶¶167-175.

Radianingtyas discloses various strains of thraustochytrids that contain more than 60% DHA by weight. *See, e.g.*, MARA-1007, 82:tbl.3 (showing the following strains having at least 60% DHA when taking the DHA amount (in mg/g) and dividing by the total lipid amount: ONC-T02 (60%), ONC-T12 (60%), and ONC-T52 (64%)); MARA-1003, ¶168. Radianingtyas also discloses that microorganisms “such as ONC-T18” can produce a lipid composition comprising an omega-3 fatty acid, such as n-3 DHA, “for example, ***at least...60% by weight.***” MARA-1007, 26:29-34. A PHOSITA would have understood that because the majority of Radianingtyas’s microbial oils are made up of triglycerides (e.g., “at least 95%” in the lipid composition), the majority of the PUFAs in Radianingtyas must be present in triglyceride form, including the DHA, and that such an oil would satisfy [4b]. MARA-1007, 89:24-26; *see also, id.*, 32:17-33:5; MARA-

1003, ¶¶169-170.

Additionally, compositions having a DHA content of the triglyceride fraction that is at least 60% by weight were also well known to a PHOSITA based on the prior art that was available before the Critical Date. MARA-1003, ¶171. It was known prior to the Critical Date that there were microorganisms of a *Thraustochytrium* strain having “a high ability of producing docosahexaenoic acid” and producing oil with at least 60% by weight DHA. MARA-1015, Abstract; *see also id.*, [0016], [0116]; *see also id.*, Fig. 3 (disclosing a *Thraustochytrium* strain with a DHA content of about 80% in triglyceride form); *see also* MARA-1019, tbl.3 (showing twenty (20) strains having more than 60% DHA, of which three (3) strains have more than 70% DHA); *see also* MARA-1009, 27; MARA-1020, 384-38, tbl.2; MARA-1032, 27-31, tbl.2.5. It was also known how to increase the yield of desired fatty acids, including DHA. For example, it was known that decreasing agitation or dissolved oxygen during culturing would result in increases of DHA. MARA-1007, 28:14-20, 27:13-21; MARA-1003, ¶171. Furthermore, Radianingtyas teaches that “if a...microorganism, for example, produces 35% DHA, this could be further ‘purified’ such that the final lipid composition was greater than 90% DHA.” MARA-1007, 8:2-4; MARA-1003, ¶172.

Additionally, a PHOSITA would also readily know how to increase the DHA content in triglyceride form using, e.g., methods disclosed by Kralovec. As

discussed above (§III.B.3, *supra*), in the combination, a PHOSITA would have been motivated to apply Kralovec's oil modification techniques (or similar techniques) to Radianingtyas's extracted microbial oil to increase its DHA content. MARA-1003, ¶173. In doing so, Kralovec discloses its methods can be used to produce "concentrated oils with triglycerides containing higher proportions of polyunsaturated fatty acid esters than the starting glycerides," such as "oils that comprise greater than or equal to about...80% DHA by weight of the total composition." MARA-1030, 35:20-27, 36:12-15. Such oils would "also have a high TG (triglyceride) content" and the method would "produce triglycerides of fatty acids." MARA-1030, 35:27-30, 37:22. The end result would be "an oil having higher levels of a PUFA...than the starting oil composition." MARA-1030, 5:24-32.

A PHOSITA would have therefore understood and/or found obvious to apply Kralovec's (or similar) methods to Radianingtyas's microbial oil to produce a DHA-enriched microbial oil containing at least 60 wt.% DHA in triglyceride form. MARA-1003, ¶174. As Dr. Curtis explains, a PHOSITA would have understood and/or found obvious that having higher levels of DHA in triglyceride form was desirable because it would mean a more homogeneous oil, desirable for use in pharmaceutical preparations. *See* MARA-1039, 20; MARA-1003, ¶175. Additionally, the presence of phospholipids, as opposed to triglycerides, was

known to make oils less stable, more cloudy, and more difficult to process efficiently. *See* MARA-1039, 17. Moreover, providing high levels of DHA in the triglyceride form closely resembles the “natural” form in which lipids are predominantly ingested. *See id.*, 19. Hence, the triglyceride form of DHA would be expected to have greater consumer acceptability and greater bioavailability. *See* MARA-1036, 352-354, tbl.2; MARA-1003, ¶175.

[4c] and wherein the oil comprises 5% by weight or less of heptadecanoic acid.

See §III.B.4[1d], *supra*.

Claim 5

[5] The microbial oil of any one of claims 1 to 4, wherein at least 20% of the triglycerides in the triglyceride fraction contain docosahexaenoic acid at two positions in the triglyceride selected from any two of the sn-1, sn-2, and sn-3 positions.

Radianingtyas-Kralovec discloses and/or renders obvious [5]. MARA-1003, ¶¶177-189.

As Dr. Curtis explains, each of claims 1-4 recites at least 40-60% DHA in triglyceride form, and this recited DHA percentage provides a presence of at least 20% of that DHA at any two of the sn-1, sn-2, and sn-3 positions. *Id.*, ¶¶178-189. A PHOSITA would have readily understood that an oil having at least 40% DHA would possess at least 20% DHA at any two of the recited sn positions. *Id.*, ¶189. A PHOSITA would have also understood that as the overall DHA percentage rises (e.g., from 40% DHA as in claim 3 to 50% DHA or 60% DHA as in claims 1 and

4), so does this probability (i.e., of at least 20% DHA at two of the recited sn positions). *Id.*

Claim 6

[6] The microbial oil of any one of claims 1 to 4, wherein at least 5% of the triglycerides in the triglyceride fraction contain docosahexaenoic acid at all three of the sn-1, sn-2, and sn-3 positions in the triglyceride.

Radianingtyas-Kralovec discloses and/or renders obvious [6]. MARA-1003, ¶¶190-194.

As Dr. Curtis explains, each of claims 1-4 recites at least 40-60% DHA in triglyceride form, and this recited DHA percentage provides a presence of at least 5% of that DHA at all three of the sn-1, sn-2, and sn-3 positions. *Id.*, ¶¶191-194. A PHOSITA would have readily understood that an oil having at least 40% DHA would possess at least 5% DHA at all three of the recited sn positions. *Id.*, ¶¶193-194. A PHOSITA would have also understood that as the overall DHA percentage rises (e.g., from 40% DHA as in claim 3 to 50% DHA or 60% DHA as in claims 1 and 4), so does this probability (i.e., of at least 5% DHA at all three of the recited sn positions). *Id.*

Claim 7

[7] A food product, cosmetic, or pharmaceutical composition for animals or humans, comprising the microbial oil of any one of claims 1 to 4.

Radianingtyas-Kralovec discloses and/or renders obvious [7]. MARA-1003, ¶¶195-196.

Radianingtyas states that its “oils can be used directly as a feed or food additive” and that its lipid can be included in “[a] *foodstuff*, supplement, *pharmaceutical composition* for both *human and animal* (including marine)[.]” MARA-1007, 42:22-23, 40:20-26; *see also id.*, 12:3-7, 43:6-8, 70:23-26, 72:4-17.

Claim 8

[8] The food product of claim 7, wherein the food product is an infant formula.

Radianingtyas-Kralovec discloses and/or renders obvious [8]. MARA-1003, ¶¶197-198.

Radianingtyas’s “compositions can be used in food products (e.g., *baby milk*).” MARA-1007, 13:15-16; *see also id.*, 40:25-26 (“infant formula”), 67:18-19, 79:12-17, claim 38.

Claim 9

[9] The food product of claim 8, wherein the infant formula can be consumed by premature infants.

Radianingtyas-Kralovec discloses and/or renders obvious [9]. MARA-1003, ¶¶199-202.

Radianingtyas’s “compositions can be used in food products (e.g., *baby milk*).” MARA-1007, 13:15-16; *see also id.*, 40:25-26, 67:18-19, 79:12-17, claim 38. Based on this disclosure, a PHOSITA would have understood and/or found obvious that Radianingtyas’s oil-containing baby milk and infant formula would also be provided to premature infants. MARA-1003, ¶200; *see also* MARA-1034,

[0016]; MARA-1003, ¶201.

Furthermore, a PHOSITA would have understood and/or found obvious the benefits of PUFAs to supplement formula for infants, including preterm infants.

See, e.g., MARA-1010, Preface; *id.* 53; MARA-1003, ¶202.

Claim 10

[10] The food product of claim 7, wherein the food product is milk, a beverage, a therapeutic drink, a nutritional drink, or a combination thereof.

Radianingtyas-Kralovec discloses and/or renders obvious [10]. MARA-1003, ¶¶203-204.

Radianingtyas’s “compositions can be used in food products (e.g., baby *milk*).” MARA-1007, 13:15-16; *see also id.*, 72:15-17, 72:5-6; 79:11-13, 79:19-21, claim 40.

Claim 11

[11] The food product of claim 7, wherein the food product is an additive for animal or human food.

Radianingtyas-Kralovec discloses and/or renders obvious [11]. MARA-1003, ¶¶205-206. For example, Radianingtyas’s compounds “are useful as...*food additives*.” MARA-1007, 11:18-21; *see also id.*, 12:3-7, 42:22-25, 43:6-8.

Claim 12

[12] The food product of claim 7, wherein the food product is a nutritional supplement.

Radianingtyas-Kralovec discloses and/or renders obvious [12]. MARA-

1003, ¶¶207-208. For example, Radianingtyas’s compounds “are useful as...*nutraceuticals*.” MARA-1007, 11:18-21; *see also id.*, 43:6-8, 12:3-7, 59:16, 59:21-24.

Claim 13

[13] The food product of claim 7, wherein the food product is an animal feed.

Radianingtyas-Kralovec discloses and/or renders obvious [13]. MARA-1003, ¶¶209-210.

Radianingtyas discloses “*foodstuff*...for both human *and animal* (including marine)” MARA-1007, 40:20-26; *see also id.*, 67:18, 12:3-7, claim 39.

Claim 14

[14] The animal feed of claim 13, wherein the animal feed is an aquaculture feed.

Radianingtyas-Kralovec discloses and/or renders obvious [14]. MARA-1003, ¶¶211-212; *see* MARA-1007, 40:20-26; *see also id.*, 79:11-18, claim 39.

Claim 15

[15] The animal feed of claim 13, wherein the animal feed is a domestic animal feed, a zoological animal feed, a work animal feed, a livestock feed, or a combination thereof.

Radianingtyas-Kralovec discloses and/or renders obvious [11]. MARA-1003, ¶¶213-214; *see* MARA-1007, 40:20-26; *see also id.*, 79:11-18, claim 39.

C. GROUND 3: Claims 1-15 are obvious over Bijl in view of Barclay

1. Overview of Bijl

Bijl, like the '363 patent, is directed to microbial oils. MARA-1008, 2:30-36, 9:5-7; MARA-1001, 1:16-21, 1:49-2:3, 2:18-37, 9:65-14:3; *see also* MARA-1008, 1:7-12, 12:22-37, 2:35-3:2; MARA-1003, ¶215.

Bijl's microbial oils contain one or more polyunsaturated fatty acids and a triglyceride content of at least 90 wt.%. MARA-1008, 2:30-33, 5:24-29; *see also* 5:14-19. Bijl's microbial oils are usable in food, nutritional supplements, and cosmetics. *Id.*, 4:13-18; MARA-1003, ¶216.

Bijl also describes processes for obtaining microbial oils. One exemplary process involves extracting microbial oil from dried granules. MARA-1008, 6:23-34. Another exemplary process involves culturing microorganisms in fermentation broth, pasteurizing the resulting broth or biomass, and then extracting microbial oil from the biomass. *Id.*, 7:2-11. These exemplary processes are combinable. *Id.*, 8:1-6, 28:28-29:19; MARA-1003, ¶217.

Bijl teaches using pasteurization to partially inactivate one or more compound degrading substance(s), such as lipases, present in the biomass or broth. MARA-1008, Abstract, 7:12-30; MARA-1003, ¶218. For example, Bijl teaches that pasteurization "inactivate[s] various lipases" that "cleave fatty acids off a triglyceride backbone," which is "disadvantageous for PUFAs where a high

triglyceride content is preferred.” MARA-1008, 7:34-37.

Bijl’s processes for obtaining microbial oils utilize less solvent for extracting microbial oils than prior methods and produce higher quality crude oils. MARA-1008, 9:5-15; MARA-1003, ¶219.

2. Overview of Barclay

Barclay discloses a process for the “extracted microbial products with a high concentration of omega-3 highly unsaturated fatty acids [HUFAs]...using biologically pure cultures of...Thraustochytriales,” a former order for thraustochytrids. MARA-1019, Abstract.

Barclay teaches that microorganisms can be “characterized by having a high concentration of fatty acids of which a high percentage are omega-3 highly unsaturated fatty acids,” and the microorganisms themselves or extracted microbial HUFAs can be included in food or pharmaceutical applications. MARA-1019, 4:54-64, Abstract; MARA-1003, ¶¶220-221. Barclay describes “process[es] for culturing [such microorganisms] for the production of *lipids* with high concentrations of omega-3 highly unsaturated *fatty acids* (HUFA).” MARA-1019, 1:23-28. A PHOSITA would have understood that the “lipids” of Barclay would include “triglycerides.” MARA-1003, ¶¶222-223; *see also* MARA-1019, 6:6-11, 13:52-58.

Barclay describes culture conditions and extraction conditions to provide

high concentrations of omega-3 HUFAs in extracted microbial oils. *See* MARA-1019, 10:17-20; 5:29-46. Barclay teaches processes that can increase both lipids (e.g., including triglycerides) and omega-3 HUFAs (e.g., DHA), in which “[i]f a product significantly *higher in lipids and omega-3 highly unsaturated fatty acids is desired*, the culture can be manipulated to become nutrient limited, preferably, nitrogen limited for a suitable time[.]” MARA-1019, 10:20-24. Extraction conditions can include a process that involves fractional crystallization. MARA-1019, 5:50-57, 33:17-66, 34:20-24; MARA-1003, ¶¶224-225.

Barclay also describes desirable characteristics for strains, as well as exemplary strains. Barclay teaches that “desirable characteristics for the production of omega-3 highly unsaturated fatty acids” include “high content of omega-3 highly unsaturated fatty acids” and “preferably low content of saturated and omega-6 highly unsaturated fatty acids.” MARA-1019, 6:45-50. Specifically, “many strains of the invention [] produce a high proportion of total omega-3 fatty acids as [DHA]” and “[f]ifteen strains had at least 94% by weight of total omega-3 fatty acids as [DHA].” MARA-1019, 22:47-54, tbls.3-4. Further, more than twenty (20) strains having greater than 50% DHA and 0.5% to 6% DPA (n-6) of total fatty acids, of which three (3) strains have more than 70% DHA. MARA-1019, tbl.3; MARA-1003, ¶¶220-227.

3. Combination of Bijl and Barclay

It would have been obvious for a PHOSITA to combine the teachings of Bijl, directed to processes to provide stable microbial oils having high levels of triglycerides (e.g., >90%) with a preferred PUFA (DHA), with Barclay, directed to high DHA microorganism strains and culture conditions for such strains, to increase the concentration of that PUFA in a stable microbial oil. MARA-1008, 2:30-33, 4:24-28; MARA-1019, 10:17-20; 5:29-57, 33:17-34:24; MARA-1003, ¶¶228-241. Specifically, a PHOSITA would have found it obvious to implement Barclay's strains and culture conditions (or similar) to Bijl's processes for at least the following reasons.

First, a PHOSITA would have been motivated to apply Barclay's strains and culture conditions to Bijl's processes to provide a high DHA oil from thraustochytrids because Bijl teaches that organisms, such as thraustochytrids, can have one predominant PUFA. Specifically, Bijl states that "[f]or example, oil of the invention can comprise *docosahexaenoic acid (DHA) preferably obtained from algae or fungi*. Algae include dinoflagellates (e.g. those of the genus) *Cryptothecodinium*. *The fungus can be of the genus Mucorales, e.g. Thraustochytrium*....Typically, the oils obtained from these organisms *predominantly contain one particular polyunsaturated fatty acid*. However, they can additionally contain other polyunsaturated fatty acids in lesser amounts."

MARA-1008, 6:3-14. This understanding is consistent with Barclay, which states that some thraustochytrid strains in Barclay “tend to have high concentrations of three omega-3 highly unsaturated fatty acids: C20:5w3 [EPA], C22:5w3 [DPA(n-3)] and C22:6w3 [DHA] and very low concentration of C20:4w6 [DPA(n-6)].”

MARA-1019, 10:42-45, Abstract. Even from the three possible omega-3 HUFAs, Barclay describes DHA as being in high amounts, as compared to EPA and DPA(n-3). MARA-1019, 10:45-60 (e.g., “Ratios of [EPA] to [DHA] can run from about 1:1 to 1:30. Ratios of [DPA(n-3)] to [DHA] can run from 1:12 to only trace amounts of [DPA(n-3)].”); MARA-1003, ¶¶230-231.

Second, a PHOSITA would have been motivated to apply Barclay’s strains and culture conditions to Bijl’s processes to provide a high triglyceride oil, which in turn can provide DHA in triglyceride form, because Bijl states that PUFA-containing high triglyceride oils with beneficial oil quality parameters can be stable. *See*, MARA-1008, 4:19-23 (“The oil of the present invention contains ***one or more polyunsaturated fatty acids*** and ***can have a high triglyceride content***.”).

This oil has a ***much higher oxidative stability*** than the microbial polyunsaturated fatty acid-containing oils described in the art.”); *see also, id.*, 5:14-24; MARA-1003, ¶232.

Moreover, a PHOSITA would have understood that Barclay’s oils included triglyceride and, based on references available before the Critical Date, likely

included high triglyceride content. MARA-1019, 6:6-11 (stating that “[l]ipids are understood to be fats or oils including the *glyceride esters of fatty acids* along with associated phosphatides, sterols, alcohols, hydrocarbons, ketones, and related compounds”); *see also, id.*, 13:52-58 (describing a process in which “[t]he solvent is removed...and the lipids hydrolyzed by using any of the well-known methods for converting *triglycerides* to free fatty acids or esters of fatty acids”); *see, e.g.*, MARA-1007, 89:24-26 (stating that “[a]nalysis of results shows that the fatty acid component which ONC-T18 produces under heterotrophic fermentation *is almost entirely triglyceride (at least 95%)* in nature”); *see also, e.g.*, MARA-1034, [0037]-[0038] (disclosing that “[t]ypically, the content of neutral lipids in the lipids of the present invention is very high (more than 90[%] of total lipids)” and that neutral lipids “contain at least 85% triacylglycerols, preferably at least 90% triacylglycerols”); MARA-1003, ¶¶232-233.

Also, a PHOSITA would have understood that PUFAs in triglyceride form are preferred and expected to have greater consumer acceptability, along with the possibility of greater bioavailability according to some literature. *See* MARA-1038, tbl.15 (stating that “PUFA should be present as triglyceride if for human consumption”); *see also* MARA-1036, 352-354, tbl.2; MARA-1040, 301 (stating that “DHA in the triacylg[l]ycerol layer is the only economically feasible form for commercialization and downstream processing”); MARA-1003, ¶234.

In addition to maximizing the amount of a preferred PUFA (e.g., DHA), it would have been well-known that increasing the amount of DHA in triglyceride form would be economically desirable. *See* MARA-1010, 37 (stating that “[c]ost-effective production of DHA from microbes would require the use of microbial strains that could produce large amounts of triacylglycerols”); MARA-1003, ¶235.

Third, a PHOSITA would have been motivated to apply Barclay’s strains and culture conditions to Bijl’s processes because Barclay’s strains possess “economically desirable characteristics for the production of omega-3 highly unsaturated fatty acids.” MARA-1019, 6:42-54. Barclay describes such strain characteristics as including “high content of omega-3 highly unsaturated fatty acids” and “preferably low content of saturated and omega-6 highly unsaturated fatty acids.” *Id.*, 6:42-54; MARA-1003, ¶¶236-237. A PHOSITA would have understood and/or found obvious that such strains provide DHA (a preferred PUFA, *see*, §III.B.3(a) and/or §III.C.2, *supra*) and that high DHA oils from thraustochytrids can simplify processing. *See* MARA-1019, 14:18:22 (stating that “[t]he advantage of this process is that it is not necessary to go through the urea complex process or other expensive extraction methods...to remove saturated and mono-unsaturated fatty acids prior to cold crystallization. This advantage is enabled by starting the purification process with an oil consisting of a simple fatty acid profile such as that produced by Thraustochytrids (3 or 4 saturated or

monounsaturated fatty acids with 3 or 4 HUFAs, two groups of fatty acids widely separated in terms of their crystallization temperatures) rather than a complex oil such as fish oil with up to 20 fatty acids (representing a continuous range of saturated, mono-, di-, tri-, and polyenoic fatty acids, and as such, a series of overlapping crystallization temperatures)').

Fourth, a PHOSITA would have been motivated to apply Barclay's strains and culture conditions to Bijl's processes because such combinations reflect nothing more than the use of a known technology (e.g., known strains and identified culture conditions) to improve similar cultures (e.g., microbial cultures) according to known methods (e.g., culture refinement methods) to yield predictable results (e.g., obtain microorganisms and microbial products with an increased concentration of DHA). *KSR*, 550 U.S. at 417; MARA-1003, ¶238.

A PHOSITA would have expected success in applying Barclay's strains and culture modifications to increase the concentration of the preferred PUFA (i.e., DHA) in the microbial oil because Bijl contemplates that its invention can "comprise *docosahexaenoic acid (DHA)* preferably obtained from algae or fungi", in which "[t]he fungus can be of the genus Mucorales, e.g. *Thraustochytrium*[" MARA-1008, 6:3-6. Thus, a PHOSITA would have looked to employ Bijl's processes in accordance with Bijl's teachings by looking to high DHA thraustochytrid strains in Barclay. MARA-1003, ¶239.

Moreover, a PHOSITA would have expected success in using Barclay's strains and culture conditions for increasing the concentration of the preferred PUFA (i.e., DHA) given that Bijl and Barclay teach that their oils are microbial in origin. MARA-1008, 13:19-22, 12:22-37; MARA-1019, 4:59-61; MARA-1003, ¶240. Bijl and Barclay both acknowledge their oils are specific to containing omega-3 PUFAs, of which DHA is an example. MARA-1008, 6:3-5, 7:18-19; MARA-1019, 10:40-60, 6:31-41. Furthermore, both Bijl and Barclay acknowledge similar uses for their oils, such as human nutritional or pharmaceutical uses. MARA-1008, 9:30-36, 14:23-27; MARA-1019, 13:35-40, 14:12-14, 14:48-68; MARA-1003, ¶241.

4. Analysis

Claim 1

[1pre] A microbial oil comprising

Bijl-Barclay discloses and/or renders obvious [1pre]. MARA-1003, ¶¶242-244.

Bijl discloses a "microbial oil" comprising "at least one polyunsaturated fatty acid (PUFA)[.]" MARA-1008, 1:8-11, 2:30-33; *see also id.*, 3:3-5, 7:10-11, 9:20-22. Consistent with Bijl, Barclay similarly disclose microbial oils. *See* MARA-1019, 4:59-61, 10:40-60; MARA-1003, ¶¶243-244.

[1a] a triglyceride fraction of at least 70% by weight,

Bijl-Barclay discloses and/or renders obvious [1a]. MARA-1003, ¶¶245-

246.

Bijl discloses a microbial oil “which has a triglyceride content of greater than 90%.” MARA-1008, 2:30-33. Bijl further discloses a triglyceride content greater than 95 wt.% and optionally higher than 97 wt.%. *Id.*, 4:24-28.

[1b] wherein the docosaehaenoic acid content of the triglyceride fraction is at least 50% by weight,

Bijl-Barclay discloses and/or renders obvious [1b]. MARA-1003, ¶¶247-255.

As discussed above in §III.C.3, a PHOSITA would have applied the teachings of using a preferred microbial strain (e.g., “strains of the invention which produce a high proportion of total omega-3 fatty acids as C22:6w3 [DHA]”), as taught by Barclay, to Bijl’s processes to yield an improved oil composition having higher amounts of DHA. MARA-1019, 22:47-54, tbls.3-4. Indeed, Barclay shows at least twenty (20) having more than 50% DHA and 0.5% to 6% DPA(n-6) of total fatty acids (TFA), of which three (3) strains have more than 70% DHA. MARA-1019, tbl.3; MARA-1003, ¶248.

A PHOSITA would have found it obvious that the DHA content of the triglyceride fraction is at least 50 wt.% in the proposed combination because more than twenty (20) of Barclay’s strains produces an oil composition with greater than 50 wt.% DHA (of TFA) and three (3) of Barclay’s strains produces an oil composition with greater than 70 wt.% DHA (of TFA). MARA-1019, tbl.4.

Consistent with Barclay's disclosure, other prior art references indicated that many microbial strains (e.g., *Thraustochytrium* strains) contained DHA in amounts greater than 50 wt.%, and even greater than 60 wt.%. MARA-1032, 27-31, tbl.2; MARA-1015, [0107]-[0108], tbl. after [0108], [0113]-[0114], [0016], [0116], Fig. 3; MARA-1019, tbls.3-4. Komazawa also discloses a *Thraustochytrium* strain that contains DHA components ranging from 62% to 84% in triglyceride form. MARA-1015, [0113]-[0114]; *see also, id.*, [0116], Fig. 3; MARA-1003, ¶¶249-251.

A PHOSITA would have understood and/or found obvious that since the majority of Bijl's microbial oil is made up of triglycerides (e.g., > 90% in the oil), the majority of the DHA in Bijl-Barclay must be present in the triglyceride form. MARA-1003, ¶252. In fact, Bijl discloses that DHA is a predominant PUFA in thraustochytrids and that its oils or "compound preferably comprises a triglyceride, such as one of the PUFAs previously mentioned." MARA-1008, 6:3-5, 7:18-19. Moreover, a PHOSITA would have understood and/or found obvious that Barclay's oils included triglycerides and, based on references available before the Critical Date, likely included high triglyceride content. MARA-1019, 6:6-11, 13:52-58; *see, e.g.*, MARA-1007, 89:24-26, 32:17-33:5; *see also, e.g.*, MARA-1034, [0037]-[0038]; MARA-1003, ¶¶252-253.

A PHOSITA would have therefore understood and/or found obvious to

apply Barclay's (or similar) strains or culture methods to Bijl's processes to produce a DHA-enriched microbial oil containing at least 50 wt.% DHA in triglyceride form, or higher such as at least 60 wt.% DHA in triglyceride form.

MARA-1003, ¶¶254-255. That in turn discloses or renders obvious [1b]. *Id.*

[1c] wherein the docosapentaenoic acid n-6 content of the triglyceride fraction is from 0.5% by weight to 6% by weight,

Bijl-Barclay discloses and/or renders obvious [1c]. MARA-1003, ¶¶256-260.

Bijl discloses microbial oils including PUFAs, which “predominantly (or only) contain[] one particular polyunsaturated fatty acid, but which may additionally contain lesser amounts of other polyunsaturated fatty acids.” MARA-1008, 5:24-29.

In the combination, Barclay describes characteristics for organisms having “preferably low content of saturated and ***omega-6 highly unsaturated fatty acids***,” in which DPA n-6 is an example of an omega-6 HUFA. MARA-1019, 6:48-50; *see, id.*, 19:46-49 (stating that “[s]trains can also be isolated which have less than 1% (as % of total fatty acids) of the undesirable C20:4w6 and C22:5w6 highly unsaturated fatty acids”). The reason for this preference is further discussed, in which “***C22:5w6 [DPA n-6] fatty acid is considered undesirable*** as a dietary fatty acid because it can retroconvert to the C20:4w6 fatty acid.” *Id.*, 10:54-57. Using the microorganisms or culture conditions of Barclay with the process of Bijl would

provide an oil with decreased DPA n-6 content. MARA-1003, ¶257-258.

A PHOSITA would have been motivated to use Barclay's microorganisms with Bijl's processes to provide an oil with high DHA content and low DPA n-6 content. MARA-1003, ¶259. Barclay discloses that its microorganisms can have low DPA n-6 component, i.e., "[t]he screening procedure outlined in this invention, however, facilitates the isolation of some strains that contain no (*or less than 1%*) omega-6 highly unsaturated fatty acids (C20:4w6 or C22:5w6)." MARA-1019, 10:57-60; *see id.*, tbl.3 (showing that, excluding "PRIOR STRAINS" (a term employed by Barclay), twenty-five (25) strains have more than 50% DHA and 0.5% to 6% DPA (n-6) of total fatty acids, of which twenty (20) strains have more than 60% DHA and of which three (3) strains have more than 70% DHA). It would have therefore been obvious and/or understood that the extracted microbial oil of the combination produces a concentration of oils that falls within the range of 0.5% by weight to 6% by weight DPA n-6 of the triglyceride fraction. MARA-1003, ¶¶259-260.

Furthermore, a PHOSITA would have understood and/or found obvious that since the majority of Bijl's microbial oil is made up of triglycerides (e.g., > 90% in the oil), the majority of PUFAs (of which DPA is an example) in Bijl-Barclay must be present in the triglyceride form. MARA-1008, 7:18-19; *see also id.*, 4:5-7, 5:30-32; MARA-1003, ¶260.

Based on at least the reasons provided above, Bijl-Barclay discloses and/or renders obvious Element [1c].

[1d] and wherein the oil comprises 5% by weight or less of heptadecanoic acid.

Bijl-Barclay discloses and/or renders obvious [1d]. MARA-1003, ¶¶261-264.

Barclay describes microbial oils having low amounts of HDA. *See* MARA-1019, tbl.3 (showing that four (4) strains have more than 50% DHA, 0.5% to 6% DPA (n-6), and less than 5% of other fatty acids (“Other FA”) of total fatty acids, in which these strains include SBG5, 46A, 27A, and 26B). A PHOSITA would have understood that a recitation of less than 5% of other fatty acids would include a composition with “5% by weight or less” of HDA. MARA-1003, ¶262.

In the combination, a PHOSITA would have applied the teachings of using a preferred microbial strain (e.g., “strains of the invention which produce a high proportion of total omega-3 fatty acids as C22:6w3 [DHA],” such as those in Table 3 or 4), as taught by Barclay, to Bijl’s processes to yield an improved oil composition having higher amounts of DHA. MARA-1019, 22:47-54, tbls.3-4. Upon employing Barclay’s oils having high DHA and low HDA content (e.g., such as oils from strains SBG5, 46A, 27A, and 26B in Table 3) with Bijl’s processes, a PHOSITA would have understood that the HDA levels in the Barclay-Bijl oils would have been maintained. MARA-1003, ¶263.

Furthermore, HDA (17:0) is an odd-chain fatty acid (OCFA), and a PHOSITA would have understood that “the physiological implications of OCFA nutrition for humans are relatively unknown” and that “15:0 and 17:0 accumulation can decrease the percentage of other fatty acids including the valuable DHA.” MARA-1041, 82-84. Also, Radianingtyas discloses production of a wide range of oils with consistently low amounts of HDA. *See* MARA-1007, 34:4-37:14. Thus, a PHOSITA would have sought out microbial oils that would contain or maintain low amounts of HDA. MARA-1003, ¶264.

Claim 2

[2] The microbial oil of claim 1, further comprising an arachidonic acid content of the triglyceride fraction of 1.5% or less by weight.

Bijl-Barclay discloses and/or renders obvious [2]. MARA-1003, ¶¶265-272.

Element [2] is an optional negative limitation, for which prior art disclosure is not necessary to meet the claim element. *AC Techs.*, 912 F.3d 1358 at 1367. In other words, an oil containing no ARA meets this limitation.

Barclay describes oils having no ARA and oils having non-zero amounts of ARA that are less than 1.5 wt.%. Specifically, Barclay’s “screening procedure...facilitates the isolation of some strains that ***contain no (or less than 1%) omega-6 highly unsaturated fatty acids (C20:4w6 [ARA] or C22:5w6 [DPA n-6])***.” MARA-1019, 10:57-60; *id.*, 19:46-49. Barclay also provides microbial oils having between 0-0.9% ARA. *See id.*, tbl.3; MARA-1003, ¶¶267-268.

In the Bijl-Barclay combination, a PHOSITA would have applied the teachings of using a preferred microbial strain (e.g., “strains of the invention which produce a high proportion of total omega-3 fatty acids as C22:6w3 [DHA]”), as taught by Barclay, to Bijl’s processes to yield an improved oil composition having higher amounts of DHA. MARA-1019, 22:47-54, tbls.3-4. Upon employing Barclay’s oils having high DHA and low ARA content (*see*, e.g., strains SBG5, 46A, 27A, and 26B in Table 3) with Bijl’s processes, a PHOSITA would have understood that ARA levels in the Barclay-Bijl oils would have been maintained. MARA-1003, ¶269.

Additionally, a PHOSITA would have understood that it was desirable to have any non-DHA component (of which ARA is just one example) present at only low levels in a primarily DHA-containing oil. As motivation, a PHOSITA would recognize that high-DHA, low-ARA concentrations would be preferable to DHA from fish oil. MARA-1034, [0005]; MARA-1003, ¶270. A PHOSITA would have wanted to achieve a high-purity, DHA-containing oil free of contaminants or other PUFAs for more efficient supplementation of human and animal food products. Indeed, a higher-purity, DHA-containing oil would be preferable because it results in a consumer needing to take fewer supplements (i.e. capsules) and reduces the “calories ingested from unwanted fatty acids.” MARA-1022, 113; MARA-1035, 381. Thus, a PHOSITA would have sought out microbial oils that contain low

amounts of a non-DHA component (e.g., ARA). MARA-1003, ¶270.

In addition, Barclay states that one of the “economically desirable characteristics for the production of omega-3 highly unsaturated fatty acids” includes “preferably *low content of* saturated and *omega-6 highly unsaturated fatty acids*”, e.g., ARA (20:4 w-6). MARA-1019, 6:42-50; MARA-1003, ¶271. Barclay further discloses strains having “high concentrations of three omega-3 highly unsaturated fatty acids: C20:5w3, C22:5w3 and C22:6w3 and *very low concentration of C20:4w6* [ARA]”. MARA-1019, 10:40-45. A PHOSITA would have understood and/or found obvious that it was desirable to have any non-DHA component (e.g., ARA) present at low levels in a primarily DHA-containing oil because higher purity oils result in more efficient processing that is economically desirable. MARA-1003, ¶272. Hence, a PHOSITA would have sought out microbial oils containing low amounts of a non-DHA component (e.g., ARA), as provided by the Bijl-Barclay combination.

Claim 3

[3pre] A microbial oil comprising

See §III.C.4[1pre], *supra*.

[3a] a triglyceride fraction of at least 70% by weight,

See §III.C.4[1a], *supra*.

[3b] wherein the docosaheptaenoic acid content of the triglyceride fraction is at least 40% by weight,

See §III.C.4[1b], supra.

[3c.1] wherein the docosapentaenoic acid n-6 content of the triglyceride fraction is from at least 0.5% by weight to 6% by weight,

See §III.C.4[1c], supra.

[3c.2] wherein the ratio of docosaheptaenoic acid to docosapentaenoic acid n-6 is greater than 6:1,

Bijl-Barclay discloses and/or renders obvious [3c.2]. MARA-1003, ¶¶277-278.

Barclay discloses that DHA is desirable and that DPA n-6 is undesirable. Regarding DHA, Barclay shows at least twenty (20) strains in Table 3 as having more than 50% DHA and 0.5% to 6% DPA (n-6), and three (3) strains in Table 3 as having more than 70% DHA. MARA-1019, tbls.3-4. Regarding DPA n-6, Barclay states that “C22:5w6 fatty acid is considered undesirable as a dietary fatty acid because it can retroconvert to the C20:4w6 fatty acid” and that its “screening procedure...facilitates the isolation of some strains that ***contain no (or less than 1%) omega-6 highly unsaturated fatty acids (C20:4w6 or C22:5w6 [DPA n-6]).***” MARA-1019, 10:55-60. Thus, Barclay discloses a ratio of DHA:DPA n-6 that is greater than 6:1. MARA-1003, ¶278.

[3d] and wherein the oil comprises 5% by weight or less of heptadecanoic acid.

See §III.C.4[1d], supra.

Claim 4

[4pre] A microbial oil comprising

See §III.C.4[1pre], supra.

[4a] a triglyceride fraction of at least 70% by weight,

See §III.C.4[1a], supra.

[4b] wherein the docosahexaenoic acid content of the triglyceride fraction is at least 60% by weight,

See §III.C.4[1b], supra.

[4c] and wherein the oil comprises 5% by weight or less of heptadecanoic acid.

See §III.C.4[1d], supra.

Claim 5

[5] The microbial oil of any one of claims 1 to 4, wherein at least 20% of the triglycerides in the triglyceride fraction contain docosahexaenoic acid at two positions in the triglyceride selected from any two of the sn-1, sn-2, and sn-3 positions.

Bijl-Barclay discloses and/or renders obvious [5]. MARA-1003, ¶¶284-286.

As Dr. Curtis explains, each of claims 1-4 recites at least 40-60% DHA in triglyceride form, and this recited DHA percentage provides a presence of at least 20% of that DHA at any two of the sn-1, sn-2, and sn-3 positions. MARA-1003, ¶¶284-286, 177-189. A PHOSITA would have readily understood and/or found obvious that an oil having at least 40% DHA would possess at least 20% DHA at any two of the sn-1, sn-2, and sn-3 positions.

Claim 6

[6] The microbial oil of any one of claims 1 to 4, wherein at least 5% of the triglycerides in the triglyceride fraction contain docosahexaenoic acid at all three of the sn-1, sn-2, and sn-3 positions in the triglyceride.

Bijl-Barclay discloses and/or renders obvious [6]. MARA-1003, ¶¶287-289.

As Dr. Curtis explains, each of claims 1-4 recites at least 40-60% DHA in triglyceride form, and this recited DHA percentage provides a presence of at least 5% of that DHA at all three of the sn-1, sn-2, and sn-3 positions. MARA-1003, ¶¶287-289, 190-194. A PHOSITA would have readily understood and/or found obvious that an oil having at least 40% DHA would possess at least 5% DHA at all three of the sn-1, sn-2, and sn-3 positions.

Claim 7

[7] A food product, cosmetic, or pharmaceutical composition for animals or humans, comprising the microbial oil of any one of claims 1 to 4.

Bijl-Barclay discloses and/or renders obvious [7]. MARA-1003, ¶¶290-292.

Bijl's oil can "be used in *foods, foods stuffs* or *food compositions* or serve as a nutritional supplement, for *humans* as well as for *animals*." MARA-1008, 4:13-16; *see also id.*, 4:17-18, 9:28-10:8, 14:23-27, cls. 33-36; *see also*, MARA-1019, 1:23-28; 17:13-15.

Claim 8

[8] The food product of claim 7, wherein the food product is an infant formula.

Bijl-Barclay discloses and/or renders obvious [8]. MARA-1003, ¶¶293-294.

Bijl's oils "are particularly suitable for inclusion in *infant formula*."

MARA-1008, 9:37-10:1; *see also id.*, 4:13-18, 9:28-10:8, 14:23-27, 29:20-25, cls. 33-36.

Claim 9

[9] The food product of claim 8, wherein the infant formula can be consumed by premature infants.

Bijl-Barclay discloses and/or renders obvious [9]. MARA-1003, ¶¶295-297.

Bijl's oil is "suitable for...*infant formula*." MARA-1008, 9:37-10:1; *see also id.*, 4:13-18, 9:28-10:8, 14:23-27, 29:20-25, cls. 33-36. Based on this disclosure, a PHOSITA would have understood and/or found obvious that Bijl's oil-containing infant formula would also be provided to premature infants. MARA-1003, ¶296; *see also* MARA-1034, [0016].

Furthermore, a PHOSITA would have understood the benefits of PUFAs to supplement formula for infants, including preterm infants. *See, e.g.*, MARA-1010, Preface at v; *id.*, 53; MARA-1003, ¶297.

Claim 10

[10] The food product of claim 7, wherein the food product is milk, a beverage, a therapeutic drink, a nutritional drink, or a combination thereof.

Bijl-Barclay discloses and/or renders obvious [10]. MARA-1003, ¶¶298-299.

Bijl's oil can be used in "*milk, health drinks*, and bread." MARA-1008, 9:28-10:8; *see also id.*, 4:13-18, 14:23-27, 29:20-25, cls. 33-36.

Claim 11

[11] The food product of claim 7, wherein the food product is an additive for animal or human food.

Bijl-Barclay discloses and/or renders obvious [11]. MARA-1003, ¶¶300-301; *see* MARA-1008, 4:13-15; *see also id.*, 4:17-18, 9:28-10:8, 14:23-27, 29:20-25, cls. 33-36; *see also*, MARA-1019, 1:23-28, 14:12-14.

Claim 12

[12] The food product of claim 7, wherein the food product is a nutritional supplement.

Bijl-Barclay discloses and/or renders obvious [12]. MARA-1003, ¶¶302-303; *see* MARA-1008, 4:13-15 (“nutritional supplement”); *see also id.*, 4:17-18, 9:28-10:8, 14:23-27, 29:20-25, cls. 33-36; *see also*, MARA-1019, 14:12-14.

Claim 13

[13] The food product of claim 7, wherein the food product is an animal feed.

Bijl-Barclay discloses and/or renders obvious [13]. MARA-1003, ¶¶304-306.

Bijl’s oil can “be used in foods...for humans as well as for animals.” MARA-1008, 4:13-15; *see also id.*, 4:17-18, 9:28-10:8, 14:23-27, 29:20-25, cls. 33-36; *see also*, MARA-1019, 1:23-28, 11:46-48.

Claim 14

[14] The animal feed of claim 13, wherein the animal feed is an aquaculture feed.

Bijl-Barclay discloses and/or renders obvious [14]. MARA-1003, ¶¶307-

308.

Barclay’s “microbial product...is of value as a source of omega-3 highly unsaturated fatty acids for fish, shrimp and other products produced by *aquaculture*” and “can be fed to...live feed organisms intended for consumption by the *aquacultured product*.” MARA-1019, 17:30-36.

Claim 15

[15] The animal feed of claim 13, wherein the animal feed is a domestic animal feed, a zoological animal feed, a work animal feed, a livestock feed, or a combination thereof.

Bijl-Barclay discloses and/or renders obvious [11]. MARA-1003, ¶¶309-310.

Bijl’s oil can “be used in foods...for humans as well as for animals.” MARA-1008, 4:13-15; *see also id.*, 4:17-18, 9:28-10:8, 14:23-27, 17:30-36, 29:20-25, cls. 33-36.

IV. DISCRETION SHOULD NOT PRECLUDE INSTITUTION

The Board should not exercise its discretion to deny institution under 35 U.S.C. §325(d) because the two-part framework set forth in *Advanced Bionics, LLC v. MED-El Elektromedizinische Geräte GmbH* is not satisfied. IPR2019-01469, Paper 6 (PTAB, Feb. 13, 2020).

The first prong of *Advanced Bionics* asks whether the art or arguments presented in the Petition are the same or substantially the same as those previously presented to the Office. *Id.*, 7-8. This inquiry is less probative, however, when art

is buried among hundreds of references on multiple pages of an information disclosure statement (IDS). *Shenzhen Zhiyi Tech. Co. v. iRobot Corp.*, IPR2017-02137, Paper 9, 9-10 (PTAB, Apr. 2, 2018) (declining discretion to deny institution because references not relied upon but instead only “included in the approximately fifteen pages of cited references”).

Here, the previously presented art includes Radianingtyas’s United States publication counterpart, Barclay, and Bijl’s European publication counterpart or Bijl’s United States family member (disclosed during the ’363 patent prosecution). Each was disclosed in an IDS during the ’363 patent prosecution. Notably, however, each of these was among 170 other cited references. And also notable is that none of Radianingtyas and Bijl were cited in a rejection or discussed substantively during prosecution of any of the ’363 family patents.

Barclay was cited in a §102 rejection and discussed substantively by the Examiner during prosecution of U.S. Patent Application No. 16/935,818, filed on July 22, 2020 (“the ’818 application”), which is a child of the ’363 patent. MARA-1043, 79.⁵ Of note, the Applicant in the ’818 application did not substantively discuss Barclay but canceled claims that were rejected under Barclay.

⁵ For this reference, page numbers are provided based on the PDF having a total of 262 pages.

MARA-1043, 65-66. A final rejection (mail date April 14, 2023) has been issued by the USPTO in which the Examiner again discussed Barclay in a §103 rejection, and the Applicant has not yet responded as of October 16, 2023. MARA-1043, 7-9. In particular, the §103 rejection raised by the Office relied on Barclay alone and not with another reference.

Patent Owner may argue that the remaining art presented in this Petition is substantially the same art or presents the same arguments as those presented in prosecution. Petitioner respectfully disagrees. Kralovec was not before the Examiner; it was cited during prosecution; and it fully discloses background teachings that were not discussed by the Examiner during prosecution. For example, the primary reference cited by the Examiner during prosecution of the '363 patent, Elswyk, was differentiated by the Applicant based on a grammatical interpretation of Elswyk as “disclos[ing] a HUFA in at least 1 of 5 forms: ‘[1] highly purified algal oil comprising 70% or more of the desired HUFA, [2] triglyceride oil combined with phospholipid, [3] phospholipid, [4] protein and phospholipid combination, or [5] dried marine microalgae.’” MARA-1002, 103. Yet, neither the Examiner nor the Petitioner considered the statement in Elswyk that HUFAs exist in triglyceride form or phospholipid form. *See* MARA-1044, [0060] (“Oxidative breakdown compromises the nutritional and sensory quality of HUFA in triglyceride form. By employing the phospholipid form, the desired

HUFA are more stable and the fatty acids are more bioavailable then when in the triglyceride form.”). In fact, the Examiner never considered arguments that any art disclosed HUFAs in triglyceride form; thus, the patent was improperly allowed.

As to the second prong of *Advanced Bionics*, that inquiry asks “whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims.” Paper 6, 8. Factors (c), (d), (e), and (f) inform this inquiry. *Id.*, 10-11. Thus, the Board inquires “(c) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection; (d) the extent of the overlap between the arguments made during examination and the manner in which petitioner relies on the prior art; (e) whether petitioner has pointed out sufficiently how the examiner erred in its evaluation of the asserted prior art; and (f) the extent to which additional evidence and facts presented in the petition warrant reconsideration of the prior art or arguments.” *Id.*, 9, n.10.

Regarding factor (c), none of Petitioner’s art (except for Barclay) was cited by, discussed by, or formed the basis of a rejection by, the Examiner in the ’363 patent family. When art cited in a petition was not applied during prosecution, the Board should not decline to institute. *See Navistar, Inc. v. Fatigue Fracture Tech., LLC*, IPR2018-00853, Paper 13 at 17 (PTAB Sept. 12, 2018) (“Under [factors] (c), (d), and (f)...the fact that [references] were of record, but not applied in any

rejection by the Examiner...provides little impetus for us to exercise our discretion to deny institution under Section 325(d).”).

Regarding factor (d), the Applicant did not substantively argue Barclay in the '818 application (a child of the '363 patent) but canceled claims that were rejected under Barclay. MARA-1043, 65-66. Further, the Petition relies on Barclay as a reference in combination with Bijl, which differs from the §103 rejection raised by the Office that relied on Barclay alone.

Regarding factors (e) and (f), the Petition highlights that the Examiner did not further consider prior art after accepting Applicant's grammatical interpretation of the cited art, Elswyk.

For example, the Petition highlights that art cited in this Petition discloses elements directly responsive to claim amendments. The Examiner allowed the patent after consideration of both Elswyk and Corley. This is because the Applicant argued that Elswyk describes “an oil comprising 70% or more of the desired HUFA, which does not require the desired HUFAs to be present in the triglyceride fraction” and that “Elswyk's disclosure regarding a highly purified algal oil comprising 70% or more of the desired HUFA cannot be construed as being equivalent to an algal oil comprising at least 70% triglycerides by weight.” MARA-1002, 103-104 (emphases in original). In light of such arguments by the Applicant, the Examiner, however, should have turned to other portions of Elswyk

itself describing PUFAs in triglyceride form or even other art. *See, e.g.*, MARA-1044, [0060] (“Oxidative breakdown compromises the nutritional and sensory quality *of HUFA in triglyceride form*. By employing the phospholipid form, the desired HUFA are more stable and the fatty acids are more bioavailable then when in the triglyceride form.”). But no rejection to any other art encompassing triglyceride forms of PUFAs followed. The Board should therefore decline to exercise its discretion under Section 325(d).

V. CONCLUSION

The Challenged Claims are unpatentable. MARA-1003, ¶¶1-312. Mara authorizes charging of fees to Deposit Account 06-1050.

VI. MANDATORY NOTICES UNDER 37 C.F.R §42.8(a)(1)

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

Mara Renewables Corporation and Algal Omega 3 Ltd. are real parties-in-interest.

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

IPRs were previously filed by Petitioner against two different patents assigned to DSM, U.S. Pat. No. 10,392,578 (IPR2023-01167, filed on July 14, 2023) and U.S. Pat. No. 10,757,959 (IPR2023-01342, filed on August 22, 2023).

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

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

Mara provides the following designation of counsel.

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D. Service Information

Please address all correspondence and service to the address listed above.

Petitioner consents to electronic service by email at IPR55973-0002IP1@fr.com.

Respectfully submitted,

Dated 11/22/2023

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CERTIFICATION UNDER 37 CFR § 42.24

Under the provisions of 37 CFR § 42.24(d), the undersigned hereby certifies that the word count for the foregoing Petition for *Inter partes* Review totals 13,873 words, which is less than the 14,000 allowed under 37 CFR § 42.24.

Dated 11/22/2023

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CERTIFICATE OF SERVICE

Pursuant to 37 CFR §§ 42.6(e)(4)(i) *et seq.* and 42.105(b), the undersigned certifies that on November 22, 2023, a complete and entire copy of this Petition for *Inter partes* Review, Power of Attorney, and all supporting exhibits were provided via Federal Express, to the Patent Owner by serving the correspondence address of record as follows:

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