

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MARA RENEWABLES CORPORATION,
Petitioner,

v.

DSM IP ASSETS, B.V.,
Patent Owner.

Case IPR2024-00070
U.S. Patent No. 8,207,363

PATENT OWNER'S PRELIMINARY RESPONSE

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PATENT OWNER'S EXHIBIT LIST

Exhibit	Description
2001	T. Yaguchi, <i>et al.</i> , <i>Production of High Yields of Docosahexaenoic Acid by Schizochytrium sp. Strain SR21</i> , JAOCS, 74(11), 1431-34 (1997).
2002	J. Huang, <i>et al.</i> , <i>Profile of Polyunsaturated Fatty Acids Produced by Thraustochytrium sp. KK17-3</i> , JAOCS, 78(6), 605-10 (2001).
2003	Marchan, <i>et al.</i> , <i>Screening on new British thraustochytrids isolates for docosahexaenoic acid (DHA) production</i> , J. APPL. PHYCOL., 29, 2831-43 (2017).
2004	S. Raghukumar, <i>Thraustochytrid Marine Protists: Production of PUFAs and Other Emerging Technologies</i> , MAR. BIOTECHNOL., 10, 631-40 (2008).
2005	U.S. Publication No. 2010/0285105
2006	Wu, <i>et al.</i> , <i>Effect of culture conditions on docosahexaenoic acid production by Schizochytrium sp. S31</i> , PROCESS BIOLOGY, 40, 3103-08 (2005).
2007	U.S. Patent No. 6,255,505

I. INTRODUCTION

Mara Renewables Corporation and real party-in-interest Algal Omega 3 Ltd. (together, "Petitioner") requested *inter partes* review and cancellation of claims 1-15 (the "Challenged Claims") of U.S. Patent No. 8,207,363 (the "'363 patent"). This is Petitioner's third challenge to a portfolio of patents covering Patent Owner's innovative microbial strains, fermentation and extraction technologies, and microbial oils. The Board rejected both of Petitioner's previous challenges to other patents in the portfolio because of evidentiary deficiencies in the petitions. (*See* IPR2023-01167, Paper 7, at 2 (P.T.A.B. Jan. 25, 2024) (denying institution for failing to demonstrate reasonable likelihood of prevailing with respect to unrelated U.S. Patent No. 10,392,578); IPR2023-01342, Paper 8, at 2 (P.T.A.B. Feb. 23, 2024) (same with respect to related U.S. Patent No. 10,757,959, which claims priority to the '363 patent through a series of divisionals)). Respectfully, the Board should do so again here.

Ground 1 challenges claims 1-3 based on alleged anticipation by WO 2008/129358 ("Radianingtyas", MARA-1007). (Pet. at 1-2). Grounds 2 and 3 challenge claims 1-15 based on alleged obviousness over the combinations of (i) Radianingtyas with WO 2009/040676 ("Kralovec", MARA 1030) and (ii) WO 97/37032 ("Bijl", MARA-1008) with U.S. Patent No. 5,130,242 ("Barclay",

MARA-1019), respectively. (*Id.*). DSM IP Assets, B.V. (“DSM” or “Patent Owner”) submits this timely Preliminary Response in opposition. 35 U.S.C. § 313. As detailed herein, the Petition fails to demonstrate a reasonable likelihood that Petitioners will prevail on at least one of the Challenged Claims, and *inter partes* review should be denied.

Fundamental deficiencies pervade each ground of alleged unpatentability. Those deficiencies are plainly illustrated in the first sentence of the challenge:

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.

(Pet. at 6). The mere disclosure of each element of the Challenged Claims in the prior art, as applied in the Petition, is not sufficient to demonstrate either anticipation or obviousness.

With respect to the anticipation challenge in Ground 1, the Petition fails to demonstrate that each and every element of claims 1-3 is disclosed in Radianingtyas *as arranged in claim 1*. Instead, the Petition improperly arrives at claims 1-3 through a mishmash of combinations of disclosures culled from distinct embodiments in Radianingtyas without explaining—much less providing supporting evidence—how a PHOSITA would at once envisage the claimed arrangement. This

is legally insufficient as “[a]nticipation is not proven by multiple, distinct teachings that the artisan might somehow combine to achieve the claimed invention.” *Microsoft Corp. v. Biscotti, Inc.*, 878 F.3d 1052, 1069 (Fed. Cir. 2017) (internal quotations and citations omitted).

The Petition similarly fails with respect to the obviousness challenges of Grounds 2 and 3. “[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art.” *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). Patentable “discoveries almost of necessity will be combinations of what, in some sense, is already known.” *Id.*, at 418-19. Under a proper Section 103 analysis, the scope and content of the prior art must be determined, differences between the prior art and the claims must be ascertained, and the level of ordinary skill in the art must be resolved. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). Only against this backdrop may the obviousness or nonobviousness of the claimed invention be determined. *Id.* Failure to adhere to this framework permits “one to fall victim to the insidious effect of a hindsight syndrome wherein that which only the invention taught is used against its teacher.” *In re Kotzab*, 217 F.3d 1365, 1369 (Fed. Cir. 2000).

Yet the Petition does not ascertain any differences between the prior art and the Challenged Claims. It does not provide any evidentiary basis for finding a

reasonable likelihood that the claimed invention *as a whole* would have been obvious in view of the prior art combinations. *See* 35 U.S.C. § 103 (requiring consideration of the invention “as a whole”). And it does not provide a legally sufficient rationale—much less supporting evidence—regarding whether a PHOSITA would have been motivated to combine the references with a reasonable expectation of success in achieving *the claimed invention* through the alleged prior art combinations. The Petition instead dissects each claim into its elements and then merely alleges that the prior art combination “discloses and/or renders obvious” each of those elements. (*See, e.g.*, Pet. at 26 (“Radianingtyas-Kralovec discloses and/or renders obvious [1pre].”), 27 (“Radianingtyas-Kralovec discloses and/or renders obvious [1a].”), 28 (“Radianingtyas-Kralovec discloses and/or renders obvious [1b].”), 28 (“Radianingtyas-Kralovec discloses and/or renders obvious [1c].”), 29 (“Radianingtyas-Kralovec discloses and/or renders obvious [1d].”)).

This is a fundamental error. The law requires a petition to demonstrate that the claimed invention as a whole would have been obvious, not the individual claim elements themselves. In each ground, the Petition impermissibly uses the individual claim elements as a hindsight-driven roadmap to reconstruct the Challenged Claims from a patchwork of purported disclosures in the prior art. However, in suggesting the specific prior art combinations, the Petition fails to demonstrate a reasonable

likelihood that a PHOSITA would have been motivated to combine the art in the manner claimed in the '363 patent with a reasonable expectation of success in doing so.

For at least the reasons detailed herein, *inter partes* review should be denied.

II. TECHNOLOGY BACKGROUND

The '363 patent generally relates to the microbial production of oils containing certain long-chain polyunsaturated fatty acids ("PUFAs")¹ primarily in triglyceride form. The Petition is devoid of any substantive discussion of the general state of the art prior to the '363 patent. However, the background technology is important for understanding why the grounds raised in the Petition are fatally deficient. DSM summarizes that background information here.

A. Long-Chain Polyunsaturated Fatty Acids Are Present in Different Structural Forms in Oils

The principal classes of lipids that make up oils include free fatty acids, glycerides (including mono-, di-, and primarily triglycerides), and phospholipids.

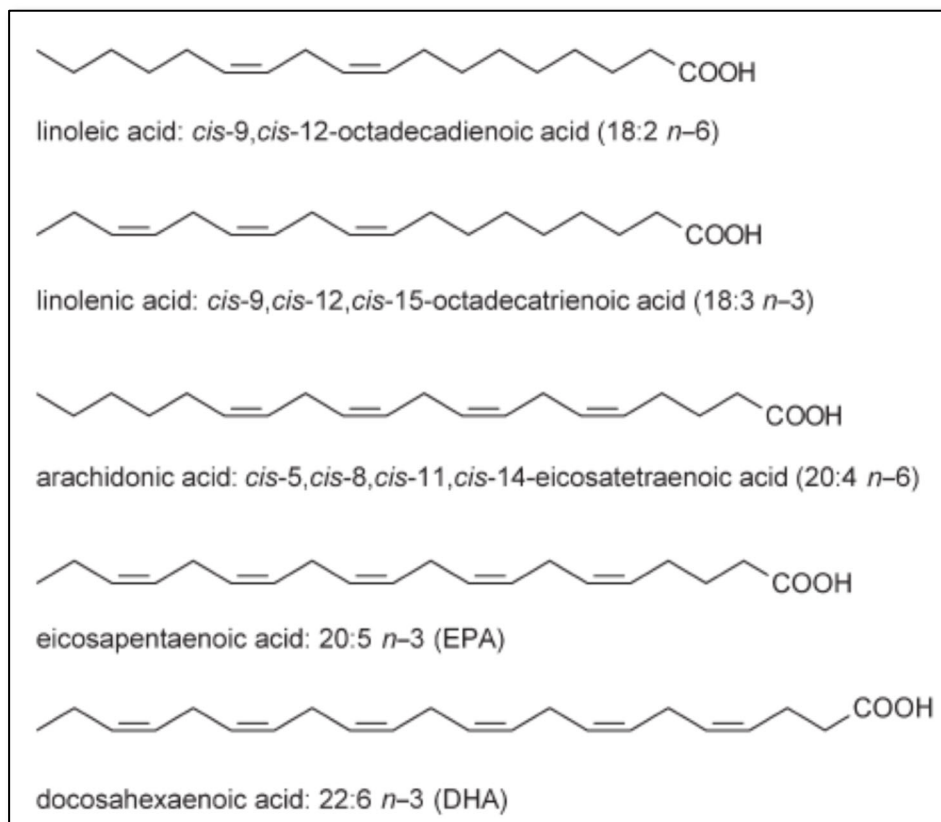
¹ As used herein, "PUFAs" generally refer to long-chain polyunsaturated fatty acids containing 20-22 carbon atoms, unless otherwise indicated.

(MARA-1027 at 1).² Monoglycerides are ester compounds that contain one fatty acid residue attached to a glycerol backbone (*i.e.*, $\text{HOCH}_2\text{CH}(\text{OH})\text{CH}_2(\text{O}_2\text{R})$, where $-\text{O}_2\text{R}$ is the fatty acid residue). (*Id.* at 1, 4-5). Diglycerides and triglycerides are similar in structure but contain two and three fatty acid residues attached as esters to the glycerol backbone, respectively. (*Id.*). Glycerides are often referred to as neutral lipids. Phospholipids are 1,2-diacyl esters of 3-glycerolphosphoric acid linked to organic bases and other moieties. (*Id.*). Phospholipids are often referred to as polar lipids.

Long-chain PUFAs are important nutritional components, for example, in maintaining cardiac health. PUFAs generally have a dual role in the cell. PUFAs may act as structural components of the cell membrane. (*Id.*). In this role, PUFAs are generally in phospholipid form. PUFAs may also be used for storage. In this

² Consistent with the Petition, DSM references the pagination for the E.N. Frankel textbook entitled *Lipid Oxidation*, rather than the pagination for the exhibit. For example, DSM cites to “MARA-1027 at 1” for page 1 of the textbook, which appears on page 19 of the exhibit. DSM cites to all other exhibits in this Preliminary Response in the same manner, except the prosecution history (MARA-1002) for which DSM cites to the pagination in the exhibit.

role, PUFAs are generally in glyceride form, including mono-, di-, and primarily triglyceride forms. (*Id.* at 4). The structures for various PUFAs include:



(*Id.* at 2, FIG. 1). To explain the terminology used in the field, docosahexaenoic acid (“DHA”) is referred to as 22:6 and is *n*-3. “22:6” means it is a fatty acid that contains **22** carbon atoms and has **6** carbon=carbon double bonds, and the “*n*-3” means the first double bond starts at the ***third*** carbon from the methyl end (or the left side of the molecule in the figure above). Similarly, arachidonic acid (“ARA”) is referred to as 20:4 and is *n*-6, which means it is a fatty acid containing **20** carbon

atoms and **4** carbon=carbon double bonds, the first of which starts at the **sixth** carbon from the methyl end. (*See generally* MARA-1027 at 1-3).

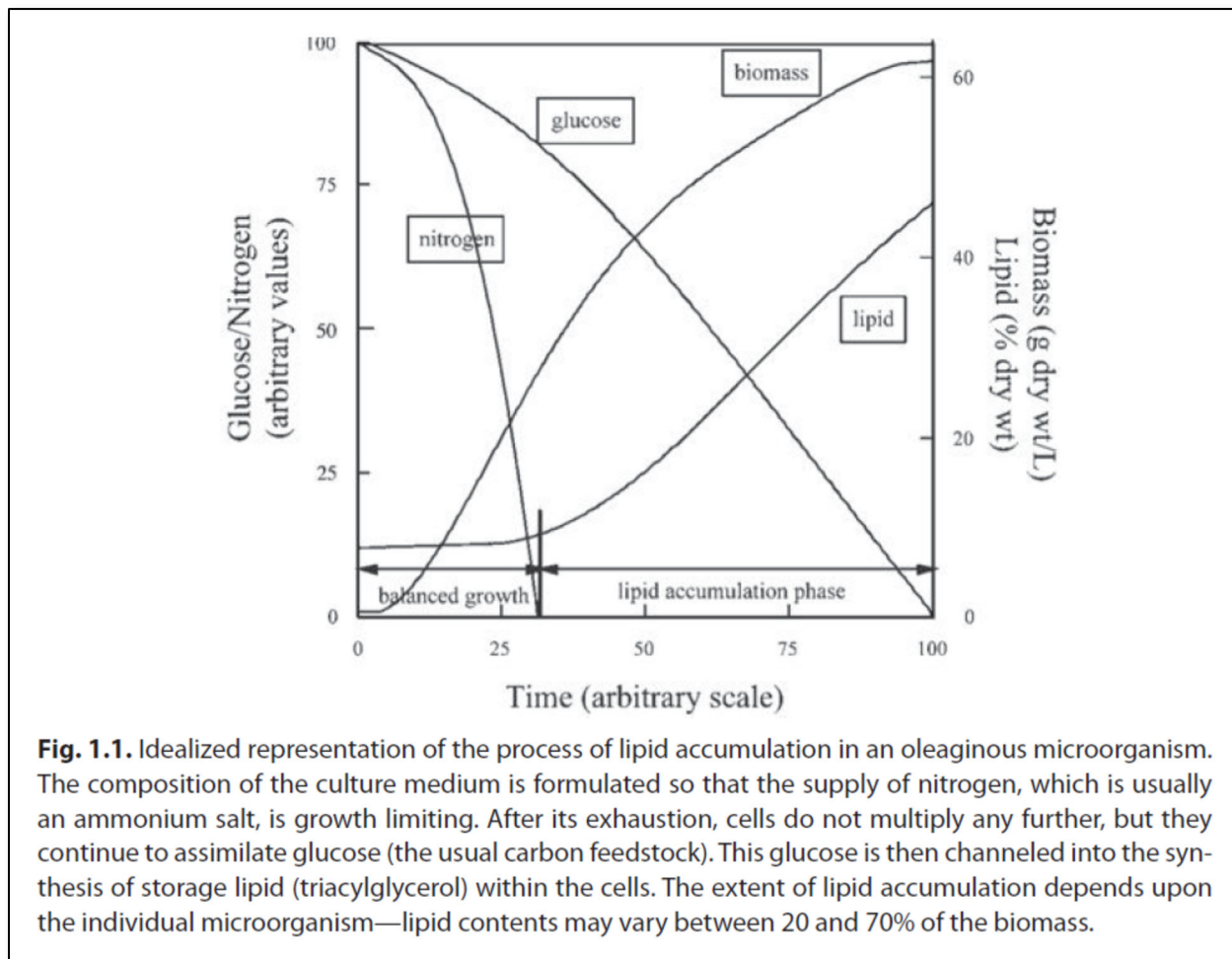
Another common long-chain PUFA is docosapentaenoic acid (“DPA”), which is referred to as 22:5. DPA can exist in two isomeric forms, *n*-3 and *n*-6. Thus, DPA is a fatty acid composed of **22** carbon atoms and **5** carbon=carbon double bonds, with the first double bond starting at either the **third** or **sixth** carbon depending on the isomer. The following chart summarizes the abbreviations and structural forms of common long-chain PUFAs relevant to this proceeding:

Fatty Acid	Abbreviation	Structural Form
Arachidonic acid	ARA (20:4)	<i>n</i> -6
Eicosapentaenoic acid	EPA (20:5)	<i>n</i> -3
Docosapentaenoic acid	DPA (22:5)	<i>n</i> -3 and <i>n</i> -6
Docosahexaenoic acid	DHA (22:6)	<i>n</i> -3

B. Microbial Fermentations Produce PUFAs in Phospholipid and Triglyceride Forms

Dietary intake is an important source of long-chain PUFAs in humans. Fish are rich in PUFAs and have been the traditional source of PUFA-based nutritional supplements (*e.g.*, fish oil). Fish-based nutritional supplements, however, have issues associated with undesirable taste characteristics as well as the potential long-term environmental impact of over-fishing. Accordingly, microbial sources of PUFAs have been sought as a means for replacement of fish-based PUFAs.

PUFAs can be produced from microbial sources using large-scale fermentation processes. These processes typically feed the cells a nitrogen source (*e.g.*, yeast extract or peptone), which is used by the cells to grow and multiply. The fermentation mixture is also supplied with a carbon source (*e.g.*, glucose). An idealized representation of a microbial fermentation process for producing PUFAs is illustrated in this figure:



(MARA-1010 at 3, FIG. 1.1). The fermentation is generally supplied with a limiting amount of the nitrogen source and an excess of the carbon source (*e.g.*, 40-50:1 C:N ratio). (*Id.* at 2-3). When the fermentation begins, a significant portion of PUFAs are produced in ***phospholipid form*** so that they can be used as a structural component and incorporated into cellular membranes to promote cellular growth in the biomass. (*Id.*). Once the nitrogen source is consumed, the ideal cells continue to consume the excess carbon source and produce PUFAs for storage in, for example, triglyceride form (also referred to as triacylglycerols). Thus, significant quantities of PUFAs can be produced and accumulated primarily in triglyceride form only after the nitrogen source is depleted and the carbon source is converted into storage lipids. (*Id.*).

The distinction between phospholipid and triglyceride production in microbial fermentations is illustrated in the prior art. For example, Yaguchi describes a microbial fermentation using thraustochytrid Strain SR21. (Ex. 2001).³ Initially, a large portion of the lipid content produced is in the form of “polar lipid”—*i.e.*,

³ Exhibit 2001 was filed by Petitioners as Exhibit 1031 in IPR2023-01167 identified in the Related Matters section of the Petition but was not included in Petitioners' exhibits in this proceeding. (*See* Pet. at iii).

phospholipid—and it is only after several days that the fermentation accumulates mostly triglycerides. (*Id.* at 1432). Notably, the neutral lipids (*i.e.*, the glycerides, including triglycerides) contained 35% DHA whereas the phospholipids contained much more (63.5%) DHA. (*Id.*). Similar trends have been observed in other thraustochytrids, such as strain KK17-3 in Huang, which produces 28% DHA in neutral lipids and 39% DHA in polar lipids. (Ex. 2002 at 608, Tbl. 4).⁴ This is consistent with Barclay's disclosure, which teaches that thraustochytrids “exhibit a ***marked decrease*** in omega-3 [PUFAs] as a percentage of total fatty acids, when undergoing nitrogen limitation” during the lipid accumulation phase. (MARA-1019 at 3:5-10 (emphasis added)).

Accordingly, the importance of the proportion of triglycerides versus phospholipids produced during a fermentation cannot be overlooked. It cannot be assumed that every microbial fermentation produces an oil containing at least 70% by weight triglycerides. For example, *S. aggregatum* (ATCC 28209) and *T. roseum* (ATCC 28210) both produce oils that contain less than 50% by weight of

⁴ Exhibit 2002 was filed by Petitioners as Exhibit 1028 in IPR2023-01167 identified in the Related Matters section of the Petition but was not included in Petitioners' exhibits in this proceeding. (*See* Pet. at iii).

triglycerides, with the remaining portions of the oil made up of substantial amounts of phospholipids and glycolipids. (MARA-1040 at 301-302, FIG. 4).

This is particularly true where the fermentation is carried out under non-optimized conditions that do not encourage complete cellular growth and exhaustion of the growth-limiting nitrogen source. In such fermentations, the cells do not adequately multiply, oil accumulation is relatively low, and a substantial portion of the PUFA content is produced in phospholipid form. (*See* Ex. 2003 at 2834 (noting that when total oil accumulation is low, “most of the fatty acids extracted are likely derived from membrane phospholipids rather than triacylglycerols”);⁵ *see also* Ex. 2004 at 636 (noting phospholipids make up a significant portion of lipids in young cells)). This is consistent with the higher concentrations of DHA in the

⁵ Exhibit 2003, which is co-authored by one of the authors of MARA-1009, published after the priority date of the '363 patent. However, the statement in Exhibit 2003 on which this Preliminary Response relies reflects the general knowledge in the field at the time of the '363 patent. It is also consistent with Figure 1.1 as well as the description of the same on pages 2-3 of MARA-1010, which explain that triglyceride accumulation does not predominate until the nitrogen source is depleted and the cells continue to consume the carbon source.

phospholipids versus triglycerides observed in Yaguchi (Ex. 2001) and Huang (Ex. 2002). (*See also* MARA-1040 at 302 (“In general, the proportion of PUFAs in polar lipid is higher than that in neutral lipid . . . owing to the regulatory role of PUFAs on membrane fluidity[.]”).

Once the fermentation is complete, the PUFAs are in various forms inside the cell and must be extracted. Extraction has traditionally been accomplished using mechanical methods and an organic solvent to disrupt the cells and extract their contents. (*See* MARA-1010 at 210-213, Fig. 13.3). The oil can then be collected and its fatty acid profile determined. (*Id.*).

C. Cellular Growth and Oil Production Are Key Considerations When Selecting Microorganisms

When screening microorganisms for use in the production of DHA-rich oils, the concentration of DHA is not the top consideration. “The *most important criterion* for selecting a microbial source for the commercial production of DHA is the potential of the microorganisms to produce substantial biomass and total lipids.” (MARA-1040 at 304 (emphasis added)). As Barclay explains it, microorganisms that produce high PUFA content but exhibit low growth and low oil production “would be considered to be very poor candidate organisms for the production of omega-3 [PUFAs].” (MARA-1019 at 4: 23-33).

Indeed, even if a microorganism produces an oil with a high concentration of DHA, that DHA will be primarily in phospholipid form and in low overall yield if the fermentation uses a microorganism that is not capable of sufficiently (i) growing in the presence of the nitrogen source and (ii) accumulating storage lipids (*e.g.*, triglycerides) derived from the carbon source once the nitrogen source is depleted. *See* Section II.B, *supra*. Thus, “[u]nless data on the total lipid content is available, one cannot evaluate an organism’s potential for use in the production of any type of fatty acid.” (MARA-1019 at 4:20-23). This is consistent with the art described in the Petition. For example, Radianingtyas explains that in its experiments, “[strain] ONC-T18 was chosen on the basis of a combination of economically desirable characteristics[,]” the first of which was its “capab[ility] of maximal heterotrophic growth[.]” (MARA-1007 at 82:2-6).

Consequently, a microorganism’s ability to sufficiently grow and produce oil are critical factors a PHOSITA would consider in evaluating that microorganism for the production of DHA.

D. Fatty Acid Profiles of Microbial Oils May Be Reported in Distinct Ways

Because (i) PUFAs make up a portion of both the triglyceride and phospholipid fractions of a microbial oil and (ii) the lipid composition of these two fractions cannot be assumed to be the same as demonstrated by Yaguchi and Huang,

it is important to appreciate the distinct ways in which fatty acid profiles of microbial oils may be reported in the art.

PUFA concentrations are measured experimentally using an indirect technique called gas chromatography ("GC"). A gas chromatogram permits the separation and identification of fatty acids based on their differing retention times. (*See, e.g.*, MARA-1015 at FIG. 1). Generally, the triglycerides and phospholipid-bound fatty acids are transesterified and converted into fatty acid methyl esters ("FAMES"). The FAMES are then analyzed by GC, and concentrations of the FAMES can be determined.

Fatty acid profiles can be reported in different ways. As in Huang, a microbial oil can first be separated into its triglyceride and phospholipid fractions before GC analysis. In such cases, the fatty acid profile for each fraction can be determined and reported independently. (*See, e.g.*, Ex. 2002 at Tbl. 4 (reporting % DHA in neutral and phospholipid fractions for two strains)). Oftentimes, however, the fatty acid profile of a microbial oil is reported as a percentage by weight of total fatty acids in the oil. (*See, e.g.*, MARA-1009 (reporting % DHA of total fatty acid composition)). When reported in this manner, the triglyceride and phospholipid fractions have not been separated prior to GC analysis, and the percent by weight reflects the concentration of each PUFA in the oil itself, not separately in the triglyceride or

phospholipid fractions. Accordingly, a PHOSITA would pay particular attention to how a reference reports the fatty acid contents of its microbial oils.

III. THE '363 PATENT CLAIMS NOVEL MICROBIAL OILS HAVING HIGH TRIGLYCERIDE CONTENT, HIGH DHA TRIGLYCERIDE CONTENT, AND LOW DPA(*n*-6) AND HEPTADECANOIC ACID CONTENT

The '363 patent discloses isolated and mutant thraustochytrid microorganisms and fermentation methods that produce novel microbial oil compositions having certain PUFA concentration and cellular biomass profiles. (*See generally* MARA-1001). These microorganisms produce relatively large amounts of oils that are high in triglyceride content. (*Id.* at 3:42-62). Despite the large production of oil output—which has traditionally been associated with microorganisms that produce relatively low concentrations of DHA—the microorganisms of the '363 patent beneficially produce oils that contain high concentrations of DHA and low concentrations of DPA(*n*-6) in the triglyceride fraction, along with low concentrations of heptadecanoic acid and, in some cases, ARA. (*Id.*) Accordingly, the '363 patent discloses microorganisms that are capable of producing new and improved omega-3 microbial oils on an industrial scale. (*See, e.g., id.* at TBLS. 5-8)

The '363 patent claims some of these novel microbial oil compositions. The '363 patent contains three independent claims:

1. A microbial oil comprising a triglyceride fraction of at least 70% by weight, wherein the docosahexaenoic acid content of the triglyceride fraction is at least 50% by weight, wherein the docosapentaenoic acid *n*-6 content of the triglyceride fraction is from 0.5% by weight to 6% by weight, and wherein the oil comprises 5% by weight or less of heptadecanoic acid.

3. A microbial oil comprising a triglyceride fraction of at least 70% by weight, wherein the docosahexaenoic acid content of the triglyceride fraction is at least 40% by weight, wherein the docosapentaenoic acid *n*-6 content of the triglyceride fraction is from at least 0.5% by weight to 6% by weight, wherein the ratio of docosahexaenoic acid to docosapentaenoic acid *n*-6 is greater than 6:1, and wherein the oil comprises 5% by weight or less of heptadecanoic acid.

4. A microbial oil comprising a triglyceride fraction of at least 70% by weight, wherein the docosahexaenoic acid content of the triglyceride fraction is at least 60% by

weight, and wherein the oil comprises 5% by weight or less of heptadecanoic acid.

(*Id.* at Claims 1, 3, 4). Claim 2 depends from claim 1, and claims 5-15 depend, directly or indirectly, from any one of claims 1-4.

The '363 patent was filed as Application No. 12/407,687 (the "'687 application") on March 19, 2009. (*Id.* at 1). An Office Action issued on March 21, 2011, requiring an election and restriction of species. (MARA-1002 at 177-185). DSM responded on April 21, 2011. (*Id.* at 155-165, 186-189). A Non-Final Office Action issued July 13, 2011, and the claims were rejected for alleged obviousness over US 2003/0060509 ("Elswyk"). (*Id.* at 139-149). DSM responded, and a Final Office Action issued October 28, 2011, again rejecting the claims over Elswyk and other art. (*Id.* at 69-79, 94-109). After two interviews with the Examiner, a Notice of Allowance issued on February 29, 2012. (*Id.* at 14-21, 58-61, 66-68). The '363 patent granted on June 26, 2012. (MARA-1001).

IV. CLAIM CONSTRUCTION

The Petition proffers no construction of any claim term other than conclusorily suggesting that each term should be given its "plain and ordinary meaning." (Pet. at 2-3). Having failed under 37 C.F.R. § 42.104(b)(3) to provide DSM with any indication as to what those "plain and ordinary meaning[s]" are, DSM

reserves its right to propose its own claim constructions should the Board institute review.

V. LEVEL OF ORDINARY SKILL IN THE ART

Any differences between Petitioners' and DSM's proffered level of ordinary skill in the art would not impact any of the arguments presented in this Preliminary Response. Accordingly, DSM reserves its right to proffer what it contends to be the appropriate level of ordinary skill in the art should the Board institute review. However, a PHOSITA would have a detailed understanding of the information provided in the Technology Background, Section II, *supra*, and, in particular, the expected impact of cellular biomass growth and oil production characteristics on the proportion of triglycerides and phospholipids produced during a microbial fermentation as well as strain selection.

VI. THE PETITION FAILS TO DEMONSTRATE THAT RADIANTINGTYAS ANTICIPATES CLAIMS 1-3

Ground 1 challenges the patentability of claims 1-3 based on alleged anticipation by Radianingtyas. (Pet. at 6-16). The Petition concedes that Radianingtyas was previously presented to the Patent Office through its U.S. Publication No. 2010/0285105 (the "105 publication", Ex. 2005), which claims

priority to and shares substantially the same specification as Radianingtyas.⁶ (Pet. at 65). In fact, the Examiner expressly considered the '105 publication during prosecution of the '363 patent. (MARA-1002 at 87). The Petition implies the Examiner missed the disclosures in Radianingtyas because it was allegedly “buried among hundreds of references on multiple pages of an information disclosure statement[.]” (Pet. at 64-65). This unfounded argument lacks merit as is demonstrated below.

Indeed, the Examiner appropriately did not rely on the reference during prosecution of the '363 patent because Radianingtyas did not invent—and therefore does not anticipate—the subject matter of claims 1-3. *See Am. Hoist & Derrick Co. v. Sowa & Sons, Inc.*, 725 F.2d 1350, 1359 (Fed. Cir. 1984) (“[A] qualified government agency [is] presumed to have properly done its job[.]”) (overruled on other grounds).

A. The Petition and Dr. Curtis Apply an Incorrect Legal Standard

“[T]he hallmark of anticipation is prior invention[.]” *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369 (Fed. Cir. 2008). To anticipate, “the prior art

⁶ The '105 publication claims priority to International Patent Application No. PCT/IB2007/004596, which published as Radianingtyas.

reference . . . must not only disclose all elements of the claim within the four corners of the document, but must also disclose those elements ‘arranged as in the claim.’” *Id.* (citing *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983); *see also id.* at 1370-72 (collecting cases). A reference does not need to expressly spell out all limitations combined as in the claim *if* a PHOSITA would at once envisage the arrangement or combination from its disclosure. *Microsoft*, 878 F.3d at 1069. But anticipation cannot be proven by pointing to multiple, distinct teachings that the artisan might somehow combine to achieve the claimed invention—as the Petition does here. *Id.*

The Petition relies on the testimony of Dr. Jonathan Curtis to prove anticipation. (MARA-1003 at ¶¶ 66-111). In forming his opinions regarding anticipation, Dr. Curtis does not apply the correct legal standard set forth above. Dr. Curtis states his understanding of anticipation as follows: “I am informed by Counsel and understand that, to anticipate a claim, a prior art reference must disclose, either expressly or inherently, each and every limitation of that claim and enable one of ordinary skill in the art to make and use the invention.” (MARA-1003 at ¶ 19). Dr. Curtis ignores the requirement that the elements must be arranged as in the claim or, if not, that a PHOSITA would at once envisage the claimed subject matter from the disclosure of Radianingtyas. (*See id.* at ¶ 100 (“Because

Radianingtyas discloses all elements of claim 1, it is my opinion that Radianingtyas anticipates claim 1.”)).

The Petition follows Dr. Curtis's lead and concludes that claims 1-3 are anticipated solely because all of their elements are purportedly disclosed somewhere in the 130-page disclosure of Radianingtyas. (Pet. at 9-16). Dr. Curtis does not explain how Radianingtyas discloses each and every element as “arranged or combined in the same way” as in claims 1-3. *Net MoneyIN*, 545 F.3d at 1371. Nor does he explain how a PHOSITA would at once envisage the claimed subject matter from the distinct disclosures of Radianingtyas. *Microsoft*, 878 F.3d at 1069. These evidentiary deficiencies are fatal to Ground 1. *See Integra Lifesciences I, Ltd. v. Merck KGaA*, 496 F.3d 1334, 1342 (Fed. Cir. 2007) (“[W]hen an expert witness' statement of the law is incorrect, that view of the law cannot be relied upon to support the verdict.”); *see also Hebert v. Lisle Corp.*, 99 F.3d 1109, 1117 (Fed. Cir. 1996) (noting expert testimony based on “markedly incorrect law” is inadmissible).

B. Radianingtyas Does Not Disclose Any Microbial Oil Containing the Claimed Triglyceride, DHA, DPA(*n*-6), Heptadecanoic Acid, and ARA Concentrations

Radianingtyas does not disclose each and every element of claims 1-3 as arranged in those claims or in such a manner that would lead a PHOSITA to at once envisage the claimed subject matter. In alleging that claims 1-3 are anticipated by

Radianingtyas, the Petition and Dr. Curtis mix and match disclosures from multiple, distinct embodiments in Radianingtyas and then cobble them together to purportedly support anticipation. (Pet. at 9-12). But mixing-and-matching is not anticipation, and Ground 1 necessarily fails. *See Net MoneyIN*, 545 F.3d at 1369 (finding no anticipation where disclosure required “combination of two disclosed examples in order to find all elements of the claim”). When the correct legal standard is applied, Radianingtyas does not anticipate claims 1-3.

1. Radianingtyas Does Not Disclose Any Microbial Oil Containing the Claimed Triglyceride, DHA and Heptadecanoic Acid Concentrations

Claim 1 recites, *inter alia*, a microbial oil comprising (i) at least 70% by weight triglycerides, (ii) at least 50% by weight of DHA in the triglycerides, and (iii) 5% by weight or less of heptadecanoic acid. (MARA-1001 at Claim 1). Claim 2 depends from claim 1 and includes these same elements. (*Id.* at Claim 2). Claim 3 is similar except that the amount by weight of DHA in the triglyceride fraction is at least 40% by weight. (*Id.* at Claim 3). In their “Analysis” sections, the Petition and Dr. Curtis rely only on a few portions of Radianingtyas for disclosure of the claimed amounts of heptadecanoic acid: (1) MARA-1007 at 34:4-37:14; (2) MARA-1007 at FIG. 11 on 11/16 (PDF page 125); and (3) MARA-1007 at 32:20-25. (Pet. at 13-14,

16; MARA-1003 at ¶¶ 95-100). These portions fail to disclose any microbial oil that contains the requisite amounts of **both** DHA **and** heptadecanoic acid.

First, page 34, line 4 through page 37, line 14 of Radianingtyas disclose the impact that certain “fatty acid production antagonist[s,]” compared to a control, have on the “fatty acid composition” of the “[l]ipid[s]” produced thereby. Although each of these exemplary microbial oils contains less than 5% by weight of heptadecanoic acid, the Petition and Dr. Curtis ignore an important teaching regarding these oils: as demonstrated in Table 1 below, none of them contain “at least 40% by weight” or “at least 50% by weight” of DHA in the triglyceride fraction. The largest amount of DHA disclosed is 33% by weight of total fatty acids.

No.	Disclosure in Radianingtyas	Heptadecanoic Acid (Margaric Acid or 17:0)	DHA	Meets Claims?
1	34:4-19	“1.16% to 1.49%”	“13.54% to 19.31%”	No
2	34:20-35:2	“0.85% to 0.74%”	“19.98% to 19.97%”	No
3	35:3-18	“0.31% to 0.28%”	“18.77% to 33.16%”	No
4	35:19-34	“0.31% to 0.17%”	“18.77% to 24.65%”	No
5	36:1-16	“2.29% to 0.19%”	“21.48% to 16.86%”	No
6	36:17-32	“1.89% to 2.69%”	“28.48% to 23.03%”	No

No.	Disclosure in Radianingtyas	Heptadecanoic Acid (Margaric Acid or 17:0)	DHA	Meets Claims?
7	36:33-37:14	"0.80% to 1.03%"	"14.13% to 20.61%"	No

Table 1. Summary of heptadecanoic acid and DHA amounts (wt.% of total fatty acids) disclosed in Paragraphs 146-152 of Radianingtyas. (MARA-1007 at 34:4-37:14). Red shading indicates amounts outside claimed ranges.

Second, although the Petition cites to FIG. 11/16 of Radianingtyas, FIG. 11/16 cannot be read separately and apart from FIG. 12/16, which together effectively provide the same information disclosed on page 34, line 4 through page 37, line 14 of Radianingtyas. Radianingtyas discloses that the fatty acid profiles for the microbial oils described in FIGS. 11/16 and 12/16 relate to Example 14, which describes the impact of fatty acid antagonist supplementations on the fatty acid profile of oils produced by strain ONC-T18. (MARA-1007 at 104:4-108:27). Again, as summarized in Table 2 below, the data provided in FIGS. 11/16 and 12/16 of Radianingtyas demonstrate that these microbial oils do not contain the requisite concentration of DHA—irrespective of the fatty acid production antagonist employed in the respective fermentations.

No.	Antagonist Experiment (FIGS. 11-12)	% TFA Heptadecanoic Acid (17:0)	% TFA DHA (22:6n3)	Meets Claims?
1	Control	1.16	13.54	No
	Sethoxydium (100 µM)	1.49	19.31	
2	Control	0.85	19.98	No
	Cerulerin (20 mg/l)	0.74	19.97	
3, 4	Oleic acid (2 g/l)	0.28	33.16	No
	Oleic acid (2 g/l) Glucose (5 g/l)	0.17	24.65	
	Control	0.31	18.77	
5	Capsaicin (0.1 g/L)	0.19	16.86	No
	Control	2.29	21.48	
6	Toluic acid (0.2 g/L)	2.69	23.03	No
	Control	1.89	28.48	
7	Norflurazon (0.2 g/L)	1.03	20.61	No
	Control	0.80	14.13	

Table 2. Summary of heptadecanoic acid and DHA amounts (wt.% of total fatty acids) disclosed in FIGS. 11/16 and 12/16 of Radianingtyas. (MARA-1007). Red shading indicates amounts outside claimed ranges.

Finally, the “Analysis” section of the Petition is left with the following disclosure of Radianingtyas:

The percentage of neutral lipids can be at least 95% by weight of total lipids. For example, the typical composition of fatty acids for ONC-T18, in the neutral lipids is as follows: 15% of myristic acid, 8% of pentadecanoic acid, 35% of palmitic acid, 7% of palmitoleic acid, 1% of stearic acid, 2% of oleic acid, 1% of eicosapentaenoic acid, 6% of decosapentaenoic [*sic*] acid and 25% docosahexaenoic acid.

(MARA-1007 at 32:20-25). The Petition contends that because these fatty acids “sum[] to 100% without disclosing [heptadecanoic acid,]” Radianingtyas “discloses a microbial oil in which [heptadecanoic acid] . . . is either absent or below the limit of detection.” (Pet. at 13-14; *see also* MARA-1003 at ¶ 98). But again, the Petition inexplicably ignores that this passage expressly discloses a “typical composition of fatty acid for ONC-T18” contains 25% DHA in the neutral lipids—not “at least 50%” or “at least 40%” as in claims 1-2 and 3, respectively. (MARA-1007 at 32:21-25).

In their “Overview of Radianingtyas” sections, the Petition and Dr. Curtis contend that Radianingtyas discloses oils with constituent fatty acids including “DHA, DPA, as well as low levels of heptadecanoic acid (HDA or 17:0 or margaric acid)” and, in support, cite to: (1) MARA-1007 at 11:4-9, 99:22-24, 99:29-32; (2) MARA-1007 at 100:23-25; (3) MARA-1007 at FIG. 9/16; and (4) as previously discussed, MARA-1007 at FIG. 11/16. (Pet. at 6-7; MARA-1003 at ¶ 68). None of these cure the deficiencies of the disclosures upon which the Petition’s and Dr. Curtis’ “Analysis” sections rely.

Further, page 11, lines 4-9 and page 99, lines 22-24 and 29-32 of Radianingtyas do not disclose heptadecanoic acid at all. Page 100, lines 23-25 of Radianingtyas disclose that the “fatty acid profile of ONC-T18” includes “the occurrence of odd-chain saturated fatty acids (15:0 and 17:0)[.]” But again, in that same section, Radianingtyas discloses that ONC-T18 produces “DHA which is approximately 35% of the total intracellular fatty acids.” (MARA-1007 at 99:22-24). Similarly, FIG. 9/16 of Radianingtyas discloses a microbial oil produced in a flask fermentation fed with oleic acid that contains less than 5% of heptadecanoic acid (17:0) but also *no more than 35% DHA*. (*Id.* at FIG. 9/16). And as previously explained, none of the microbial oils disclosed in FIGS. 11/16 and 12/16 of Radianingtyas contain the claimed concentration of DHA.

Radianingtyas does not expressly disclose heptadecanoic acid in any manner aside from these identified disclosures. The Petition evidence further demonstrates that the claimed heptadecanoic acid range is not inherent to all microbial oils produced by *Thraustochytrium* strains such as those disclosed in Radianingtyas. (See, e.g., MARA-1007 at 82-83 (noting that strains ONC-T01 through ONC-T68 are “believed to be a Thraustochytrid”)). For example, Ground 1 relies on a strain described in US 2004/0161831 (“Komazawa”) (MARA-1015) as purportedly having high DHA content in the triglyceride fraction.⁷ (Pet. at 10). Aside from being improperly relied on in an anticipation context, Komazawa’s strain, which is a *Thraustochytrium* referred to as LFF1, also produces heptadecanoic acid in an amount of 9.7% by weight of total fatty acids, which exceeds the claimed range.

⁷ Ground 1 relies on Komazawa to support Petitioners’ argument that “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 oil would satisfy [1b].” (Pet. at 10). But as noted, the claimed triglyceride concentration is not inherent to all microbial oils, including those disclosed in Radianingtyas. See generally Section II.B, *supra*, and Section VI.B.2.b, *infra*.

(MARA-1015 at Example 2, ¶¶ [0073]-[0108]; *see also id.* at ¶ [0184] (identifying strain LFF1 as *Thraustochytrium*)).

Accordingly, the Petition fails to demonstrate that Radianingtyas discloses any microbial oil that contains the requisite DHA and heptadecanoic acid concentrations recited in claims 1-3.

2. *Radianingtyas Does Not Disclose Any Microbial Oil Containing the Claimed Triglyceride and DHA Concentrations*

None of the microbial oils disclosed in Radianingtyas contains, either expressly or inherently, a triglyceride fraction that makes up at least 70% by weight of the microbial oil and the requisite concentration of DHA in that triglyceride fraction. Accordingly, Radianingtyas does not anticipate claims 1-3 for this additional reason.

a. *Strain ONC-T18 Does Not Produce a Microbial Oil Containing the Claimed DHA Concentrations*

The only microbial oils for which Radianingtyas purportedly discloses triglyceride content are oils produced by strain ONC-T18. According to Radianingtyas,

[t]he disclosed oil producing microbes, including the oil producing microbe, ONC-T18, are able to produce lipid thus obtained, any of its variants and any associations between members of the same species of eukaryotic

microorganisms whereby the lipid profile is as follows.

The percentage of neutral lipids can be at least 95% by weight of total lipids.

(MARA-1007 at 32:17-21). Radianingtyas further discloses that

[t]he percentage of mono-, di- and tri-glycerides in the neutral lipid fraction of ONC-T18 is 0% to about 2%, 0 to about 2% and 96 to about 100%, respectively. While the polar lipid fraction with [sic] comprises between 5% and about 10% of the lipid fraction, comprises phosphatidylcholine, phosphatidylserine and phosphatidic acid both bound and unbound to neutral lipids.

(*Id.* at 33:1-5). “Analysis of results shows that the fatty acid component which ONC-T18 produces under heterotrophic fermentation is almost entirely triglyceride (at least 95%) in nature.” (*Id.* at 89:22-26). But, as Radianingtyas conclusively demonstrates, strain ONC-T18 does not produce “at least 40% by weight” or “at least 50% by weight” DHA.

As an initial matter, the Petition and Dr. Curtis distort the express disclosure of Radianingtyas with respect to how much DHA strain ONC-T18 can produce. In

particular, Dr. Curtis quotes page 26, lines 29-34 of Radianingtyas in a misleading manner. (MARA-1003 at ¶ 82 (alleging ONC-T18 produces up to 60% DHA (citing MARA-1007 at 26:29-34))). Dr. Curtis uses an ellipsis to suggest that ONC-T18 produces up to 60% by weight of DHA. (*Id.*). The Petition also suggests that strain ONC-T18 produces a microbial oil containing up to 60% by weight DHA. (Pet. at 10 (citing MARA-1007 at 26:29-34)).

But this is what the misquoted paragraph of Radianingtyas actually states:

The eukaryotic microorganism, for example, such as ONC-T18, can produce at least about 30 wt.%, 40 wt.%, 50 wt.%, 60 wt.%, 70 wt.% or 80 wt.% (e.g. about 80 wt.%) of a lipid composition per dried cellular biomass. For example, the oil producing microbe 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 0% to about 3% of the omega-3 fatty acid, EPA, (for example, at least 1% or 2% 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 at 26:29-27:3). A PHOSITA would not interpret this paragraph as teaching that strain ONC-T18 produces a microbial oil containing “at least 50% by weight” or “at least 40% by weight” of DHA in the triglyceride fraction. The only mention of strain ONC-T18 in this particular paragraph is in the first sentence, which is directed to the amount of lipid composition produced per dried weight of cellular biomass. The sentence that purportedly discloses a range of about 15-60% by weight of DHA (*see* MARA-1003 at ¶ 82 n.4) does not mention strain ONC-T18 at all.

In view of the other disclosures in Radianingtyas, a PHOSITA would understand that strain ONC-T18 does not produce microbial oils that contain at least 40% by weight DHA in the triglyceride fraction. Radianingtyas selects strain ONC-T18 due to, *inter alia*, its favorable growth and oil production characteristics under heterotrophic fermentation conditions and conducts numerous fermentations with this strain to optimize its oil production. (*See* MARA-1040 at 304 (noting biomass and total lipid production is the “most important criterion” for selecting microbial source for DHA production)). But none of these optimized fermentations produce a microbial oil containing at least 40% by weight DHA in the triglycerides.

In Example 4, carbon sources, nitrogen sources, and salt types were all varied in twenty-three different fermentations, and the amount of DHA produced varied between 16-38% by weight of total fatty acids. (MARA-1007 at 87-88, Tbl. 4). Example 4 does not disclose the amounts of DPA(*n*-6) and ARA produced in any of its fermentations. Example 8 discloses that ONC-T18 produces DHA and DPA in amounts of 24-34% and 6-10% by weight of total fatty acids, respectively. (*Id.* at 90-91, Tbl. 5). Example 8 does not disclose the amount of ARA produced in any of its fermentations. Example 9 performed similar fermentations with alternative carbon sources, which produced DHA at a maximum of 26% by weight of total fatty acids but also produced 9% by weight DPA(*n*-6). (*Id.* at 92, Tbl. 6).

In the fermentations of Example 10, strain ONC-T18 produced DHA in amounts of 30% and 38% by weight of total fatty acids. (*Id.* at 93:1-19). Example 10 does not disclose how much DPA(*n*-6) and ARA were produced in these fermentations. Similar results were shown in Example 11, which demonstrated DHA production in strain ONC-T18 to be between 13-30% by weight of total fatty acids. (*Id.* at 93-94, Tbl. 7). Example 12 discloses the impact of the extraction technique on the microbial oil composition, and none of the various extraction techniques produce DHA in an amount greater than 25% by weight of total fatty

acids.⁸ (*Id.* at 94:6-95:27). Example 13 discloses fermentations designed to “limit the factors inhibiting both biomass and omega-3 PUFA production in ONC-T18,” but once again these fermentations produce no more than 32% by weight DHA of total fatty acids. (*Id.* at 101:33-102:7). As described in Section VI.B.1, *supra*, the fermentations disclosed in Example 14 do not produce any microbial oil containing “at least 40%” by weight of DHA.

Accordingly, strain ONC-T18 does not produce an oil containing the claimed amount of DHA in the triglyceride fraction under any of the multitude of fermentation conditions disclosed in Radianingtyas.

Effectively conceding as much, the Petition contends that Radianingtyas discloses microbial oils containing up to 90% DHA. (Pet. at 11 (citing MARA-1007 at 8:2-4; MARA-1003 at ¶ 86)). But the Petition ignores the full context of such

⁸ The Bligh and Dyer technique produces about 25% by weight DHA ($125.24/505.63 \times 100$). (*Id.* at 95:11-14). Direct transesterification produces about 24% by weight DHA ($98.65/408.17 \times 100$). (*Id.* at 95:15-17). Simultaneous saponification produces about 25% by weight DHA ($197.20/779.31 \times 100$). (*Id.* at 95:18-19). And solid phase extraction produces about 22% by weight DHA ($171.69/784.34 \times 100$). (*Id.* at 95:20-27).

purported disclosure. In defining the term “purify” as referring to the state in which a substance is in a state of greater homogeneity than it was before, Radianingtyas provides a lexicographical 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-1007 at 7:26-8:4). The Petition does not identify any actual microbial oil, purified or not, that contains at least 70% by weight triglycerides and 90% DHA in the triglyceride fraction, much less one that also contains 0.5-6% by weight DPA(*n*-6), 5% or less by weight of heptadecanoic acid, and 1.5% by weight or less of ARA. Nor is one disclosed in Radianingtyas.

b. The Petition Fails to Demonstrate That Any Other Radianingtyas Strain Produces an Oil Containing at Least 70% By Weight Triglycerides

The Petition identifies eleven strains disclosed in Radianingtyas that purportedly produce more than 50% by weight DHA. (Pet. at 11 (citing MARA-1003 at ¶ 85)). But Radianingtyas does not disclose how much of the microbial oils produced by these strains is made up of a triglyceride fraction. Nor does Radianingtyas tie the claimed triglyceride concentration with any particular DHA concentration in such triglyceride fraction.

Moreover, as illustrated in Table 3 below, all of these strains exhibit a significant inhibition of cellular growth, as evidenced by the 74-96% decrease in biomass production compared to strain ONC-T18. These other *Radianingtyas* strains also exhibit substantially decreased (66-87%) oil production compared to ONC-T18. (MARA-1007 at 82-83, TBL. 3 (noting the total lipid production for strains); *see also* MARA-1045 at FIG. 11 (comparing lipid production of strains); MARA-1025 at FIG. 2 (same)). As explained in Section II.B, *supra*, oils produced by microbial strains that exhibit relatively low growth and low oil production are expected to contain fatty acids that are primarily in phospholipid form, not triglyceride form.

Strain	DHA (mg/g)	Total Lipid (mg/g)	DHA (wt.% total lipid)	Oil Production Difference (%Δ)	Biomass (g/l)	Biomass Difference (%Δ)
ONC-T02	31.84	52.88	60	-84	0.50	-78
ONC-T07	33.02	61.81	53	-81	0.50	-78
ONC-T09	63.82	109.12	58	-66	0.80	-65
ONC-T10	22.22	40.99	54	-87	0.10	-96
ONC-T12	57.96	96.26	60	-70	0.60	-74

Strain	DHA (mg/g)	Total Lipid (mg/g)	DHA (wt.% total lipid)	Oil Production Difference (%Δ)	Biomass (g/l)	Biomass Difference (%Δ)
ONC-T18	83.63	321.14	26	N/A	2.30	N/A
ONC-T19	34.71	66.14	52	-79	0.60	-74
ONC-T25	26.99	45.67	59	-86	0.60	-74
ONC-T46	33.34	63.76	52	-80	0.30	-87
ONC-T52	26.57	41.36	64	-87	0.60	-74
ONC-T67	23.71	43.24	55	-87	0.50	-78
ONC-T68	22.72	41.37	55	-87	0.50	-78

Table 3. Comparison of growth characteristics of ONC-T18 and other strains disclosed in Radianingtyas. (MARA-1007 at 82-83, TBL. 3). Oil production and biomass differences are calculated as percent difference in the production of oil and biomass, respectively, compared to strain ONC-T18.

Furthermore, the claimed triglyceride fraction is not inherent to all microbial oils. (See, e.g., MARA-1040 at FIG. 4 (noting *S. aggregatum* ATCC 28209, *T. aureum* ATCC 34304, and *T. roseum* ATCC 28210 produce oils that do not contain at least 70% by weight of a triglyceride fraction)). Thus, the evidence in the Petition

does not demonstrate that any of these other Radianingtyas strains necessarily produces a microbial oil that contains at least 70% by weight of triglycerides. Moreover, Radianingtyas does not disclose any fatty acid profile for any of these additional strains, including the amount of heptadecanoic acid and DPA(*n*-6) produced in fermentations employing these strains.

Accordingly, none of the other strains disclosed in Radianingtyas cure the deficiencies of strain ONC-T18. Radianingtyas does not disclose any microbial oil produced by any of these strains that meet, either expressly or inherently, each and every element of claims 1-3.

3. Radianingtyas Does Not Disclose Any Microbial Oil Containing the Claimed DHA and ARA Concentrations

The Petition fails to demonstrate anticipation of claim 2 for an additional reason: Radianingtyas does not disclose any strain that produces a microbial oil containing at least 50% by weight of DHA in the triglyceride fraction in combination with 1.5% by weight or less of ARA, as recited in claim 2.

According to the Petition, Radianingtyas discloses that “approximately 80%” of its isolated strains “synthesized the omega-6 PUFAs, arachidonic acid (AA) . . . at concentrations varying between 1 and 18%.” (Pet. at 14 (citing MARA-1007 at 96:1-3, 99:8-12, 29-32; MARA-1003 at ¶ 102)). The Petition then contends that Radianingtyas anticipates claim 2 because a range of 1-18% of ARA ever so slightly

overlaps the claimed range of 1.5% or less. (Pet. at 14-15). This argument lacks merit.

This is not a case in which the only difference between the prior art disclosure and the claimed invention is an overlapping range. Here, Radianingtyas does not disclose any strain that produces at least 50% by weight of DHA in the triglyceride fraction in combination with the requisite concentration of ARA. Indeed, the paragraph of Radianingtyas on which the Petition relies for its 1-18% range discloses only the amount of DHA produced by ONC-T18, which was approximately 35% of the total intracellular fatty acids—notably below the claimed threshold. (MARA-1007 ant 99:16-32). Radianingtyas does not disclose, either expressly or inherently, that any of the other 53 strains produce oils having the claimed concentration of DHA in combination with the claimed concentration of ARA. (Id. at 82-83, Tbl. 3 (disclosing only DHA production in various strains)).

The Petition again effectively concedes this point but asserts that Radianingtyas discloses that strain ONC-T18 “can produce a wide range of oils that all consistently contain low amounts of ARA.” (Pet. at 15 (citing MARA-1007 at 34:4-37:14; FIG. 11/16; MARA-1003 at ¶ 103)). But this argument fails for the same reasons described in Section VI.B.2.a, *supra*. Again, in each of the examples that purportedly produce oils with “low amounts of ARA[,]” (Pet. at 15), they also

consistently produce low amounts of DHA that fall outside the claimed range under all fermentation conditions. (*See, e.g.*, MARA-1007 at 34:4-19 (disclosing 0.36-0.2% ARA and 13.54-19.31% DHA), 34:20-35:2 (disclosing 0.16-0.30% ARA and 19.98-19.97% DHA), 35:3-18 (disclosing 0.22-0.72% ARA and 18.77-33.16% DHA), 35:19-34 (disclosing 0.22-0.46% ARA and 18.77-24.65% DHA), 36:1-16 (disclosing 0.17-0.78% ARA and 21.48-16.86% DHA), 36:17-32 (0.38-0.90% ARA and 28.48-23.03% DHA), 36:33-37:14 (disclosing 0.14-0.19% ARA and 14.13-20.61% DHA); *see also* Section VI.B.2.a, *supra* (noting ONC-T18 does not produce at least 50% by weight of DHA)).

The Petition further prophetically contends that in some embodiments, “ARA is not disclosed at all, and is either absent or below the limit of detection.” (Pet. at 15 (citing MARA-1007 at 32:20-25; MARA-1003 at ¶ 104)). But the single embodiment that purportedly discloses 0% ARA also discloses only 25% DHA. (MARA-1007 at 32:20-25).

Accordingly, the Petition fails to demonstrate a reasonable likelihood that claim 2 is anticipated by Radianingtyas.

4. *The Petition Provides No Evidence Demonstrating That A PHOSITA Would at Once Envisage Claims 1-3 From the Distinct Embodiments of Radianingtyas*

Having failed to demonstrate that Radianingtyas discloses each and every element *as arranged in* claims 1-3, the Petition and Dr. Curtis were required to provide evidence showing that a PHOSITA would at once envisage the claimed subject matter from the disclosure of Radianingtyas. *Microsoft*, 878 F.3d at 1069. Neither the Petition nor Dr. Curtis provides such evidence. Consequently, the Petition does not establish a reasonable likelihood that Petitioner will prevail in establishing anticipation of claims 1-3 by Radianingtyas. Nor does it demonstrate material error by the Examiner in allowing claims 1-3 over Radianingtyas.

VII. THE PETITION FAILS TO DEMONSTRATE A REASONABLE LIKELIHOOD THAT ANY CHALLENGED CLAIM WOULD HAVE BEEN OBVIOUS

The obviousness grounds raised in the Petition fare no better than the anticipation ground. In each case, the Petition mixes and matches disparate teachings from the various prior art references without proper consideration of the claimed subject matter as a whole and fails to demonstrate a reasonable likelihood that any claim will be found to have been obvious. For at least the reasons detailed below, the Petition should be rejected.

A. Ground 2 Fails to Meet the Institution Threshold

Ground 2 challenges the patentability of claims 1-15 based on alleged obviousness over the combination of Radianingtyas and Kralovec. (Pet. 16-41). The Petition fails to demonstrate a reasonable likelihood that a PHOSITA (i) would have been motivated to combine Radianingtyas and Kralovec to arrive at the claimed invention and (ii) would have had a reasonable expectation of success in achieving the claimed invention through that combination. The Petition reconstructs the claimed invention using improper hindsight based on the teachings of the '363 patent. Consequently, the Petition fails to demonstrate a reasonable likelihood that any of claims 1-15 will be found to have been obvious in view of the combination of Radianingtyas and Kralovec.

1. *Kralovec's Enrichment Methods Significantly Increase the Concentration of PUFAs in Microbial Oils, Not Just DHA*

Ground 2 contends that a PHOSITA would have used the enrichment techniques disclosed in Kralovec to increase the amount of DHA in the microbial oils produced in fermentations using strains disclosed in Radianingtyas. (Pet. at 18-26). Ground 2 relies on the very same disclosures in Radianingtyas as identified in Ground 1. (*Id.* at 16, 26-34). Radianingtyas was discussed in detail with respect to Ground 1. *See* Section VI, *supra*.

Kralovec discloses a method by which an extracted oil can be enriched to increase the concentration of PUFA-containing triglycerides in the oil. (MARA-1030 at 2:25-31). According to Kralovec's enrichment methods, an extracted microbial oil is hydrolyzed with a lipase enzyme to liberate saturated fatty acids from the triglyceride to produce a mixture of free fatty acids and a glyceride fraction containing a mixture of mono-, di-, and triglycerides. (*Id.* at 6:1-26, 8:20-12:11, 38-39, Example 1). After separation of the free fatty acid and glyceride fractions, the resulting glyceride fraction is reacted with added polyunsaturated fatty acids (in their free fatty acid form) from a different source in the presence of a different lipase enzyme to re-form the triglycerides. (*Id.* at 12:12-32, 13:26-15:6). By selectively removing saturated fatty acids from the starting oil, "concentrated oils with triglycerides containing higher proportions of *polyunsaturated fatty acid esters* than the starting triglycerides" may be formed. (*Id.* at 35:20-25 (emphasis added)).

Not surprisingly, Kralovec discloses that its methods increase not only the amount of DHA in an oil but also other PUFAs, including DPA(*n*-6) and ARA. (*Id.* at 15:7-22 (noting DPA(*n*-6) and ARA as exemplary PUFAs), 19:28-30 (same)). This is illustrated in Example 4 of Kralovec. In this example, Kralovec discloses a starting microbial oil that contains almost 60% saturated fatty acids and only 30% PUFAs, including 4.6% DPA and 0.9% ARA (20:4). (*Id.* at 42:1-43:35, Tbl. 9.1).

After hydrolysis using a lipase enzyme, the free fatty acid fraction is separated from the glyceride fraction. The resulting glyceride fraction, which contains only 57% triglycerides—significantly below the 70% threshold recited in the Challenged Claims—contains 8.1% DPA and 1.4% ARA (20:4). (*Id.* at Tbl. 9.1, 9.2). The glyceride fraction is then re-esterified to re-form the triglycerides, and the resulting oil contains 7.3% DPA and 2.5% ARA, both of which fall outside of the claimed range. (*Id.* at Tbl. 9.1). In fact, none of the re-esterified oils produced by Kralovec's enrichment methods contain 0.5-6% by weight DPA and 1.5% or less by weight ARA. (*Id.* at Tbl 8.2 (disclosing 17.8%, 16.8% and 16.5% DPA and 2.9%, 4.1%, and 3.0% ARA in re-esterified oils)⁹, Tbl. 9.1 (disclosing 7.3% DPA in re-esterified oil compared to 4.6% in starting oil and 2.5% ARA in re-esterified oil compared to 0.9% in starting oil)). This is illustrated in Table 4 below.

⁹ Example 3 of Kralovec does not disclose the amount of ARA in the starting microbial oil. Consequently, the amount by which ARA in Example 3 is increased in the resulting re-esterified oil cannot be determined.

Fatty Acid	Composition of Kralovec Example 4 Before Enrichment	Composition of Kralovec Example 4 After Re-esterification	Meets Claims?
Myristic Acid (14:0)	19.4	11.6	N/A
Palmitic Acid (16:0)	35.4	17.3	N/A
ARA (20:4)	0.9	2.5	No
DPA (22:5)	4.6	7.3	No
DHA (22:6)	22.0	34.5	No

Table 4. Fatty acid composition (% wt. total fatty acids) of the microbial oil of Example 4 of Kralovec before and after enrichment. (MARA-1030 at Tbl. 9.1). Red shading indicates amounts outside claimed ranges.

A PHOSITA therefore would understand that Kralovec’s enrichment methods are not selective for increasing only the concentration of DHA in an oil. Importantly, Kralovec’s methods also increase the concentration of other PUFAs, including DPA and ARA, in the resulting oil—and do so substantially. (*See id.* at Tbl. 9.1 (disclosing 7.3% DPA in re-esterified oil compared to 4.6% in starting oil and 2.5% ARA in re-esterified oil compared to 0.9% in starting oil)). This is consistent with the Petition, which notes that “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.”
(Pet. at 25 (citing MARA-1007, 42:14-16, 42:19-20) (emphasis added)).

2. *A PHOSITA Would Not Have Been Motivated to Combine Radianingtyas and Kralovec to Achieve Claims 1-3 and Their Dependent Claims*

Because “claimed discoveries almost of necessity will be combinations of what, in some sense, is already known[,]” *KSR*, 550 U.S. at 418-19, the Petition must provide a reason that a PHOSITA “would have combined elements from specific references *in the way the claimed invention does*[,]” *ActiveVideo Networks, Inc. v. Verizon Communs., Inc.*, 694 F.3d 1312, 1328 (Fed. Cir. 2012) (emphasis in original). The overly generic and conclusory reasons for combining Radianingtyas and Kralovec in the Petition fail to provide a sufficient motivation to combine under the correct legal standard.

The Petition proffers seven alleged motivations for combining Radianingtyas and Kralovec, all of which are limited in their rationale solely to increasing the DHA content of the resulting oil but are not tied to any specific range of DHA concentrations, much less the claimed ranges:

- “[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.” (Pet. at 19 (emphasis added)).

- “[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.” (*Id.* at 20 (emphasis added)).
- “[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.” (Pet. at 22 (citations and quotations omitted) (emphasis added)).
- “[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.” (Pet. at 23 (citations and quotations omitted) (emphasis added)).

- “[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*).” (Pet. at 23-24 (emphasis added)).
- “[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.” (Pet. at 24).

Although long in length, these motivations are short on substance and do not address the alleged combination in the context of the claimed subject matter. Indeed, the Petition fails to provide a sufficient reason why a PHOSITA would have been motivated to modify any of the microbial oils in Radianingtyas using the enrichment methods of Kralovec to increase the DHA concentration in the resulting modified oil *while, at the same time, maintaining DPA(n-6) and ARA concentrations within the claimed ranges*.

With respect to the claimed DPA(*n*-6) concentration in claims 1-3, the Petition contends that:

- “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.” (Pet. at 28-29).
- “[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.” (Pet. at 29).

Neither of these is sufficient to support a motivation to combine Radianingtyas and Kralovec.

Although Radianingtyas discloses that strain ONC-T18 can produce a lipid composition comprising “at least 4% by weight” of DPA(*n*-6), this does not control the obviousness inquiry here. The proper inquiry is whether a PHOSITA would have been motivated to subject the microbial oil disclosed in Radianingtyas, which contains “at least 4% by weight” of DPA(*n*-6), to the enrichment technique disclosed

in Kralovec to achieve the claimed invention. The answer to that question is an unequivocal “no” because Kralovec itself teaches away from the combination. As explained above, Kralovec expressly discloses that when a microbial oil containing 4.6% by weight DPA is subjected to its enrichment methods, the resulting oil contains 7.3% by weight DPA, which falls outside the claimed maximum of 6% by weight.

This substantial increase in the concentration of DPA is not surprising because Kralovec's stated goal is to produce “concentrated oils with triglycerides containing higher proportions of *polyunsaturated fatty acid esters* than the starting triglycerides”—not simply to increase the DHA concentration in an oil. (MARA-1030 at 35:20-25 (emphasis added); *see also id.* at 1:9-11 (“The disclosed subject matter relates . . . to a process for increasing the concentration of polyunsaturated fatty acid in an oil composition.”)). This demonstrates the importance of considering the teachings of the combination, not their disclosures individually. Accordingly, Dr. Curtis's opinion that “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” is conclusory, is contradicted by the teachings of Kralovec, and should be afforded no weight. (Pet. at 28-29 (citing MARA-1003 at ¶ 147)).

With respect to the claimed ARA range of claim 2, the Petition contends that “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” and “[a]s motivation, a PHOSITA would recognize that high-DHA, low-omega-6 (of which low ARA is only one example) concentrations would be preferable” because “high-purity” oils resulted in “more efficient [nutritional] supplementation.” (Pet. at 30-31). But these rationales would have dissuaded a PHOSITA from combining Radianingtyas with Kralovec. As detailed in Section VII.A.1, *supra*, Kralovec's methods increase the amount of PUFAs such as ARA in the modified oil compared to the starting oil, and this increase is substantial. Table 9.1 of Kralovec demonstrates a nearly ***three-fold increase*** in the amount of ARA (20:4) (0.9% to 2.5%) in the resulting, re-esterified oil. (MARA-1030 at Tbl. 9.1).

Thus, a PHOSITA—attempting to maintain low amounts of DPA(*n*-6) and ARA for the reasons set forth in the Petition—would not have been motivated to subject Radianingtyas' microbial oils to the enrichment methods disclosed in Kralovec. Kralovec demonstrates that doing so would result in oils containing too much DPA(*n*-6) and ARA. Because the Petition ignores the internal inconsistencies

with its proffered motivations, it is deficient. Ground 2 fails with respect to claims 1-3 and their dependent claims at least on this basis alone.

3. *The Petition Fails to Demonstrate a Reasonable Expectation of Success in Combining Radianingtyas and Kralovec to Achieve Claims 1-3 and Their Dependent Claims*

Ground 2 fails for another similar reason. To prove obviousness, “[t]he reasonable-expectation-of-success analysis must be tied to the scope of the claimed invention.” *Teva Pharms. USA, Inc. v. Corcept Therapeutics, Inc.*, 18 F.4th 1377, 1381 (Fed. Cir. 2021). Yet in considering the reasonable expectation of success in achieving the Challenged Claims through the combination of Radianingtyas and Kralovec, the Petition fails to consider the impact that Kralovec’s methods would have been expected to have on the concentration of the DPA(*n*-6) and ARA contained in Radianingtyas’s microbial oils.

According to the Petition:

- “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 the 50% DHA by weight.” (Pet. at 21 (emphasis added)).

- “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 the omega-3 and omega-6 PUFAs may be further concentrated by hydrolyzing the lipids and concentrating the highly saturated fraction by employing traditional methods.” (Pet. at 25 (emphasis added)).
- “[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.” (Pet. at 25-26 (emphasis added)).

Like the Petition’s proffered motivations to combine, all of these statements regarding a purported reasonable expectation of success notably fail to consider the claimed DPA(*n*-6) and ARA ranges in claims 1-3 and their dependent claims.

The Petition does not provide any competent evidence with respect to whether a PHOSITA would have reasonably expected any microbial oil disclosed in Radianingtyas to meet the claimed DPA(*n*-6) and ARA ranges after being modified with Kralovec’s enrichment methods. In fact, the data provided in Kralovec conclusively demonstrates the opposite. As explained above, when subjected to

Kralovec's enrichment techniques, an oil containing "at least 4% by weight" of DPA(*n*-6) (such as Radianingtyas's oils produced by strain ONC-T18) contains more than 6% by weight of DPA(*n*-6) after enrichment. The same is true for ARA, the amount of which falls outside the claimed range in each enriched oil. (*See* MARA-1030 at Tbl 8.2 (disclosing 2.9%, 4.1%, and 3.0% ARA in re-esterified oils), Tbl. 9.1 (disclosing 2.5% ARA in re-esterified oil compared to 0.9% in starting oil)).

The Petition and Dr. Curtis inexplicably ignore these teachings in Kralovec. The Petition's separate consideration of the individual DPA and ARA disclosures in Radianingtyas and Kralovec instead of in the combination is indisputable proof of improper reconstruction of claims 1-3 and their dependent claims based on hindsight. The relevant inquiry under a proper obviousness analysis is whether the modified oils produced by the prior art combination would have reasonably been expected to contain DPA(*n*-6) and ARA within the claimed concentration ranges. On this point, the Petition is entirely silent. The Petition contains no argument—much less any evidence—to support a reasonable likelihood of establishing a reasonable expectation of success in achieving the claimed invention through the combination of Radianingtyas and Kralovec. Given that Kralovec's enrichment methods increase the concentration of both DPA(*n*-6) and ARA beyond the claimed

ranges, this evidentiary deficiency dooms Ground 2 with respect to claims 1-3 and their dependent claims.

4. The Petition Fails to Demonstrate That Claim 4 and Its Dependent Claims Would Have Been Obvious Over the Combination of Radianingtyas and Kralovec

With respect to claim 4 and its dependent claims, Ground 2 is deficient for a separate reason: the combination of Radianingtyas and Kralovec does not disclose any oils that contain at least 70% by weight of a triglyceride fraction and at least 60% by weight DHA in the triglyceride fraction.

The Petition relies on strains ONC-T02, ONC-T12, and ONC-T52 of Radianingtyas for purportedly disclosing at least 60% by weight of DHA in the triglyceride fraction. (Pet. at 34-35). But Radianingtyas does not disclose the triglyceride concentration of any oil produced by these strains. Moreover, as explained in Section VI.B.2.b, *supra*, a PHOSITA would reasonably expect the DHA produced by these strains to be in phospholipid form, not triglyceride form, due to low cellular growth and oil output when cultured. Kralovec's teachings do not cure this fundamental deficiency. Neither the Petition nor Dr. Curtis points to any teaching in Kralovec that would suggest forming a triglyceride-based oil from a phospholipid-based oil. (See MARA-1003 at ¶¶ 115, 117 (explaining that Kralovec's lipase hydrolyzes and reforms triglycerides), ¶ 218 (explaining lipases

“cleave fatty acids off a triglyceride backbone”)). Nor does the Petition explain why a PHOSITA would have selected these low-growth, low-oil-producing strains in the first place, especially given that growth and oil production capabilities are the “most important criteri[a] for selecting a microbial source” for the production of DHA. (MARA-1040 at 304; *see also* Section II.C, *supra*). Finally, there is nothing in the general disclosure of Radianingtyas that ties a DHA concentration of at least 60% by weight in the triglyceride fraction to a microbial oil containing at least 70% by weight triglycerides.

The Petition is left with strain ONC-T18 of Radianingtyas. (Pet. at 34-35). As explained in Section VI.B.2.a, *supra*, ONC-T18 does not produce microbial oils containing at least 40% by weight of DHA, much less at least 60% by weight. And a PHOSITA would not reasonably expect any oil produced by ONC-T18 to achieve an amount of at least 60% by weight of DHA *even after* being subjected to the enrichment techniques disclosed in Kralovec. Indeed, Kralovec's actual data demonstrates that its techniques do not achieve oils containing the claimed DHA concentration in the triglyceride fraction. For instance, the oil of Example 1 of Kralovec contains 43.8% DHA (*i.e.*, “22:6”). (MARA-1030 at Tbl. 6). This amount of DHA is more than the amount of DHA produced by strain ONC-T18 of Radianingtyas. After Kralovec's enrichment techniques, the amount of DHA (22:6)

in the triglyceride fraction falls far below the claimed minimum of 60% under all re-esterification conditions. (MARA-1030 at Tbl. 8.2 (noting 22:6 amounts under 60% by weight of total fatty acids for FFA20/48, FFA24/54, and FFA55/16 re-esterifications)). Similar results were observed in Example 4 of Kralovec. (*Id.* at Tbl. 9.1 (showing DHA in starting oil is increased from 22.0% to only 34.5% by weight after Kralovec enrichment)).

The Petition attempts to fill this gap with (i) Komazawa, (ii) Barclay, (iii) Nichols-II (MARA-1020), and (iv) the Lewis Thesis (MARA-1032). (Pet. at 35-36). But these references suffer the same fatal deficiency: they do not disclose what portion of their microbial oils are made up of a triglyceride fraction. (*See* Pet. at 27-28 (relying only on Radianingtyas and Kralovec for disclosure of at least 70% by weight triglyceride fraction)). Nichols-II and the Lewis Thesis are entirely silent with respect to the triglyceride fraction. Barclay is addressed in detail in Section VII.B. *infra*. And the example in Komazawa that purportedly produces 80% DHA in the triglyceride fraction was performed at a pH of 8.5, which resulted in a low-growth, low oil-output fermentation consistent with the production of primarily phospholipids. (MARA-1015 at [0116]). As was known in the field, thraustochytrids exhibit significantly reduced growth and oil production in basic conditions. (Ex. 2006 at 3105, Tbl. 1 (showing trace growth and significantly

reduced oil production at pH 8)). And the Petition does not explain why a PHOSITA would have ignored “the most important criterion . . . for the commercial production of DHA” and selected Komazawa’s strain in view of its low growth and low oil production at pH of 8.5. (MARA-1040 at 304).

Consequently, a PHOSITA would not have reasonably expected the Radianingtyas/Kralovec combination to provide an extracted microbial oil containing at least 70% by weight triglycerides and at least 60% by weight DHA in the triglyceride fraction.

* * * * *

For at least these reasons, the Petition fails to demonstrate a reasonable likelihood that any of claims 1-15 will be found to have been obvious in view of the combination of Radianingtyas and Kralovec.

B. Ground 3 Fails to Meet the Institution Threshold

Ground 3 challenges the patentability of claims 1-15 based on alleged obviousness over the combination of Bijl and Barclay. (Pet. at 42-64). The Petition concedes that Bijl, through U.S. Patent No. 6,255,505 (the “’505 patent”, Ex. 2007)¹⁰

¹⁰ Bijl and the ’505 patent claim priority to the same foreign patent applications and share substantially the same specification.

and Barclay were previously presented to the Patent Office. (Pet. at 65). In fact, the Examiner expressly considered the '505 patent (*i.e.*, Bijl's US counterpart) and Barclay during prosecution of the '363 patent. (MARA-1002 at 84). The Petition implies the Examiner missed the disclosures in Bijl and Barclay because they were allegedly "buried among hundreds of references on multiple pages of an information disclosure statement[.]" (Pet. at 64-66). But again, the Examiner did not err. The Bijl/Barclay combination does not render any of the Challenged Claims unpatentable. Accordingly, the Board may "defer to [the Examiner's] previous . . . evaluation[]" and determination that claims 1-15 are patentable over Bijl and Barclay. *Advanced Bionics, LLC v. Med-El Elektromedizinische Gerate GmbH*, IPR2019-01469, Paper 6 at 9 (P.T.A.B. Feb. 13, 2020).

1. There Are Substantial Differences Between the Combination of Bijl and Barclay and the Claimed Invention

Bijl generally discloses methods of (1) fermenting various microorganisms using specified fermentation conditions, (2) pasteurizing the fermentation broth, (3) and extracting PUFA compounds from the oil after it has been processed to produce dried granular particles. (MARA-1008, 7:2-11, 45-47, Example 22). Bijl discloses separating the biomass from the fermentation broth. (*Id.* at 17:6-18:16). The biomass can then be extruded to form granular particles. (*Id.* at 18:17-21:37). The PUFA is then extracted from the granular particles using an organic solvent such as

hexane. (*Id.* at 27:2-29:18; *see also* Pet. at 42-43 (describing Bijl's fermentation and extraction processes)).

Bijl discloses only one working example in which its fermentation and extraction methods were employed to produce a DHA-containing microbial oil. (MARA-1008 at 42-43, Example 19). In this example, the microorganism *Cryptocodinium cohnii* was cultured in a fed-batch process employing Ocean[®]-brand artificial seawater (250 g/L) with 6 g/L yeast extract and 12 g/L glucose at pH of 7-7.8 and a temperature of 20-28° C. for 70-80 hours. (MARA-1008 at 45-47, Example 22). Next, the fermentation broth was pasteurized, and granular particles were formed by the addition of starch followed by extrusion, which were then dried. (*Id.* at 42-43). The dried particles were extracted with hexane to produce a crude oil containing 67% triglycerides, which is below the claimed 70% threshold. (*Id.*). This amount is also far below the "greater than 90%" triglyceride content touted in Bijl's general disclosure.¹¹ (*Id.* at 4:24-28). The crude oil also contained 32.6% DHA, which falls below the claimed DHA thresholds of at least 50%, 50%, 40%, and 60%

¹¹ Consistent with Bijl's disclosure that triglycerides may be greater than 90% in some embodiments, the ARA-based oil produced by *Mortierella alpina* in Example 16 of Bijl contains 93% triglycerides after extraction. (Ex. 1008 at 38:17-40:10).

in claims 1, 2, 3, and 4, respectively. (*Id.* at 42-43). Additionally, Bijl does not disclose how much of the triglyceride fraction in this example is made up of DHA.

Barclay pre-dates the '363 patent by nearly two decades. As Barclay explains, the fatty acid content of microbial oils differs significantly depending on whether they are produced under growth-limited conditions:

An additional problem with the cultivation of algae for omega-3 highly unsaturated fatty acid production, is that even though omega-3 highly unsaturated fatty acids comprise 20-40% of some strains, total fatty acids, *the total fatty acid content of these algae is generally very low*, ranging from 5-10% of ash-free dry weight. *In order to increase the fatty acid content of cells, they must undergo a period of nitrogen limitation which stimulates the production of lipids. However, of all the strains noted to date in the literature, and over 60 strains evaluated by the inventor, all exhibit a marked decrease in omega-3 highly unsaturated fatty acids as a percentage of total fatty acids, when undergoing nitrogen limitation[.]*

(MARA-1019 at 2:65-3:10 (emphasis added)).

In other words, the fatty acid profile of a composition can differ significantly depending on whether it is sampled during the balanced growth phase (*i.e.*, before nitrogen depletion) or the lipid accumulation phase (*i.e.*, after nitrogen depletion). This is entirely consistent with the state of the art described in Section II.B, *supra*, which demonstrates that phospholipids (produced during the balanced growth phase) typically contain a higher concentration of PUFAs than triglycerides (produced during the lipid accumulation phase) do. (See Ex. 2001 at 1432 (noting strain SR21 produces 63.5% DHA in phospholipids and 35% DHA in triglycerides); Ex. 2002 at 608, Tbl. 4 (noting strain KK17-3 produces 39% DHA in phospholipids and 28% DHA in triglycerides)).

Barclay explains that, at the time, thraustochytrid strains were known to be difficult to grow and propagate under culture conditions:

Some single-celled members of the order Thraustochytriales are also known to produce omega-3 highly unsaturated fatty acids . . . but they are known to be difficult to culture. Sparrow (1960) noted that the minuteness and simple nature of [thraustochytrids] make them exceedingly difficult to propagate.

(MARA-1019 at 3:58-66). Barclay further explains that its microorganisms “generally exhibited restricted growth, with vegetative growth terminating after a few generations[.]” (*Id.* at 9:54-59).

To address this problem, Barclay formulated growth media containing “relatively high concentrations of phosphorus (*e.g.*, $\text{KH}_2\text{PO}_4 > 0.2 \text{ g/l}$) and/or . . . a nutritional supplement” and then cultured numerous strains using the media. (*Id.* at 9:60-68). In Example 5 of Barclay, 151 isolated strains were cultured in accordance with its methods, and their fermentations were “quantitatively analyzed for highly unsaturated fatty acid content[.]” (*Id.* at 21:54-58). Although the fatty acid profile for each strain is provided in Table 3 of Barclay, Barclay does not disclose any information regarding the growth characteristics or oil production exhibited by these strains.

Not surprisingly, Barclay does not disclose the amount of triglycerides produced by any of its microbial strains, which is confirmed by Petitioner's own expert. (See MARA-1003 at ¶¶ 222-223 (concluding that at best, “a PHOSITA would have understood and/or found obvious that the ‘lipids’ of Barclay **would include** ‘triglycerides,’ depending on the context”) (emphasis added), ¶¶ 245-246 (relying only on Bijl for disclosure of claimed “at least 70%” by weight triglyceride fraction)).

2. *The Petition Does Not Demonstrate a Reasonable Expectation of Success in Achieving the Claimed Invention*

The evidence in the Petition fails to demonstrate that a PHOSITA, through the combination of Bijl and Barclay, would have reasonably expected to achieve a microbial oil comprising at least 70% by weight triglycerides and at least 50%, 50%, 40%, and 60% by weight DHA in the triglyceride fraction, as recited in independent claims 1, 2, 3, and 4, respectively.

The Petition contends that a PHOSITA would have had a reasonable expectation of success in combining Bijl and Barclay for increasing DHA concentrations in an oil because Bijl and Barclay both disclose DHA-based oils produced by thraustochytrids that are microbial in origin. (Pet. at 49-50). This rationale, however, is not “tied to the scope of the claimed invention.” *Teva Pharms. USA*, 18 F.4th at 1381. The only example of a microbial DHA-based oil disclosed in Bijl contains less than 70% by weight of triglycerides and less than 40% by weight DHA of total fatty acids. (MARA-1008 at 42-43, Example 19 (disclosing oil containing 67% by weight triglycerides and 32.6% by weight DHA)). Thus, strains cultured and processed according to the methods of Bijl do not necessarily produce microbial oils with the claimed concentrations of triglycerides and DHA in the triglyceride fraction. This is consistent with other art cited in the Petition, which demonstrates that an “at least 70% by weight” triglyceride fraction is not necessarily

a characteristic of oils produced by microbial strains—even strains that grow well. (See, e.g., MARA-1040 at 301-302, FIG. 4 (showing *S. aggregatum* (ATCC 28209) and *T. roseum* (ATCC 28210) both produce oils that contain less than 50% by weight of triglycerides)).

The Petition seeks to cure this deficiency through the combination of Barclay's microbial strains and culture conditions—which purportedly produce oils containing the requisite amount of DHA—with Bijl's pasteurization and extraction processes. (Pet. at 45-50). This attempt misses the mark. As noted above, Barclay does not disclose (i) the amount of triglycerides produced by any of its strains under its culture conditions, (ii) the extent to which its strains grow (or do not grow) under its culture conditions, and (iii) the extent to which its strains produce (or do not produce) oils and accumulate lipids under its culture conditions. In the absence of such information, Barclay itself advises "one cannot evaluate an organism's potential use in the production of any type of fatty acid." (MARA-1019 at 4:20-33). Thus, a PHOSITA would have no basis to reasonably expect any of Barclay's strains, either alone or when subjected to Bijl's teachings, would contain at least 70% by weight of triglycerides and the requisite levels of DHA, DPA, and ARA.

The Petition and Dr. Curtis ignore these fundamental differences between the prior art combination and the Challenged Claims. Instead, they contend that: (1)

“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[;]” and (2) “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 include high triglyceride content.” (*See, e.g.,* Pet. at 52 (citing MARA-1003 at ¶¶ 252-253)). But Dr. Curtis’s opinion—and the Petition’s reliance thereon—is conclusory.

As noted above, the only DHA-based oil produced by Bijl does not contain the claimed amount of triglycerides or DHA. Moreover, the Petition does not point to any evidence that would lead a PHOSITA to reasonably expect the fatty acid profile of any microbial strain disclosed in Barclay to contain at least 70% by weight of a triglyceride fraction. In fact, Barclay is entirely silent on the triglyceride content produced by its microbial strains. The other art on which the Petition relies does not cure this deficiency because those references do not disclose any information about any strain disclosed in Barclay or Bijl. (*See* Pet. at 51-52 (citing MARA-1007, MARA-1015, MARA-1019, MARA-1032 and MARA-1034)). The Petition and Dr. Curtis arrive at the Challenged Claims through hindsight bias derived from the teachings of the ’363 patent.

Consequently, Ground 3 fails to demonstrate the obviousness of any of the Challenged Claims.

3. *The Petition Fails to Demonstrate Examiner Error*

As explained above, even though the Examiner did not cite Bijl or Barclay in a formal rejection during prosecution (*Advanced Bionics*, IPR2019-01469, Paper 6 at 9 n.10, factor (c)), the evidence and arguments presented in the Petition do not warrant reconsideration of those references here (*id.* at 9 n.10, factor (f)). The Petition proffers two purported errors the Examiner committed (*id.* at 9 n.10, factor (e)), neither of which justify instituting *inter partes* review.

First, the Petition implies that the Examiner erred by not rejecting the Challenged Claims over Barclay. (Pet. at 65-68). According to the Petition, Barclay was used in a rejection by the Examiner in a subsequent, related U.S. Patent Appl. No. 16/935,818 (the “’818 application”), which purportedly resulted in abandonment of that application. (*Id.* at 65-66). Whatever the Petition attempts to imply from this argument is inapposite: the rejected claims in the ’818 application are substantially different from the Challenged Claims and, importantly, do not contain any triglyceride or DHA concentration range limitations. (MARA-1043 at 16-17). Moreover, the fact that the Examiner relied on Barclay during prosecution of the ’818 application demonstrates that the Examiner was well aware of its

teachings during prosecution of the '363 patent but appreciated the significant differences between Barclay and the Challenged Claims.

Second, the Petition accuses the Examiner of erring by allowing the Challenged Claims to grant over Elswyk (MARA-1044). (Pet. at 68-69). During prosecution of the '363 patent, the Examiner agreed with the Applicant's argument 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." (*Id.* (citing MARA-1002 at 103-104)). Accordingly, the Challenged Claims were allowed because the prior art did not disclose a microbial oil containing the requisite amounts of triglycerides and DHA in the triglycerides. (Pet. at 68-69). The Petition contends this was in error because the Examiner should have looked "to other art encompassing triglyceride forms of PUFAs[.]" (*Id.*). But Bijl and Barclay fail for the very same reason as Elswyk: the references, either alone or in combination, do not disclose any microbial oil that contains at least 70% by weight of a triglyceride fraction or the requisite concentration of DHA in that triglyceride fraction. Bijl discloses a single microbial oil containing DHA, but it does not contain the claimed amount of triglycerides or DHA. (*See* Section VII.B.1, *supra*). And like Elswyk, Barclay does not disclose the amount of triglycerides produced by its strains at all. (*Id.*).

Consequently, the Petition does not demonstrate that the Examiner erred in allowing the Challenged Claims to grant over Bijl and Barclay. *Inter partes* review should be denied.

VIII. CONCLUSION

The Petition fails to demonstrate a reasonable likelihood that any claim of the '363 patent is unpatentable, and *inter partes* review should be denied.

Dated: February 29, 2024

Respectfully submitted,

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

I hereby certify that this **PATENT OWNER'S PRELIMINARY RESPONSE** contains 13,735 words, as counted using Microsoft Word in accordance with 37 C.F.R. § 42.24(c) and inclusive of footnotes. This wordcount is less than the allotted 14,000 words permitted under 37 C.F.R. § 42.24(b)(1).

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CERTIFICATE OF SERVICE

I hereby certify that on this 29th day of February, 2024, a copy of this **PATENT OWNER'S PRELIMINARY RESPONSE** was served by electronic mail to the attorneys of record, at the following address:

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