

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MARA RENEWABLES CORPORATION AND ALGAL OMEGA 3 LTD.,
Petitioners,

v.

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

Case IPR2023-01342
U.S. Patent No. 10,757,959

PATENT OWNER'S PRELIMINARY RESPONSE

Mail Stop **Patent Board**
Patent Trial and Appeal Board
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

TABLE OF CONTENTS

	Page(s)
TABLE OF AUTHORITIES	iv
PATENT OWNER'S EXHIBIT LIST	vi
ARGUMENT	1
I. INTRODUCTION	1
II. TECHNOLOGY BACKGROUND.....	4
A. Long-Chain Polyunsaturated Fatty Acids Are Present in Different Structural Forms in Oils	4
B. Microbial Fermentations Produce PUFAs in Both Phospholipid and Triglyceride Forms	7
C. Fatty Acid Profiles of Microbial Oils May Be Reported in Distinct Ways	11
III. THE '959 PATENT CLAIMS NOVEL MICROBIAL OILS HAVING HIGH TRIGLYCERIDE CONTENT, HIGH DHA TRIGLYCERIDE CONTENT, AND LOW ARA CONTENT	12
IV. CLAIM CONSTRUCTION	14
V. LEVEL OF ORDINARY SKILL IN THE ART	15
VI. THE PETITION Fails to demonstrate anticipation of claim 1 BY RADIANTINGTYAS	15
A. The Petition and Dr. Curtis Apply an Incomplete Legal Standard.....	16
B. Radiantingtyas Does Not Disclose Any Microbial Oil Containing the Requisite DHA and ARA Concentrations.....	18
VII. THE PETITION FAILS TO DEMONSTRATE A REASONABLE LIKELIHOOD THAT ANY CHALLENGED CLAIM WOULD HAVE BEEN OBVIOUS	26

-

A.	Ground 2 Fails to Meet the Institution Threshold.....	26
1.	Kralovec's Enrichment Methods Significantly Increase the Concentration of ARA in Microbial Oils.....	27
2.	A PHOSITA Would Not Have Been Motivated to Combine Radianingtyas and Kralovec to Achieve the Claimed Invention.....	29
3.	The Petition Fails to Demonstrate a Reasonable Expectation of Success With Respect to the ARA Ranges	33
B.	Ground 3 Fails to Meet the Institution Threshold.....	38
1.	Ground 3 Is Based on Art That Does Not Qualify as a Patent or Printed Publication and Was Not Publicly Available By the Priority Date.....	39
2.	The Petition Does Not Demonstrate a Sufficient Motivation to Combine and Reasonable Expectation of Success in Achieving the Claimed Invention Based on Bijl/Nichols-I/Kralovec.....	43
3.	The Other Art Identified in Ground 3 Does Not Cure the Deficiencies of the Bijl/Nichols-I/Kralovec Combination	49
C.	Ground 4 Fails to Meet the Institution Threshold and Has Already Been Considered By the Examiner	51
1.	The Board May Exercise Its § 325(d) Discretion and Deny Institution of Ground 4.....	52
a.	Bijl and Komazawa Differ Significantly From the Challenged Claims.....	54
b.	A PHOSITA Would Not Have Been Motivated to Combine Bijl and Komazawa to Achieve the Claimed Invention or Have a Reasonable Expectation of Success in Doing So.....	59
c.	The Examiner Did Not Err in Allowing the Claims After the ARA Amendment.....	62

-

d.	The Petition Does Not Demonstrate Material Examiner Error	64
2.	Ground 4 Is Based on Art That Does Not Qualify as a Patent or Printed Publication	65
VIII.	CONCLUSION.....	67

TABLE OF AUTHORITIES

	Page(s)
Cases	
<i>ActiveVideo Networks, Inc. v. Verizon Communs., Inc.</i> , 694 F.3d 1312 (Fed. Cir. 2012)	29
<i>Advanced Bionics, LLC v. MED-El Elektromedizinische Gerate GmbH</i> , IPR 2019-01469, Paper 6, (P.T.A.B. Feb. 13, 2020).....	53, 54, 64
<i>Connell v. Sears Roebuck & Co.</i> , 722 F.2d 1542 (Fed. Cir. 1983)	16
<i>Elekta, Inc. v. Varian Med. Sys., Inc.</i> , IPR2016-00315, Paper 12 (P.T.A.B. June 13, 2016)	40, 66
<i>Graham v. John Deere Co.</i> , 383 U.S. 1 (1966).....	2
<i>Hebert v. Lisle Corp.</i> , 99 F.3d 1109 (Fed. Cir. 1996)	18
<i>Integra Lifesciences I, Ltd. v. Merck KGaA</i> , 496 F.3d 1334 (Fed. Cir. 2007)	17
<i>In re Kotzab</i> , 217 F.3d 1365 (Fed. Cir. 2000)	2
<i>KSR Int'l Co. v. Teleflex Inc.</i> , 550 U.S. 398 (2007).....	2, 29
<i>Net MoneyIN, Inc. v. VeriSign, Inc.</i> , 545 F.3d 1359 (Fed. Cir. 2008)	16, 17, 18
<i>Novartis Pharms. Corp. v. Accord Healthcare, Inc.</i> , 38 F.4th 1013 (Fed. Cir. 2022).....	63
<i>In re Oelrich</i> , 666 F.2d 578 (C.C.P.A. 1981)	25

Case IPR2023-01342
Patent Owner’s Preliminary Response

<i>Samsung Elecs. Co. v. Infobridge Pte. Ltd.</i> , 929 F.3d 1363 (Fed. Cir. 2019)	43
---	----

<i>Teva Pharms. USA, Inc. v. Corcept Therapeutics, Inc.</i> , 18 F.4th 1377 (Fed. Cir. 2021)	33
---	----

Statutes

35 U.S.C. § 103	2, 3
35 U.S.C. § 311	40
35 U.S.C. § 311(b)	66
35 U.S.C. § 313	1

Other Authorities

37 C.F.R. § 42.104(b)(3).....	14
-------------------------------	----

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	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).
2006	T.E. Lewis, <i>et al.</i> , <i>The Biotechnological Potential of Thraustochytrids</i> , MAR. BIOTECHNOL., 1, 580-87 (1999).
2007	U.S. Patent No. 10,362,794.
2008	List of References Considered by Examiner dated March 22, 2019, in U.S. Patent No. 10,362,794.

ARGUMENT

I. INTRODUCTION

Mara Renewables Corporation and real party-in-interest Algal Omega 3 Ltd. (together, "Petitioners") request *inter partes* review and cancellation of claims 1-14 (the "Challenged Claims") of U.S. Patent No. 10,757,959 (the "'959 patent"). Ground 1 challenges claim 1 based on alleged anticipation by Radianingtyas (MARA-1007). (Pet. at 1-2). Grounds 2 through 4 contend that the Challenged Claims would have been obvious in view of several alleged prior art combinations. (*Id.*). Pursuant to 35 U.S.C. § 313, DSM IP Assets, B.V. ("DSM" or "Patent Owner") submits this timely Preliminary Response. The Petition 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 1-14 of the '959 patent unpatentable.

(Pet. at 6). But disclosure of each element of the Challenged Claims in the prior art 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 claim 1 is disclosed in Radianingtyas

as arranged in claim 1. Instead, the Petition at best arrives at claim 1 through a mishmash of combinations of disclosures from distinct embodiments in Radianingtyas. That is not anticipation.

The Petition similarly fails with respect to the obviousness challenges of Grounds 2-4. “[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). Indeed, 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 an adequate explanation—much less supporting evidence—regarding any 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 20 (“Radianingtyas-Kralovec discloses and/or renders obvious [1pre].”), 21 (“Radianingtyas-Kralovec discloses and/or renders obvious [1a].”), 22 (“Radianingtyas-Kralovec discloses and/or renders obvious [1b].”), 22 (“Radianingtyas-Kralovec discloses and/or renders obvious [1c].”)).

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 '959 patent with a reasonable expectation of success in doing so.

For at least the reasons detailed in this Preliminary Response, institution of *inter partes* review should be denied.

II. TECHNOLOGY BACKGROUND

The '959 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 '959 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. (MARA-1027 at 1).² Monoglycerides are ester compounds that contain one fatty

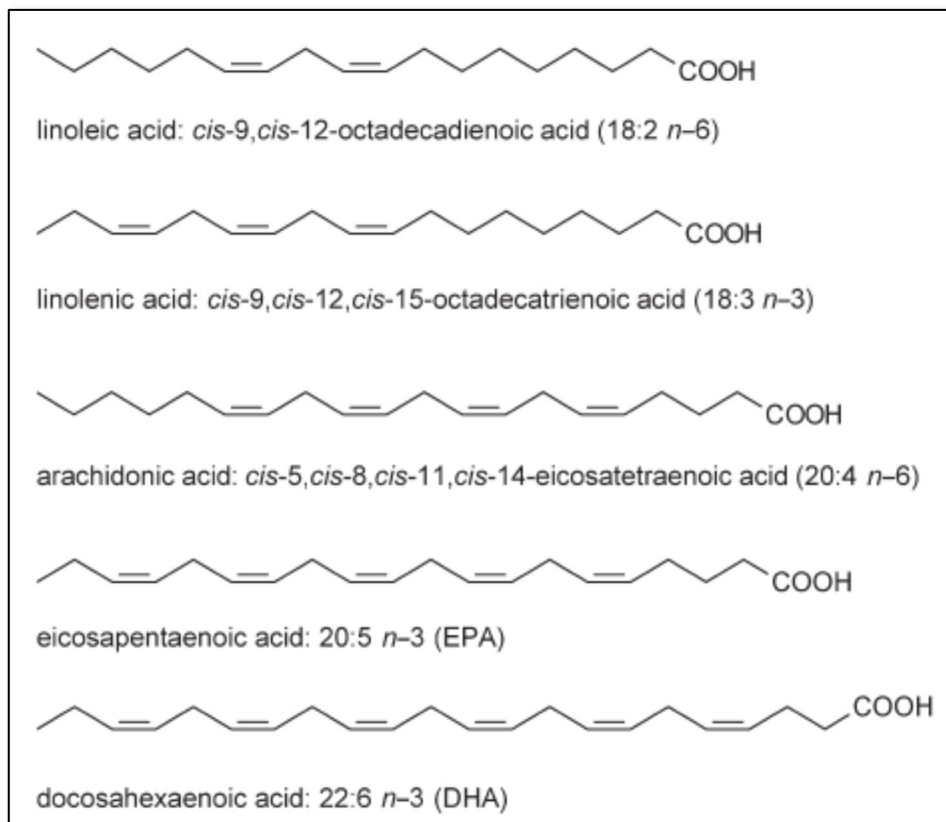
¹ As used herein, "PUFAs" generally refer to long-chain polyunsaturated fatty acids containing 20-22 carbon atoms, unless otherwise indicated.

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

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

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 (Ex. 1002) for which DSM cites to the pagination in the exhibit.



(*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:

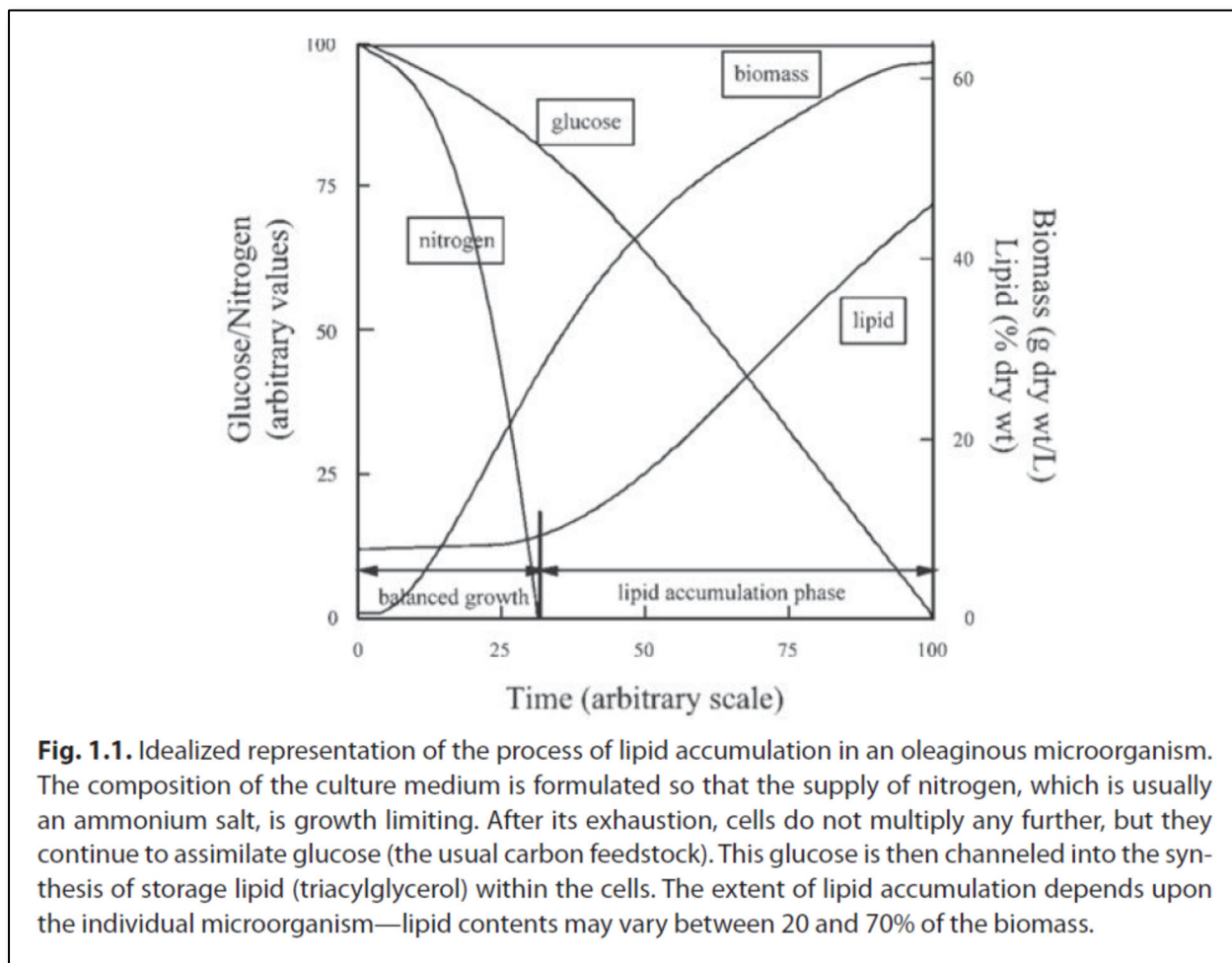
Fatty Acid	Abbreviation	Structural Form
Arachidonic acid	ARA (20:4)	<i>n</i> -6
Eicosapentaenoic acid	EPA (20:5)	<i>n</i> -3
Docosapentaenoic acid	DPA (22:5)	<i>n</i> -3 and <i>n</i> -6
Docosahexaenoic acid	DHA (22:6)	<i>n</i> -3

B. Microbial Fermentations Produce PUFAs in Both 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). (MARA-1010 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 cells continue to consume the excess carbon source and produce PUFAs for storage in, for example, triglyceride form. Thus, significant quantities of PUFAs can be produced and accumulated primarily in triglyceride form only after the nitrogen source is depleted. (*Id.*).

This 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.*, 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 produced 28% DHA in neutral lipids and 39% DHA in polar lipids. (Ex. 2002 at

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 72).

608, Tbl. 4).⁴ Accordingly, the importance of the proportion of triglycerides versus phospholipids produced during a fermentation cannot be overlooked.

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 PUFAs 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

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 72).

⁵ Exhibit 2003, which is co-authored by one of the authors of MARA-1009, published after the priority date of the '959 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 '959 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.

see also Ex. 2004 at 636 (noting phospholipids make up significant portion of lipids in young cells)). This is consistent with the higher concentrations of DHA in the phospholipids versus triglycerides observed in Yaguchi and Huang.

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 lyse and disrupt the cells. (See MARA-1010 at 210-213, Fig. 13.3). The oil can then be collected and its fatty acid profile determined. (*Id.*).

C. 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, one must pay particular attention to how a reference reports the fatty acid contents of its microbial oils.

III. THE '959 PATENT CLAIMS NOVEL MICROBIAL OILS HAVING HIGH TRIGLYCERIDE CONTENT, HIGH DHA TRIGLYCERIDE CONTENT, AND LOW ARA CONTENT

The '959 patent discloses isolated and mutant *thraustochytrid* microorganisms and fermentation methods that produce novel microbial oil

compositions having certain PUFA concentration and cellular biomass profiles. These microorganisms produce relatively large amounts of oils that are high in triglyceride content. 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 '959 patent beneficially produce oils that contain high concentrations of DHA and low concentrations of ARA. Accordingly, the '959 patent discloses improved microbial oils.

The '959 patent claims some of these novel microbial oil compositions. The '959 patent contains one independent claim directed to microbial oils. Claim 1 recites:

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 45% by weight, and wherein the oil comprises 1.5% by weight or less of arachidonic acid.

(MARA-1001). Claims 2-14 depend either directly or indirectly from claim 1. Except for claim 1, the Petition effectively concedes that the claimed microbial oil compositions of the '959 patent are novel and does not raise any grounds of unpatentability based on anticipation.

The '959 patent was filed as Application No. 16/132,992 (the "'992 application") on September 17, 2018. The '959 patent is a divisional in a long line of divisional applications with priority dating back to March 19, 2009. (MARA-1001 at Related U.S. Application Data). Prior to the allowance of the '992 application, the Office had already granted four patents in the broader patent family and was therefore familiar with the relevant prior art. An Office Action was issued on November 22, 2019, requiring an election and restriction of species. (MARA-1002 at 142-147). DSM filed a response January 20, 2020. (*Id.* at 150-154). A Non-Final Office Action issued February 7, 2020, and the claims were rejected for alleged obviousness over US 2007/0003686 ("Fichtali"). (*Id.* at 155-161). In response to the Office Action, the claims were amended to recite that the claimed microbial oil comprises 1.5% by weight or less of arachidonic acid. (*Id.* at 184-196). A Notice of Allowance was mailed on April 23, 2020. (*Id.* at 200-204). The '959 granted on September 1, 2020.

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 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 characteristics on the proportion of triglycerides and phospholipids produced during a microbial fermentation.

VI. THE PETITION FAILS TO DEMONSTRATE ANTICIPATION OF CLAIM 1 BY RADIANTINGTYAS

Ground 1 challenges the patentability of claim 1 based on alleged anticipation by WO 2008/129358 to Radianingtyas *et al.* ("Radianingtyas"). (Pet. at 7-12). The Petition concedes that Radianingtyas, through its U.S. publication (US2010/0285105), was previously presented to the Patent Office. (Pet. at 69). In fact, it was presented to the Patent Office during prosecution of U.S. Patent No. 10,362,794 (Ex. 2007 at 2 (identifying US2010/0285105 in References Cited section)), of which the '959 patent is a divisional (Ex. 1001 at Related U.S.

Application Data) and against which the '959 patent is terminally disclaimed (Ex. 1002 at 190). The Petition accuses the examiner of “fail[ing] to consider . . . Radianingtyas” because it was allegedly “buried among hundreds of references on multiple pages of an information disclosure statement[.]” (Pet. at 69-71). The examiner did no such thing and certainly did not err in allowing claim 1 over Radianingtyas. As demonstrated below, the examiner did not rely on the reference during prosecution of the '959 patent because, under a proper anticipation analysis, Radianingtyas did not invent—and therefore does not anticipate—the subject matter of claim 1.

Accordingly, *inter partes* review based on Ground 1 should be denied.

A. The Petition and Dr. Curtis Apply an Incomplete 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 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)).

The Petition relies on the testimony of Dr. Jonathan Curtis to prove anticipation. (MARA-1003 at ¶¶ 66-91). 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. I further understand from counsel that an overlap in a range can demonstrate anticipation.

(MARA-1003 at ¶ 20). Dr. Curtis ignores the requirement that the elements must be arranged as in the claim. (*See id.* at ¶ 91 (“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 claim 1 is anticipated solely because all of its elements are purportedly disclosed somewhere in Radianingtyas. (Pet. at 7-12). Neither the Petition nor Dr. Curtis explains how Radianingtyas discloses each and every element as “arranged or combined in the same way” as in claim 1. *Net MoneyIN*, 545 F.3d at 1371. This evidentiary deficiency is 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). As explained below, Radianingtyas does not anticipate claim 1 when the correct anticipation standard is applied to the reference.

B. Radianingtyas Does Not Disclose Any Microbial Oil Containing the Requisite DHA and ARA Concentrations

In alleging that claim 1 is anticipated by Radianingtyas, the Petition and Dr. Curtis mix and match disclosures from distinct embodiments in Radianingtyas and then cobble them together to purportedly support anticipation of claim 1. (Pet. at 9-12). But mixing-and-matching is not anticipation. *See Net MoneyIN*, 545 F.3d at 1369 (finding no anticipation where disclosure required “combination of two examples in order to find all elements of the claim”). The primary disclosure on which the Petition relies relates to microbial oils made by a strain referred to as ONC-T18. (Pet. at 9-12). Yet Radianingtyas does not disclose any microbial oil produced by strain ONC-T18—or any other strain—that contains at least 45% by weight of DHA in the triglyceride fraction and 1.5% by weight or less of ARA. None of the other disclosures on which the Petition relies cures this deficiency. Consequently, Radianingtyas does not anticipate claim 1.

As an initial matter, the Petition and Dr. Curtis distort the express disclosure of Radianingtyas with respect to how much DHA strain ONC-T18 produces. In particular, the Petition quotes page 26, lines 29-34 in a misleading manner. (*See* Pet. at 10 (alleging ONC-T18 produces up to 60% DHA (citing MARA-1007 at 26:29-34)); MARA-1003 at ¶ 82 (same)). The Petition uses an ellipsis to suggest that ONC-T18 produces up to 60% by weight of DHA. But this is what that particular 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). Contrary to the Petition and Dr. Curtis's unsupported opinion, a PHOSITA would not interpret this paragraph as teaching that strain ONC-T18 produces a microbial oil containing "at least 45% by weight" of DHA in the triglyceride fraction, especially in view of all the other disclosures in Radianingtyas relating to DHA production by strain ONC-T18. The only mention of strain ONC-T18 in this particular paragraph of Radianingtyas 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.1) does not mention strain ONC-T18 at all. Nor does this paragraph disclose any concentration of ARA, either alone or in combination with DHA.

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 45% by weight DHA in the triglyceride fraction. Radianingtyas selects strain ONC-T18 due to its growth characteristics and conducts numerous fermentations with this strain to optimize its oil production. But none of these optimizations

produce a microbial oil containing at least 45% 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 8 discloses that ONC-T18 produces DHA in an amount of 24-34% by weight of total fatty acids. (*Id.* at 90-91, Tbl. 5). Example 9 performed similar fermentations with alternative carbon sources, which produced DHA at a maximum of 26% by weight of total fatty acids. (*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). 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.⁶ (*Id.* at 94:6-95:27).

⁶ The Bligh and Dyer technique produces about 25% by weight DHA ($125.24/505.63 \times 100$). Direct transesterification produces about 24% by weight DHA ($98.65/408.17 \times 100$). Simultaneous saponification produces about 25% by

Example 13 discloses fermentations designed to “limit 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).

Accordingly, strain ONC-T18—the strain specifically chosen based on its capability of maximum heterotrophic growth and ability to produce “a high percentage” of *n*-3 PUFAs (*id.* at 82:2-6)—does not produce an oil containing the claimed amount of DHA in the triglyceride fraction under any 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)). But the Petition ignores the full context of such 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

weight DHA ($197.20/779.31 \times 100$). And solid phase extraction produces about 22% by weight DHA ($171.69/784.34 \times 100$). (*Id.* at 95:11-27).

Petition does not identify any actual microbial oil, purified or not, that contains 90% DHA in the triglyceride fraction, much less one that also contains 1.5% by weight or less of ARA. Nor is one disclosed in Radianingtyas.

The Petition is left with the remaining strains disclosed in Radianingtyas. Yet Radianingtyas does not disclose that any of these other strains produces a microbial oil containing at least 45% by weight of DHA in the triglyceride fraction in combination with 1.5% by weight or less of ARA, as recited in claim 1. According to the Petition, Radianingtyas discloses that “approximately 80%” of its strains “synthesized the omega-6 PUFAs, arachidonic acid (AA) . . . at concentrations varying between 1 and 18%.” (Pet. at 11 (citing MARA-1007 at 96:1-3, 99:29-32, FIG. 11)). The Petition then contends Radianingtyas anticipates claim 1 because a range of 1-18% of ARA ever so slightly overlaps the claimed range of 1.5% or less. (Pet. at 11-12). 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 45% 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 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 its oil producing microbes can produce a wide range of oils that all consistently contain low amounts of ARA.” (Pet. at 12 (citing MARA-1007 at 32:20-25, 34:4-37:14)). But the Petition ignores the full disclosure of Radianingtyas. In each of the examples that purportedly produce oils with “low amounts of ARA[,]” (Pet. at 12), they also consistently produce low amounts of DHA that fall outside of claim 1 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).

The Petition further prophetically contends that “[i]n some embodiments, ARA is not disclosed at all, and is either absent or below the limit of detection.” (Pet. at 12 (citing MARA-1007 at 32:20-25); *see also* MARA-1003 at ¶ 90). But this argument is inapposite. The single embodiment that purportedly discloses 0% ARA also discloses 25% DHA, far below the claimed threshold of at least 45%. (MARA-1007 at 32:20-25). And Dr. Curtis’s conclusory opinion that “it is also *possible* that arachidonic acid is present in these oils, but below detectable levels” is not supported by the evidence. (MARA-1003 at ¶ 90 (emphasis added)). Radianingtyas discloses that measurable amounts of ARA are produced in each and every actual fermentation involving strain ONC-T18. (*See, e.g.*, MARA-1007 at Tbl. 6 (AA), Figs. 11-12 (C20:4w6)). In any event, inherent disclosure cannot be established by mere possibilities. *In re Oelrich*, 666 F.2d 578, 581 (C.C.P.A. 1981)

The Petition fails to demonstrate that Radianingtyas discloses a microbial oil meeting all of the elements as they are arranged in claim 1. Accordingly, the Petition does not establish a reasonable likelihood that Radianingtyas anticipates claim 1, and *inter partes* review based on Ground 1 should be denied.

**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 due consideration of the claimed subject matter as a whole and fails to demonstrate a reasonable likelihood that any claim will be found obvious. For the reasons detailed below, the Petition should be denied.

A. Ground 2 Fails to Meet the Institution Threshold

Ground 2 challenges the patentability of claims 1-14 based on alleged obviousness over the combination of Radianingtyas and International Publication No. WO 2009/040676 to Kralovec *et al.* (“Kralovec”, MARA-1030). 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 '959 patent. Consequently, *inter partes* review of claims 1-14 based on Ground 2 should be denied.

1. Kralovec's Enrichment Methods Significantly Increase the Concentration of ARA in Microbial Oils

Ground 2 relies on the very same disclosures in Radianingtyas as identified in Ground 1. (Pet. at 13). Radianingtyas was discussed in detail with respect to Ground 1. *See* Section VI, *supra*. Effectively conceding that strain ONC-T18 disclosed in Radianingtyas does not produce the claimed amounts of DHA in claims 1-4 (and their dependent claims), 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 strain ONC-T18 disclosed in Radianingtyas. (Pet. at 14-19, 22, 24-30).

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). As shown in Table 6, this hydrolysis process liberates from the triglycerides not only saturated fatty acids but also significant amounts of PUFAs, including DHA. (*Id.* at Tbl. 6 (noting FFA fraction contains ~45% palmitic acid (16:0) and ~19% DHA)). 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 ARA. (*Id.* at 15:7-22 (noting ARA as an exemplary PUFA), 19:28-30 (same)). This is illustrated in the working 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 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 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 2.5% ARA, which also falls 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 1.5% or less by weight ARA. (*Id.* at Tbl 8.2 (disclosing 2.9%, 4.1%, and 3.0% ARA in re-esterified oils)⁷, Tbl. 9.1 (disclosing 2.5% ARA in re-esterified oil compared to 0.9% in starting oil)).

A PHOSITA therefore would understand that Kralovec's enrichment methods are not selective for increasing only the concentration of DHA in an oil. Importantly, a PHOSITA would appreciate that Kralovec's methods also increase the concentration of other PUFAs, such as ARA, in the resulting oil—and do so substantially. (*See id.* at Tbl. 9.1 (disclosing 2.5% ARA in re-esterified oil compared to 0.9% in starting oil)).

2. *A PHOSITA Would Not Have Been Motivated to Combine Radianingtyas and Kralovec to Achieve the Claimed Invention*

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*

⁷ Example 3 of Kralovec does not disclose the amount of ARA in the starting microbial oil. Consequently, the amount by which ARA is increased in the resulting re-esterified oil cannot be determined.

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 six 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:

- “[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 15 (emphasis added)).
- “[A] PHOSITA would have been motivated *to increase DHA* content in Radianingtyas’s microbial oil because Kralovec teaches that DHA is an omega-3 fatty acid, known to be vital to everyday life and function.” (Pet. at 16 (citations and quotations omitted) (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.* (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 18 (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 that have better color and lower levels of trans-isomers as well as better sensory properties.” (Pet. at 18 (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 18-19 (emphasis added)).

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 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 an ARA concentration within the claimed ranges.*

Other motivations described in the Petition contradict the aforementioned rationales and demonstrate that a PHOSITA would not have been motivated to combine Radianingtyas and Kralovec to achieve the claimed invention in view of Kralovec's express teachings. For example, in addressing the claimed ARA ranges, the Petition contends that "a PHOSITA would have understood that it was desirable to have low levels of ARA in a primarily DHA-containing oil" and "[a]s motivation, a PHOSITA would recognize that high-DHA, low-ARA concentrations would be preferable" "because higher purity oils resulted in more efficient [nutritional] supplementation." (Pet. at 23, 32). 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 ARA for the reasons set forth in the Petition—would not have been motivated to subject Radianingtyas's microbial oils to the enrichment methods disclosed in Kralovec. Kralovec demonstrates that doing so would result in oils containing too much ARA. The Petition ignores the internal inconsistencies with its proffered motivations and is therefore deficient. Ground 2 should be denied in its entirety on this basis alone as the ARA ranges are elements of each Challenged Claim.

3. The Petition Fails to Demonstrate a Reasonable Expectation of Success With Respect to the ARA Ranges

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 ARA found in Radianingtyas's microbial oils.

According to the Petition:

- “A PHOSITA would have expected to be successful in pursuing *increased DHA* in an extracted oil because Radianingtyas identifies DHA as one of two desirable PUFAs.” (Pet. at 17 (emphasis added)).
- “[A] PHOSITA would have expected success in pursuing extracted oils *with high levels of DHA* given that it was already known that certain strains of microbes contained very high levels of DHA (61%).” (Pet. at 17 (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 19 (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 are microbial/algal in origin and so have similar characteristics.” (Pet. at 19-20 (emphasis added)).

Like the Petition's proffered motivations to combine, all of these notably fail to consider the claimed ARA ranges in the Challenged Claims. Indeed, the Petition does not provide any competent evidence with respect to whether a PHOSITA would have reasonably expected the microbial oil disclosed in Radianingtyas to meet the claimed ARA ranges after being modified with Kralovec's enrichment methods. The Petition instead contends that the ARA elements would have been obvious because Radianingtyas and Kralovec separately disclose microbial oils having the requisite ARA concentration. (Pet. at 22-24, 30-32). This is not legally sufficient.

First, the Petition mischaracterizes the ARA disclosures in Kralovec. According to the Petition, “Kralovec teaches that in an embodiment using Kralovec's method for increasing DHA, ARA is present at no more than 1.4% of the glyceride fraction.” (Pet. at 23 (citing MARA-1030, 43-44 & Tbl. 9.1), 32 (same)). But the Petition overlooks a critical fact with respect to that “glyceride fraction.” The starting oil in this particular embodiment contains 0.9% ARA. (MARA-1030 at 42-43). When hydrolyzed to remove the free fatty acid fraction,

the concentration of ARA in the “glyceride fraction” increases to 1.4%. But Kralovec’s “glyceride fraction” contains only 57% triglycerides, with the remaining 43% being diglycerides. (*Id.* at Tbl. 9.2). This level of triglycerides falls far outside the range of the Challenged Claims. When the “glyceride fraction” containing 1.4% ARA is re-esterified to produce an oil containing the requisite concentration of triglycerides, the resulting oil contains 2.5% by weight ARA, which is outside the claimed ARA ranges. (*Id.* at Tbl. 9.1 (20:4)).

This substantial increase in the concentration of ARA 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. (*Id.* 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 individual disclosures, especially given that the Petition concedes the vast majority of strains in Radianingtyas produce ARA in an amount of 1-18%. (Pet. at 23, 31). It also directly contradicts Dr. Curtis’s unsupported opinion that a PHOSITA would have understood that the ARA concentration in the triglycerides “would not deviate significantly” from the

amounts disclosed in Radianingtyas. (Pet. at 31 (citing MARA-1003 at ¶¶ 157-159)). Consistent with its stated goals, Kralovec conclusively demonstrates that its methods substantially increase the concentration of ARA in its enriched oils compared to the starting microbial oils.

Second, the Petition also mischaracterizes the ARA disclosures in Radianingtyas. (Pet. at 23, 31). As noted in Section VI.B, *supra*, Radianingtyas's fermentation data demonstrates that its strains produce measurable amounts of ARA—directly contradicting Dr. Curtis's unsupported opinion that some embodiments disclose zero ARA or at most ARA concentrations that are below the limit of detection. (Pet. at 23). That the strains in Radianingtyas produce ARA is not surprising. Figure 1 of Radianingtyas illustrates that arachidonic acid is a key component of the fatty acid metabolic pathway in its microorganisms and is a precursor to other PUFAs, including omega-3 PUFAs. (MARA-1007 at FIG. 1). Moreover, there is nothing in the Petition sufficient to demonstrate that a PHOSITA would reasonably expect any of Radianingtyas's oils to lead to compositions containing ARA in the claimed amounts after being subjected to Kralovec's enrichment methods. Yet, Kralovec's methods expressly produce re-esterified oils that contain more than 1.5% by weight ARA in each instance. (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)).

Third, the Petition's separate consideration of the ARA disclosures in Radianingtyas and Kralovec instead of in the combination is conclusive proof of improper reconstruction of the Challenged 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 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 ARA beyond the claimed ranges, this evidentiary deficiency dooms Ground 2.

The Petition is therefore deficient, and Ground 2 should be denied in its entirety on this additional basis, as the ARA ranges are elements of each Challenged Claim.

B. Ground 3 Fails to Meet the Institution Threshold

Ground 3 challenges the patentability of claims 1-14 based on alleged obviousness over the combination of WO 97/37032 ("Bijl"), Nichols-I (MARA-

1009), and Kralovec. (Pet. at 37-56). In forming its purported basis of unpatentability, Ground 3 improperly relies on the *use of microbial strain O* in Nichols-I. This microbial strain is not a patent or printed publication, and the Petition fails to demonstrate that this strain was, as a matter of fact, publicly available as of the priority date of the '959 patent. Furthermore, the Petition fails to provide a sufficient motivation to combine and reasonable expectation of success in achieving claims 1-14 of the '959 patent based on the combination of Bijl, Nichols-I, and Kralovec. Consequently, *inter partes* review of claims 1-14 based on Ground 3 should be denied.

1. Ground 3 Is Based on Art That Does Not Qualify as a Patent or Printed Publication and Was Not Publicly Available By the Priority Date

Ground 3 relies on the *use* of a particular microbial strain referenced in Nichols-I, not on the disclosure of Nichols-I itself. The Petition plainly states it multiple times: “a PHOSITA would have been motivated to *use Nichols-I's preferred microbial strains* (e.g., strain O thraustochytrids) as a microbial source for Bijl's extracted microbial oil[.]” (Pet. at 40-41 (emphasis added)). In other words, strain O in Nichols-I is being *used* as the microbial source in Bijl's fermentation and extraction process:

It would have been obvious for a PHOSITA to combine the teachings of Bijl, *directed to microbial oils and processes of cultivating, processing, and extracting microbial oils* from natural sources, with Nichols-I, which teaches *using specific beneficial strains of microorganisms* (e.g., thraustochytrids).

(*Id.* at 40 (emphasis added)). But strain O, a microorganism, is not a patent or printed publication, as required under 35 U.S.C. § 311(b), and institution of Ground 3 should be denied on this basis alone. *See Elekta, Inc. v. Varian Med. Sys., Inc.*, IPR2016-00315, Paper 12, at *13-14 (P.T.A.B. June 13, 2016) (refusing institution of ground based on use of system rather than on what prior art discloses about that system).

The Petition's reliance on the *use* of Nichols-I's strain O in Bijl's fermentation process rather than on Nichols-I's disclosure is not surprising. Nichols-I says very little about the microbial oil produced by strain O and the conditions under which it was produced:

Representative fatty acid profiles for selected Australian thraustochytrids recently isolated and maintained by CSIRO are shown in Table 2. Strain O is particularly

attractive as it contains very high levels of DHA (61%).

Other PUFA are present at less than 5% each. High DHA-containing thraustochytrids often also contain high proportions of 22:5 ω 6, docosapentaenoic acid (DPA(6)), as is observed for strains A, C and H. DPA(6) is only a minor component in our strain O under the culture conditions employed, making this strain particularly interesting. Further work is required to assess the proportion of these two components across a range of culture and other conditions.

(Ex. 1009 at 27). Similar statements regarding strain O are provided in Nichols-II (MARA-1020 at 385) and Singh (MARA-1018 at [0571]), all of which share overlapping co-authors and inventors. However, these purported disclosures do nothing to demonstrate that strain O was publicly available as of the priority date of the '959 patent.

Nichols-I does not disclose any identifying information with respect to strain O such as its genus and species or any morphological characteristics and genetic sequencing from which its genus and species can be determined. (*See, e.g.*, MARA-1007 at 83-86 (demonstrating identification of genus and species using 18s

ribosomal RNA technique)). It does not disclose where strain O was isolated other than somewhere in all of Australia, much less how it was isolated. Aside from a general fatty acid profile based on total fatty acids, it does not disclose anything about the microbial oil. For example, it does not disclose what portion of the oil is triglycerides and what portion is phospholipids. It does not disclose any growth characteristics of the fermentation such that a PHOSITA could surmise whether cellular growth was inhibited by non-optimal fermentation conditions, in which case PUFA-containing phospholipids would be expected to be produced in significant quantities. Nichols-I does not even disclose the conditions under which its fermentation of strain O was conducted and, in fact, specifically states that “[f]urther work *is required* to assess” its DHA production “across a range of culture and other conditions.” (MARA-1009 at 27 (emphasis added)).

Moreover, although it states that strain O is “maintained by CSIRO,” Nichols-I does not identify any depository qualified under the Budapest Treaty in which this alleged strain has been deposited such that the public could have accessed it at the time of the '959 patent. Nor does the Petition. And even if such a strain were somehow available from CSIRO, there is no identifying information regarding the strain that would permit a PHOSITA to have actually obtained it. The same is true for the substantially similar descriptions of strain O in Nichols-II

and Singh. (See MARA-1020 at 385; MARA-1018 at [0571]). Petitioners therefore have failed to meet their burden of proving that the art on which it relies—strain O of Nichols-I—was a patent or printed publication and publicly available prior to the ’959 patent. See *Samsung Elecs. Co. v. Infobridge Pte. Ltd.*, 929 F.3d 1363, 1372 (Fed. Cir. 2019) (“[A] work is not publicly accessible if the only people who know how to find it are the ones who created it.”).

Accordingly, institution of *inter partes* review of claims 1-14 based on Ground 3 should be denied for this reason alone.

2. *The Petition Does Not Demonstrate a Sufficient Motivation to Combine and Reasonable Expectation of Success in Achieving the Claimed Invention Based on Bijl/Nichols-I/Kralovec*

Even if the Board permits Petitioners’ reliance upon the *use* of Nichols-I’s strain O in this proceeding, the Petition still fails to sufficiently demonstrate a reasonable expectation of success in achieving the claimed invention based on the combination of Bijl, Nichols-I’s strain O, and Kralovec.

Nichols-I and Kralovec have been discussed extensively above. 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, 7:1-11, 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 37-38 (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*—one of Kralovec's preferred microorganisms (*see* MARA-1030 at 7:18-21)—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). 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 and produced a crude oil containing 67% triglycerides, which is below the claimed 70% threshold. (*Id.*). The crude oil also contained 32.6% DHA, which falls below the claimed DHA thresholds of at least 45%, 60%, 80%, and 90% in claims 1, 2, 3,

and 4, respectively. (*Id.*). Additionally, Bijl does not disclose how much of the triglyceride fraction is made up of DHA.

The Petition contends that “[a] PHOSITA would . . . have a reasonable expectation of success in combining Bijl with Nichols-I” because:

- Both relate to the creation of microbial oils using culturing techniques;
- Both references teach the same sources of those microbial oils;
- Both teach that the desired product is one of high enough quality for use in the human diet, including in infant formula; and
- Bijl discloses that its processes are compatible with a wide range of natural sources, including thraustochytrids, which are disclosed in Nichols-I.

(Pet. at 42). These reasons are not sufficient to support the alleged obviousness of the Challenged Claims.

First, none of these assertions address the reasonable expectation of success ***in achieving the claimed invention***, which is required under the law. The fact that Bijl and Nichols-I are analogous art and allegedly disclose the same microbial sources of PUFA-containing lipids does not address the question of whether a PHOSITA would have had a reasonable expectation of success in achieving the

claimed invention through their combination. The same is true regarding the references' desire to produce oils of high enough quality for human consumption. The Challenged Claims are not defined by any human consumption criteria. They are defined by specific concentrations of specific components. And there are certainly a multitude of microbial oils that are of high enough quality for human consumption but which do not fall within the scope of the claims.

Second, in alleging that Bijl is compatible with the thraustochytrid strain O disclosed in Nichols-I, the Petition ignores the express teaching in Nichols-I that “[f]urther work is *required* to assess the proportion of [its] components across a range of *culture and other conditions*.” (MARA-1009 at 27 (emphasis added)). Nichols-I does not disclose the culture and extraction conditions under which its purported fatty acid profile was produced. Nor does it disclose the proportion of triglycerides that make up the oil purportedly produced by strain O under such undisclosed conditions. The Petition fails to identify any culture conditions to which a PHOSITA would have subjected strain O to achieve the fatty acid profile described therein. It instead uses strain O as the source of the microbial oil produced under the culture and extraction conditions of Bijl—presumably, because Bijl purportedly discloses that its fermentation processes produce oils that may contain greater than 90% by weight triglycerides. (*See* Pet. at 46-47). But the only

fermentation conditions disclosed in Bijl for producing DHA are for a dinoflagellate microorganism (*i.e.*, *Crypthecodinium cohnii*), which is not a thraustochytrid like strain O of Nichols-I. And that fermentation does not produce an oil containing at least 70% by weight triglycerides. (MARA-1008 at 42-43).

The Petition does not provide any evidence demonstrating that a PHOSITA would have expected strain O to perform in the same or similar manner disclosed in Nichols-I under the culture and extraction conditions of Bijl. And there is nothing in the Petition demonstrating that, under the culture and extraction conditions of Bijl, a PHOSITA would have expected strain O to produce the claimed glyceride levels, the claimed DHA levels, and the claimed ARA levels. These failures are fatal given the clear instruction in Nichols-I itself that further work is ***required*** before any reasonable assessment can be made with respect to the fatty acid profiles produced by strain O under other culture and extraction conditions such as those in Bijl.

Nichols himself has explained the basis for that statement in other publications. For example, in a prior review article Nichols co-authored, it states:

Table 2 gives an indication of ***how variations in culture conditions can influence the biomass and amount of PUFA produced*** by various thraustochytrid strains. ***It is***

apparent from these results that changes to culture conditions do not have uniform effects on PUFA production by different thraustochytrid strains. Optimization and manipulation of culture conditions to produce the amounts and types of PUFA required for specific applications are definitely areas that will require extensive research for each strain taken towards commercial production.

(Ex. 2006 at 582 (emphasis added)). Accordingly, at the time of the '959 patent, it was known that changing culture conditions affects the PUFA fatty acid profiles ultimately produced, both within the same thraustochytrid strain and across different strains. Yet the Petition and Dr. Curtis fail to address in any manner this point when considering the combination of using Nichols-I's strain O under the culture and extraction conditions of Bijl. This is classic hindsight reconstruction of the Challenged Claims based on the teachings of the '959 patent itself.

Finally, even assuming *in arguendo* that strain O produces an oil having the same fatty acid profile disclosed in Nichols-I when subjected to Bijl's fermentation and extraction conditions, that oil contains 0.7% by weight ARA. As explained above with respect to the Radianingtyas/Kralovec combination, subjecting the

Nichols-I microbial oil to the enrichment process of Kralovec would be expected to result in an enriched oil containing an ARA concentration that falls outside of the claimed ARA ranges. *See* Section VII.A.3, *supra*. Thus, a PHOSITA would not have been motivated to apply Kralovec's enrichment methods to the microbial oil produced by Nichols-I's strain O under the fermentation and extraction conditions of Bijl. Nor would a PHOSITA have had a reasonable expectation of success in doing so.

For at least these reasons, the Petition does not establish a reasonable likelihood that a PHOSITA would have been motivated to combine of Bijl, Nichols-I, and Kralovec to achieve the Challenged Claims with a reasonable expectation of success in doing so. Institution of Ground 3 should be denied.

3. The Other Art Identified in Ground 3 Does Not Cure the Deficiencies of the Bijl/Nichols-I/Kralovec Combination

In addition to Bijl, Nichols-I, and Kralovec, Ground 3 of the Petition relies on several other references for disclosure of certain elements of the claims. For example, the Petition identifies Singh (MARA-1018), Nichols-II (MARA-1020), the Lewis Thesis (MARA-1032), Komazawa (MARA-1015), and Barclay (MARA-1019). (Pet. at 47-48). Even if the Board were to consider these extraneous references as part of Ground 3, none cure the deficiencies in Bijl, Nichols-I, and Kralovec.

First, the disclosures of Singh and Nichols-II are substantially the same as the relevant disclosure in Nichols-I. They therefore suffer the same deficiencies as Nichols-I.

Second, the Petition fails to demonstrate that Lewis is a “printed publication” for purposes of *inter partes* review. Lewis purports to be a doctoral thesis from the University of Tasmania. (MARA-1032 at 1). It expressly states the following:

This thesis is not to be made available for loan or copying for two years following the date this statement was signed. Following that time the thesis may be made available for loan and limited copying in accordance with the Copyright Act of 1968.

(MARA-1032 at 3). Despite these non-publication restrictions, the Petition provides no evidence that the Lewis thesis was ever actually made available to the public or that it could be freely copied by the public. Notably, the Munford Declaration (MARA-1021) attempts to authenticate the public availability of other articles cited in the Petition but does not address the public availability of the Lewis Thesis at all. Accordingly, the Petition fails to qualify the Lewis Thesis as a “printed publication.”

In any event, the Lewis Thesis does not disclose how much of its measured DHA resides in the triglyceride fraction versus, for example, the phospholipid fraction. Additionally, reflecting graduate-level, academic research, the Lewis Thesis does not demonstrate that any of the microbial strains therein were publicly available as of the '959 patent. Nor does the Petition provide any motivation to combine the Lewis Thesis with Bijl and Nichols-I.

Third, neither Komazawa⁸ nor Barclay disclose how much of their oils are made up of triglycerides. Barclay does not disclose how much of its measured DHA resides in the triglyceride fraction versus, for example, the phospholipid fraction. Nor does the Petition provide any motivation to combine Komazawa and/or Barclay with Bijl, Nichols-I, and Kralovec.

Accordingly, institution of *inter partes* review of claims 1-14 based on Ground 3 should be denied.

C. Ground 4 Fails to Meet the Institution Threshold and Has Already Been Considered By the Examiner

Having failed to demonstrate a reasonable likelihood of success on Grounds 1-3, the Petition is left with Ground 4. Ground 4 challenges the patentability of claims 1-4 and 6-14 based on alleged obviousness over the combination of Bijl and

⁸ Komazawa is described in detail in Section VII.C, *infra*.

U.S. Publ. No. 2004/0161831 (“Komazawa”). (Pet. at 56-68). Both of these references were previously presented to the Office. The Petition fails to demonstrate that the examiner materially erred in allowing claims 1-4 and 6-14 over the combination of Bijl and Komazawa. Indeed, the Petition fails to demonstrate that a PHOSITA would have been motivated to combine Bijl and Komazawa to achieve the claimed subject matter with a reasonable expectation of success in doing so. Consequently, *inter partes* review of claims 1-4 and 6-14 based on Ground 4 should be denied.

1. The Board May Exercise Its § 325(d) Discretion and Deny Institution of Ground 4

The Petition concedes that both Bijl and Komazawa were “previously presented” to the Office. (Pet. at 69). In fact, both references were presented during prosecution of the parent ’794 patent, (Ex. 2007 at 2 (identifying US2004/0161831 and WO 1997/037032 in References Cited section)), and were considered by the examiner, (Ex. 2008 at 6 (Komazawa), 11 (Bijl)). The ’959 patent is a divisional of and is terminally disclaimed over the ’794 patent. (MARA-1001 at Related U.S. Application Data; MARA-1002 at 190). And as illustrated below, the subject matter of the parent ’794 patent is similar to that of the ’959 patent, including the claimed range of ARA concentrations:

Claim 1 of the '794 patent	Claim 1 of the '959 patent
1. A microbial oil comprising a triglyceride fraction of from 75% to 95% by weight, wherein the docosahexaenoic acid content of the triglyceride fraction is from 40% to 80% by weight, wherein the arachidonic acid content of the triglyceride fraction is from 0.1% by weight to 1.5% by weight, wherein said microbial oil further comprising an effective amount of at least one added antioxidant to provide oxidative stability.	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 45% by weight, and wherein the oil comprises 1.5% by weight or less of arachidonic acid.

(Compare Ex. 2007 with MARA-1001). Thus, the first prong of *Advanced Bionics* is met. See *Advanced Bionics, LLC v. MED-El Elektromedizinische Gerate GmbH*, IPR 2019-01469, Paper 6, at 7-8 (P.T.A.B. Feb. 13, 2020) (noting first prong asks whether art in petition is same or substantially the same as those previously presented).

Because the first prong is met, if “the petitioner fails to make a showing of material error, the Director generally will exercise discretion not to institute inter partes review.” *Id.*, at 8-9. The Petition fails to demonstrate material examiner error in allowing claims 1-4 and 6-14 over the combination of Bijl and Komazawa and institution should be denied. The Petition correctly notes that the Examiner did not rely on Bijl or Komazawa in making any substantive rejections during prosecution of the parent ’794 patent and ’959 patent. *See id.*, at 9 n.10 (factor (c) considers the extent to which a reference was used as the basis for a rejection). However, this is not a case in which the Examiner simply overlooked teachings in those references. As explained in the following sections, the Examiner did not rely on Bijl and Komazawa in rejecting the claims during prosecution because their combination would not have rendered the ’959 patent obvious, even upon consideration of the arguments and evidence presented in the Petition. Accordingly, and respectfully, the Board should “defer to [the Examiner’s] previous . . . evaluation[.]” and determination that the Challenged Claims are patentable over Bijl and Komazawa. *Id.* at 9.

a. Bijl and Komazawa Differ Significantly From the Challenged Claims

Bijl has been discussed extensively above. *See generally* Section VII.B, *supra*. Komazawa discloses the isolation, characterization, and classification of a

certain thraustochytrid microorganism referred to as strain LFF1 and its use in microbial fermentations to produce oils containing polyunsaturated fatty acids. (MARA-1015). Example 1 of Komazawa discloses the isolation and identification of its LFF1 strain, which was determined to be a microorganism from the genera Thraustochytrium. (MARA-1015 at [0072]).

In Example 2, Komazawa's LFF1 strain was placed in an agitation fermenter at 28° C with a growth medium containing a carbon source (glucose) at a ratio of 3:1 to the nitrogen source (yeast extract). (*Id.* at [0074]- [0094]). Notably, this ratio is much lower than the 40-50:1 typically used "to ensure that nitrogen is exhausted" during the fermentation. (MARA-1010 at 3). Agitation culture was conducted for 40 hours with aeration at 500 rpm. (MARA-1015 at [0092]). pH was not regulated in this fermentation. (*Id.*). The resulting oil was extracted with a mixture of chloroform and methanol, which resulted in an extracted lipid composition containing 58.8% DHA by weight of total fatty acids. (*Id.* at [0094]-[0108]). In this Example, Komazawa does not disclose how much DHA is in its triglyceride fraction or how much of the oil is made up of the triglyceride fraction. (*Id.* at [0093]-[0108]). However, this fermentation produced 5.95 g of total amount of fat and oil and 3.50 g DHA per liter of culture. (*Id.* at [0105]-[0107]).

Example 4 of Komazawa⁹ discloses increasing the concentration of PUFAs in its oil by selectively hydrolyzing it with a lipase enzyme and removing the free fatty acids (*Id.* at [0112]-[0114]), but this forms a glyceride fraction that would be expected to contain a mixture of mono- and diglycerides, not triglycerides. (*See, e.g.,* MARA-1027 at 5, FIG. 2 (depicting hydrolysis of triglyceride into di- and monoglycerides by lipase enzyme)). Komazawa does not disclose a post-extraction enrichment process like Kralovec in which PUFA concentrations are increased via a subsequent enzymatic lipase reaction between a glyceride fraction and free fatty acids to form a predominantly triglyceride fraction.

Example 5 is similar to Example 2 except that pH was controlled at 4.5, 7.5, and 8.0. (MARA-1015 at [0115]-[0116]). At pH 7.5, the resulting oil contained about 30% DHA in the triglycerides (*id.* at Fig. 3), but Komazawa does not disclose any growth information or production yields for this fermentation. (*Id.* at [0116], Fig. 3). At pH 4.5 and 8.0, the resulting oils purportedly contained about 60% and 80% DHA in the triglycerides, respectively. (*Id.*). Importantly, Komazawa does not disclose how much of the oil in any of its examples is made up of the triglyceride fraction.

⁹ Example 3 of Komazawa relates to the conversion of DHA into behenic acid, which is not relevant to the claimed microbial oils.

Komazawa further explains that “the production amount of fat and oil is decreased but the content of [DHA] in fat and oil is increased by adjusting pH to 8.0 to 9.0.” (*Id.* at [0046]). Indeed, Komazawa discloses that at pH 8.5, the DHA yield was only 0.8 g per liter of culture. (*Id.* at [0116]). This is consistent with a fermentation in which the cells have not grown to capacity, resulting in low oil accumulation, and therefore are likely producing a significant amount of PUFAs in the form of phospholipids. (*See* Section II.B, *supra*). Thus, although Komazawa purportedly discloses an oil having 80% DHA in the triglycerides when cultured at pH of 8.5, there is nothing to indicate that the triglycerides make up at least 70% by weight of that oil.

The same is true for Komazawa's fermentation run under highly acidic conditions such as a pH of 4.5—where cellular growth would be expected to be inhibited significantly. As was known in the field, thraustochytrids generally exhibit optimal growth near neutral pH, but their growth is significantly impeded under acidic and basic conditions. (*See* Ex. 2005 at 3105, Tbl. 1 (showing reduced growth of biomass and DHA yield at pH 5 and trace growth of biomass and DHA yield at pH 8)). Yet the Petition and Dr. Curtis ignore these differences with the fermentations in Example 5 of Komazawa and do not explain why a PHOSITA would have selected highly acidic or basic fermentation conditions given the

known negative impact on cellular growth.

In Examples 6 and 7, the amount of glucose (*i.e.*, the carbon source) in the culture medium was increased to 15%. (MARA-1015 at [0122], [0159]). As expected, this substantially increased the production of fat and oil. Example 6 produced 52 g of fat and oil and 16.6 g of DHA per liter of culture. (*Id.* at [0146]). The DHA content in the triglycerides was only 32%. (*Id.*). Similarly, Example 7 produced 45 g of fat and oil and 15.3 g of DHA per liter of culture. (*Id.* at [0183]). The DHA content in the triglycerides was only 34%. (*Id.*) The amount of oil produced in Examples 6 and 7 is significantly higher than those produced in Example 2 and the pH 8.0 fermentation of Example 5, which is consistent with better growth conditions in Examples 6 and 7 compared to Examples 2 and 5. Importantly, the fermentations with the highest production of oil—*i.e.*, the oils that would likely be expected to contain the highest amount of triglycerides—contained the least amount of DHA in the triglyceride fraction.

Accordingly, a PHOSITA would appreciate that in Komazawa, the fermentations that produce oils likely expected to contain primarily triglycerides also produce DHA in the triglycerides in an amount substantially below the “at least 45%” threshold of claim 1. (*See* Section II.B, *supra*). In fermentations in which growth was inhibited (*e.g.*, at pH 4.5 and 8.5), the percentage of DHA in the

triglycerides was comparatively increased in the triglycerides, but a PHOSITA would have also expected that those oils would contain a substantial portion of phospholipids. (*Id.*). The Petition and Dr. Curtis fail to consider the full disclosure of Komazawa and do not address in any manner the fermentation results disclosed in Examples 6 and 7.

b. A PHOSITA Would Not Have Been Motivated to Combine Bijl and Komazawa to Achieve the Claimed Invention or Have a Reasonable Expectation of Success in Doing So

The Petition fails to provide a motivation to combine Bijl and Komazawa sufficient to support *inter partes* review. The Petition once again provides conclusory and generic motivations that do not address why a PHOSITA would have combined the disclosures of Bijl and Komazawa in the same manner as in the Challenged Claims. (Pet. at 58-61). In so doing, the Petition ignores the full disclosures of Bijl and Komazawa.

As noted above, Komazawa discloses several fermentations using its LFF1 strain to produce microbial oils. Komazawa demonstrates that in those fermentations that produce high amounts of oil (i.e., Examples 6 and 7), the microbial oil contained less than 40% DHA in the triglyceride fraction. And because high amounts of oil were produced in those examples, those oils would likely be expected to contain primarily triglycerides. (See Section II.B, *supra*). In

contrast, in those fermentations that produce low amounts of oil (i.e., Examples 2 and 5 (pH 8.5)), the microbial oil purportedly contained up to 80% DHA in the triglyceride fraction. But because low amounts of oil were produced in those examples, a PHOSITA would have expected those oils to contain a substantial amount of phospholipids. (*Id.*). Accordingly, a PHOSITA would not have been motivated to select Komazawa's LFF1 strain for use in Bijl's fermentation and extraction process because Komazawa's strain does not produce the requisite concentration of DHA in an oil that contains at least 70% by weight of a triglyceride fraction.

The Petition and Dr. Curtis overlook these critical disclosures in Komazawa and instead contend that a PHOSITA would understand that all oils in Komazawa contain predominantly triglycerides for two reasons. (Pet. at 62-63). **First**, they contend that Komazawa teaches the use of a lipase enzyme for triglyceride-specific oils. (Pet. at 62 (citing MARA-1003 at ¶ 270)). Although that may be true, there is nothing in Komazawa that indicates its oils are free of phospholipids. Petitioners' own evidence shows that microbial oils often contain substantial amounts of fatty acids in phospholipid form, particularly in low-growth fermentations. (See Section II.B, *supra*).

Second, they contend that instead of using the term "lipid," Komazawa uses

the term “fat and oil”, which a PHOSITA purportedly associates with an oil that is predominantly triglycerides. (Pet. at 62-63 (citing MARA-1003 at ¶ 271)). But Dr. Curtis’s conclusory opinion is contradicted by Komazawa itself, which uses “fat and oil” and “lipid” interchangeably—as is common in the field. For example, Komazawa notes that “Table 1 shows the fatty acid composition of the extracted *lipid*.” (MARA-1015 at [0112] (emphasis added)). And the title of Table 1 is “Fatty acid composition of the *fat and oil* extracted from LFF1 strain[.]” (*Id.* at Tbl. 1 (emphasis added)). Komazawa expressly equates “lipid” with “fat and oil.”

Thus, contrary to the Petition and Dr. Curtis, a PHOSITA would not have understood that all of Komazawa’s microbial oils contain predominantly triglycerides such that they meet the “at least 70% by weight” triglyceride threshold. And a PHOSITA certainly would not have expected a microbial oil produced via a fermentation with low oil output (such as when growth in pH-inhibited) to contain a high level of triglycerides. (*See generally* Section II.B, *supra*). When total oil accumulation is low, “most of the fatty acids extracted are likely derived from membrane phospholipids rather than triacylglycerols”. (Ex. 2003 at 2834).

Accordingly, a PHOSITA would not have been motivated to combine Bijl and Komazawa to arrive at the claimed invention and would not have reasonably

expected to achieve the claimed invention in doing so. The combination of Bijl and Komazawa does not teach or suggest any microbial oil that contains at least 70% by weight of a triglyceride fraction and at least 45% by weight DHA in the triglyceride fraction.

c. The Examiner Did Not Err in Allowing the Claims After the ARA Amendment

The Petition acknowledges that claims 1-4 and 6-14 were allowed after the claims were amended to include the element “wherein the oil comprises 1.5% by weight or less of arachidonic acid.” (Pet. at 71). According to the Petition, the Examiner erred in not considering Bijl and Komazawa after the amendment. But the Petition expressly concedes that “Bijl and Komazawa do not disclose ARA values at all[.]” (*Id.*). Accordingly, it is difficult to comprehend how the Examiner could have erred when Bijl and Komazawa admittedly do not disclose any ARA values whatsoever. The Petition proffers two arguments in an attempt to overcome this deficiency, both of which fail.

First, the Petition contends that the ARA element “is an optional negative limitation, for which prior art disclosure is not necessary to meet the claim element.” (Pet. at 64). This is a fundamental error. The ARA element is not an optional negative limitation. The plain language of claims 1-4 and 6-14 requires that the microbial oil “comprises 1.5% by weight or less of arachidonic acid.”

Accordingly, the Petition must demonstrate that this element is disclosed in the prior art combination. And a reference's silence with respect to a particular claim element is not a disclosure that such claim element is necessarily absent from the reference. See *Novartis Pharms. Corp. v. Accord Healthcare, Inc.*, 38 F.4th 1013, 1017 (Fed. Cir. 2022) ("Silence is generally not disclosure.").

Second, the Petition contends that Table 1 in Komazawa discloses an oil that contains "no detectable amount of ARA" because the fatty acid composition purportedly contains five fatty acids, the amounts of which add up to 100%. (Pet. at 64). Even if that were true, which Patent Owner denies,¹⁰ the Petition overlooks a critical fact with respect to the oil described in Table 1: it has been subjected to hydrolysis using a lipase enzyme and therefore would be expected to contain a substantial amount of mono- and diglycerides and fall outside the claimed range of triglycerides. (See, e.g., MARA-1027 at 4-5, FIG. 2 (depicting hydrolysis of triglyceride into di- and monoglycerides by lipase enzyme)). And the oil from

¹⁰ Figure 1 of Komazawa demonstrates that strain LFF1 produces an oil that contains measurable amounts of substantially more than five fatty acids, which Komazawa does not expressly report. (Compare MARA-1015 at FIG. 1 (showing numerous fatty acid peaks) with MARA-1015 at Example 2 (identifying only six fatty acids)).

which it was derived contains 5.5% of unidentified fatty acids, which could potentially include ARA. (MARA-1015 at [0108] (disclosing lipid composition containing 1.8% C15:0, 18.8% C16:0, 9.7% C17:0, 2.2% EPA, 3.2% DPA, 58.8% DHA, and 5.5% other unidentified components; *see also id.* at Fig. 1 (identifying more than 5 fatty acids in gas chromatography analysis)). Thus, Komazawa does not necessarily disclose any oil that excludes ARA. The Petition and Dr. Curtis ignore this fact.

Accordingly, the Petition does not point out sufficiently how the Examiner erred in her evaluation of Bijl and Komazawa in view of the claim amendment that led to allowance of the claims. *See Advanced Bionics*, at 9 (“If reasonable minds can disagree regarding the purported treatment of the art or arguments, it cannot be said that the Office erred in a manner material to patentability.”).

d. The Petition Does Not Demonstrate Material Examiner Error

In sum, the second prong of *Advanced Bionics* weighs strongly in favor of denying institution of Ground 4. The Examiner expressly considered Bijl and Komazawa during prosecution of the parent '794 patent, which contains claims similar in scope to those in the '959 patent and against which the '959 patent is terminally disclaimed. Although the Examiner did not use either Bijl or Komazawa as the basis for any rejection, that is not surprising. The Examiner

allowed the Challenged Claims upon the addition of the claimed ARA range over the combination because as the Petition concedes “Bijl and Komazawa do not disclose ARA values at all[.]” (Pet. at 71). The only disclosure in Komazawa and Bijl to which the Petition points for purportedly disclosing a microbial oil with the requisite amount of ARA is an oil that has been reacted with a lipase enzyme to form mono- and diglycerides, not triglycerides. Moreover, in the fermentations of Komazawa that produce oil expected to be high in triglyceride content, the DHA production in the triglycerides falls far below the threshold of “at least 45% by weight.” Thus, the evidence presented in the Petition fails to demonstrate material Examiner error and does not warrant reconsideration of the patentability of claims 1-4 and 6-14 over the combination of Bijl and Komazawa. It also fails to demonstrate the alleged obviousness of claims 1-4 and 6-14 on the merits irrespective of the Board’s Section 325(d) discretion. Institution should therefore be denied.

2. *Ground 4 Is Based on Art That Does Not Qualify as a Patent or Printed Publication*

In addition Ground 4, like Ground 3, relies on the *use* of a particular microbial strain referenced in Komazawa, not on the disclosure of Komazawa itself. The Petition plainly states it multiple times: “a PHOSITA would have been motivated to *use Komazawa’s preferred microbial strains* (e.g., strain LFF1

thraustochytrids) as a microbial source for Bijl's extracted microbial oil[.]” (Pet. at 59-61 (emphasis added)). In other words, strain LFF1 in Komazawa is being *used* as the microbial source in Bijl's fermentation and extraction process. But strain LFF1, a microorganism, is not a patent or printed publication, as required under 35 U.S.C. § 311(b), and institution of Ground 3 should be denied on this additional basis. *See Elekta*, IPR2016-00315, at *13-14 (refusing institution of ground based on use of system rather than on what prior art discloses about that system).

Moreover, the Petition does not provide any evidence demonstrating that a PHOSITA would have expected strain LFF1 to perform in the same or similar manner disclosed in Komazawa under the culture and extraction conditions of Bijl. And there is nothing in the Petition demonstrating that, under the culture and extraction conditions of Bijl, a PHOSITA would have expected strain LFF1 to produce the claimed glyceride levels, the claimed DHA levels, and the claimed ARA levels. These failures are fatal to Ground 4 given that Komazawa itself demonstrates that fermentation conditions significantly impact the fatty acid compositions of the oils produced by strain LFF1. (*Compare* MARA-1015 at Example 5 *with* MARA-1015 at Examples 6-7).

Accordingly, institution of *inter partes* review of claims 1-4 and 6-14 based on Ground 4 should be denied for this additional reason.

VIII. CONCLUSION

The Petition fails to demonstrate a reasonable likelihood that any claim of the '959 patent is unpatentable. Ground 1 fails to demonstrate how Radianingtyas discloses each and every element of claim 1 as those elements are arranged in the claim. Ground 2 fails to demonstrate that a PHOSITA would have been motivated to combine Radianingtyas with Kralovec to achieve claims 1-14 with a reasonable expectation of success in doing so. Ground 3 is based on art that does not qualify as a patent or printed publication that was publicly available as of the priority date of the '959 patent and that otherwise does not render claims 1-14 obvious. Ground 4 is based on art that was previously presented to the Office during prosecution. Yet, the Petition fails to demonstrate that the Examiner materially erred in allowing claims 1-4 and 6-14 over that art. In view of these fundamental failures, *inter partes* review should be denied.

DSM believes the legal and evidentiary deficiencies highlighted in this Preliminary Response are dispositive and preclude institution of *inter partes* review of the '959 patent. Should the Board disagree and institute review, DSM reserves its right to fully address all of the deficiencies and merits with respect to the grounds and issues raised in the Petition.

Case IPR2023-01342
Patent Owner's Preliminary Response

Dated: November 30, 2023

Respectfully submitted,

/Erick J. Palmer/

Erick J. Palmer (Lead Counsel)

Reg. No. 64,456

MAYER BROWN LLP

71 South Wacker Drive

Chicago, IL 60606

(312) 701-8352

ejpalmer@mayerbrown.com

Joseph A. Mahoney (Backup Counsel)

Reg. No. 38,956

MAYER BROWN LLP

300 South Tryon Street

Suite 1800

(704) 444-3654

jmahoney@mayerbrown.com

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

I hereby certify that this **PATENT OWNER'S PRELIMINARY RESPONSE** contains 13,878 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).

Respectfully submitted,

Date: November 30, 2023

By: /Erick J. Palmer/

Erick J. Palmer
Reg. No. 64,456
MAYER BROWN LLP
71 South Wacker Drive
Chicago, IL 60606
(312) 701-8352
ejpalmer@mayerbrown.com

CERTIFICATE OF SERVICE

I hereby certify that on this 30th day of November, 2023, a copy of this **PATENT OWNER'S PRELIMINARY RESPONSE** was served by electronic mail to the attorneys of record, at the following address:

IPR55973-0004IP1@fr.com

Respectfully submitted,

Date: November 30, 2023

By: /Erick J. Palmer/

Erick J. Palmer
Reg. No. 64,456
MAYER BROWN LLP
71 South Wacker Drive
Chicago, IL 60606
(312) 701-8352
ejpalmer@mayerbrown.com