

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MARA RENEWABLES CORPORATION,
Petitioner,

v.

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

Case IPR2023-01167
U.S. Patent No. 10,392,578

PATENT OWNER'S PRELIMINARY RESPONSE

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PATENT OWNER'S EXHIBIT LIST

Exhibit	Description
2001	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).
2002	S. Raghukumar, <i>Thraustochytrid Marine Protists: Production of PUFAs and Other Emerging Technologies</i> , MAR. BIOTECHNOL., 10, 631-40 (2008).
2003	Office Action dated August 7, 2007, issued during prosecution of U.S. Serial No. 10/518,146, which published as US Publ. No. 2005/0220958 to Schaap <i>et al.</i> (Ex. 1005)
2004	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).
2005	T.E. Lewis, <i>et al.</i> , <i>The Biotechnological Potential of Thraustochytrids</i> , MAR. BIOTECHNOL., 1, 580-87 (1999).

I. INTRODUCTION

Mara Renewables Corporation and real party-in-interest Algal Omega 3 Ltd. (together, "Petitioners") request *inter partes* review and cancellation of claims 1-7 (the "Challenged Claims") of U.S. Patent No. 10,392,578 (the "'578 patent"). 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.

The Petition does not raise any ground of unpatentability based on anticipation, effectively conceding the novelty of the Challenged Claims. The Petition instead raises four grounds of unpatentability based on alleged obviousness. But fundamental deficiencies pervade each ground. Those deficiencies are plainly illustrated in the first sentence of the challenge:

This request describes how the prior art discloses each of the elements of the Challenged Claims, thereby rendering claims 1-7 of the '578 patent unpatentable.

(Pet. at 8). Of course "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements is, independently, known in the prior art." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418-19 (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 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 15 (“Schaap-Kralovec discloses and/or renders obvious [3pre].”), 16 (“Schaap-Kralovec discloses and/or renders

obvious [3a].”), 18 (“Schaap-Kralovec discloses and/or renders obvious [3b].”), 22 (“Schaap-Kralovec discloses and/or renders obvious [3c].”), 23 (“Schaap-Kralovec discloses and/or renders obvious [3d].”).

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 provide evidence sufficient to demonstrate that a person of ordinary skill in the art would have reasonably expected to achieve the claimed invention based on those purported combinations.

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

II. TECHNOLOGY BACKGROUND

The '578 patent generally relates to the microbial production of oils containing certain long-chain polyunsaturated fatty acids (“PUFAs”)¹ primarily in

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

triglyceride form. The Petition is devoid of any substantive discussion of the general state of the art prior to the '578 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

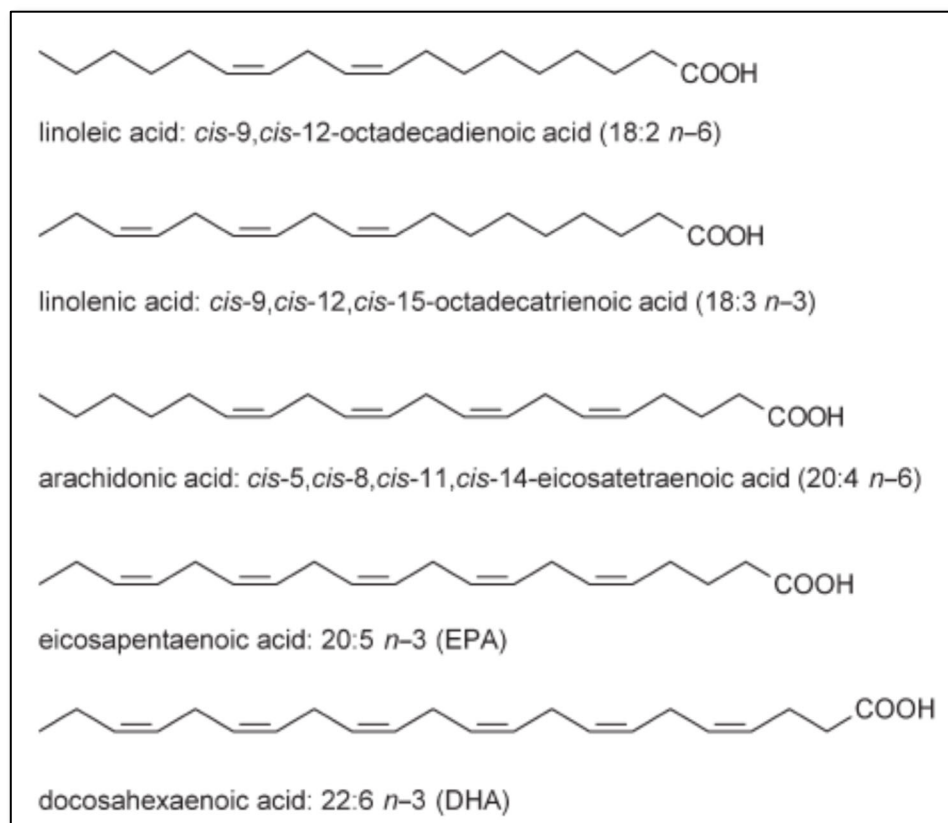
The principal classes of lipids that make up oils include free fatty acids, glycerides (including mono-, di-, and primarily triglycerides), and phospholipids. (MARA-1027 at 1).² Monoglycerides are ester compounds that contain one fatty acid residue attached to a glycerol backbone (*i.e.*, $\text{HOCH}_2\text{CH}(\text{OH})\text{CH}_2(\text{O}_2\text{R})$, 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

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

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:



(*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).

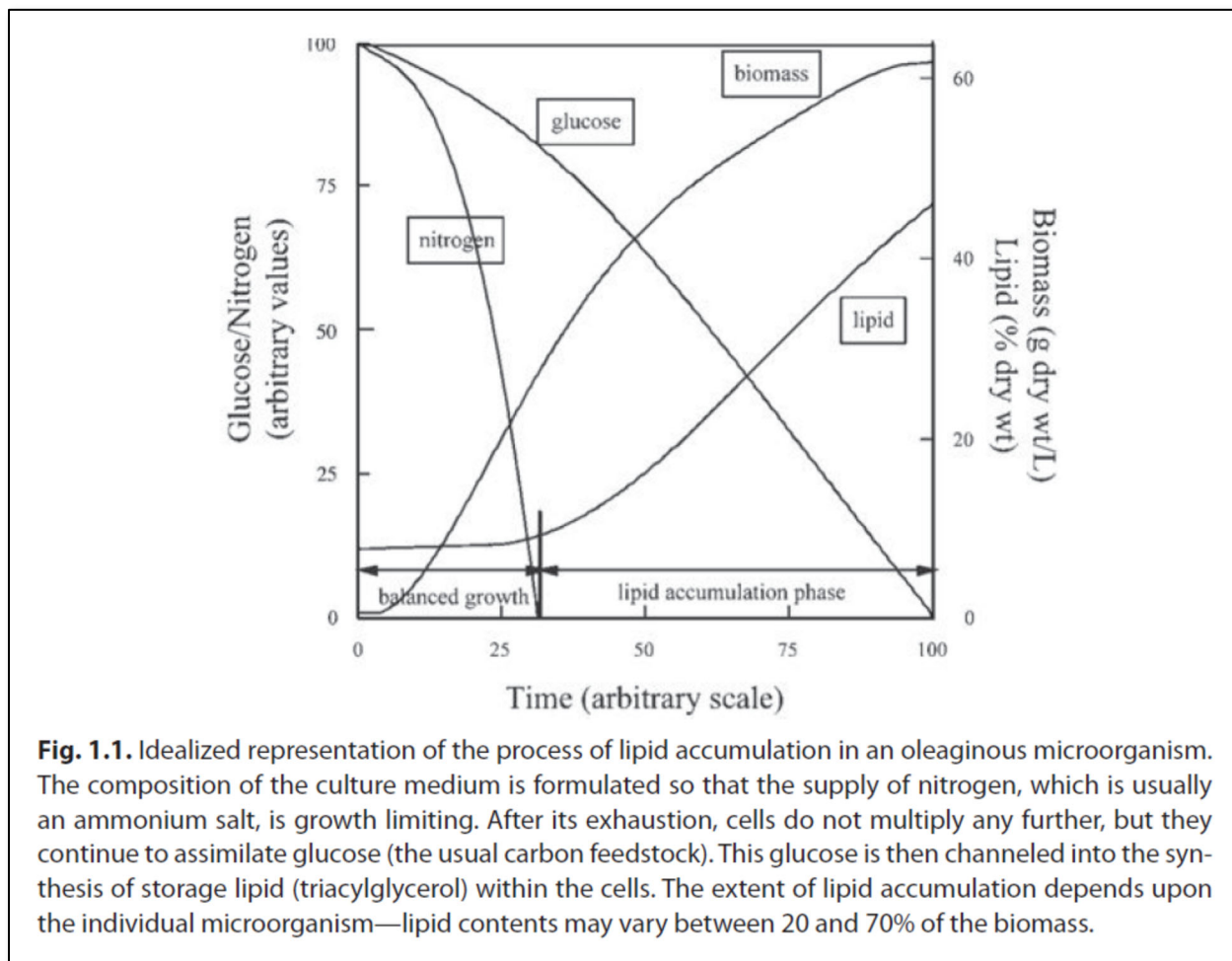
Another common long-chain PUFA is docosapentaenoic acid (“DPA”), which is referred to as 22:5. DPA can exist in two isomeric forms, *n*-3 and *n*-6. Thus, DPA is a fatty acid composed of **22** carbons atoms and **5** carbon=carbon double bonds, with the first double bond starting at either the ***third*** 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 6, FIG. 1.1). The fermentation generally is 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 5). 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 are 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. (MARA-1031). 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. (MARA-1028 at 608, Tbl. 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. 2001 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”);³ *see also* Ex. 2002 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 125-26, Fig. 6.4). The oil can then be collected and its fatty acid profile determined. (*Id.*).

³ Exhibit 2001, which is co-authored by one of the authors of MARA-1009, published after the priority date of the '578 patent. However, the statement in Exhibit 2001 on which this Preliminary Response relies reflects the general knowledge in the field at the time of the '578 patent. It is also consistent with Figure 1.1 as well as the description of the same on pages 4-6 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.

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.*, Ex. 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.*, MARA-1028 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.

D. Susceptibility to Oxidation Is a Significant Problem With Microbially-Produced PUFAs

As Petitioners' own declarant concedes, "PUFA containing oils are particularly susceptible to oxidation[.]" (MARA-1003 at ¶ 48(c)(iii)). In fact, PUFAs are known to undergo autoxidation, which refers to the direct reaction of molecular oxygen with the PUFA under mild conditions. (MARA-1027 at 15). The oxidation of lipids proceeds via a free-radical chain mechanism involving initiation, propagation, and termination processes. (*Id.* at 15-18). Not surprisingly, PUFAs exhibit different oxidation behavior based on differences in their structure. For example, studies have demonstrated that "the oxidizability of each PUFA [is] increased approximately two fold for each active bis-allylic methylene group" contained in its backbone. (*Id.* at 21). As illustrated in the table below, DHA

(22:6) is nearly twice as oxidizable as ARA (20:4) and exhibits a relative oxidation rate that is almost 70% greater than ARA:

Table 1.1. Rates of autoxidation of unsaturated fatty esters ^{a,b}					
Fatty esters	Number of -CH₂-	mole O₂ per 100 hr ^a	Relative rates ^a	Oxidizability M^{-1/2}sec^{-1/2} ^b	Relative rates ^b
18:1	0	0.04	1		
18:2	1	1.63	41	0.020	1
18:3	2	3.90	98	0.041	2.1
20:4	3	7.78	195	0.058	2.9
22:6	5			0.102	5.1
Trilinolein	1 × 3	1.99	50	0.080	4.0

^a Holman and Elmer (1947): neat methyl or ethyl esters were autoxidized at 37°C and rates were measured by oxygen absorption with a Warburg respirometer.

^b Cosgrove *et al.* (1987): chlorobenzene solution were oxidized at 37°C in the presence of 2,2'-azobis(2-methylpropionitrile) and rates were measured by oxygen absorption with a pressure transducer in an automated recording gas apparatus.

(MARA-1027 at 21, Tbl. 1.1). A common way to determine the extent of oxidation in an oil is to measure its anisidine value. (*Id.* at 106-107).

The propensity of PUFAs to undergo autoxidation is particularly problematic under the conditions generally employed in microbial fermentations. Microbial fermentations typically are carried out under aerobic—*i.e.*, oxidative—conditions. Aeration is important to ensure adequate cellular growth and microbial production of PUFAs in thraustochytrids, which are the microorganisms on which much of the Petition relies. (MARA-1010 at 89 (noting aeration rate is “important variable” for DHA production)). Moreover, typical extraction processes employ solvents to lyse and disrupt the cells. This extraction process is known to result in

dissociated metal ions (*e.g.*, iron and copper) from other cellular components, which can form salts with PUFAs and catalyze PUFA oxidation reactions. (*See* Ex. 1027 at 302 (noting solvent extraction causes metal ion dissociation that may form metal salts with fatty acids and catalyze autoxidation); *see also id.* at 22-23 (noting metals accelerate autoxidation in oils)).

Not surprisingly, PUFA oxidation is particularly problematic in industrial-scale fermentation processes. For example, the FRIOLEX[®] process is a commercial process for extracting lipids using an organic solvent. (MARA-1001 at 55:42-66). The '578 patent demonstrates that when this process is used to extract a high-concentration DHA oil from a broth of microbial cells, the oil has an anisidine value of 73.9, indicating significant oxidation. (*Id.* at Tbl. 7).

III. THE '578 PATENT CLAIMS NOVEL EXTRACTED MICROBIAL OILS HAVING HIGH TRIGLYERIDE AND DHA CONTENT WITH LOW ANISIDINE VALUES

The '578 patent discloses methods that produce novel extracted microbial oil compositions having certain PUFA concentration profiles and low levels of oxidation by-products and solvent impurities. The '578 patent claims some of these novel extracted microbial oil compositions.

A. The Extraction Methods Disclosed in the '578 Patent Eliminate the Use of Organic Solvents

Traditionally, extraction of oils from microbial cells has been accomplished using organic solvents. Bucking this convention, the inventors of the '578 patent developed an alternative extraction process that eliminates the use of costly and flammable organic solvents. (MARA-1001 at 1:62-65). The methods disclosed in the '578 patent may comprise raising the pH of the cell composition to 8 or above to lyse and/or demulsify the cell composition, adding a salt, heating, and agitating the composition as well as other modifications of this general process. (*Id.* at 2:16-3:2, 7:62-8:3, FIGS. 1-4).

The extraction technology disclosed in the '578 patent represents a significant advance in the field and has led to novel microbial lipid compositions with industrial application. Indeed, the extraction methods disclosed in the '578 patent surprisingly permit the production of extracted microbial oils that have high concentrations of DHA but which have low levels of oxidation as evidenced by anisidine values—and they do so on an industrial scale. This is illustrated in Example 8 of the '578 patent. (MARA-1001 at 45:63-46:47). In Example 8, the pH of a 20,000 kg (*i.e.*, **over 22 tons**) batch of a microbial fermentation broth was raised to 10.5, 2% NaCl was added, and the composition was heated overnight to lyse the microbial cells. (*Id.*). The crude oil was produced in high yield, contained

more than 60% of DHA, and had an anisidine value of 15—all while not requiring an organic solvent for extraction. (*Id.*). Given its industrial applicability, this technology is exactly the type that the patent laws are intended to protect.

B. The Claimed Compositions Are Novel Advancements Over the Prior Art

The '578 patent contains three independent claims directed to extracted microbial oils. Claim 1 recites:

1. An extracted microbial lipid comprising a triglyceride fraction of at least 70% by weight of the lipid fraction, wherein the docosahexaenoic acid content of the triglyceride fraction is at least 50% by weight, wherein the docosapentaenoic acid n-6 content of the triglyceride fraction is from at least 0.5% by weight to 6% by weight, and wherein the oil has an anisidine value of 0.5 to 26, and wherein the lipid has less than 5% by weight of an organic solvent.

(MARA-1001). Thus, the extracted microbial lipid of claim 1 comprises at least 70% by weight triglycerides containing at least 50% by weight DHA and 0.5-6% by weight *n*-6 DPA. The extracted microbial lipid has an anisidine value of 0.5-26

and less than 5% by weight of an organic solvent. Claims 4-7 all depend, directly or indirectly, from claim 1.

Claim 2 is similar to claim 1 but recites a DHA threshold of 40% DHA in the triglycerides and a DHA to DPA, *n*-6 ratio of greater than 6 to 1:

2. An extracted microbial lipid comprising a triglyceride fraction of at least 70% by weight of the lipid fraction, wherein the docosahexaenoic acid content of the triglyceride fraction is at least 40% by weight, wherein the docosapentaenoic acid *n*-6 content of the triglyceride fraction is from at least 0.5% by weight to 6% by weight, wherein the ratio of docosahexaenoic acid to docosapentaenoic acid *n*-6 is greater than 6:1, and wherein the oil has an anisidine value of 0.5 to 26, and wherein the lipid has less than 5% by weight of an organic solvent.

Claim 3 is not limited by its DPA, *n*-6 content but requires a higher concentration of DHA in the triglycerides (*i.e.*, at least 60% by weight):

3. An extracted microbial lipid comprising a triglyceride fraction of at least about 70% by weight, of

the lipid fraction wherein the docosahexaenoic acid content of the triglyceride fraction is at least 60% by weight and wherein the oil has an anisidine value of 0.5 to 26, and wherein the lipid has less than 5% by weight of an organic solvent.

(MARA-1001).

The Petition effectively concedes that these extracted microbial oil compositions are novel and does not raise any grounds of unpatentability based on anticipation.

C. The '578 Patent Issued After Eight Years of Prosecution

The '578 patent did not sail through prosecution unimpeded. It endured more than eight years of a robust back-and-forth with the Patent Office before being granted. (*See generally* MARA-1002).

During that time, the examiner was fully engaged in prosecution. The examiner conducted a multitude of prior art searches. (MARA-1002 at 236-241, 278, 308, 346, 505-506, 555-556, 592-593, 612-613, 657-658, 908-909, 1026-1028, 1036-1037, 1086-1088). In assessing the patentability of the Challenged Claims, the examiner considered hundreds of prior art references. (*Id.* at 273-277, 347-349, 354-355, 560-568, 662-668, 912-999, 1031-1035, 1089-1100, 1108-

1122). The examiner issued numerous Office Actions containing substantive claim rejections. (*Id.* at 194-199, 264-272, 494-503, 544-553, 587-591, 1014-1024). And the claims were amended multiple times along the way. (*Id.* at 202-209, 283-295, 511-522, 569-579, 604-606, 1067-1074).

The '578 patent is not an example of a patent that was improvidently granted early in the prosecution stage without due consideration. It is the result of eight long years of the Patent Office's careful consideration of the claims that were ultimately granted. If ever there were a case where it may be presumed that the examiner did her job correctly, this is the one.

In an attempt to avoid Section 325(d) discretionary denial, the Petition strategically selects art that was either not part of a substantive rejection (*i.e.*, Bijl and Schaap) or was not included in the hundreds of references the examiner considered (*i.e.*, Kralovec, Komazawa, Nichols-I, Radianingtyas, and Wang). (Pet. at 68-71). As demonstrated below, the art raised in the Petition fares no better than the voluminous art already raised and considered during prosecution, and *inter partes* review should be denied.

IV. CLAIM CONSTRUCTION

The Petition proffers a construction of the term “the oil” to mean “the extracted microbial lipid.” (Pet. at 4). Under Petitioners' proposed construction,

the scope of the claims are such that the extracted microbial lipid has an anisidine value of 0.5 to 26.” (*Id.*). For the purpose of this Preliminary Response, DSM does not dispute this proposed construction. DSM reserves its right to propose alternative and additional 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.

VI. THE PETITION FAILS TO DEMONSTRATE A REASONABLE LIKELIHOOD THAT ANY CHALLENGED CLAIM IS UNPATENTABLE

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). All of the grounds raised in the Petition suffer the same fatal legal and evidentiary deficiency, namely, the purported combinations do not support a reasonable expectation of success in achieving an extracted microbial oil that has (i) the requisite amount of triglycerides, (ii) the requisite amount of DHA, and (iii) the requisite anisidine values. The Petition merely contends that the claimed anisidine values are “explicitly disclosed” in Schaap, Bijl, and Wang and are otherwise “an inherent

property of extracted oils from microbial sources.” (Pet. at 71). The Petition mixes and matches disparate teachings from the various prior art references and conclusorily contends that such combinations render the Challenged Claims obvious without any substantive consideration of the requisite reasonable expectation of success. The evidence of record does not support these contentions. For the reasons detailed below, the Petition should be denied.

A. Ground 1 Fails to Meet the Institution Threshold

Ground 1 of the Petition challenges the patentability of claim 3 based on the combination of U.S. Publ. No. 2005/0220958 (“Schaap”) and WO 2009/040676 (“Kralovec”). (Pet. at 8). Despite Petitioners’ contention that “[t]he Examiner[] fail[ed] to consider Schaap,” Schaap’s international counterpart—whose “disclosure is the same”—appears on the face of the ’578 patent and therefore was considered by the Examiner. (*Id.* at 68, 71; Ex. 1001 at page 3 (citing WO 2004/001021 A1); Ex. 1002 at 665 (considering WO 2004/001021)). The Examiner did not err in allowing claim 3 to grant over Schaap and the other prior art cited during prosecution.

Claim 3 recites an extracted microbial lipid comprising, *inter alia*, a triglyceride fraction that (i) is at least 70% by weight of the lipid fraction and (ii) contains at least 60% by weight of DHA. Claim 3 further recites that the oil (*i.e.*,

the extracted microbial lipid) has an anisidine value of 0.5 to 26. (MARA-1001). The Petition does not provide evidence sufficient to demonstrate that a PHOSITA would have reasonably expected to achieve such an extracted microbial lipid based on the combination of Schaap and Kralovec.

Consequently, *inter partes* review of claim 3 based on Ground 1 should be denied.

1. There Are Significant Differences Between Schaap/Kralovec and Claim 3

Schaap discloses “a process for pasteurizing microbial cells, the process comprising heating the cells at (a temperature comprising) from 40° C. to (60° C. or) 70° C. in no more than 30 minutes or heating the cells at a rate of at least 0.5° C./minute.” (MARA-1005 at [0014]). According to Schaap:

While the art gives pasteurization temperatures, there is no appreciation or discussion of the rate of heating, or that this parameter would be important and that a relatively rapid rate can provide benefits. Indeed, high heating rates are counter-intuitive as they might be expected to cause oxidation or otherwise degrade the PUFA or oil that can be extracted from the cells.

(*Id.*). Schaap discloses generally that its microbial oils may contain one or more PUFAs, including various linoleic and linolenic acids, ARA, EPA, and DHA. (*Id.* at [0045]-[0052]).

Schaap discloses three working examples, each involving the fermentation and pasteurization of microbial oils produced by *Mortierella alpina* containing about 40% of ARA when extracted with hexane, an organic solvent. (*Id.* at [0102]-[0132]). *M. alpina* is known to produce oils rich in ARA, not DHA. (MARA-1010 at 16, 30). In its working examples, Schaap provides experimental data showing that its pasteurization process can reduce anisidine values for oils that contain about 40% ARA. (MARA-1005 at [0102]-[0132]). Schaap does not disclose any experimentally determined anisidine values for any other pasteurized oils, including any oils containing 60% by weight of DHA in the triglyceride fraction.

Kralovec discloses a method by which an extracted oil can be enriched with PUFAs to increase the concentration of PUFA-containing triglycerides in the oil. (MARA-1030 at 2:25-31). According to Kralovec's method, an extracted microbial oil is reacted with a lipase enzyme to liberate saturated fatty acids from the triglyceride to produce free fatty acids and a mixture of mono-, di-, and triglycerides. (*Id.* at 6:1-26, 8:20-12:11). After separation of the free saturated

fatty acids, the resulting glycerides are reacted with added polyunsaturated fatty acids (in the 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). This purportedly results in an enriched oil that has an increased amount of polyunsaturated fatty acids compared to the starting extracted oil. (*Id.* at 35:20-25). Kralovec does not disclose the anisidine value of any of its oils.

Accordingly, the combination of Schaap and Kralovec does not provide any experimental data describing an extracted microbial oil that contains at least 60% by weight DHA in the triglycerides and also exhibits an anisidine value of 0.5 to 26, as recited in claim 3.

2. *The Petition Does Not Demonstrate a Reasonable Expectation of Success in Achieving Extracted Microbial Oils Having the Claimed Anisidine Value Based on Schaap/Kralovec*

As far as DSM can decipher, Petitioners make several arguments with respect to a purported reasonable expectation of success. For example, the Petition makes several general statements regarding alleged success in combining Schaap and Kralovec to achieve increased concentrations of DHA. (Pet. at 12,14-15). However, this is not sufficient to demonstrate a reasonable expectation of success in achieving *the claimed invention*—*i.e.*, an extracted microbial oil having (i) a

lipid fraction containing *at least 70% triglycerides* made up of *at least 60% DHA* and (ii) *an anisidine value of 0.5-26*.

With respect to the claimed range of anisidine values, the Petition offers only the following:

A PHOSITA would have understood from Schaap's disclosure that the combination would be expected to have anisidine values between 0.5 and 26. MARA-1005, [0082]-[0083]. Schaap discloses that preferable anisidine values of its oils range from 5 to 25. *Id.* Experimental results from Schaap demonstrate that its oils have anisidine values ranging from 5 to 15. *Id.* And Figure 5 also demonstrates that Schaap's exemplary extracted oils have anisidine values under 25. *Id.* Fig. 5, [0011], [0132].

(Pet. at 22). In effect, the Petition's reasonable expectation of success is based solely on Schaap's disclosure. Yet the Petition fails to address the significant differences between Schaap's disclosures and the claimed invention.

For example, the experimental data in Schaap is limited to microbial oil compositions obtained from a single microorganism, *Mortierella alpina*, that

produces about 40% of ARA, not the claimed concentration of DHA. (MARA-1005, at EXAMPLES 1-3). As noted above, in relation to oxidative stability, ARA and DHA are vastly different. Due to DHA's increased level of unsaturation, DHA is twice as oxidizable as ARA and exhibits a nearly 70% increase in its relative oxidation rate. *See* Section II.D, *supra*. And although Schaap generally discloses "preferred" anisidine values of its microbial oils, (*id.* at [0083]), Schaap does not disclose experimental data for any microbial oil that contains 60% by weight DHA in the triglyceride fraction, much less one that also meets the claimed anisidine value. Nor does it specifically tie any preferred anisidine value to an oil composition containing 60% of DHA in the triglyceride fraction. In fact, Schaap discloses that its oils may contain a number of other PUFAs, all of which are more oxidatively stable than DHA. (MARA-1005 at [0045]-[0052]).

Schaap even acknowledges that its pasteurization process is "counter-intuitive" because its "high heating rate . . . might be expected to cause oxidation or otherwise degrade the PUFA[.]" (MARA-1005 at [0014]). Yet Schaap does not provide any disclosures or experimental data that would have led a PHOSITA to reasonably expect Schaap's pasteurization process to successfully achieve the claimed anisidine values across all PUFAs and PUFA concentrations, much less when performed on an extracted microbial oil containing at least 60% by weight

DHA in the triglyceride fraction. Not surprisingly, during prosecution of Schaap, the Patent Office determined that Schaap's "method of pasteurizing microbial cells or organisms *may or may not* result in the microbial oil[s]" disclosed and claimed therein. (Ex. 2003 at 2 (emphasis added)). This is contrary to the Petition's contention that the claimed range of anisidine values is inherent to the disclosure of Schaap, which itself is bare attorney argument without any evidentiary support whatsoever. (Pet. at 71).

The Petition ignores these differences between the disclosures in Schaap and the claimed invention. Petitioner's declarant, Dr. Curtis, whose conclusory testimony on this point is wholesale copied and pasted from the Petition, similarly fails to address the expected differences in the oxidizability and oxidation rate—and their expected impact on anisidine values—of an oil containing 42% ARA (for which Schaap discloses limited experimental data) versus one containing 60% DHA in the triglyceride fraction (for which Schaap does not). (MARA-1003 at ¶¶ 101-103). Dr. Curtis's failure to do so is inexcusable given his acknowledgement that oxidative stability issues with PUFAs are a well-known problem in the field. (MARA-1003 at ¶ 48(c)(iii) ("PUFA containing oils are particularly susceptible to oxidation and hence to changes in [anisidine value].")). Accordingly, Dr. Curtis's assertion that "a PHOSITA would have understood and/or found obvious from

Schaap's disclosure that its compositions have anisidine values between 0.5 and 26" is conclusory and not supported by any facts. (MARA-1003 at ¶ 102).

Kralovec does not cure these deficiencies in Schaap. Kralovec does not disclose anisidine values at all. Additionally, the Petition does not address the extent to which a PHOSITA would have expected Kralovec's enrichment techniques to impact the anisidine value of the resulting enriched oil.

These shortcomings are fatal to Ground 1. There is no evidence in the Petition showing that a PHOSITA would have read the limited disclosures in Schaap and Kralovec to support a reasonable expectation of success in achieving the claimed invention. Schaap's "counter-intuitive" and "[un]expected" experimental data is limited to a microbial oil containing a PUFA (*i.e.*, ARA) that is substantially more oxidatively stable than the claimed DHA and present at a substantially lower concentration than the claimed "at least 60%."

Accordingly, the Petition fails to demonstrate the obviousness of claim 3. The combination of Schaap and Kralovec was improperly constructed based on hindsight bias using the elements of claim 3 as a roadmap.

3. *The Petition Does Not Demonstrate a Reasonable Expectation of Success in Achieving Extracted Microbial Oils Having the Claimed DHA Concentration Based on Schaap/Kralovec*

Ground 1 is deficient for at least another reason: the combination of Schaap and Kralovec does not disclose any oils that contain at least 60% by weight DHA in the triglyceride fraction.

Even after employing the enrichment techniques disclosed in Kralovec, Kralovec's techniques do not achieve oils containing 60% DHA in the triglyceride fraction. For example, the oil of Example 1 of Kralovec contains 43.8% DHA (*i.e.*, "22:6"). (MARA-1030 at Tbl. 6). This amount of DHA is similar to the amount of ARA disclosed in the Examples of Schaap. After Kralovec's enrichment techniques, the amount of DHA in the triglyceride fraction falls below the claimed minimum of 60% under all re-esterification conditions. (MARA-1030 at Tbl. 8.2). Consequently, a PHOSITA would not reasonably expect the Schaap/Kralovec combination to provide an extracted microbial oil containing at least 60% by weight DHA in the triglyceride fraction.

Implicitly acknowledging this deficiency in the Schaap/Kralovec combination, the Petition argues that Schaap discloses using *Thraustochytrium* microbial sources and that such microbial strains (*e.g.*, strain O thraustochytrid) were known to contain high levels (*e.g.*, 61%) of DHA, citing to the Nichols-I

reference (MARA-1009) and Lewis Thesis (MARA-1032). (Pet. at 19). It is unclear what is intended by the Petition.

To the extent the Petition is contending that the Schaap/Kralovec combination inherently discloses the claimed 60% DHA threshold, it is mistaken. Schaap, which has a priority date three years before Nichols-I, does not disclose the strain O thraustochytrid of Nichols-I, and not all thraustochytrid strains produce 60% DHA in the triglyceride fraction. For example, the thraustochytrid Strain SR21 disclosed in Yaguchi (MARA-1031) produces at most 35% DHA in the triglycerides (assuming *in arguendo* that 100% of the neutral lipids in Yaguchi are in the form of triglycerides). (MARA-1031 at 1432 (“Neutral lipids were composed of 35% DHA[.]”). Similar results were observed with *Thraustochytrium* sp. Strain KK17-3 in Huang, which produced less than 30% DHA in the triglycerides. (MARA-1028 at Tbl. 4 (28.2% DHA in neutral lipids). Thus, production of 60% DHA in the triglyceride fraction is not an inherent property of the *Thraustochytrium* microbial strains disclosed in Schaap.

To the extent the Petition is contending that the 60% threshold would have been obvious over the Schaap/Kralovec combination further in view of Nichols-I and/or Lewis, it is again mistaken. **First**, 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 Lewis as a “printed publication.”

In any event, Lewis does not disclose anisidine values for any of its microbial oils or disclose how much of its measured DHA resides in the triglyceride fraction versus, for example, the phospholipid fraction. Additionally, reflecting graduate-level, academic research, Lewis does not demonstrate that any of the microbial strains therein were publicly available as of the '578 patent. Nor

does the Petition provide any motivation to combine Lewis with Schaap and Kralovec.

Second, the Petition does not provide any explanation whatsoever—much less a rational underpinning—as to why a PHOSITA would have selected strain O of Nichols-I to combine with the various teachings of Schaap and Kralovec. This omission is particularly troubling given that Nichols-I does not disclose (1) how much of its DHA is in triglyceride form, (2) what the anisidine value of its oil is, (3) the conditions under which its fermentations were performed, (4) where and how strain O was isolated, (5) to what genus and species of thraustochytrid strain O belongs, or (6) even whether strain O has been deposited in an appropriate depository such that it is deemed “publicly available” under the law. Nichols-I just states that its oil contains 61% DHA as a percentage of total fatty acids. The Petition fails to provide any motivation to combine Nichols-I with the Schaap/Kralovec combination as well as evidence supporting any reasonable expectation of success in achieving the claimed invention based on the combination of Schaap/Kralovec and Nichols-I. The only reason Ground I discusses the Nichols-I's thraustochytrid Strain O is because it purportedly produces an oil with 61% DHA based on total fatty acids. The selection of Nichols-I is based on classic hindsight bias.

Accordingly, Ground 1 fails to demonstrate the obviousness of claim 3.

B. Ground 2 Fails to Meet the Institution Threshold

Ground 2 challenges the patentability of claims 1-7 based on the combination of Schaap and U.S. Publ. No. 2004/0161831 (“Komazawa”, MARA-1015). Ground 2 suffers the same deficiencies as Ground 1 above. The Petition fails to support a reasonable expectation of success in achieving claims 1-7 of the ’578 patent based on the combination of Schaap and Komazawa. Consequently, *inter partes* review of claims 1-7 based on Ground 2 should be denied.

1. Schaap and Komazawa Differ Substantially From the Claimed Invention

Ground 2 relies on the very same disclosures in Schaap as identified in Ground 1. Ground 2 substitutes Komazawa for Kralovec—presumably because Kralovec’s methods produce oils that contain far more than the 6% DPA recited in Claims 1-2 and 4-7. (*See, e.g.*, MARA-1030 at Tbl. 8.2 (disclosing re-esterified triglyceride fractions containing 17.8%, 16.8%, and 16.5% DPA, 22:5)). According to the Petition, “a PHOSITA would have been motivated to apply Komazawa’s organism culturing techniques to Schaap’s teachings” for several general reasons. (Pet. at 28-29). However, the Petition does not identify with particularity which of Komazawa’s culturing techniques should be combined with

Schaap. *See* 35 U.S.C. § 312(a)(3) (requiring Petition to identify grounds and supporting evidence “with particularity”).

As far as DSM can decipher from the Petition, Ground 2 relies on the microbial fermentations described in Examples 2 and 5 of Komazawa. (Pet. at 32-33 (citing MARA-1015 at [0108], [0116], Fig. 3). 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). (MARA-1015 at [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 5). Agitation culture was conducted for 40 hours ***with aeration at 500 rpm***. (MARA-1015 at [0094]). pH was not regulated in Komazawa's 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. (*Id.*). 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]).

Example 5 is similar to Example 2 except that pH was controlled at 4.5, 7.5, and 8.0. (*Id.* at [0115]-[0116]). At pH 7.5, the resulting oil contained less than 40% DHA in the triglycerides. (*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. Komazawa does not disclose how much of the oils in these examples are made up of the triglyceride fraction.

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]). 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 8.0, there is nothing to indicate that the triglycerides make up at least 70% by weight of that oil.

The same is true for a fermentation run under highly acidic conditions such as a pH of 4.5—where cellular growth would be expected to be inhibited significantly. (*See, e.g.,* MARA-1010 at 89 (noting growth profile of *thraustochytrids* depends on initial pH) (citing Ex. 2004); *see also* MARA-1010 at 67 (noting EPA production in strains was optimal at pH 7.0)). 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. 2004 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.

Notably, as explained above, Komazawa discloses fermentations that implement rigorous agitation and aeration at 500 rpm and organic solvent extractions—*i.e.*, oxidative conditions—but does not disclose anisidine values for any of its microbial oils.

2. The Petition Does Not Demonstrate a Reasonable Expectation of Success in Achieving Extracted Microbial Oils Having the Claimed Anisidine Values Based on Schaap/Komazawa

With respect to the anisidine values recited in the Challenged Claims, the Petition incorporates by reference (i) the arguments set forth in Ground 1 with respect to the Schaap/Kralovec combination and (ii) conclusory testimony from Petitioners' declarant through bald citation to Paragraphs 134-136 of MARA-1003 without any analysis whatsoever:

[1d]

See §III.A.4[3d], *supra*. MARA-1003, ¶¶134-136.

(Pet. at 33). This is improper procedurally and substantively.

Procedurally, “[a]rguments must not be incorporated by reference from one document into another document.” 37 C.F.R. § 42.6(a)(3). By doing so here, Petitioner afforded themselves an improper end-run around the word limit for the Petition.⁴ Consequently, Dr. Curtis’s opinions set forth in Paragraphs 134-136 of his declaration should not be considered.

Substantively, the Schaap/Komazawa combination of Ground 2 is significantly different from the Schaap/Kralovec combination of Ground 1. In Ground 1, the teachings of Kralovec were used to enrich an extracted microbial oil that had already been subjected to Schaap’s fermentation, pasteurization, and extraction processes. Here, the teachings of Komazawa are being used to produce a microbial oil that can then be subjected to the pasteurization techniques disclosed in Schaap. Komazawa does not disclose a post-extraction enrichment process like Kralovec in which PUFA concentrations are increased in the triglycerides after initial extraction. Example 4 of Komazawa discloses increasing the concentration

⁴ Petitioners also afforded themselves an end-run around the word count limit by removing spaces between paragraph symbols and numbers throughout the Petition. *See Tesla, Inc. v. Unicorn Energy GmbH*, IPR2022-00110, Paper 19, at *10 (P.T.A.B. Feb. 17, 2022) (noting “better practice would be to use spaces between paragraph symbols and paragraph numbers”).

of PUFAs in its oil by selectively hydrolyzing the saturated fatty acids (MARA-1015 at [0112]-[0114]), but this forms 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)).

Because Ground 2 relies on the same arguments as Ground 1 with respect to the reasonable expectation of success in achieving an oil high in DHA content but having an anisidine value between 0.5 and 26, Ground 2 fails for the very same reasons. *See* Section VI.A.2, *supra*. The Petition does not provide any evidence demonstrating that the extracted microbial oils disclosed in Komazawa, which are cultured under highly aerobic and oxidative conditions and extracted with an organic solvent, would reasonably be expected to exhibit the claimed anisidine values when subjected to Schaap's pasteurization process. Again, the Petition ignores the significant differences in oxidative stability of ARA (for which Schaap provides limited experimental anisidine values) and DHA (for which Schaap and Komazawa, either alone or in combination, does not). This failure is notable here given that Komazawa expressly discloses that its fermentations are carried out under agitation and aeration at 500 rpm for 40 hours and extracted with an organic solvent—conditions known to promote oxidation of DHA.

Without knowing the anisidine values of the extracted microbial oils produced in Komazawa and the extent to which Schaap's pasteurization technique can reduce those anisidine values in a high-concentration DHA-based oil, a PHOSITA would have no reasonable basis to expect success in achieving the claimed invention through the combination of Komazawa and Schaap. Not surprisingly, Petitioners and their declarant instead contend that the claimed anisidine values are inherent to Schaap's disclosure. (MARA-1003 at ¶ 136 ("A PHOSITA would have understood from Schaap's disclosure that the combination would have anisidine values between 0.5 and 26."); Pet. at 71 (asserting that Schaap "discloses that anisidine values under 25 were an inherent property of extracted oils from microbial sources"). As noted above, the Patent Office has held otherwise, noting that Schaap's pasteurization technique "may or may not" produce the compositions in Schaap. (Ex. 2003 at 2).

In any event, a proper inherency analysis requires consideration of whether the extracted microbial oils produced according to the combination of Schaap and Komazawa would necessarily exhibit the claimed anisidine values. *See Par Pharm., Inc. v. Twi Pharms., Inc.*, 773 F.3d 1186, 1195 (Fed. Cir. 2014) ("[T]he concept of inherency must be limited when applied to obviousness, and is present only when the limitation at issue is the 'natural result' of the combination of prior

art elements.”). On this point, aside from the unsupported and conclusory testimony of Dr. Curtis, the Petition is silent. It therefore fails to meet the “high standard” of establishing that the combination of Schaap and Komazawa inherently discloses the claimed anisidine values. *Id.* at 1195-96.

The Petition fails to demonstrate a reasonable likelihood that claim 1 and its dependent claims are unpatentable over the combination of Schaap/Komazawa. According to the Petition, the patentability of claims 2 and 3 rise and fall with claim 1. (*See* Pet. at 33-34 (correlating elements of claim 1 with those of claims 2 and 3). Because the Petition fails with respect to claim 1 (and its dependent claims), it also fails with respect to claims 2 and 3.

C. Ground 3 Fails to Meet the Institution Threshold

Ground 3 challenges the patentability of claims 1-7 based on the combination of WO 97/37032 (“Bijl”), the microbial strain O in Nichols-I (MARA-1009), and Schaap. (Pet. at 35-58). Despite Petitioners’ contention that the examiner failed to consider Bijl and Schaap, both Bijl and Schaap’s international counterpart—whose “disclosure is the same”—are listed on the face of the ’578 patent and were expressly considered by the Examiner. (*Id.* at 68, 71; Ex. 1002 at 665 (considering WO 2004/001021), 920 (considering WO 1997/037032)).

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 '578 patent. Furthermore, the Petition fails to support a reasonable expectation of success in achieving claims 1-7 of the '578 patent based on the combination of Bijl, Nichols-I, and Schaap. Consequently, *inter partes* review of claims 1-7 based on Ground 3 should be denied.

1. The Petition Fails to Identify Ground 3 With Particularity

Although Ground 3 purports to be based on the combination of Bijl, Nichols-I, and Schaap, it goes far beyond those references. As summarized in the following chart, Ground 3 identifies numerous prior art references to support disclosure of the various claim elements:

Element	Prior Art Cited for Disclosure	Petition Pages
[Ipre]	MARA-1008 (Bijl) MARA-1018 (Singh)	43-44
[Ia]	MARA-1008 (Bijl) MARA-1005 (Schaap) MARA-1018 (Singh)	44-45

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Element	Prior Art Cited for Disclosure	Petition Pages
[Ib]	MARA-1009 (Nichols-I) MARA-1018 (Singh) MARA-1020 (Nichols-II) MARA-1032 (Lewis Thesis) MARA-1015 (Komazawa) MARA-1008 (Bijl) MARA-1017 (Apt)	45-48
[Ic]	MARA-1008 (Bijl) MARA-1009 (Nichols-I) MARA-1020 (Nichols-II) MARA-1018 (Singh) MARA-1032 (Lewis Thesis)	48-50
[Id]	MARA-1008 (Bijl)	50-51
[Ie]	MARA-1008 (Bijl) MARA-1005 (Schaap)	51-56

In total, this represents more than 400 unique combinations of prior art disclosures.

Aside from Bijl, Nichols-I, and Schaap, the Petition does not provide any motivations to combine with respect to Singh (MARA-1018), Nichols-II (MARA-1020), the Lewis Thesis (MARA-1032) (which is not prior art as explained in Section VI.A.3, *supra*), Komazawa (MARA-1015), or Apt (MARA-1017). (Pet. at 38-43).

Accordingly, Ground 3 should be limited to the combination of Bijl, Nichols-I, and Schaap.

2. 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 differs significantly from the other grounds raised in the Petition. Ground 1 modifies a pasteurized microbial oil disclosed in Schaap using the enrichment method disclosed in Kralovec. Ground 2 subjects the microbial oils produced in Komazawa to the pasteurization process disclosed in Schaap. And as explained in Section VI.D, *infra*, Ground 4 subjects the microbial oil compositions disclosed in Radianingtyas to the purification process disclosed in Wang.

Unlike all the other grounds, 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 38-39 (emphasis added)). In other words, strain O in Nichols-I is being *used* as the microbial source in Bijl’s fermentation and extraction process. 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 is not surprising because Nichols-I says very little about this microorganism or the conditions under which its purported oil was produced:

Representative fatty acid profiles for selected Australian thraustochytrids recently isolated and maintained by CSIRO are shown in Table 3. 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 '578 patent.

Nichols-I does not disclose any identifying information with respect to strain O such as its genus and species or any 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 fatty acid profiles “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 '578 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 '578 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 1-7 based on Ground 3 should be denied for this reason alone.

3. *The Petition Does Not Demonstrate a Reasonable Expectation of Success in Achieving the Claimed Invention Based on Bijl/Nichols-I/Schaap*

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 Schaap.

Nichols-I and Schaap 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).

Bijl discloses only one working example in which anisidine values for an oil were measured. (*Id.* at 49-50, EXAMPLE 23). This oil was produced via fermentation using *Mortierella alpina*, the same type of microorganism disclosed in the working examples of Schaap that is known to produce oils rich in ARA.

However, Bijl does not disclose any fatty acid profile for any of its fermentations using *Mortierella alpina*, including the fermentation on which the anisidine values were measured. Accordingly, a PHOSITA would not know the amount of ARA in this example.

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 Schaap's preferred microorganisms (*see* Ex. 1005 at [0054])—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. (*Id.* at 45, 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 threshold of 50%, 40%, and 60% in claims 1, 2, and 3, respectively. (*Id.*). Bijl does not disclose the anisidine value of this or any other DHA-containing oil.

The Petition contends that “[a] PHOSITA would . . . have reasonably expected success in combining” Bijl, Nichols-I, and Schaap for a hodge-podge of purported reasons:

- Bijl, Nichols-I, and Schaap all relate to the creation of microbial lipids using culturing techniques;
- All three references teach the same sources of microbial lipids;
- All three teach that their desired product is one of high enough quality for use in the human diet; and
- Bijl and Schaap disclose that their processes are compatible with a wide range of natural sources, including thraustochytrids, which are disclosed in Nichols-I.

(Pet. at 40, 43). 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, Nichols-I, and Schaap 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 with specific anisidine values. And there are certainly a multitude of extracted 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 and Schaap are 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 [DPA and DHA] 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. 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. But Bijl discloses culture conditions for a dinoflagellate microorganism (*i.e.*, *Crypthecodinium cohnii*), which is not a thraustochytrid like strain O of Nichols-I.

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, the claimed DPA levels, the claimed proportion of DHA to DPA, or the claimed anisidine values. 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 and proportions of DHA to DPA produced by strain O under other culture and extraction conditions.

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. 2005 at 582 (emphasis added)). Accordingly, at the time of the '578 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, pasteurization, and extraction conditions of Bijl and Schaap.

Moreover, the Petition argues Bijl discloses that the claimed anisidine values "are an inherent property of extracted oils from microbial sources." (Pet. at 71). This statement is not supported by any evidence and therefore is entitled to no weight. The only microbial oils in Bijl for which anisidine values are disclosed are a crude and refined version of an oil containing an unknown amount of ARA produced by *Mortierella alpina*. There is nothing in Bijl that teaches, suggests, or discloses, either alone or in combination with Nichols-I and Schaap, an extracted

microbial oil containing the claimed DHA and triglyceride levels and having the claimed anisidine value.

Finally, even if the Board considers the extraneous Singh (MARA-1018), Nichols-II (MARA-1020), the Lewis Thesis (MARA-1032), Komazawa (MARA-1015), and Apt (MARA-1017) references as part of Ground 3, none of these cure the deficiencies in Bijl, Nichols-I, and Schaap. They do not disclose or suggest an extracted microbial oil containing at least 70% triglycerides, the requisite concentrations of DHA and DPA, and anisidine values between 0.5 and 26, as recited in the Challenged Claims.

The Petition's conclusory reasons do not provide any rational underpinning as to why a PHOSITA would have reasonably expected to achieve the Challenged Claims based on Bijl, Nichols-I, and Schaap. The Petition therefore fails, and institution of Ground 3 should be denied.

D. Ground 4 Fails to Meet the Institution Threshold

Ground 4 challenges the patentability of claim 3 based on the combination of WO 2008/129358 ("Radianingtyas") and U.S. Publ. No. 2009/0118525 ("Wang"). The Petition fails to support a reasonable expectation of success in achieving claim 3 of the '578 patent based on the combination of Radianingtyas

and Wang. Consequently, *inter partes* review of claim 3 based on Ground 4 should be denied.

1. Radianingtyas and Wang Are Substantially Different From the Claimed Invention

Radianingtyas discloses the isolation, characterization, and classification of certain thraustochytrid microorganisms and their use in microbial fermentations to produce oils containing DHA, EPA, and DPA. (MARA-1007 at 1:22-26). Radianingtyas describes the isolation and characterization of a specific strain referred to as ONC-T18 as well as its performance in producing microbial oils under a variety of fermentation conditions. (*Id.* at 16:1-30, EXAMPLES 3-11). Under various fermentation conditions designed to optimize the production of DHA disclosed in Radianingtyas, this strain does not produce DHA in quantities greater than 40% by weight. Radianingtyas does not disclose any anisidine values for any microbial oils produced by its fermentation methods.

Wang discloses a specific method for purifying extracted marine oils such as fish oils. (MARA-1006 at [0021]). The method comprises contacting the oil with an adsorbent such as a clay to provide a mixture, heating the mixture up to about 210° C., and then removing the adsorbent from the mixture to provide a purified oil with reduced levels of compounds such as cholesterol. (*Id.* at [0075]).

2. *The Petition Misinterprets the Claim Language*

As an initial matter, the Petition confusingly contends as follows:

As discussed previously (*see* §III.A.2), since [3a] requires a triglyceride fraction of at least about 70 wt.% of the lipid fraction, the DHA content of at least 60 wt.% of such a triglyceride fraction (i.e., 70 wt.% of the lipid fraction) is expressed as the DHA content constituting at least 42 wt.% of the lipid fraction. MARA-1003, ¶285.

(Pet. at 63). **First**, this argument was not raised in Section III.A.2 of the Petition or anywhere else. **Second**, this statement is factually incorrect and potentially misleading because it does not account for DHA content that may be in the other portions of the lipid fraction (*e.g.*, phospholipids, monoglycerides, diglycerides, etc.). Moreover, a disclosure in the prior art of an oil containing 42% DHA does not necessarily meet claim 3. To illustrate, an oil that contains 100% triglycerides and 42% DHA in the triglycerides would be an oil containing 42% DHA but which does not fall within the scope of claim 3.

Accordingly, to the extent the Petition relies on it, this statement does not support the unpatentability of claim 3. Nor does disclosure of a microbial oil containing 42% DHA necessarily meet the requisite DHA concentration in claim 3.

3. *The Petition Does Not Demonstrate a Reasonable Expectation of Success in Achieving Extracted Microbial Oils Having 60% DHA and the Claimed Anisidine Value Based on Radianingtyas and Wang*

The Petition contends that a PHOSITA would have been motivated to apply Wang's method of eliminating and/or reducing undesirable compounds to Radianingtyas' oil compositions to yield a higher quality oil. (Pet. at 60-61). Thus, Ground 4 relies on the microbial oils produced in Radianingtyas that are then subjected to Wang's purification process.

The Petition contends that "[a] PHOSITA would have a reasonable expectation of success in combining Radianingtyas' and Wang's teachings to produce *an improved oil composition*" because they are in "the same field" and disclose obtaining different yields of fatty acids by "culturing marine microorganisms in differing conditions." (Pet. at 61-62 (emphasis added)). This is the only statement regarding the expectation of success when combining Radianingtyas and Wang, and it falls far short of complying with the proper legal standard. Claim 3 does not claim an "improved oil composition." It claims an extracted microbial lipid composition containing at least 70% triglycerides, at least 60% of which is DHA in the triglyceride fraction, and which has an anisidine value of 0.5-26. The Petition fails to demonstrate that any microbial oil produced according to Radianingtyas and purified according to Wang would reasonably be

expected to exhibit the claimed anisidine value as well as the claimed 60% by weight DHA threshold recited in claim 3.

First, the Petition contends that Radianingtyas discloses microbial oils containing up to 90% DHA. (Pet. at 64). 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 Petition does not identify any actual microbial oil, purified or not, that contains 90% DHA in the triglyceride fraction. Nor is one disclosed in Radianingtyas. Further, nothing in Radianingtyas suggests that a microbial oil with such a high concentration of DHA would be oxidatively stable enough to maintain an anisidine value within the claimed range even if in such hypothetically “purified” form.

Second, the Petition does not point to any microorganism disclosed in Radianingtyas that actually produces 60% DHA in the triglyceride fraction. Radianingtyas highlights strain ONC-T18 due to its growth characteristics and conducts numerous fermentations with this strain to optimize its oil production.

None of these fermentations produce an extracted microbial oil containing 60% DHA. 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. (MARA-1007 at 87-88, Tbl. 4). Example 9 performed similar fermentations with alternative carbon sources, which produced DHA at a maximum of 26% by weight. (*Id.* at 92, Tbl. 6). Similar results were shown in Example 11, which demonstrated DHA production in strain ONC-T18 to be between 13-30% by weight. (*Id.* at 94, Tbl. 7). Accordingly, 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 DHA in the claimed amount under any fermentation conditions disclosed in Radianingtyas. Dr. Curtis effectively concedes as much. (MARA-1003 at ¶ 261 (“[I]t is my opinion that the resultant lipids [in Radianingtyas] comprise from about 25 wt.% to about 40 wt.% of *n*-3 DHA[.]”))

Third, even if Radianingtyas is deemed to disclose an extracted microbial oil containing 60% DHA in the total lipid (*see* Pet. at 63-64), it would not reasonably be expected to contain 60% DHA in the total lipid, let alone in the triglyceride fraction, after undergoing Wang's purification process. As Wang explains:

High temperature can destroy EPA and DHA, especially in the presence of absorbents. As the temperature and time increased, the loss of EPA and DHA increased (see Table 5). There are about 6 to 7 wt.% EPA and 8 to 9 wt.% DHA losses in the cholesterol free oil . . . using the disclosed methods.

(MARA-1006 at [0155]). In other words, Wang's purification process decreases the amount of DHA in its oils by almost 10%, and an oil containing 60% DHA in the total lipid before Wang's purification process would be expected to contain much less after. The Petition and Dr. Curtis ignore this important disclosure in Wang. Although Wang suggests using a shorter treatment time "[t]o minimize losses of EPA and DHA[,]" (*Id.*), there is nothing in Wang demonstrating that shorter reaction times would reasonably be expected to result in the claimed DHA concentration or anisidine values when combined with Radianingtyas.

Fourth, the oil compositions for which Wang reports anisidine values after purification contain far less than 60% by weight of DHA. (MARA-1006 at Tbl. 4). For example, Table 4 provides anisidine values for an oil referred to as TG18/12, lot #3929, crude oil ("3929 Crude Oil") that has been purified under a variety of Wang's conditions. (*Id.*). 3929 Crude Oil is a crude triglyceride marine oil

containing about 18 wt.% EPA and only about 12 wt.% DHA. (*Id.* at [0146])). The claimed amount of at least 60% by weight DHA in the triglyceride fraction is about, or more than, ***5 times greater than*** the amount of DHA in Wang's total 3929 Crude Oil. There is nothing in the disclosure of Wang (either alone or in combination with Radianingtyas) that would lead a PHOSITA to reasonably expect that Wang's purification process could produce an oil that falls within the claimed range of anisidine values when it contains at least 60% by weight of DHA.

Without knowing the anisidine values of the extracted microbial oils produced in Radianingtyas and the extent to which Wang's purification technique can reduce anisidine values in a high-concentration DHA-based oil, a PHOSITA would have no basis to reasonably expect success in achieving the claimed invention through the combination of Radianingtyas and Wang. Not surprisingly, Petitioners instead contend that the claimed anisidine values are inherent to Wang's disclosure. (Pet. at 71 (asserting that Wang "discloses that anisidine values under 25 were an inherent property of extracted oils from microbial sources"))). However, this contention is not supported by any evidence and is nothing more than attorney argument entitled to no weight. Moreover, there is nothing in the disclosure of Wang that ties an anisidine value of 0.5-26 to any oil composition containing at least 60% DHA from a microbial source. Wang

discloses experimentally determined anisidine values of a fish oil with a substantially different fatty acid profile—one that contains much less DHA than claimed.

Finally, Ground 4 relies on Komazawa, Nichols-I, and the Lewis Thesis. (Pet. at 64). But none of these references cures the deficiencies of the Radianingtyas/Wang combination for the reasons already discussed with respect to Grounds 1-3. Indeed, none of these references disclose anisidine values for their oils. Nor does the Petition provide any explanation as to why a person of ordinary skill in the art would combine any of these references with Radianingtyas and Wang to achieve the claimed invention—other than hindsight bias based solely on the '578 patent.

Accordingly, the Petition fails to demonstrate that purifying the microbial oils disclosed in Radianingtyas with the process disclosed in Wang would reasonably be expected to successfully achieve the claimed invention. Once again, the Petition dissects claim 3 into its elements, purports to find those elements individually in Radianingtyas and Wang, and then conclusorily combines those disclosures without consideration of whether they would reasonably be expected to achieve the claimed invention. This analysis is legally and factually deficient, and *inter partes* review of claim 3 based on Ground 4 should be denied.

VII. RESERVATION OF RIGHTS

DSM believes the legal and evidentiary deficiencies highlighted in this Preliminary Response are dispositive and preclude institution of *inter partes* review of the '578 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.

VIII. CONCLUSION

The '578 patent granted after eight years of robust prosecution. The Petition provides no reason why the Patent Office should question its original determination that the Challenged Claims are patentable. The grounds in the Petition reconstruct the Challenged Claims from the purported prior art combinations in a manner that demonstrates improper reliance on hindsight bias. Each ground argues that the combination “discloses and/or render obvious” each claim element but does not consider the purported obviousness of the claimed invention as a whole. Moreover, the Petition largely ignores the requirement that a PHOSITA must have had a reasonable expectation of success in achieving the claimed invention in view of the purported combinations. As demonstrated above, the evidence set forth in the Petition fails to demonstrate that any of the combinations in Grounds 1-4 would have reasonably been expected to achieve the

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Challenged Claims. In view of these fundamental failures, *inter partes* review should be denied.

Dated: October 30, 2023

Respectfully submitted,

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

I hereby certify that this **PATENT OWNER'S PRELIMINARY RESPONSE** contains 12,320 words, as counted using Microsoft Word in accordance with 37 C.F.R. § 42.24(c) and inclusive of footnotes. This wordcount is less than the allotted 14,000 words permitted under 37 C.F.R. § 42.24(b)(1).

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CERTIFICATE OF SERVICE

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

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