IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

PRONOVA BIOPHARMA NORGE AS,	)	
	)	
Plaintiff,	)	
	)	
v.	)	Civ. No. 09-286-SLR
	)	
TEVA PHARMACEUTICALS USA, INC., PAR PHARMACEUTICAL, INC. and PAR PHARMACEUTICAL COMPANIES, INC.,	)	
	)	
Defendants.	)	

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OPINION

Dated: May 29, 2012
Wilmington, Delaware

ROBINSON, District Judge

I. INTRODUCTION

This action arises out of the filing of Abbreviated New Drug Applications ("ANDAs") by Teva Pharmaceuticals, USA, Inc. ("Teva") and Par Pharmaceutical, Inc. and Par Pharmaceutical Companies, Inc. (collectively, "Par") seeking to market versions of Lovaza® (omega-3-acid ethyl esters), used to treat hypertriglyceridemia. Plaintiff Pronova Biopharma Norge AS ("Pronova") is the holder of approved New Drug Application ("NDA") No. 021654 for Lovaza®. Pronova is the owner by assignment of U.S. Patent Nos. 5,656,667 ("the '667 patent") and 5,502,077 ("the '077 patent"), which are listed in the Food and Drug Administration's ("FDA's") publication titled "Approved Drug Products with Therapeutic Equivalence Evaluations" (known as the "Orange Book") for Lovaza®. (Civ. No. 09-286, D.I. 74 at ¶¶ 8, 11, 21, 24)

In March 2009, Pronova received notification from Teva that Teva had filed ANDA No. 91-208 with a Paragraph IV certification alleging that the '667 and '077 patents are invalid, unenforceable, and/or not infringed by Teva's generic erlotinib hydrochloride tablets. (*Id.* at ¶ 15) Pronova also received notification from Par that Par had filed ANDA No. 91-108 with a Paragraph IV certification as to the '667 and '077 patents. (Civ. No. 09-505, D.I. 78 at ¶ 17) On April 23, 2009, Pronova filed Civ. Nos. 09-286 and 09-305, alleging infringement of the '667 and '077 patents by Teva and Par, respectively. Teva and Par (collectively, "defendants") asserted defenses of noninfringement and invalidity. (Civ. No. 09-286, D.I. 96; Civ. No. 09-305, D.I. 99) The cases were consolidated.

The parties filed their respective claim construction briefing, and a seven-day

bench trial commenced March 29, 2011. The infringement and validity issues have been fully briefed post-trial. (D.I. 232, 233, 234) The 30-month statutory stay expired on or about May 10, 2012. (D.I. 208 at 2) On May 7, 2012, the court entered an order enjoining defendants from launching their generic products until the court's decision issued. (D.I. 243, *amended at* D.I. 244)

The court has jurisdiction pursuant to 28 U.S.C. §§ 1331, 1338(a) and 1400(b). Having considered the documentary evidence and testimony, the court makes the following findings of fact and conclusions of law pursuant to Fed. R. Civ. P. 52(a).

II. FINDINGS OF FACT AND CONCLUSIONS OF LAW

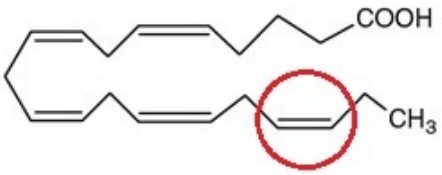
A. Technological Background

1. This case involves fatty acid compositions and pharmaceutical compositions containing fatty acids for the treatment or prophylaxis of hypertriglyceridemia, or high blood levels of triglycerides, a type of fat in the bloodstream that can contribute to the hardening or narrowing of arteries.[1] Eicosapentaenoic acid ("EPA"), docosahenaeonic acid ("DHA"), henicosapentaenoic acid ("HPA"), docosapentaenoic acid ("DPA") and arachidonic acid ("AA") are examples of omega-3 and omega-6 fatty acids at issue in this case.

2. EPA and DHA are "lipids," or fats, that can exist as free fatty acids, ethyl esters, or triglycerides. (D.I. 204 at 723:25-725:11) Fatty acids containing carbon-carbon double bonds are called "unsaturated" fatty acids. (D.I. 200 at 53:15-22) EPA and DHA may also be described as "omega-3 fatty acids" or "ω-3," which

[1] *See, gen.,* Triglycerides, MedlinePlus, *available at http://www.nlm.nih.gov/medlineplus/triglycerides.html* (last accessed May 2, 2012).

designates them as polyunsaturated fatty acids ("PUFAs") having a terminal double bond 3 carbons away from the methyl ($–CH_3$) end of the fatty acid chain. (D.I. 200 at 53:23-54:8)



Eicosapentaenoic Acid [EPA]

3. Alternatively, compounds may be referred to by the number of carbon atoms and double bonds. EPA, which contains 20 carbons and 5 double bonds, can be represented as C20:5. Likewise, DHA, which contains 22 carbons and 6 double bonds, can be denoted as C22:6. (D.I. 200 at 57:17-58:18)

4. High blood plasma levels of triglycerides are strongly associated with a risk of heart attack. (D.I. 203 at 545:25-546:10) For that reason, clinical practice guidelines recommend lowering triglyceride levels when they are elevated. (*Id.* at 545:25-546:10) Very high triglyceride levels can cause pancreatitis, an inflammatory condition of the pancreas that can be fatal if uncorrected. (*Id.* at 546:14-23) Hyperlipidemia is the medical term for several disorders of lipid metabolism that cause high levels of triglycerides or cholesterol. The standard classifications of hyperlipidemia denote the various patterns of blood lipid elevation, with Types IIb, IV and V involving high triglycerides. (*Id.* at 547:2-23)

B. Patented Technology

1. '667 patent

5. The '667 patent, entitled "Fatty acid composition," was filed June 6, 1995 and

issued August 12, 1997. Priority is claimed to United Kingdom application no. GB 8819110, filed August 11, 1988.

6. The specification explains that numerous prior art publications have reported that "dietary fish oil preparations containing omega-3 polyunsaturated fatty acids have an effect on serum cholesterol and blood platelet aggregation" by affecting the prostanoid system. ('667 patent, col. 1:37-45) The available data, however, conflicts on several points. (*Id.*) While EPA has been considered to be "the most important of the marine omega-3 polyunsaturated fatty acids partly because of its potent antiaggregatory action," recent reports showed that "EPA alone does not have a significant effect on hypertension" and EPA with DHA did not affect blood pressure. (*Id.*, col. 1:58-col.2:16) EPA does combat hypertension in pregnancy, however, which is thought to have a different biological cause. (*Id.* at col. 2:17-25) Further, while early studies indicated that fish oils lower total cholesterol and LDL-cholesterol (the "bad" cholesterol) and raise HDL-cholesterol (the "good" cholesterol), later studies revealed the opposite. (*Id.* at col. 2:28-39)

7. The inventors disclosed that they had now found that

> fatty acid compositions containing a high concentration, of at least 80% by weight, of omega-3 fatty acids, salts or derivatives thereof, where EPA and DHA are present in relative amounts of 1:2 to 2:1, and constitute at least 75% of the total fatty acids, ha[ve] a surprisingly advantageous effect on all the above mentioned risk factors for cardiovascular diseases, but especially a good effect on mild hypertension, hypertriglyceridemia and on the coagulation factor VII phospholipid complex activity. It lowers serum LDL-cholesterol, increases serum HDL-cholesterol, lowers serum triglycerides, lowers systolic and diastolic blood pressure and the pulse rate and lowers the activity of the blood coagulation factor VII-phospholipid complex. Although the detailed biological mechanisms for the effects of the compositions according to present application are not explicitly known,

> there are indications of a surprising synergism between the action of EPA and of DHA.

(*Id.* at col. 2:50-67) The compositions of the invention are also described as being well-tolerated, without severe side effects. (*Id.* at col. 3:1-3) An "especially preferred composition" according to the invention "comprises at least 90% by weight of long chain, polyunsaturated omega-3 fatty acids of which EPA and DHA constitute at least 85% by weight of the total fatty acids and are present in a ratio of EPA:DHA from 1:1 to 2:1 especially about 3:2." (*Id.* at col. 3:4-9)

8. The '667 patent also discloses a method for preparing the compositions of the invention, which results in a very low concentration of by-products and the significant reduction of contaminants. (*Id.* at col. 3:22-4:39)

9. It was determined that the test composition (described in table 1, below)

TABLE 1

	Typical product variation	Test Sample
C 20:4 omega-6	1–2	1.4
C 20:5 omega-3	40–60 wt %	54 wt %
C 21:5 omega-3	1–4 wt %	1.5 wt %
C 22:5 omega-3	1–3 wt %	2 wt %
C 22:6 omega-3	25–45 wt %	32.6 wt %
lower acids	3–8.5 wt %	7.5 wt %
unknown	1 wt %	1 wt %
sum Omega-3 FA		90.1 wt %
sum EPA + DHA		86.6 wt %
EPA:DHA		3.3:2

lowered total serum cholesterol "significantly" in patients with a total cholesterol over 7.0 mmol/liter and raised HDL cholesterol "significantly in the whole population." (*Id.*, col. 8:58-63) LDL cholesterol was also lowered (5-10%) in these patients but no significant effect was noted for patients with a total cholesterol less than 7.0 mmol/liter. (*Id.* at col.8:64-67)

10. Pronova asserts that Teva's ANDA infringes claims 20, 44 and 50 of the '667 patent; only claims 20 and 44 are asserted against Par. Claim 20 is a dependent claim, referring back to independent claim 14. Claims 14-20 are reproduced below.

> 14. A pharmaceutical mixed-fatty-acids composition in which
>
> a) at least 80% by weight of the composition is comprised of a combination of (all-Z omega-3)-5,8,11,14,17-eicosapentaenoic acid (EPA) and (all-Z omega-3)-4,7,10,13,16,19-docosahexaenoic acid (DHA) in a weight ratio of EPA:DHA of from 1:2 to 2:1 and
>
> b) (all-Z omega-3)-6,9,12,15,18-heneicosapentaenoic acid is present in an amount of at least one percent by weight.
>
> 15. The composition of claim 14, wherein at least 85% by weight of the composition is comprised of long chain omega-3 fatty acids.
>
> 16. The composition of claim 15, wherein the EPA constitutes 40 to 60% by weight of the composition and the DHA constitutes 25 to 45% by weight of the composition.
>
> 17. The composition of claim 16, wherein C 20:4 omega-6 fatty acid constitutes at least one percent by weight of the composition.
>
> 18. The composition of claim 17, wherein C 22:5 omega-3 fatty acid constitutes at least one percent by weight of the composition.
>
> 19. The composition of claim 16, wherein the (all-Z omega-3) -6,9,12,15,18-heneicosapentaenoic acid is present in an amount of from 1 to 4% by weight.
>
> 20. The composition of any of claims 17, 18, or 19, wherein the EPA and DHA are present in an EPA:DHA weight ratio of from 1:1 to 2:1.

Asserted claim 40 is also a dependent claim, which refers back to independent claim 28, as follows.

> 28. A pharmaceutical mixed-fatty-acids composition in which
>
> a) at least 80% by weight of the composition is comprised of a combination of (all-Z omega-3)-5,8,11,14,17-eicosapentaenoic acid (EPA) and (all-Z omega-3)-4,7,10,13,16,19-docosahexaenoic acid

(DHA) in a weight ratio of EPA:DHA of from 1:2 to 2:1 and

b) at least 3% by weight of the composition is comprised of omega-3 fatty acids other than EPA and DHA that have 20, 21, or 22 carbon atoms.

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30. The composition of claim 28, wherein at least 85% by weight of the composition is comprised of long chain omega-3 fatty acids.

31. The composition of claim 30, wherein the EPA constitutes 40 to 60% by weight of the composition and the DHA constitutes 25 to 45% by weight of the composition.

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38. The composition of claim 31, wherein (all-Z omega-3)-6,9,12,15,18-heneicosapentaenoic acid is present in an amount of at least one percent by weight.

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40. The composition of claim 38, wherein the (all-Z omega-3)-6,9,12,15,18-heneicosapentaenoic acid is present in an amount of from 1 to 4% by weight.

Finally, claim 50, asserted against Teva, depends from claim 49, which reads:

49. A pharmaceutical mixed-fatty-acids composition in which

a) at least 90% by weight of the composition is comprised of long chain, polyunsaturated, omega-3 fatty acids;

b) at least 80% by weight of the composition is comprised of a combination of (all-Z omega-3)-5,8,11,14,17-eicosapentaenoic acid (EPA) and (all-Z omega-3)-4,7,10,13,16,19-docosahexaenoic acid (DHA) in a weight ratio of EPA:DHA of from 1:1 to 2:1, with the EPA constituting 40 to 60% by weight of the composition and the DHA constituting 25 to 45% by weight of the composition;

c) at least 4.5% by weight of the composition is comprised of omega-3 fatty acids other than EPA and DHA that have 20, 21, or 22 carbon atoms;

d) from 1 to 4% by weight of the composition is comprised of (all-Z omega-3)-6,9,12,15,18-heneicosapentaenoic acid; and

> e) the composition is in oral dosage form and includes an effective amount of a pharmaceutically acceptable antioxidant.

Claim 50 further requires that the fatty acids of the composition of claim 49 are present in ethyl ester form.

2. '077 patent

15. The '077 patent is related to the '667 patent; both patents are continuations of a common application (U.S. Patent Application No. 389,902 ("the '902 application"))[2] and, therefore, share the same specification. The '077 patent was filed on June 23, 1992 and issued March 26, 1996. As with the '667 patent, priority is claimed to August 11, 1989.

16. Pronova asserts that defendants' ANDAs infringe claim 9 of the '077 patent. Claim 9 is a dependent claim that incorporates the limitations of "any of [dependent] claims 5, 6 or 7," and claims 5, 6 and 7 further depend on claims that reach back through their dependency to independent claim 1 of the '077 patent. Claim 1 reads as follows.

> 1. A method for the treatment or prophylaxis of hypertriglyceridemia in a human patient, which comprises orally administering to the patient a pharmaceutical composition in which the active ingredients consist essentially of a mixture of fatty acids of which at least 80% by weight is comprised of a combination of (all-Z omega-3)-5,8,11,14,17-eicosapentaenoic acid (EPA) and (all-Z omega-3)-4,7,10,13,16,19-docosahexaenoic acid (DHA) in a weight ratio of EPA:DHA of from 1:2 to 2:1, said composition being administered in amounts providing a daily dosage of 1 to 10 grams of said mixture of fatty acids.

Each of claims 5-7 of the '077 patent incorporates the limitations of claim 4 which, in

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[2]While the '077 patent was filed directly from this application, the '667 patent issued from a second continuation application in the chain.

turn, incorporates the limitations of claim 3, and so on, through independent claim 1.

Thus, by reason of its dependency, claim 9 contains the following additional limitations:

- at least 85% by weight of the mixture of fatty acids is comprised of long chain omega-3 fatty acids (dependent claim 2);
- the EPA constitutes 40 to 60% by weight of the mixture of fatty acids and the DHA constitutes 25 to 45% by weight of the mixture of fatty acids (dependent claim 3);
- the EPA and DHA are present in the composition in an EPA:DHA weight ratio of from 1:1 to 2:1 (dependent claim 4).

Additionally, at least one of the following limitations must also be present:

- at least 4.5% by weight of the mixture of fatty acids is comprised of fatty acids other than EPA and DHA that have 20, 21, or 22 carbon atoms (dependent claim 5);
- at least 3% by weight of the mixture of fatty acids is comprised of omega-3 fatty acids other than EPA and DHA that have 20, 21, or 22 carbon atoms (dependent claim 6)
- at least 1% by weight of the mixture of fatty acids is comprised of (all-Z omega-3)-6,9,12,15,18-heneicosapentaenoic acid (dependent claim 7)

Finally, claim 9 itself requires that the fatty acids are present in the composition in ethyl ester form.

3. Claim summary

17. For ease of reference, the court reproduces below defendants' chart summarizing the asserted claims' requirements.

	'077 Patent Composition of Claim 9	'667 Patent Claim 20	'667 Patent Claim 44	'667 Patent Claim 50
EPA + DHA at least 80% by weight	●	●	●	●
Ratio (at least 1:2 to 2:1 or 1:1 to 2:1)	●	●	●	●
40-60% EPA, 25-45% DHA	●	●	●	●
At least 3% other C20, C21 or C22 ω-3	●	N/A	●	N/A
At least 4.5% other C20, C21 or C22 ω-3	N/A	N/A	N/A	●
At least 1% C21:5 (HPA)	●	●	N/A	N/A
From 1%-4% C21:5 ω-3 (HPA)	N/A	N/A	N/A	●
At least 1% C22:5 ω-3 (DPA)	N/A	●	N/A	N/A
At least 1% C20:4 ω-6 (AA)	N/A	●	N/A	N/A
At least 85%, 90% long chain ω-3	●	●	●	●
Ethyl Ester	●	N/A	●	●
Oral Dosage Form	●	N/A	N/A	●
Antioxidant (Tocopherol)	N/A	N/A	N/A	●

(D.I. 209 at 24)

C. Claim Construction

1. Standards

18. Claim construction is a matter of law. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1330 (Fed. Cir. 2005) (en banc). Claim construction focuses on intrinsic evidence - the claims, specification and prosecution history – because intrinsic evidence is "the most significant source of the legally operative meaning of disputed claim language." *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996); *Markman v. Westview Instruments, Inc.,* 52 F.3d 967, 979 (Fed. Cir. 1995) (en banc), *aff'd*, 517 U.S. 370 (1996). Claims must be interpreted from the perspective of one of ordinary skill in the relevant art at the time of the invention. *Phillips*, 415 F.3d at 1313.

19. Claim construction starts with the claims, *id.* at 1312, and remains centered

on the words of the claims throughout. *Interactive Gift Express, Inc. v. Compuserve*, *Inc.*, 256 F.3d 1323, 1331 (Fed. Cir. 2001). In the absence of an express intent to impart different meaning to claim terms, the terms are presumed to have their ordinary meaning. *Id.* Claims, however, must be read in view of the specification and prosecution history. Indeed, the specification is often "the single best guide to the meaning of a disputed term." *Phillips*, 415 F.3d at 1315.

2. Intrinsic evidence

a. Specification

20. The abstracts of the patents-in-suit describe a "[f]atty acid composition comprising at least 80% by weight of omega-3 fatty acids, salts or derivatives thereof[.]" (*See* '077 patent, abstract) The summary of the invention provides that

> [i]t has now been found that fatty acid compositions containing a high concentration, of at least 80% by weight, of omega-3 fatty acids, salts or derivatives thereof, where EPA and DHA are present in relative amounts of 1:2 to 2:1, and constitute at least 75% of the total fatty acids, has a surprisingly advantageous effect on all the above mentioned risk factors for cardiovascular diseases, but especially a good effect on mild hypertension, hypertriglyceridemia and on the coagulation factor VII phospholipid complex activity. . . .

(*Id.* at col. 2:50-58) The summary also provides that "[t]he analysis in % by weight was based on the ethyl esters even if other derivatives or salts or the acids themselves are part of the present invention." (*Id.* at col. 3:16-19)

b. Prosecution history

21. As noted previously, the patents-in-suit issued from continuations of the '902 application; the court's review of the relevant prosecution history begins there. Independent claim 1 of the '902 application was directed to a "[f]atty acid composition

comprising at least 80% by weight of omega-3 fatty acids" with specified relative amounts and weights for the EPA and DHA components. (D.I. 133 at JA-76) Dependent claims 7, 8 and 10 claimed compositions according to claim 1 "wherein the fatty acids are present in the form of pharmaceutically acceptable salts" (claim 7), "derivatives" (claim 8), or "ethyl esters" (claim 10). (*Id.* at JA-77) Dependent claim 9 depended from claim 8, and further required that "the derivative is an ester, especially an alkyl ester." (*Id.*) These claims were rejected as obvious in view of three prior art references, including U.S. Patent No. 3,158,541 to Sutherland ("Sutherland"). (*Id.* at JA-150-53) After removal of the "especially" language of dependent claim 9 (and other amendments) (*id.* at JA-158), the examiner maintained the obviousness rejection, and made the rejection final. (*Id.* at JA-213-14)

22. Thereafter, the inventors cancelled claim 1 and added a new claim 19, claiming

> [a] fatty acid composition for the treatment or prophylaxis of multiple risk factors for cardiovascular diseases, comprising at least 80% by weight of omega-3 fatty acids, whereof (all-Z)-5,8,11,14,17-eicosapentaeonic acid (EPA) C 20:5 and (all-Z)-4,7,10,13,16,19-docosahexaeonic acid (DHA) C 22:6 are present in relative amounts of from 1:2 to 2:1 and constitute at least 75% by weight of the total fatty acids.

(*Id.* at JA-228) Dependent claims 7 and 8 were amended to depend on new claim 19. (*Id.* at JA-229) The examiner maintained that the prior art disclosed pharmaceutical compositions containing eleanosanoic and docosahexanoic acid esters. (*Id.* at JA-232)

23. After a request for reconsideration, the examiner deemed further prosecution

necessary,[3] and issued a rejection of claims 7 to 10 as being: (1) "of improper dependent form for failing to further limit the subject matter of a previous claim;" and (2) "improperly dependent from claim 19 because claim 19 recites the acid, and claims 7 to 10 recite 'derivatives,' 'salts,' and 'esters.'" (*Id.* at JA-239) The examiner also stated that the term "'derivative(s)' is vague and indefinite because it can mean amides, as well as salts and esters and other undefined derivatives." (*Id.*)

24. Following a telephonic interview, the examiner noted that the "composition claims will be amended to include other omega fatty acids, and declarations will be presented to overcome the prior art." (*Id.* at JA-244) The applicants proceeded to cancel claim 19 in favor of new claim 21, reciting:

> 21. A fatty acid composition for the treatment or prophylaxis of multiple risk factors for cardiovascular diseases, comprising at least 80% by weight of **omega-3 fatty acids or pharmaceutically acceptable salts or other derivatives of said acids**, whereof (all-Z)-5,8,11,14,17-eicosapentaeonic acid (EPA) C 20:5, or a pharmaceutically acceptable salt or other derivative of said acid, and (all-Z)-4,7,10,13,16,19-docosahexaeonic acid (DHA) C 22:6, **or a pharmaceutically acceptable salt or other derivative of said acid**, are present in relative amounts of from 1:2 to 2:1 and constitute at least 80% by weight of the total fatty acids or pharmaceutically acceptable salts or other derivatives of said acids, and omega-3 fatty acids other than said EPA and DHA are present in an amount of at least 1.5% by weight of the total fatty acids.

(*Id.* at JA-247) (emphasis added) The dependent claims were amended to depend from claim 21 (rather than 19). (*Id.* at JA-248) In their remarks, the applicants stated that,

> [i]n view of the rejection of claims 7-10 under the fourth paragraph of

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[3]The applicants pointed out in their Request for Reconsideration that the examiner had previously indicated that claims 11, 13 and 14 would be allowable if rewritten in independent form; the newly-presented independent claims (13, 19, 20) were again rejected. (D.I. 133 at JA-233)

> 35 U.S.C. [§] 112, each of new claims 21 and 22[4] recites pharmaceutically acceptable salts or other derivatives of the acids (**in addition to the free acids as originally recited**), thus rendering the rejection moot. The salts and derivatives are set forth in claims 7-10.

(*Id.* at JA-249) (emphasis added)

25. A final office action was then issued, in which the examiner maintained the §103 rejection in view of Sutherland, and added an anticipation rejection based on a previously-cited obviousness reference. (*Id.* at JA-336) The examiner also maintained the §112 rejection over the term "derivatives." (*Id.* at JA-337) The examiner explained that the "[a]pplicants argue that the term 'derivatives' is defined and claims stating 'derivatives of fatty acids' have been allowed in the past. However, in the instant specification, what the possible derivatives are have not been defined[.]" (*Id.*)

26. In an amendment after final rejection, the applicants amended their claims to the esters of claim 9. (*Id.* at 359-60 ("Applicants have now decided to limit the derivatives to the esters.")) On obviousness, a declaration was submitted which purported to demonstrate unexpected superior results of the DHA and EPA concentration of the invention. (*Id.* at JA-363) An advisory action was issued in which only the obviousness rejection in view of Sutherland was maintained by the examiner. (*Id.* at JA-382) After further prosecution, the applicants filed a notice of appeal, but ultimately abandoned the '902 application in favor of continuation application no. 07/902,500 ("the '500 application"), filed June 23, 1992. (*Id.* at JA-464-65, JA-468, JA-473-77) Also on June 23, 1992, a substitution of counsel was effected. (*Id.* at JA-478-

[4]Claim 22 was directed to a method of treatment of cardiovascular disease, not at issue here.

49)

27. On November 18, 1992, then-pending claims 2-8, 10, 16-18, and 21-22 in the '500 application were rejected by the examiner.[5] (*Id.* at JA-776-77) The claims remained rejected as obvious in view of Sutherland, and the examiner also stated with respect to §112 that

> [c]laims 2 to 8, 21 and 22 are rejected . . . as being indefinite . . . . The term "derivative" is unduly functional because the type of derivative has not been defined. Do applicants intend to include heavy metal salts and amides?

(*Id.* at JA-779)

28. In response, the applicants noted confusion over the rejection given that "the word 'derivative' did not appear in any of those claims[.]" (*Id.* at JA-828) Notwithstanding, the applicants cancelled all pending claims and substituted new claims 23-78, which also did not utilize the term "derivative." (*Id.*) New claim 23 read as follows:

> 23. A mixed-fatty-acids composition for the treatment or prophylaxis of multiple risk factors for cardiovascular diseases in which
> a) at least 80% by weight of the composition is comprised of omega-3 fatty acids,
> b) at least 80% by weight of the total fatty acid content of the composition is comprised of a combination of (all-Z omega-3)-5,8,11,14,17-eicosapentaeonic acid (EPA) and (all-Z)-4,7,10,13,16,19-docosahexaeonic acid (DHA) in a weight ratio of EPA:DHA of from 1:2 to 2:1, and
> c) omega-3 fatty acids other than EPA and DHA are present in an amount of at least 1.5% by weight of the total fatty acids.

(*Id.* at JA-803-04) New dependent claims further required that "the fatty acids are

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[5]There does not appear to be a resuscitation of claims prior to this office action. Presumably, the claims carried over from the '902 application, although the examiner's rejection (discussed *infra*) reveals some confusion in this regard.

present in the form of pharmaceutically acceptable salts" (claim 29), "an ester" (claim 30), and "ethyl esters" (claim 31). (*Id.* at JA-805) New independent claim 34 was also added, and claimed as follows:

> 34. A mixed-fatty-acids composition for the treatment or prophylaxis of multiple risk factors for cardiovascular diseases in which
> a) at least 80% by weight of the composition is comprised of a combination of (all-Z omega-3)-5,8,11,14,17-eicosapentaeonic acid (EPA) and (all-Z)-4,7,10,13,16,19-docosahexaeonic acid (DHA) in a weight ratio of EPA:DHA of from 1:2 to 2:1 and
> b) (all-Z omega-3)-6,9,12,15,18-heneicosaptentaeonic acid is present in an amount of at least one percent by weight.

(*Id.* at JA-806-07) New dependent claims 45-48, which depended from 24 or 34, further required that "the fatty acids are present in esterified form" (claim 45), "ethyl ester form" (claim 46), "salt form" (claim 47) and "free acid form" (claim 48). (*Id.* at JA-807-09)

29. As is custom, the applicants identified the support for their new claims in the specification, noting the locations of disclosure of the "use of the acids in esterified form," "ethyl ester form," "salt form" and the "free acid form." (*Id.* at JA-818) With respect to the lingering obviousness rejection based on Sutherland, the applicants noted, *inter alia*, that Sutherland teaches "the use of a mixed-fatty-acids composition" to treat hypercholesterolemia and "places no emphasis on any particular fatty acids[.]" (*Id.* at JA-819) Further, the applicants argued that "[a]ll of the present claims (23-78) differ from Sutherland in at least one particular [way]: They specify that at least 80% of the fatty acid content is comprised of a combination of EPA and DHA." (*Id.* at JA-820)

30. Subsequently, the applicants presented new claims 79-105 for prosecution. Independent claim 94 would eventually issue, unchanged, as claim 1 of the '077 patent. The claim reads:

> A method for the treatment or prophylaxis of hypertriglyceridemia in a human patient, which comprises orally administering to the patient a pharmaceutical composition in which the active ingredients consist essentially of a mixture of fatty acids of which at least 80% by weight is comprised of a combination of (all-Z omega-3)-5,8,11,14,17-eicosapentaenoic acid (EPA) and (all-Z omega-3)-4,7,10,13,16,19-docosahexaenoic acid (DHA) in a weight ratio of EPA:DHA of from 1:2 to 2:1, said composition being administered in amounts providing a daily dosage of 1 to 10 grams of said mixture of fatty acids.

31. In a subsequent office action, the examiner rejected the pending claims as anticipated and as obvious in view of U.S. Patent No. 5,130,611 to Cornieri et. al., disclosing at least a 69% mixture of EPA and DHA. (*Id.* at JA-989) After further prosecution, claims 94-105 were deemed allowable in view of evidence showing improved results in the treatment of hypertriglyceridemia. (*Id.* at JA-1049) The applicants canceled the remaining claims (*id.* at JA-1052) and the '500 application was allowed as the '077 patent (*id.* at JA-1058).

3. Discussion

32. Of pivotal import in this case is the court's construction of the term "fatty acid" as used in the claims of the '077 and '667 patents. The issue presented, specifically, is whether "fatty acid" includes free fatty acids, salts and derivatives such as esters.

33. The intrinsic evidence supports defining "fatty acids" as broader than "free acids" or "omega-3 fatty acids," as used in the claims. The structure of the claims of the '902 application support this broad interpretation of "fatty acids," insofar as the dependant claims required that "the fatty acids are present in the form of" derivatives, esters or salts. (D.I. 133 at JA-77) Claim 19 also used the term "total fatty acids" to

signify a broader class of compounds than "omega-3 fatty acids," which subgroup further includes EPA and DHA. Similar terminology was also repeated in '500 application claims 23 ("total fatty acids") and the dependent claims 24 or 34 (e.g., "the fatty acids are present in esterified form"). (*Id.* at JA-804, JA-807-09) Consequently, there is a presumption that "fatty acids" should be construed broadly. *See gen., Marine Polymer Techs., Inc. v. HemCon, Inc.*, 672 F.3d 1350, 1368 (Fed. Cir. 2012) ("Where a particular construction of an independent claim would nullify claims that depend from it, the doctrine of claim differentiation creates a presumption that such a construction is improper.") (citing *Liebel-Flarsheim Co. v. Medrad, Inc.*, 358 F.3d 898, 910 (Fed. Cir. 2004).

34. In arguing for a narrow construction, defendants emphasize that the examiner rejected claims 7 to 10 of the '902 application for improper dependency because "claim 19 recites the acid, and claims 7 to 10 recite 'derivatives,' 'salts,' and 'esters.'" (D.I. 119 at 7 (citing D.I. 133 at JA-239)) Claim 19 was drawn to a fatty acid composition comprising at least 80% "omega-3 fatty acids" where EPA and DHA is present in "at least 75% by weight of the total fatty acids." (D.I. 133 at JA-228) The examiner's primary concern was with the vagueness and redundancy of the term "derivative," and required that the claims "be amended to include **other fatty acids.**" (*Id.* at JA-244) (emphasis added) The applicants cured the dependency by amending the independent claim[6] to require at least 80% "omega-3 fatty acids **or** pharmaceutically acceptable salts or other derivatives of **said** acids," ergo, specific derivatives of "the

[6]By the substitution with new claim 21, and amending dependent claims 7-10 to depend therefrom.

[omega-3] **free acids** as originally recited." (*Id.* at JA-244, JA-248-49) (emphasis added) Later, the concern over "derivatives" was mooted by the applicants' selection of esters.

35. The foregoing supports a broad construction of "fatty acids," as the addition of "pharmaceutically acceptable salts or other derivatives of said [omega-3 fatty] acids" appears to have satisfied the examiner's request to amend the claims to include "other fatty acids." Where the specification distinguishes between the terms, it does so in the context of "omega-3 fatty acids" rather than "fatty acids" absent any qualifying terms. ('077 patent, col. 3:16-18; *see also id.* at abstract, col. 2:52 ("omega-3 fatty acids, salts **or** derivatives thereof") (emphasis added)) There is no clear disclaimer vis-a-vis "fatty acids," as was used in the "total fatty acids" limitation in claims 21 or 23 of the '500 application, or "fatty acids" as used in claim 94 (issuing as claim 1 of the '077 patent).

36. The court does not find defendants' evidence sufficient to rebut the presumption established by claim differentiation. *See Marine Polymer Techs.*, 672 F.3d at 1368 (construction of a term which renders claims meaningless is appropriate "only where a contrary construction is 'dictated'—i.e., compelled—by the written description or prosecution history") (citations omitted).

37. The court also notes extrinsic evidence consistent with its finding, as follows. Scientific and medical dictionaries customarily define a "fatty acid" broadly. *See* MCGRAW-HILL DICTIONARY OF SCIENTIFIC AND TECHNICAL TERMS 780 (6th ed. 2003) ("[a]n organic monobasic acid of the general formula $C_nH_{2n+1}COOH$ derived from the saturated series of aliphatic hydrocarbons"); DORLAND'S ILLUSTRATED MEDICAL DICTIONARY 693 (31st ed. 2007) ("any straight chain monocarboxylic acid, especially those naturally

occurring in fats"); *see also* Alan W. Cuthbert, *Fats*, THE OXFORD COMPANION TO THE BODY (Colin Blakemore and Shiela Jennett, ed., Oxford University Press 2001)[7] (describing fatty acids as "long chains of carbon atoms linked to a carboxyl (acidic) group").[8]

38. For the foregoing reasons, the court declines to limit "fatty acids" to the free fatty acid, ester or salt form as advocated by defendants, nor does the court find "fatty acids" to be indefinite, as asserted by defendants. (D.I. 209 at 44) Having declined to adopt defendants' construction, the court also declines to find the dependent claims of the '077 and '667 patents invalid for improper dependency under § 112, ¶ 4. (*Id.* at 43-44)

D. Infringement

1. Standards

39. A patent is infringed when a person "without authority makes, uses or sells any patented invention, within the United States . . . during the term of the patent." 35 U.S.C. § 271(a). A two-step analysis is employed in making an infringement determination. *See Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995). First, the court must construe the asserted claims to ascertain their meaning and scope. *See id*. Construction of the claims is a question of law subject to de novo review. *See Cybor Corp. v. FAS Techs.*, 138 F.3d 1448, 1454 (Fed. Cir. 1998). The

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[7]Available from Oxford Reference Online *at http://www.oxfordreference.com/views/ENTRY.html?subview=Main&entry=t128.e368*.

[8]Defendants' cited secondary reference is not inconsistent with the foregoing. (D.I. 119 at 5 (citing JA-5305))

trier of fact must then compare the properly construed claims with the accused infringing product. *See Markman*, 52 F.3d at 976. This second step is a question of fact. *See Bai v. L & L Wings, Inc.*, 160 F.3d 1350, 1353 (Fed. Cir. 1998).

40. "Direct infringement requires a party to perform each and every step or element of a claimed method or product." *BMC Res., Inc. v. Paymentech, L.P.*, 498 F.3d 1373, 1378 (Fed. Cir. 2007). "If any claim limitation is absent from the accused device, there is no literal infringement as a matter of law." *Bayer AG v. Elan Pharm. Research Corp.*, 212 F.3d 1241, 1247 (Fed. Cir. 2000). If an accused product does not infringe an independent claim, it also does not infringe any claim depending thereon. *See Wahpeton Canvas Co. v. Frontier, Inc.*, 870 F.2d 1546, 1553 (Fed. Cir. 1989). However, "[o]ne may infringe an independent claim and not infringe a claim dependent on that claim." *Monsanto Co. v. Syngenta Seeds, Inc.*, 503 F.3d 1352, 1359 (Fed. Cir. 2007) (quoting *Wahpeton Canvas*, 870 F.2d at 1552) (internal quotations omitted). A product that does not literally infringe a patent claim may still infringe under the doctrine of equivalents if the differences between an individual limitation of the claimed invention and an element of the accused product are insubstantial. *See Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 24, 117 S. Ct. 1040, 137 L. Ed. 2d 146 (1997). The patent owner has the burden of proving infringement and must meet its burden by a preponderance of the evidence. *See SmithKline Diagnostics, Inc. v. Helena Lab. Corp.*, 859 F.2d 878, 889 (Fed. Cir. 1988) (citations omitted).

41. Under 35 U.S.C. § 271(b), "[w]hoever actively induces infringement of a patent shall be liable as an infringer." To demonstrate inducement of infringement, the patentee must establish, first, that there has been direct infringement and, second, that

the alleged infringer had "knowledge that the induced acts constitute patent infringement." *Global-Tech Appliances, Inc. v. SEB S.A.*, 131 S. Ct. 2060, 2068 (2011). "Inducement requires evidence of culpable conduct, directed to encouraging another's infringement, not merely that the inducer had knowledge of the direct infringer's activities." *DSU Medical Corp. v. JMS Co., Ltd.*, 471 F.3d 1293, 1306 (Fed. Cir. 2006) (en banc in relevant part).

42. Under 35 U.S.C. § 271(c), a patentee must demonstrate that an alleged contributory infringer has sold, offered to sell or imported into the United States a component of an infringing product "knowing the same to be especially made or especially adapted for use in an infringement of such patent, and not a staple article or commodity of commerce suitable for substantial noninfringing use." Therefore, § 271(c) "require[s] a showing that the alleged contributory infringer knew that the combination for which [its] component was especially designed was both patented and infringing." *Aro Mfg. Co. v. Convertible Top Replacement Co.*, 377 U.S. 476, 488 (1964).

2. Discussion

43. There is no dispute that defendants' ANDA products are composed of fatty acid ethyl esters ("FAEEs"). Defendants' only noninfringement argument occurs under their proposed construction of "fatty acids" as excluding FAEEs. (D.I. 214)

44. Notwithstanding, as Pronova had the burden to prove infringement by a preponderance of the evidence, the court notes that it found convincing Pronova's evidence of infringement. Pronova presented testimony by Dr. Jonathan Curtis ("Curtis"), an associate professor in the analytical lipid chemistry group at the University of Alberta, Department of Agriculture, Food and Nutritional Sciences, and an expert in

analytical chemistry and the quantitative analysis of fish oil. The court also heard testimony by Dr. John Kane ("Kane"), Professor of Medicine at the University of California, San Francisco, Associate Director of the Cardiovascular Research Institute and Director of the Genomic Resource in Arteriosclerosis and Metabolic Disease, and an expert in the fields of lipid biology and lipid disorders.

45. Curtis compared Teva's ANDA product to the asserted claims and concluded that Teva's ANDA product directly infringes the asserted claims of the '667 patent and meets the composition limitations of the asserted claims of the '077 patent. (D.I. 200 at 65:10-19, 74:10-92:22; PTX-1240A (summary of supporting exhibits)) Curtis also compared Par's ANDA product to the asserted claims and concluded that Par's ANDA product will directly infringe the asserted claims of the '667 patent, and that Par's ANDA product will meet the composition limitations of the asserted claims of the '077 patent. (D.I. 201 at 129:8-137:15; PTX-1242A (summary of supporting exhibits))

46. With respect to indirect infringement, defendants' labels indicate that their products are intended for oral administration. (PTX-331 at TOMEG0005250; PTX-516 at PAR00004813-4814) Kane testified that Teva and Par's prescribing information for their generic products indicate that each is intended to be used to treat hypertriglyceridemia in patients with triglyceride levels of greater than or equal to 500 mg/dL and, thus, the proposed indications of defendants' generic products are encompassed by the claim language of "a method for the treatment or prophylaxis of hypertriglyceridemia in a human patient." (D.I. 201 at 162:3-164:3, 165:10-166:2) Furthermore, as physicians are expected to follow prescribing information, defendants' proposed prescribing information would instruct physicians on how to use Teva's and

Par's generic products in the same way as Lovaza®. (*Id.* at 166:9-167:7) Defendants conducted no cross examination of Dr. Kane and presented no rebuttal evidence in their case-in-chief.

47. The court finds plaintiff's infringement evidence credible and, for the above reasons, concludes that defendants' ANDA products infringe the patents-in-suit.

E. Anticipation

The court next addresses defendants' argument that the asserted composition claims (of the '677 patent) are invalid for public use before the statutory bar date.

48. There is no dispute between the parties that, on September 8, 1987, Norsk Hydro sent Dr. Victor Skrinska ("Skrinska"), then-director of biochemistry research within the cardiovascular research group at the Cleveland Research Institute,[9] liquid vials of "K-80" ethyl esters from Batch No. 222. (D.I. 209 at 35; D.I. 215 at 43; DTX-81A; DTX-82; DTX-83; DTX-84; DTX-85; DTX-86) Pronova does not contest that the Batch 222 samples meet all of the claimed limitations, as they contained 86.5 by weight EPA EE + DHA EE (53.2% by weight EPA, 33.3% by weight DHA), as well as the other omega-3 and omega-6 fatty acids and Vitamin E (as an antioxidant) recited in the asserted claims. (D.I. 209 at 35 (citing DTX-86; D.I. 203 at 698:3-699:12; D.I. 202 at 483:24-484:6; D.I. 204 at 743:24-748:19); D.I. 215 at 43-47)

49. Defendants contend that

> Norsk Hydro made commercial public use of its product by disclosing its contents and providing product samples to, among others, Dr. Skrinska. Dr. Skrinska made public use of the Skrinska material by testing to confirm its contents and discussing it with colleagues. In addition, Dr. Skrinska made

[9](D.I. 202 at 471:17-24)

> further public use of the Skrinska material by administering capsules to himself and others. No confidentiality agreement restricted these public uses.

(D.I. 209 at 34) Pronova argues that there is no corroborating evidence to support Skrinska's testimony about using the samples in a study or for any other purpose. (D.I. 215 at 43-47)

50. Defendants also point to the following shipments as preceding invalidating public uses by the recipients: (1) shipments of "K80" to Dr. Fran Peterson ("Peterson") of General Mills on February 17, 1987; (2) shipments of 1000 capsules of "K85" to Professor Arne Nordøy ("Nordøy") at the University of Oregon in January 1988; and (3) shipments of samples of "K80" to Professor Roger Davis ("Davis") at the University of Colorado in January 1988. (D.I. 209 at 38 (citing DTX-99, DTX-150, DTX-113 and DTX-114))

1. Public use standard

51.

> Public use under 35 U.S.C. § 102(b) includes any use of the claimed invention by a person other than the inventor who is under no limitation, restriction or obligation of secrecy to the inventor. Whether a patent is invalid due to a § 102(b) public use is a question of law based on underlying questions of fact.

Minnesota Min. & Mfg. Co. v. Chemque, Inc., 303 F.3d 1294, 1301-02 (Fed. Cir. 2002) (internal citations omitted).

2. Discussion

a. Work by Nordøy

52. Pronova does not contest that it sent 1000 capsules of "K85" to Nordøy in

January 1988 for study. (D.I. 215 at 47) Rather, it notes that Nordøy conducted an experimental bioavailability study that was detailed to the PTO during prosecution of the '667 and '077 patents.[10] (*Id.* (citing PTX-9 at PRV409076-86, PRC409089-123, PRV407448-55; PTX-10 at PRV407448-55)) Additionally, Pronova argues that defendants waived this argument because it was not raised in discovery or in the pretrial order. (*Id.*) Defendants do not attempt to rebut Pronova's evidence in these regards in their reply papers. (D.I. 218 at 18-22) The court does not invalidate the '667 or '077 patents on the basis of Nordøy's work.

b. Peterson and Davis

53. While Pronova does not contest that K80 was shipped to Peterson and Davis in 1987 and 1988, respectively, Pronova also (correctly) points out that defendants do not point to any evidence that those samples were ever used. (D.I. 215 at 18, 43) Defendants emphasize testimony by Norsk Hydro's former business development manager that his role was to contact companies and determine potential medical markets for drug samples. (D.I. 209 at 39 (citations omitted)) As defendants' cited evidence does not demonstrate that Peterson, Davis or others actually used the samples they received, the court does not find defendants' evidence of invalidity clear and convincing in this regard.

[10]Defendants' documentary evidence with respect to Nordøy's work is a letter from inventor Knut Dahl ("Dahl") enclosing "1000 capsules of K85" on January 29, 1988. (DTX-150) In this correspondence, Dahl states that he understands that Nordøy wants to investigate uptake and distribution of the drug, and provides restrictions on the use of the samples, for example, that human trials must be approved by Norsk Hydro. (*Id.*) The foregoing is not clear and convincing evidence of an invalidating public use by Nordøy.

c. Skrinska

54. The documents demonstrate that Skrinska was sent two, 100mL samples of Batch 222 on September 8, 1987, with a specification sheet. (DTX-84, DTX-85, DTX-86) There are no confidentiality concerns or other mentions of the potential uses in the cover letter accompanying the liquid samples. (*Id.*) Pronova does not identify any such restrictions in its answering papers. (D.I. 215 at 42-47)

55. The pivotal question is whether Skrinska actually used "the claimed invention" and, if so, in what manner. *See id.* at 1307 ("Although there is evidence in the record that samples of Ricoseal were sent to various corporations, there is no [direct] evidence of their use") (declining to invalidate based on anticipation). "Although 'public use' for purposes of § 102(b) is defined differently from 'use' for purposes of § 102(a), both require actual use by someone at some point." *Id.*

56. As to this issue, Skrinska testified that he tested the amounts of fatty acids within these two samples and found that the certificate of analysis supplied by Norsk Hydro was correct. (D.I. 202 at 483:24-484:6) Defendants do not point to any particular "use" of the two Batch 222 liquid vials.[11]

57. Skrinska further testified[12] that he "believe[s]" that Norsk Hydro sent him "maybe 500 to 1000 capsules [of concentrated fish oil] to do some studies." (D.I. 202 at 477:10-17, 485:16-25) He could not remember whether he ever received any fish oil

[11]Pronova emphasizes that the liquid samples were not "capsules" and, by implication, were not the "claimed invention." While it is clear that claim 50 of the '667 patent requires an "oral dosage form," the parties do not address whether the other asserted "fatty acid composition" claims require encapsulation specifically.

[12]By deposition designation.

capsules from anyone besides Norsk Hydro. (*Id.* at 480:8-20) He could also not remember any specific data from assays on the capsules, although Skrinska recalled that they were in conformity with the previous samples. (*Id.* at 484:7-16) Skrinska stated that six volunteers were selected from the Cleveland Research Institute staff for a study using the Norsk Hydro capsules (including himself as one of the volunteers), which study involved taking "approximately six capsules a day for two weeks," and after which they looked at fatty acid composition in the membranes of platelets. (*Id.* at 484:25-485:15) Skrinska recorded the results of this study in a notebook, although no one from Norsk Hydro asked to see the results of the study, and he did not send them any data. (*Id.* at 486:1-22) Skrinska testified that "everyone related to the Cleveland Research Institute was aware of what [they] were doing through just regular meetings and updates," including the board members, and they also "freely exchange[d] information at conferences and with colleagues" in the field. (*Id.* at 493:4-14)

58. Defendants proffer no corroborating documentary evidence for these extensive claims, for example, Skrinska's notebooks, proposals, meeting minutes, or conference documentation. The only documentary evidence cited with respect to Skrinska's activities are two letters. The first is from Dr. Irene Wei ("Wei"), assistant professor of medicine at Case Western Reserve University School of Medicine, to Sigurd Gulbrandsen at Norsk Hydro. In this communication, Wei states that she learned "of the existence of your concentrated product of omega-3 fatty acids (80%) as ethyl esters" from Skrinska, a colleague. (DTX-111) Wei asks for more information about the product and literature related to its clinical usage. (*Id.*) The other letter is addressed to Wei and Dr. John Sheehan, M.D. of the Diabetes Management Center of

Case Western Reserve University from Dr. Hans Krokan, M.D. ("Krokan") at Norsk Hydro. (DTX-112) Therein, Krokan responds to Wei's request for information and references Norsk Hydro's present work on K85, including (not yet published) clinical studies. (*Id.*) Krokan states that it is "likely that we can supply you with capsules or oil" but requests more information on "how the preparations are to be used before reaching a final decision." (*Id.*)

59. The court found Skrinska's generalized testimony (twenty years after the fact) less than compelling; the foregoing is insufficient to corroborate Skrinska's testimony regarding the purported invalidating public "uses." *See Minnesota Mining & Mfg. Co.*, 303 F.3d at 1307; *see also Finnigan Corp. v. International Trade Com'n,* 180 F.3d 1354, 1369 (Fed. Cir. 1999) ("[C]orroboration is required of any witness whose testimony alone is asserted to invalidate a patent, regardless of his or her level of interest"). As discussed above, the court does not find persuasive defendants' evidence that Norsk Hydro was shopping K80 and/or K85 in the market, as this evidence is not indicative of any actual prior public "use" of the invention as claimed. For the foregoing reasons, the court does not invalidate either the '667 or '077 patent on public use grounds.

F. Obviousness

1. Standards

60. "A patent may not be obtained . . . if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. § 103(a). Obviousness is a question of law, which

depends on underlying factual inquiries.

> Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented.

KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 406 (2007) (quoting *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966)).

61. "[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*, 550 U.S. at 418. Likewise, a defendant asserting obviousness in view of a combination of references has the burden to show that a person of ordinary skill in the relevant field had a reason to combine the elements in the manner claimed. *Id*. at 418-19. The Supreme Court has emphasized the need for courts to value "common sense" over "rigid preventative rules" in determining whether a motivation to combine existed. *Id*. at 419-20. "[A]ny need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." *Id*. at 420. In addition to showing that a person of ordinary skill in the art would have had reason to attempt to make the composition or device, or carry out the claimed process, a defendant must also demonstrate that "such a person would have had a reasonable expectation of success in doing so." *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1360 (Fed. Cir. 2007).

62. A combination of prior art elements may have been "obvious to try" where

there existed "a design need or market pressure to solve a problem and there [were] a finite number of identified, predictable solutions" to it, and the pursuit of the "known options within [a person of ordinary skill in the art's] technical grasp" leads to the anticipated success. *Id.* at 421. In this circumstance, "the fact that a combination was obvious to try might show that it was obvious under § 103." *Id.* Federal Circuit precedent has also established that "[s]tructural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds," and that particular types of structural similarity can give rise to a case of prima facie obviousness. *Genetics Institute, LLC v. Novartis Vaccines and Diagnostics, Inc.*, 655 F.3d 1291, 1312 (Fed. Cir. 2011) (citing *In re Deuel*, 51 F.3d 1552, 1558 (Fed. Cir. 1995)).

63. A court is required to consider secondary considerations, or objective indicia of nonobviousness, before reaching an obviousness determination, as a "check against hindsight bias." *See In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1079 (Fed. Cir. 2012). "Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented." *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17–18 (1966).

64. "Because patents are presumed to be valid, *see* 35 U.S.C. § 282, an alleged infringer seeking to invalidate a patent on obviousness grounds must establish its obviousness by facts supported by clear and convincing evidence." *Kao Corp. v. Unilever U.S., Inc.*, 441 F.3d 963, 968 (Fed. Cir. 2006) (citation omitted). In conjunction

with this burden, the Federal Circuit has explained that,

> [w]hen no prior art other than that which was considered by the PTO examiner is relied on by the attacker, he has the added burden of overcoming the deference that is due to a qualified government agency presumed to have properly done its job, which includes one or more examiners who are assumed to have some expertise in interpreting the references and to be familiar from their work with the level of skill in the art and whose duty it is to issue only valid patents.

PowerOasis, Inc. v. T-Mobile USA, Inc., 522 F.3d 1299, 1304 (Fed. Cir. 2008) (quoting *Am. Hoist & Derrick Co. v. Sowa & Sons*, 725 F.2d 1350, 1359 (Fed. Cir. 1984)).

2. Composition claims

65. Defendants summarize their obviousness position as follows.

> The prior art disclosed at least five concentrated fish oil compositions containing 80% or higher ("≥80%") EPA + DHA, including EE species, in a 1:2 to 2:1 ratio of EPA:DHA, having the minor components, and including compositions with antioxidant and in an oral dosage form. In addition, at least five other prior art references disclosed concentrates containing between 70-80% EPA + DHA. The unrebutted trial record is that this prior art both (1) disclosed the claimed compositions to a [person of ordinary skill in the art ("POSA")] and (2) provided a POSA with everything necessary to make the claimed compositions: (i) starting material [ ]; (ii) target percentages of ≥80% EPA + DHA [ ]; (ii) motivation to make very concentrated compositions; (iv) the techniques to prepare such compositions; and (v) a reasonable expectation that the resulting concentrate would meet all of the claim limitations, including the limitations relating to the minor components.

(D.I. 209 at 24) (internal citations omitted). In support, defendants cite to their expert, Dr. Bruce Ganem ("Ganem"),[13] who identified five asserted prior art references published before August 4, 1988 and describing omega-3 compositions having 80% by weight of EPA and DHA in the 1:2-2:1 ratio: (1) a paper entitled "Purification of Omega-

[13]Ganem is the Franz and Elizabeth Roessler Professor of Chemistry at Cornell University, and also holds the position of the J. Thomas Clark Professor of Entrepreneurship at that institution. (D.I. 204 at 712:18-24)

3 Fatty Acids from Fish Oils using HPLC: An Overview" by Judith Krzynowek et al. ("Krzynowek") (DTX-699);[14] (2) an abstract entitled "Compared Absorption of Marine Fatty Acids in Humans after Two Weeks Oral Intake of a Triglyceride or an Ethylester Concentrate" by inventor Knut Dahl et al. (the "Dahl abstract") (DTX-137A);[15] (3) Batch 222 vials and capsules sent to Skrinska, as discussed *supra* (DTX-80-86) ("the Skrinska material"); (4) a publication entitled "Study of Perinatal and Postnatal Effects in Rats After Oral Administration of a New Drug Containing Eicosapentaenoic Acid and Docosahexaenoic Acid at 85%" by M. De Bernardini et al. ("De Bernardini") (DTX-1429);[16] (5) international patent application (PCT) no. WO 87/03899, entitled "A Refined Fish Oil Concentrate and the Production Process for Sample," naming Harald Breivik et. al as inventors ("Brevik") (DTX-177). (D.I. 204 at 734:10-735:14 (cited at D.I. 209 at 24))

66. Defendants' argument in their post-trial papers does not mirror this cited testimony. Defendants assert that a skilled artisan could have readily started with fish oil manufactured by the NMFS (at least 70% by weight of EPA EE + DHA EE in a 1:1 to

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[14]The paper indicates that it was associated with the June 1988 conference of the Tropical and Subtropical Fisheries Technological Society of the Americas held jointly with the Atlantic Fisheries Technological Society, from November 9-11, 1987 in Orlando, Florida. (DTX-699) The compilation itself bears a "June 1988" date; the cover page bears a University of Florida Central Science Library stamp dated August 3, 1988. (*Id.*)

[15]The abstract has a handwritten notation on it stating that it was associated with the "NATO Advanced Research Workshop on Dietary ω-3 and ω-6 fatty acids" in Belgirante, Italy in 1988. (DTX-137A)

[16]De Bernardini was published in the International Journal of Toxicology Pharmacology and Therapy in the September-December 1987 edition. (DTX-1429) The article bears a date of March 1987. (*Id.*)

2:1 ratio), and adopted a target percent of EPA + DHA over 80% from Krzynowek, De Bernardini, Skrinska or Dahl. (D.I. 209 at 24-25)

67. It is not abundantly clear what disclosures (or uses) by the NMFS constitute prior art. In describing the NMFS compositions, defendants cite the testimony of inventor Dahl and its expert Galem that the NMFS had compositions available for use. (D.I. 209 at 12) In connection with their obviousness argument, defendants rely on the Krzynowek, Joseph, Nilssen, Brevik and De Bernardini prior art references. (*Id.* at 24-26) That is, a skilled artisan would have started with the 88% EPA EE + DHA EE composition disclosed in Krzynowek, or the 85% EPA EE + DHA EE composition disclosed in De Bernardini, added tocopherol (an antioxidant) and prepared an oral dosage form.[17] (D.I. 209 at 25-26) Alternatively, a skilled artisan could have started with an EPA + DHA composition lower than the claimed 80% by weight from various sources (including Breivik, at 75-77%) and "readily concentrated" them.[18] (D.I. 209 at 25) Defendants describe in detail three separation methods which were well-known in the art for concentrating EPA, DHA and other omega-3 fatty acids: distillation, urea

[17]While this argument appears to be geared to '667 patent claim 50 given the presence of antioxidant, as discussed *infra*, defendants do not differentiate between particular composition claims.

[18]One such reference identified in defendants' briefing is a handout presented at a May 11-14, 1986 ACOS conference in Hawaii by Dr. Jeanne D. Joseph of the U.S. National Marine Fisheries Service ("Joseph"), disclosing a mixed omega-3 EE concentrate product containing 73% EPA EE + DHA EE and an EPA:DHA ratio of 1.92:1. (PTX-547; D.I. 204 at 772:19-773:13) The other cited reference is an article entitled "Fractionation of Menhaden Oil Ethyl Esters Using Supercritical Fluid CO_2," published in January 1988 in the Journal of the American Oil Chemists' Society ("Nilsson"). (D.I. 209 at 25; DTX-1448) According to Ganem, Nilsson discloses a sample (labeled "PUFA2") containing 70.8% by weight EPA + DHA in ethyl ester form in a ratio of 2.1:1. (D.I. 204 at 777:6-20)

fractionation, and supercritical fluid extraction. (D.I. 209 at 9-12)

68. Having considered all of the proffered evidence of obviousness, as well as the secondary indicia of nonobviousness proffered by Pronova and defendants' counterevidence,[19] the court finds that defendants have failed to meet their burden to prove invalidity by clear and convincing evidence for the following reasons. Even if the court were to accept that ≥80% EPA EE + DHA EE was disclosed in, or readily producable according to, the prior art, defendants do not sufficiently address the asserted claims as a whole. As defendants' chart illustrates (*supra* p.10), the claims are directed to unique mixed-fatty-acid compositions that include, among other limitations, a specific combination of omega-3 and omega-6 fatty acids, other than just EPA and DHA, in particular amounts. There is no separate discussion of the composition included within '077 patent claim 9 or the composition that is the subject of '667 patent claims 20, 44 or 50, and there is no detailed comparison of the prior art compositions to the full scope of the claimed inventions.

69. The components other than EPA and DHA are grouped together by defendants in what they call "minor components." (D.I. 209 at 28-29) Defendants point to testimony by their expert, Dr. Syed Rizvi ("Rizvi"), Professor of Food Process Engineering at Cornell University, that: (1) a person of ordinary skill in the art would

[19]To the extent secondary considerations must be considered prior to reaching a nonobviousness determination. *Compare In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d at 1079. The court does not read this authority as requiring a regurgitation of all of defendants' evidence it finds does not amount to clear and convincing evidence of obviousness, or all of plaintiffs' secondary consideration evidence, in the event defendants fail to demonstrate a *prima facie* case of obviousness.

recognize that the process described in Joseph would "preserve[ ] and concentrate[ ]" the remaining 12% components present in the original menhaden oil (DPA, HPA and AA); and (2) Nilsson's PUFA2 sample (obtained from NMFS) contained "each of the minor components," and those less than 1% would be concentrated during the process. (*Id.* (citing D.I. 204 at 908:13-910:5 (concluding that the minor components "should be preserved"), 916:13-920:25) Defendants broadly conclude that "[t]he same would be true for any of the prior art compositions." (*Id.* at 29)

70. The foregoing is insufficient evidence to support a conclusion that each of the composition claims, containing particular combinations of C20, C21 or C22 omega-3 acids, HPA, DPA, AA, long chain omega-3 acids, EE, and antioxidant in particular concentrations in addition to EPA and DHA, are obvious in view of the cited prior art. There is no particular articulated motivation to combine the asserted references in the specific manners claimed,[20] or a reasonable expectation of success in doing so.[21]

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[20]In connection with its proffered motivation to combine, defendants cite the testimony of their expert, Dr. Frank Sacks, Professor of Cardiovascular Disease Prevention in the Department of Nutrition at Harvard, that ≥80% EPA+DHA compositions would have had similar benefits, yet provide a lower amount of fat and calories. (D.I. 209 at 31 (citing D.I. 203 at 572:22-574:9)) Defendants also cite testimony by Ganem that the fact that others were already making ≥80% compositions would provide motivation. Ganem also referenced an article stating that it was "a recent trend" to make more and more concentrated fish oil. (*Id.* (citing D.I. 204 at 788:2-790:2)) Even assuming that the foregoing were true, defendants have focused only on the ≥80% limitation, and have not proffered a motivation to combine the prior art to result in each claimed combination as a whole.

[21]Defendants' discussion of the reasonable expectation of success focuses on the presence of the minor components. (D.I. 209 at 28-29) Elsewhere in its papers, defendants broadly assert that the overlap in EPA + DHA ranges in the claims and prior art are "close enough that one skilled in the art would have expected them to have the same properties." (*Id.* at 32) No testimony is cited in support. (*Id.* at 32-33)

These omissions are especially troublesome given that Pronova provided credible evidence that concentrating the NMFS test materials would have been contrary to concerns of artisans at the time about potential detrimental effects of fish oils, such as adverse increases in LDL cholesterol levels. (D.I. 203 at 600:7-607:3; PTX-1083; PTX-1080; PTX-1078; D.I. 204 at 955:6-956:23; DTX-938-R)

71. As a final matter, the court notes (and rejects) defendants' argument that the Skrinska materials render the composition claims obvious for the same reasons discussed with respect to anticipation. (D.I. 209 at 26) Defendants did not meet their burden to demonstrate a prior public use of Batch 222, ending that inquiry.[22]

72. Having found that defendants have not demonstrated obviousness of the composition claims by clear and convincing evidence, the court declines to hold claim 9 of the '077 patent (claiming a method of treatment of hypertriglyceridemia by orally administering the novel composition) obvious. *See gen., Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc.*, 520 F.3d 1358, 1365 (Fed. Cir. 2008) (ruling that since independent claim directed to a drug composition was not obvious, the method of use claims were also not obvious).

G. Inequitable Conduct

73. The court turns next to defendants' argument that inventor Dahl committed inequitable conduct by preparing and submitting to the PTO a false declaration and by concealing data revealing of the declaration's falsity. (D.I. 209 at 44)

[22]The court notes that defendants did not separately brief the issue of whether the Skrinska materials render the composition claims obvious; they simply reference their section on anticipation. (D.I. 209 at 26)

1. Inequitable conduct standards

74. The Federal Circuit has recently stated that,

> [t]o successfully prove inequitable conduct, the accused infringer must provide evidence that the applicant (1) made an affirmative misrepresentation of material fact, failed to disclose material information, or submitted false material information, and (2) did so with intent to deceive the PTO. Both materiality and intent must be proven by clear and convincing evidence. While deceptive intent can be inferred from indirect and circumstantial evidence, that inference must not only be based on sufficient evidence and be reasonable in light of that evidence, but it must also be the single most reasonable inference able to be drawn from the evidence to meet the clear and convincing standard.

Cancer Research Technology Ltd. v. Barr Laboratories, Inc., 625 F.3d 724, 732 (Fed. Cir. 2010) (internal quotations and citations omitted). The court must recognize that "materiality and intent are separate requirements, and intent to deceive cannot be found based on materiality alone." *Id.* (citing *Larson Mfg. Co. of S.D., Inc. v. Aluminart Prods. Ltd.*, 559 F.3d 1317, 1340 (Fed. Cir. 2009)). The court cannot simply infer that an applicant "should have known" the materiality of the withheld information; other evidence "that indicates that the applicant appreciated the information's materiality" is required. *Id.* (citation omitted).

2. Background

75. The alleged inequitable conduct in this case is Dahl's omission, from a July 1990 declaration submitted to the PTO, of three of the five sets of results from a controlled study in human volunteers designed to test the inventors' "K85" product (a concentrate of omega-3 fatty acids containing approximately 55% EPA and 30% DHA of the ethyl ester form) against a prior art product ("TG30," having an EPA+DHA

concentration of about 30%). (DTX-141 at PRV1148250; DTX-9 at PRV408246) The parties do not dispute that K85 was the product Norsk Hydro later deemed the preferred embodiment of the '667 and '077 patents.

a. The Absorption Comparison Study

76. The controlled study was designed to prove the "safety as well as absorption" of PUFAs in ethyl ester form, for example, whether they are "absorbed from the gut as efficient as the triglycerides," and "enter the same lipid pools in the organism as those from the triglycerides." (DTX-141 at PRV1148249) The absorption of EPA and DHA was measured into different blood lipids. (*Id.* at PRV1148250)

77. The data examined in the controlled study was generated from two sources. First, in a study called "Ethylester K85: a 14 day multiple dose rising tolerance study" (hereinafter, the "Hazleton K85 study"), the absorption of K85 was measured in three groups of eight volunteers over a two-week period. (DTX-1574 at PRV10877; DTX-141 at PRV1148250) Second, in the study entitled "Absorption of marine fatty acids from 'TG30' in healthy volunteers (ABS of TG30)" (hereinafter, the "Norsk Hydro TG30 study"), the absorption of TG30 was measured in two groups of eight volunteers over a two-week period. (DTX-1026 at PRV950086) The results from both the Hazleton K85 and Norsk Hydro TG30 studies were analyzed in a report dated September 21, 1988 entitled "Absorption of different forms of omega-3 fatty acids in man – comparison between an ethylester (K85) and a triglyceride (TG30)." (DTX-141 at PRV1148250) The court hereinafter refers to this document as the "Absorption Comparison Study."

78. The doses in the Absorption Comparison Study were chosen such that the amounts of EPA and DHA taken in Groups 1 and 2 (K85) were equivalent to the

amounts taken in Groups 4 and 5 (TG30), respectively. (*Id.* at PRV1148251) The Absorption Comparison Study provided results for all five test groups, as indicated in the table below.

GROUP (Compound)	DOSES TAKEN (g/day) Oil	EPA	DHA	RECOVERED FATTY ACIDS FROM SERUM: Fatty acid	Total lipids Predose	Day 15	Diff.	Phospholipids Predose	Day 15	Diff.
1 (EE K85)	4	2.2	1.2	EPA	0.8 (0.2)	5.4 (1.2)	4.6	1.3 (0.3)	6.2 (1.1)	4.9
				DHA	1.7 (0.3)	4.4 (0.5)	2.7	5.1 (0.9)	9.2 (0.7)	4.1
2 (EE K85)	8	4.4	2.4	EPA	0.9 (0.5)	9.1 (1.1)	8.2	1.3 (0.6)	10.3 (1.3)	9.0
				DHA	2.3 (0.7)	5.3 (0.7)	3.0	5.5 (0.9)	10.3 (1.0)	4.8
3 (EE K85)	14	7.7	4.2	EPA	0.8 (0.4)	9.7 (2.7)	8.9	1.2 (0.7)	11.0 (2.7)	9.8
				DHA	1.8 (0.3)	4.5 (0.6)	2.7	4.4 (0.7)	8.5 (1.0)	4.1
4 (TG-30)	12	2.2	1.4	EPA	0.9 (0.5)	6.0 (1.5)	5.1	1.5 (0.6)	7.0 (1.4)	5.5
				DHA	2.4 (1.2)	4.7 (1.5)	2.3	6.5 (2.1)	8.7 (1.8)	2.2
5 (TG-30)	24	4.4	2.9	EPA	1.1 (0.8)	8.6 (1.5)	7.5	1.7 (1.4)	9.2 (0.6)	7.5
				DHA	3.0 (1.4)	5.3 (0.5)	2.3	6.8 (1.5)	9.5 (1.2)	2.7

(DTX-141 at PRV1148283) As the table indicates, absorption of EPA and DHA were measured in serum lipids as well as serum phospholipids.

79. The data for the low doses of K85 and TG30 (Groups 1 and 4), showed a 4.9 and 5.5% net gain, respectively, in phospholipid absorption for the EPA, and a 4.1 and 2.2% net gain in phospholipid absorption for DHA. That is, DHA absorbed to a much greater extent in phospholipids in patients taking the K85. With respect to the high doses (Groups 2 and 5), EPA absorbed to yield a 9.0 and 7.5% increase in the phospholipids, and DHA increased 4.8% and 2.7% in the phospholipids. Again, DHA absorption was noticeably higher in the K85 group. (*Id.*)

80. In contrast to table 4, however, the text of the Absorption Comparison Study stated that, for the phospholipid extract, the higher dose of K85 (Group 2) resulted in a 2.5 percent unit increase for DHA content. (*Id.* at PRV1148255) There is, of course, much less difference between the absorption of K85 and TG30 when comparing a

2.5%/2.7% increase in the phospholipids than a 4.8%/2.7% increase.

81. Dahl concluded that, "[w]hen the same amount of EPA was taken as ethylester [as was taken as] triglyceride, a similar increase in the fraction of serum EPA was observed. It is concluded that EPA/DHA absorption is similar for ethylester [K85] and triglyceride [TG30]" as "[b]oth formulations exerted a shift in the serum triglyceride fatty acids to a higher degree of unsaturation." (*Id.* at PRV1148248) Similarly, "[t]he differences observed between the two forms of EPA (ethylester and triglyceride) are concluded to be within individual and experimental variation." (*Id.* at PRV1148257) While the Absorption Comparison Study revealed that omaga-3 fatty acids in ethylester and triglyceride form absorbed with the same efficacy, "still the mechanism of absorption of ω-3 fatty acids can be different for triglycerides and ethylesters." (*Id.* at PRV1148261)

b. The 1988 presentations

82. The Dahl abstract was presented at the Belgirate, Italy NATO Advanced Workshop in June 1988.[23] (DTX-137A; D.I. 204 at 748:25-749:23) The Dahl abstract discloses a study administering a composition of 85% EPA EE + DHA EE (55% EPA EE, 30% DHA EE), having a 1.83:1 ratio of EPA:DHA, identified as "K85." (DTX-137A; D.I. 204 at 734:10-735:14, 748:25-749:23) The the results of the two-week study "show[ ] that a[n] EPA-ethylester is absorbed with the same efficacy as an EPA-triglyceride." (DTX-137A) The Dahl abstract was not disclosed to the PTO during the

[23]The workshop was attended by many people from industry and research. (D.I. 202 at 433:4-434:6; D.I. 203 at 585:18-586:1 ("this is a major conference")) The NATO Abstract was later published in a book that recorded the NATO meeting proceedings. (DTX-1572; D.I. 202 at 437:21-439:25)

prosecution of the ’077 and ’667 patents. (D.I. 202 at 433:7-434:14)

83. The finding that “ethyl and glycerol esters of EPA are absorbed to the same extent” was echoed in another abstract listing Dahl as an inventor from an October 1988 symposium in Rome (“the Rome Abstract”). (DTX-95; DTX-101) The Rome Abstract also stated that [t]here were no statistically significant differences between the K85 and TG30 groups in their phospholipid concentrations of EPA or DHA.” (DTX-95) The Rome Abstract was not provided to the PTO.

c. The Bioavailability Study

84. Dahl authored a report in January 1990 entitled “Bioavailability of the Ω-3 Fatty Acids EPA and DHA from K85 Compared to that from TG30” (hereinafter, the “Bioavailability Study”). (DTX-213) In the Bioavailability Study, Dahl again compared the results from the Hazleton K85 and Norsk Hydro TG30 studies, this time doing a statistical analysis of the phospholipid absorption data for two of the five groups reported in the Absorption Comparison Study, labeled “Groups A and B.” (*Id.* at PRV833052) Groups A and B correlate to Groups 2 and 5 of the Absorption Comparison Study. (DTX-141 at PRV01148283; DTX 213 at PRV833052 (Group 2 (8 g/day of K85 providing 4.4 g/day EPA and 2.4 g/day DHA) and Group 5 (24 g/day of TG30 providing 4.4 g/day EPA and 2.9 g/day of DHA))

85. For purposes of the Bioavailability Study, Dahl assumed that “since much of the biological action of EPA and DHA depends on their incorporation into phospholipids of the organism, the relative content of these fatty acids in the plasma phospholipids will

depict the efficacy of different ω-3 preparations taken."[24] (*Id.* at PRV833051) Utilizing the same underlying data as the Absorption Comparison Study, Dahl compared the phospholipid bioavailability for Groups 2 and 5 by conducting a statistical analysis. (D.I. 202 at 316:5-318:9; DTX-213 at PRV833051-53) His analysis included calculating p-values between groups. (DTX-213 at PRV833053-55, PRV833055-T) Importantly, Dahl's data for the difference in DHA phospholipid content for the higher-dose K85 group (Group 2, now Group "A") was now reported to be 4.8%, as was reported in table 4 of the Absorption Comparison Study. (*Id.* at PRV833053) In addition, Dahl provided a 3.1% difference in phospholipid serum DHA absorption for the high-dose TG30 group (Group 5, now Group "B"), whereas table 4 of the Absorption Comparison Study listed that value as 2.7%. (*Id.*) Put most simply, higher values for DHA absorption were utilized in the Bioavailability Study.

86. In performing his analysis, Dahl found that the increase in phospholipid EPA level after intake of K85 was larger than obtained after intake of TG30, and that the difference between the groups was statistically "significant." (*Id.* at PRV833053) He further determined that the increase in phospholipid DHA level after intake of K85 was also larger than obtained after intake of TG30, and that the difference between those two groups was "highly significant." (*Id.* at PRV833053) The K85 group showed a

[24]Kaare Bønaa ("Bønaa"), a medical doctor at the University of Tromsø and colleague of Krokan's, performed a study to evaluate the efficacy of K85 in reducing blood pressure, entitled "Blood Pressure Efficacy Study for K85," which was published in the New England Journal of Medicine (hereinafter, the "Blood Pressure Study"). (PTX-1255) The Blood Pressure Study concluded that K85 reduced blood pressure and that this effect depended "on the increase in plasma phospholipid n-3 fatty acids." (*Id.* at PRV1053738; D.I. 202 at 312:17-314:5)

larger increase in both EPA and DHA than the TG30 group. (*Id.* at PRV833054) Dahl concluded that there was "a difference in the bioavailability of EPA and DHA from K85 and from TG30" and that "the bioavailability of EPA and DHA and thus their therapeutic effect is enhanced when they are taken as K85 rather than as the less concentrated triglyceride preparations." (*Id.* at PRV00833054)

d. July 1990 declaration

87. In July 1990, Dahl, along with Bønaa, jointly executed a declaration to the PTO in connection with U.S. Patent Application Serial No. 07/389,902 ("the '902 application").[25] (DTX-9) The July 1990 declaration was responsive to an office action rejecting all claims then-pending during prosecution of the '902 application issued on March 22, 1990. (DTX-7) The July 1990 declaration contained the results of "study I" and "study II" to the PTO. "Study I" was described as follows:

> Two groups (each of eight persons) were given either K85 or TG30 twice daily for two weeks. . . The doses of K85 or TG30 were chosen so that for both preparations a similar amount of EPA and DHA was taken. The design of the study is described in Table I.

Table I

Group (N)	Compound	Doses taken (g/day) Oil	EPA	DHA
A (8)	K85	8.0	4.4	2.4
B (8)	TG30	24.0	4.4	2.9

(DTX-9 at PRV408246-47) The results from Groups A and B were provided in table II, as follows:

[25]The '667 and '077 patents issued from (direct or subsequent) continuations to the '902 application.

Group A (K85):

Fatty Acid	Day 1	Day 15	Diff.	p-value
EPA	1.3 (0.6)	10.3 (1.3)	9.0	<0.001
DHA	5.5 (0.9)	10.3 (1.0)	4.8	<0.001

Group B (TG30):

Fatty Acid	Day 1	Day 15	Diff.	p-value
EPA	1.7 (1.4)	9.2 (0.6)	7.5	<0.001
DHA	6.6 (1.4)	9.7 (1.0)	3.1	<0.005

The increase in phospholipid EPA level after intake of K85 (9.0 percent units) was larger than that obtained after intake of TG30 (7.5 percent units) and the difference between the two groups is significant (p 0.025). The increase in phospholipid DHA level after intake of K85 (4.8 percent units) is also larger than that obtained after intake of TG30 (3.1 percent units) and the difference between the two groups is highly significant (p 0.005).

The results obtained in this experiment show that the intake of omega-3 concentrates as an ethyl ester or as a less concentrated triglyceride markedly increased the relative content of EPA and DHA in the serum phospholipid fraction. These changes are highly significant for both fatty acids in both groups.

Id. at PRV408248) As the foregoing indicates, Dahl and Bønaa provided the PTO with only the comparison for the phospholipid fraction, not the serum lipid fraction. (*Id.*; D.I. 202 at 443:17-18) Further, the PTO was informed with respect to "Study I":

> The observations made in this study are interpreted as a difference in the bioavailability of EPA and DHA from K85 and from TG30. It is our conclusion that the bioavailability of EPA and DHA and thus their therapeutic effect is enhanced when they are taken as K85 rather than as the less concentrated triglyceride preparations.

(*Id.* at PRV402249) Bønaa's Blood Pressure Study data and conclusions constituted

the "Study II" referenced in the July 1990 declaration, and is not at issue here.[26]

e. 1993 Krokan draft

88. In 1993, after the July 1990 declaration to the PTO but before the '667 and '077 patents issued, Dahn was listed as a co-author (with inventor Krokan and other co-authors) on a draft publication discussing the Absorption Comparison Study (hereinafter, the "1993 Krokan draft"). (DTX-143; D.I. 202 at 460:17-461:2) Dahl was a consultant for Pronova at the time. (D.I. 202 at 463:8-10) The conclusion of the 1993 Krokan draft (as described in the abstract) was that "[e]nteral absorption by healthy male volunteers of [EPA] and [DHA] from an ethyl ester enriched in EPA and DHA (K85) and from natural fish oil (TG30) was found to be similar after intake of equivalent doses." (DTX-143; D.I. 202 at 461:3-13) Dahl later notified the publisher that he withdrew as an author of the paper. (DTX-215) According to Dahl, he withdrew from the article because it was after the July 1990 declaration to the PTO and "at this time, [he] knew more and [he] did not agree to this publication as it was written." (D.I. 202 at 461:16-21) Krokan wrote in a March 3, 1993 letter to the publisher that Dahl's withdrawl "ha[d] nothing to do with the scientific soundness of the paper," but was the result of "conflict of interest in his present position as a consultant for a pharmaceutical company involved with omega-3 fatty acids." (DTX-216)

89. On July 24, 2007, Dahl sent a letter to Pronova responsive to an offer letter from Pronova for additional compensation for the patents-at-issue pursuant to an "employee inventions law." (DTX-1157) Therein, Dahl stated as follows:

[26]Defendants do not allege inequitable conduct by Bønaa in this case.

> In 1993[,] I (along with three other authors) wrote a manuscript for publication based on work done at the Research Center. The manuscript was accepted for publication in *Biochemica et Biophysica Acta*. Before publication, the manuscript was presented to [Pronova], and for fear that the publication might harm the Omacor patent I was strongly requested to withdraw as author. I then withdrew as author, but was not able to prevent the other three from publishing the work.

(*Id.* at PRV1832203 (emphasis added))

2. Motion to strike

90. Dahl was deposed in connection with this litigation on August 12 and 13, 2010. The following exchanges took place:

> Q: Now, let's turn to your declaration [DTX-9]. Do you see where it says on page PRV408246, under "Study Design and Methods," "A study in healthy volunteers which gave their informed consent to participate in the study was designed as follows: Two groups each of eight persons were given either K85 or TG30 twice daily for two weeks. Do you see that?
>
> A: Yes.
>
> Q: Now, was there ever a single study in which there were two groups, each of eight persons, who were given either K85 or TG30 twice daily for two weeks?
>
> A: No. There were five groups. But we have selected two of these five groups.
>
> Q: And what was the basis for choosing to report in your declaration only two of the five groups?
>
> A: [Assertion of privilege].
>
> * * *
>
> Q. So even though there were five groups, three relating to K85 and two relating to TG30, you chose only to disclose in your declaration two of the five groups? You cannot tell me today why it is that you chose to disclose in your declaration only two out of the five groups?
>
> A: [Assertion of privilege].

(D.I. 229, ex. A at 197:3 – 199:21) On the basis of privilege, Dahl thereafter refused to explain why his July 1990 declaration did not include from the Absorption Comparison Study: (1) data from Groups 1, 3 and 4 (*id.* at 200:7-18); (2) data relating to the total serum lipid levels for any group (*id.* at 200:20-201:4); (3) data from tables 3 and 4 (*id.* at 201:9-16); or (4) the conclusion that "the differences observed between the two forms of EPA (ethyl esters and triglycerides) are concluded to be within individual and experimental variation" (*id.* at 204:15- 205:4). Dahl did not explain why he: (1) did not disclose the Dahl Abstract or the data set forth therein in his July 1990 declaration (*id.* at 205:10-206:5); or (2) why he prepared the Bioavailability Study report in January 1990 (*id.* at 156:16-157:1). Dahl testified that, aside from particular disagreements with the content of the 1993 Krokan manuscript, "[t]here was [ ] also another reason for the withdrawl from the manuscript;" this "main reason" was not provided on the basis of privilege. (D.I. 229, ex. B at 343:22-348:13)

91. After hearing arguments from both parties at the pretrial conference, the court held that the scope of the questions to be asked of Dahl by Pronova at trial "have to be narrowly circumscribed to what he answered in the deposition," not going any further. (D.I. 229, ex. C at 65:9-65:21; 67:7-8)

92. On direct examination at trial, Dahl touched upon reasons for his creation of the Bioavailability Study report. (D.I. 202 at 317:3-318:9) Similarly, Dahl attempted to discuss why the data and conclusions from the Absorption Comparison Study were not included in the July 1990 declaration to the PTO. (*Id.* at 325:5-11) Defendants did not object during Dahl's direct. On cross-examination, Dahl also attempted to explain why

he had failed to provide all of the data with regard to phospholipid absorption of EPA and DHA to the PTO. Defendants moved to strike. (*Id.* at 446:21-449:10) Dahl commented on why he withdrew as an author of the 1993 Krokan manuscript. (*Id.* at 461:3-21) Defendants did not object to this particular excerpt. In connection with their post-trial briefing, defendants have moved to strike all of the foregoing portions of testimony, as well as the portions of Pronova's post-trial papers referencing these excerpts. (D.I. 228)

93. The court grants defendants' motion to strike certain excerpts of Dahl's testimony elicited by Pronova's counsel during direct examination. (D.I. 202 at 317:3-318:9, 325:5-11) To this end, the court does not allow Pronova to use privilege as both a sword and a shield. However, as defendants elicited the additional complained-of testimony during cross-examination, Pronova did not violate the court's previous order in this regard; the court denies defendants' motion in all other respects. (D.I. 228 at 1) Having determined the appropriate record before the court, the court turns next to the merits of defendants' inequitable conduct arguments.

3. Defendants' evidence

94. From a scientific perspective, there were three tacks defendants could have taken with the facts at bar. There is no dispute that Dahl omitted the Group 1/Group 4 comparison data from the July 1990 declaration. Additionally, Dahl did not report any total serum lipid data to the PTO, only data corresponding to the phospholipid serum fractions. Finally, there are the inconsistencies between the table 4 DHA data (4.8% increase in phospholipid serum) and the data analyzed in the accompanying text of the

Absorption Comparison Study (2.5% increase in phospholipid serum), and the reversion to the table 4 DHA data (4.8% increase in phospholipid serum) in the Bioavailability Study.

95. Defendants assert that the results from the three groups of the Absorption Comparison Study not before the examiner "disclosed that EPA and DHA were absorbed with 'equal efficacy' from K85 and TG30," in contrast to the representations in the patent. (D.I. 209 at 54) The court draws a distinction between "absorption," per the Absorption Comparison Study, and "bioavailability," a concept requiring separate analysis and necessitating the Bioavailability Study. Defendants, however, use "absorption or bioavailability" synonymously in their papers. (D.I. 209 at 46) While the Absorption Comparison Study was concerned with proving safety and efficacy, i.e., whether ethylesters are taken up from the gut similarly to naturally-occurring triclycerides (DTX-141 at PRV1148249), the Bioavailability Study was concerned with proving that K85 increased phospholipid EPA and DHA more than TG30 (DTX-213 at PRV833053).[27] By their design, the studies were at odds with each other, as a heightened EPA or DHA content in the Absorption Comparison Study vis-a-vis TG30 indicated a safety concern, while in the Bioavailability Study, it was indicative of greater efficacy.

96. Defendants do not focus on the scientific validity of the 2.5% versus 4.8% values. Rather, defendants emphasize that Dahl testified that all of the data for the Absorption Comparison Study was valid. (D.I. 209 at 47 (citing D.I. 202 at 449:25-

[27]Consistent with Dahl's testimony to this effect. (D.I. 202 at 323:21-325:11, 458:13-22)

451:23) Defendants' focus is on Dahl's omission of the Group 1/Group 4 phospholipid data, rather than why he might have changed the DHA data from 4.8% to 2.5% to 4.8% again. (*Id.* at 48 et seq.)

a. Intent to deceive

97. The court proceeds to address the remaining issues in the broader context of defendants' evidence of Dahl's intent to deceive the PTO. The relied-upon excerpts of Dahl's testimony are as follows. Defendants devote significant resources to discrediting Dahl's testimony on direct examination that, when he prepared the July 1990 declaration, he "had no efficacy data from which to compare TG30 with K85."[28] (D.I. 202 at 391:19-23 (cited at D.I. 209 at 55)) For example, Dahl confirmed that the Absorption Comparison Study reported that "[t]he differences observed between the two forms of EPA (ethylester and triglyceride) are concluded to be within individual and experimental variation." (DTX-141 at PRV1148257; D.I. 202 at 451:13-23 (cited at D.I. 209 at 54)) Defendants also emphasize that efficacy data is provided in the Norsk Hydro TG30 study report, which states that TG30 had a "marked hypotriglyceridemic effect," i.e., it lowered triglycerides. (DTX-1026 at PRV950080; D.I. 202 at 428:20-429:5)

98. In addition to Dahl's testimony, defendants rely on testimony by their expert Dr. Frank M. Sacks ("Sacks"), Professor of Cardiovascular Disease Prevention in the Department of Nutrition and Professor of Medicine at Harvard, that there is no plausible scientific explanation for why Dahl omitted the total lipid data from his July 1990

[28]Defendants did not move to strike this testimony.

declaration. (D.I. 209 at 55 (citations omitted)) Even if the court were to credit all of Sacks' testimony in these regards, the foregoing is not informative with respect to intent, which may not be inferred simply from the relevance of the omitted data, i.e., the materiality of the omission of the total lipid data.[29]

99. With respect to the omission of the Group 1/Group 4 phospholipid data from the July 1990 declaration, defendants stress that Dahl testified that all of the data in table 4 of the Absorption Comparison Study is valid.[30] (DTX-212; D.I. 202 at 449:25-450:21) Taking into account data for **all** of the Groups 1-5, Dahl considered the test results to show that absorption for EPA was the same regardless if K85 or TG30 was administered (within individual and experimental variation). (D.I. 202 at 451:2-452:7) Only upon isolation of Groups 2 and 5 did the absorption results for K85 exhibit statistical significance vis-a-vis TG30. Notwithstanding, this evidence goes primarily to the materiality of the omission of the Group 1/Group 4 data.

100. The chronology of events is not indicative of an intent to deceive the PTO. Importantly, there is no indication that Dahl conducted the Bioavailability Study for the purpose of justifying the later-filed declaration. The Bioavailability Study was completed two months before a first office action was initiated by the PTO. (D.I. 203 at 637:18-21, 638:6-8) There is no evidence that the Bioavailability Study was unsound. Defendants have not challenged Dahl's statistical analysis. Furthermore, the Absorption

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[29]With respect to materiality, the court notes that while Sacks focuses on the lack of a justification for withholding the total lipid serum data, there is no equivalent focus on why the total lipid serum data was needed. (D.I. 209 at 55)

[30]As noted previously, table 4 includes the 4.8% increase for DHA in the larger dosing group for K85.

Comparison Study did not preclude the possibility that, while omega-3 fatty acids in ethylester and triglyceride form absorbed with the same efficacy, "still the mechanism of absorption of ω-3 fatty acids can be different." (DTX-141 at PRV1148261)

101. While his data changed (for reasons unknown), Dahl's position has been consistent: the early Hazleton K85 and Norsk Hydro TG30 studies (from which defendants cite triglyceride-lowering "efficacy data") were safety/tolerability and absorption studies, not efficacy studies. (D.I. 202 at 297:12-15, 323:21-325:11, 348:3-9, 424:19-25, 426:15-427:7, 428:15-16, 429:10-11) The 1988 Dahl and Rome Abstracts, as well as the Absorption Comparison Study, all concerned absorption generally. On the stand, Dahl disagreed that the purpose of the Absorption Comparison Study was to document any hypolipidemic effect. (D.I. 209 at 56-57 (citing D.I. 202 at 429:15-431:17)) It was only after he analyzed the data differently in the January 1990 Bioavailability Study that Dahl claims to have appreciated that (1) phospholipid bioavailability was an indication of the biological action of EPA and DHA, and (2) the increase in phospholipid EPA and DHA levels after intake of K85 was larger than obtained after intake of TG30. (DTX-213 at PRV833053-54)

102. With respect to the 1993 Krokan draft, years after the July 1990 declaration, Dahl testified that at that time he "knew more and [he] did not agree with this publication as it was written" in stating that TG30 and K85 had similar enteral absorption. (*Id.* at 461:14-21 (cited at D.I. 209 at 56)) Defendants describe evidence of record conflicting with this statement as a factual matter, yet concurrently move to strike

this statement in the first instance.[31] (D.I. 209 at 56-57; D.I. 228 at 1)

103. Dahl's withdrawl from the 1993 Krokan draft, which stated that "enteral absorption" was "similar" for equivalent doses of K85 and TG30, appears unnecessary given the distinction between absorption and bioavailability. Technically speaking, Dahl's withdrawl casts more doubt on the 2.5% DHA increase reported within the Absorption Comparison Study than it does the Bioavailability Study. It is apparent that Dahl changed his view of the data between 1988 and 1990 and, regardless of the merits, thereafter consistently viewed the data as a positive indication of bioavailability without regard to toxicity or absorption. That there are differences of opinion with respect to the data may be indicative of materiality,[32] but not Dahl's deceptive intent.

104. In sum, the court cannot conclude that defendants have met their burden to prove inequitable conduct by clear and convincing evidence, as defendants have not proffered evidence of deceptive intent separate and apart from materiality. *See Cancer Research Technology Ltd.*, 625 F.3d at 732. Even if it could be reasonably inferred

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[31]When Pronova claimed the privilege, defendants did not voice concern that Dahl's withholding of the reasons for his decision to submit data from two groups of the Absorption Comparison Study would hinder their ability to prove inequitable conduct. Rather, defendants appear to have made the strategic decision to take advantage of Pronova's inability to ask Dahl exculpatory questions at trial, yet delve into the topic on cross-examination. Unsatisfied with Dahl's responses, defendants moved to strike select portions of Dahl's cross-examination from the record. Yet defendants concurrently rely on interspersed portions of Dahl's cross-examination as their primary evidence of deceptive intent – in this particular instance, citing testimony that they also sought to strike. (*Compare* D.I. 228 at 1 *with* D.I. 209 at 56 (citing D.I. 202 at 461:16-21))

[32]Krokan testified that he could not rule out the possibility that "there can be different ways of doing statistical analysis" on the Absorption Comparison Study data. (D.I. 205 at 1058:17-24)

from the above-cited evidence that Dahl changed his position on the data (if not the data itself), the facts do not permit the reasonable inference that Dahl did so with the intent to deceive the PTO, rather than for some other purpose.[33] *See Therasense, Inc. v. Becton, Dickinson and Co.*, 649 F.3d 1276, 1293 (Fed. Cir. 2011) ("[T]o meet the clear and convincing evidence standard, the specific intent to deceive must be the **single most** reasonable inference able to be drawn from the evidence.") (internal quotation and citation omitted) (emphasis added).

V. CONCLUSION

105. For the forgoing reasons, the court finds that Pronova has met its burden to prove infringement of the '667 and '077 patents by a preponderance of the evidence; defendants have not proven that the asserted claims of either patent are invalid by clear and convincing evidence; and defendants have not proven, by clear and convincing evidence, that either patent is unenforceable due to inequitable conduct. Judgment shall be entered for Pronova.

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[33]The court notes that defendants assert that the materiality of the July 1990 declaration is established in two ways: (1) Dahl engaged in affirmative misconduct via a "deliberately planned and carefully executed scheme to defraud the PTO;" and (2) "but for" Dahl's conduct, the PTO would not have allowed the claims of the '667 and '077 patents to issue. (D.I. 209 at 52-53) The first ground has been called the "egregious misconduct exception" to the general rule requiring but-for materiality. *Therasense, Inc.*, 649 F.3d at 1293 ("When the patentee has engaged in affirmative acts of egregious misconduct, such as the filing of an unmistakably false affidavit, the misconduct is material. . . . Because neither mere nondisclosure of prior art references to the PTO nor failure to mention prior art references in an affidavit constitutes affirmative egregious misconduct, claims of inequitable conduct that are based on such omissions require proof of but-for materiality."). Insofar as the court finds no evidence of a deliberate scheme to defraud the PTO, it follows that the omitted test results are not material pursuant to this exception.