

1 of ordinary skill would not have found the results of Hayashi reliable. The study involved 28
2 patients and it was conducted for only 8 weeks. Hayashi shows that changes in Apo-B and LDL-
3 C were not statistically significant.⁴²⁰⁸ Further, the person of skill in the art would not have
4 looked to this patient population to predict the Apo-B or LDL-C effect of EPA therapy on very
5 high TG patients. Hayashi does not provide a motivation or reasonable expectation of success
6 for administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA
7 and substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL,
8 to effect a reduction in triglycerides without increasing LDL-C when purified EPA is
9 administered to the very high TG patient population.

10 Further, Hayashi was a small study conducted in only Japanese patients and was not
11 placebo controlled. This study would not have been extrapolated to Western populations
12 because the Japanese diet contains much more fish and has a number of other different attributes.
13 The Japanese consume a higher amount of EPA and DHA in their diets than Western
14 populations. In fact, Defendants' own reference states that the results from studies where the
15 patient population is exclusively Japanese cannot be generalized to other populations.⁴²⁰⁹ The
16 Japanese diet comprises between 8 and 15 times more EPA and DHA than typical the typical
17 Western diet. The Western diet typically consists of higher amounts of polyunsaturated omega-6
18 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand that
19 the Japanese respond differently to lipid lowering agents than Westerners.

20 Further, Defendants have failed to offer a purported combination of references as part of
21 their obviousness contentions that include Nozaki and Hayashi. Similarly, they fail to offer any

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23 ⁴²⁰⁸ Hayashi at 26, Table I.

24 ⁴²⁰⁹ Yokoyama 2007 at 1097 (“Because our population was exclusively Japanese, we cannot generalise our results to other populations.”).

1 motivation to combine Nozaki and Hayashi with the other references of their purported
2 obviousness combinations. Therefore, Defendants should be precluded from relying on these
3 references.

4 (iii) Grimsgaard, Mori 2000
5 and/or Maki Do Not Disclose
6 Purported Knowledge that
7 DHA was Responsible for the
8 Increase in LDL-C

9 Defendants assert, incorrectly, that “it was known in the art as of February 2009 that
10 administration of DHA (alone or in a mixture) resulted in the negative effect of increasing LDL-
11 C levels.”⁴²¹⁰ Defendants’ caveat of DHA being “alone or in a mixture” is telling that it was *not*
12 known that DHA alone resulted in an increase in LDL-C levels. Further, the prior art Defendants
13 rely on to support this statement does not categorize the increase in LDL-C as a “negative effect”
14 in light of the overall impact of the disclosed composition on all lipid parameters. Further, the
15 patients in Grimsgaard, Mori 2000 and Maki had normal to borderline-high baseline TG levels.
16 As discussed above in Section III, a person of ordinary skill would not expect the same LDL-C
17 effect in patients with lower baseline TG levels—the subjects of Grimsgaard, Mori 2000 and/or
18 Maki—as in very-high TG patients because patients with higher TG levels had different lipid
19 responses compared to patients with lower TG levels. Patients with very-high TG levels were
20 considered fundamentally different from patients with borderline-high or high triglycerides from
21 a lipid chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint. A person of
22 ordinary skill in the art would have expected that fish oils (and other TG lowering agents) would

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24 ⁴²¹⁰ Defendants’ Joint Invalidation Contentions at 577.

1 not increase LDL-C substantially in patients with normal to borderline high TG levels, but would
2 substantially increase LDL-C in patients with very high TG levels.

3 Defendants rely on Grimsgaard, Mori 2000 and/or Maki to demonstrate that it was known
4 that “DHA was responsible for the increase in LDL-C levels.”⁴²¹¹ The discussion related to
5 Grimsgaard in Section V.I.3.c.1.a.ii.a.i and Mori 2000 in Section V.I.3.c.1.a.i.a.iii is incorporated
6 herein by reference.

7 Defendants argue that Maki discloses the administration of purified DHA resulted in the
8 desired reduction of TGs, but also significantly increased LDL-C levels.⁴²¹² Maki was designed
9 to assess the impact of 1.52g/day DHA supplements on the serum lipid profile of patients with
10 below-average levels of HDL-C levels.⁴²¹³ The DHA supplemented group was administered
11 capsules containing 1.52 g/day DHA **and** 0.84 g/day palmitic acid, in addition to other saturated,
12 monounsaturated and polyunsaturated fatty acids.⁴²¹⁴ Therefore, Maki demonstrated that when
13 1.52 g/day DHA **and** 0.84 g/day palmitic acid is administered to patients with below-average
14 levels of HDL-C levels and borderline-high TG levels, a significant increase in LDL-C is
15 observed.⁴²¹⁵ However, one cannot attribute the rise in LDL-C solely to DHA, because the
16 authors admit that “changes in fatty acid intake other than DHA, particularly palmitate, may have
17 also contributed to the elevation in LDL cholesterol.”⁴²¹⁶ Further, Maki admits that the
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⁴²¹¹ Defendants’ Joint Invalidity Contentions at 575.

20 ⁴²¹² Defendants’ Joint Invalidity Contentions at 577.

21 ⁴²¹³ Maki at 190.

22 ⁴²¹⁴ Maki at 191.

23 ⁴²¹⁵ Maki at 195.

24 ⁴²¹⁶ Maki at 197; Yu et al., *Plasma Cholesterol-Predictive Equations Demonstrate that Stearic Acid is Neutral and Monounsaturated Fatty Acids are Hypocholesterlemic*, 61 AM J CLIN NUTR 1129, 1136 (1995).

1 “mechanism(s) responsible for the changes in the lipid profile associated with DHA
2 supplementation are not fully understood.”⁴²¹⁷ Therefore, the results of Maki are inconclusive as
3 to DHA’s effect alone on LDL-C levels.

4 Defendants mischaracterize the rise in LDL-C associated with the administration of
5 omega-3 fatty acids as being a “negative effect” because they incorrectly focus on only the LDL-
6 C effect and fail to look at the lipid effects as a whole. In fact, Maki does not find the increase in
7 LDL-C to be troublesome; Maki states that “the lack of increase in the total/HDL cholesterol
8 ratio, the decline in the triglyceride/HDL cholesterol ratio and the reduction in the proportion of
9 cholesterol carried by small, dense LDL particles render the changes in LDL cholesterol level
10 less worrisome.”⁴²¹⁸ Therefore, when one of ordinary skill in the art reviewed all the lipid effects
11 of the DHA-rich algal triglycerides, they would have understood that the increase in LDL-C was
12 “less worrisome” because of the “potentially favorable effects on triglycerides, the
13 triglyceride/HDL cholesterol ratio and the fraction of LDL cholesterol carried by small, dense
14 particles.”⁴²¹⁹

15 Therefore, Grimsgaard, Mori 2000 and/or Maki fail to substantiate Defendants’ assertion
16 that it was known that DHA was responsible for the increase in LDL-C levels. Further,
17 Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or
18 has little effect on LDL-C levels.⁴²²⁰ Defendants identify no other basis upon which a person of
19 ordinary skill would have sought to combine the Omacor PDR/Lovaza PDR with Katayama,
20 Matsuzawa, Takaku, Grimsgaard, Mori 2000 and/or Maki.

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22 ⁴²¹⁷ Maki at 197.

23 ⁴²¹⁸ Maki at 197.

24 ⁴²¹⁹ Maki at 197.

⁴²²⁰ See e.g., Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

1 (iii) The ‘560 Patent is not Obvious Over the
2 Omacor PDR/Lovaza PDR, in Combination
3 with Katayama in View of Satoh and/or in
View of Satoh or Shinozaki in Further View
of Contacos

4 With respect to the ‘560 patent, Defendants present a combination of five references: “the
5 Omacor PDR/Lovaza PDR, in combination with the known clinical benefits of administering
6 pure EPA as evidenced by Katayama in view of Satoh and/or in view of Satoh or Shinozaki in
7 further view of Contacos.”⁴²²¹ Defendants also present charts purporting to assert that an
8 additional 60 references may be combined in order to render the Claims obvious. Not only do
9 Defendants ignore the improbability that a person of ordinary skill would combine 60 separate
10 references, they additionally do not suggest any identify for combining these references.
11 Although Defendants need not point to an explicit statement in the prior art motivating the
12 combination of these references, any assertion of an “apparent reason” to combine must find a
13 basis in the factual record.⁴²²² Defendants’ unsupported cobbling of selective disclosures
14 represents hindsight reconstruction.⁴²²³ Defendants’ contentions are no more than an assertion
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16 ⁴²²¹ Defendants’ Joint Invalidity Contentions at 575.

17 ⁴²²² See, e.g., *In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the
18 formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did
19 not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply
20 the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi
Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must
21 avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to
select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and
22 elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp.
2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie*
obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding
that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been
motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

23 ⁴²²³ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under
24 *KSR*, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention
without any explanation as to how or why the references would be combined to produce the claimed invention”).

1 that certain claim elements were known in the prior art. Throughout their contentions,
2 Defendants’ selectively cite to data points in a reference without considering other disclosures or
3 even the reference as a whole. Each reference, however, must be evaluated for all that it
4 teaches.⁴²²⁴ Accordingly, Defendants fail to meet their burden to establish *prima facie*
5 obviousness.

6 The Lovaza PDR fails to disclose or even suggest the claimed method of reducing
7 triglycerides in a subject with the claimed pharmaceutical composition with the specified fatty
8 acid compositions or administration period. The Lovaza PDR further does not disclose a method
9 to effect the specified TG reduction without substantially increasing LDL-C. Indeed, the Lovaza
10 PDR discloses the exact opposite, that the EPA/DHA composition contained within the reference
11 would cause a significant increase in LDL-C levels in the very high TG patient population, for
12 whom the product is indicated. At most, the Lovaza PDR discloses administration of a
13 prescription fish oil, a combination of approximately 465 mg EPA and 375 mg DHA, as an
14 adjunct to diet to reduce TG levels in adult patients with very-high (at least 500 mg/dL) TG
15 levels.

16 Defendants formulate an obviousness argument that relies on Contacos.⁴²²⁵ However,
17 Defendants fail to provide any factual or legal basis as to why Contacos discloses a claim
18 element or an “apparent reason” or motivation to combine the elements in the manner
19 claimed,⁴²²⁶

21 ⁴²²⁴ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

22 ⁴²²⁵ *Id.*

23 ⁴²²⁶ *KSR*, 550 U.S. at 417–19; *TriMed, Inc. v. Stryker Corp.*, 608 F.3d 1333, 1341 (Fed. Cir. 2010). Hindsight may
24 not be employed to identify relevant prior art and relevant teachings therein: *Heidelberger Druckmaschinen AG v. Hantscho Comm. Prods., Inc.*, 21 F.3d 1068, 1071–72 (Fed. Cir. 1994); *Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 881 (Fed. Cir. 1998).

1 Contacos disclosed administration of fish oil, pravastatin, and combination of fish oil and
2 pravastatin, but it does not disclose administration of EPA of the recited composition. Therefore,
3 Contacos fails to provide motivation to administer purified EPA to a very high TG patient
4 population. Contacos also fails to provide motivation to administer purified EPA to a very high
5 TG patient population.

6 The proposed combinations do not render the independent claims of the '560 patent
7 obvious and Defendants' burden to prove otherwise is especially difficult because the PTO
8 considered Katayama, Satoh, Shinozaki, Contacos, Geppert, Kelley and Lovaza (both generally
9 and the Lovaza package insert specifically) during prosecution.⁴²²⁷

10 The analysis of the independent claims of the '560 patent is incorporated into all asserted
11 claims that depend from those Claims.

12 (a) A Person of Ordinary Skill Would
13 Not Have Been Motivated to
14 Replace the Mixed Fish Oil Active
Ingredient in Lovaza with EPA of
the Recited Composition

15 For an invention to be obvious, there must have been an "apparent reason" to make it.
16 The subject matter of the '560 patent claims would not have been obvious in light of these
17 references because a person of ordinary skill would not have been motivated to purify EPA or
18 been able to reasonably expect that the claimed pharmaceutical composition would reduce TG
19 levels without an increase in LDL-C levels.

20 (i) Katayama, Satoh and/or
21 Shinozaki Do Not Disclose
Purported Known Clinical

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23 ⁴²²⁷ See, e.g., *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012)(taking into account that "the
24 examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention.
Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear
and convincing standard came into play").

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3 Defendants rely on Katayama, Satoh and/or Shinozaki to demonstrate the “known clinical
4 benefits of administering pure EPA - lowering triglycerides without raising LDL-C.” As
5 discussed in Section V.I.3.c.1.a.i.a.i, incorporated herein by reference, Katayama merely
6 confirms the safety of long term treatment of Epadel and its ability to lower both serum total
7 cholesterol and triglyceride levels. Katayama does not mention LDL-C levels at all, let alone
8 discuss any purported “benefits” observed related to LDL-C. Katayama does not disclose or
9 suggest that the LDL-C results obtained were a clinical benefit, nor would a person of ordinary
10 skill view these references as teaching such a benefit for very-high TG patients.

11 Satoh administered 1.8g/day of >98% EPA to patients in order to measure the effects of
12 EPA on C-reactive protein and examine how alteration of lipoprotein profile by EPA affects
13 systemic inflammation. Satoh reported a statistically significant reduction in LDL-C only when
14 compared to baseline, there was no significant effect when compared to placebo.⁴²²⁸

15 Defendants’ characterization of Satoh as disclosing the lowering of TG levels without increasing
16 LDL-C to be a “clinical benefit” is incorrect.⁴²²⁹ Satoh does not disclose or suggest that the
17 LDL-C results obtained were a clinical benefit, nor would a person of ordinary skill view these
18 references as teaching such a benefit for very-high TG patients. As discussed above, one of
19 ordinary skill in the art would not expect LDL-C to increase in a patient with TG below 500
20 mg/dL and Satoh provides no evidence to the contrary. A person of ordinary skill in the art,
21 however, would have expected that fish oils (and other TG lowering agents) would substantially

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23 ⁴²²⁸ Satoh at 145.

24 ⁴²²⁹ Defendants’ Joint Invalidity Contentions at 574.

1 increase LDL-C in patients with very high TG levels. Satoh fails to provide motivation to
2 administer purified EPA to a very high TG patient population.

3 Further, Satoh was a small study conducted in only Japanese patients. This study would
4 not have been extrapolated to Western populations because the Japanese diet contains much
5 more fish and has a number of other different attributes. The Japanese consume a higher amount
6 of EPA and DHA in their diets than Western populations. In fact, Defendants' own reference
7 states that the results from studies where the patient population is exclusively Japanese cannot be
8 generalized to other populations.⁴²³⁰ The Japanese diet comprises between 8 and 15 times more
9 EPA and DHA than typical the typical Western diet. The Western diet typically consists of
10 higher amounts of polyunsaturated omega-6 fatty acids and saturated fatty acids. Therefore, a
11 person of ordinary skill would understand that the Japanese respond differently to lipid lowering
12 agents than Westerners.

13 Shinozaki studied the long-term effect of EPA on serum levels of Lipoprotein (a) (Lp(a))
14 and lipids such as triglycerides, total cholesterol, and low density lipoprotein particles.
15 Defendants' characterization of Shinozaki as disclosing the lowering of TG levels without
16 increasing LDL-C to be a "clinical benefit" is incorrect.⁴²³¹ Shinozaki says nothing about an
17 LDL-C effect because it measured LDL particle number, not LDL-C. The finding disclosed by
18 Shinozaki was that "long term administration of EPA may lower Lp(a) and serum lipids."⁴²³² In
19 addition to Shinozaki's lack of disclosure regarding LDL-C, Defendants identify no other basis
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22 ⁴²³⁰ Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to
other populations.").

23 ⁴²³¹ Defendants' Joint Invalidation Contentions at 575.

24 ⁴²³² Shinozaki at 107-109.

1 upon which a person of ordinary skill would have sought to combine the composition disclosed
2 in Shinozaki.

3 Therefore, Katayama, Satoh and/or Shinozaki fail to substantiate Defendants' assertion
4 that pure EPA lowers triglycerides without raising LDL-C. Further, other studies cited by
5 Defendants suggest that EPA increases LDL-C.⁴²³³ Defendants identify no other basis upon
6 which a person of ordinary skill would have sought to combine the Lovaza PDR with Katayama,
7 Satoh, Shinozaki and/or Contacos.

8 (ii) Geppert and/or Kelley Do
9 Not Disclose Purported
10 Knowledge that DHA was
11 Responsible for the Increase
12 in LDL-C

11 Defendants assert, incorrectly, that “it was known in the art as of February 2009 that
12 administration of DHA (alone or in a mixture) resulted in the negative effect of increasing LDL-
13 C levels.”⁴²³⁴ Defendants' caveat of DHA being “alone or in a mixture” is telling that it was *not*
14 known that DHA alone resulted in an increase in LDL-C levels. Further, the prior art Defendants
15 rely on to support this statement do not categorize the increase in LDL-C as a “negative effect”
16 in light of the overall impact of the disclosed composition on all lipid parameters. Further, the
17 patients in Geppert and Kelley had normal and borderline-high/high baseline TG levels,
18 respectively. As discussed above in Section III, a person of ordinary skill would not expect the
19 same LDL-C effect in patients with lower baseline TG levels—the subjects of Geppert and/or
20 Kelley—as in very-high TG patients because patients with higher TG levels had different lipid
21 responses compared to patients with lower TG levels. Patients with very-high TG levels were

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23 ⁴²³³ See, e.g., Rambjor.

24 ⁴²³⁴ Defendants' Joint Invalidity Contentions at 577.

1 considered fundamentally different from patients with borderline-high or high triglycerides from
2 a lipid chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint. Although a
3 person of ordinary skill in the art would have expected that fish oils (and other TG lowering
4 agents) would not increase LDL-C substantially in patients with normal to borderline high TG
5 levels, a person of ordinary skill in the art would expect a substantial increase in LDL-C in
6 patients with very high TG levels.

7 Defendants rely on Geppert and/or Kelley to demonstrate that it was known that “DHA
8 was responsible for the increase in LDL-C levels.”⁴²³⁵ Both Geppert and Kelley administer
9 DHA-rich oil that is contaminated with other saturated and polyunsaturated fatty acids.
10 Therefore, a person of ordinary skill would have known it is unsuitable for evaluating the
11 independent effects of DHA because it is not clear how much of the supplement’s effects can be
12 attributed to DHA.⁴²³⁶ For example, Defendants’ own prior art teaches that changes in fatty acid
13 intake other than DHA, particularly palmitate, may contribute to elevations in LDL-C.⁴²³⁷

14 In Geppert, 0.94 g/day of DHA derived from microalgae oil was administered to
15 normolipidaemic vegetarians for 8 weeks. A person of ordinary skill would not have been
16 convinced that DHA increases LDL-C based on Geppert. As Geppert acknowledges, prior
17 studies have shown “[i]nconsistent effects of DHA on LDL cholesterol.”⁴²³⁸ Rather than reading
18 Geppert in isolation, a person of ordinary skill would have read Geppert together with the prior
19 studies cited in Geppert. As such, a person of ordinary skill would have concluded that there
20 was confusion in the art and it was unclear whether DHA increased LDL-C.

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22 ⁴²³⁵ Defendants’ Joint Invalidity Contentions at 575.

23 ⁴²³⁶ See Mori 2006 at 96.

24 ⁴²³⁷ Maki at 197.

⁴²³⁸ Geppert at 784.

1 A person of ordinary skill would have expected that Geppert's results would be
2 applicable to other components of fish oil such as EPA. Nothing in Geppert suggests that DHA
3 was the only component of fish oil to increase LDL-C. For example, there is no data comparing
4 DHA to fish oil or EPA. In fact, Geppert discusses DHA and fish oil together when trying
5 explain the mechanism of LDL-C increase.⁴²³⁹ A person of ordinary skill would have not
6 expected that EPA and DHA would have different effects on LDL-C based on Geppert.

7 Defendants contend that Kelley shows that DHA was responsible for the increase in
8 LDL-C.⁴²⁴⁰ In Kelley, patients fasting serum TG levels of 150 to 400 mg/dL received 7.5 g/day
9 of DHA oil containing 3 g of DHA for 90 days. Kelley does not show that DHA is responsible
10 for the increase in LDL-C. Kelley suggests that increase in LDL-C is a general phenomenon
11 associated with triglyceride-lowering drugs, stating that a similar increase was induced by fibrate
12 therapy.⁴²⁴¹ Further, Kelley teaches that the increase in LDL-C is not harmful when viewed in
13 context with the other lipid effects reported in the study. Kelley states that:

14 DHA supplementation may lower the risk of CVD by reducing
15 plasma triacylglycerols; triacylglycerol:HDL; the number of small,
16 dense LDL particles; and mean diameter of VLDL particles. An
17 increase was observed in fasting LDL cholesterol, but it is unlikely
18 this increase is detrimental because no increase was observed in the
19 overall number of LDL particles; actually, there was an 11%
20 reduction that was statistically not significant. The reason LDL
21 cholesterol increased despite no change in LDL particle number was
22 that the LDL particles were made larger and hence more cholesterol
23 rich by DHA treatment.⁴²⁴²

22 ⁴²³⁹ *Id.*

23 ⁴²⁴⁰ Defendants' Joint Invalidity Contentions at 588.

24 ⁴²⁴¹ Kelley at 329.

⁴²⁴² Kelley at 329

1 Kelley specifically teaches that the increase in LDL-C caused by DHA supplementation
2 is unlikely to be “detrimental” because there was not a parallel increase in overall LDL particle
3 number. Kelley’s ultimate conclusion is that “[o]verall, DHA supplementation reduced the
4 concentrations of atherogenic lipids and lipoproteins and increased concentrations of
5 cardioprotective lipoproteins” and that “DHA supplementation may improve cardiovascular
6 health.”⁴²⁴³ Rather than concluding that DHA was uniquely responsible for a rise in LDL-C
7 levels, a person of ordinary skill would understand Kelley to disclose that DHA had uniquely
8 beneficial cardioprotective effects. Indeed, instead of identifying DHA as composition with
9 negative attributes, a person of ordinary skill would understand that the reference taught towards
10 the use of DHA. In addition, none of the study subjects in Kelley had a TG level above 400
11 mg/dL and, for the reasons previously discussed, a person of ordinary skill would understand the
12 very high TG patient population to be different in terms of their response to lipid therapy,
13 including administration of DHA. A person of ordinary skill in the art would have expected that
14 fish oils (and other TG lowering agents) would not increase LDL-C substantially in patients with
15 normal to borderline high TG levels, but a person of ordinary skill in the art would expect a
16 substantial increase in LDL-C in patients with very high TG levels.

17 Therefore, Geppert and/or Kelley fail to substantiate Defendants’ assertion that it was
18 known that DHA was responsible for the increase in LDL-C levels.

19 Throughout their contentions, Defendants’ selectively cite to data points in a reference
20 without considering other disclosures or even the reference as a whole. Each reference,
21 however, must be evaluated for all that it teaches.⁴²⁴⁴ As is the case with Kelley, Defendants use

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23 ⁴²⁴³ Kelley at 324, 332.

24 ⁴²⁴⁴ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

1 hindsight to characterize a reference based on LDL-C levels alone without considering the other
2 lipid effects studied, considered and reported.⁴²⁴⁵ The isolated manner in which Defendants
3 select such data points is not the approach that a person of ordinary skill would have taken at the
4 time of the invention. Defendants' approach represents the use of impermissible hindsight bias.
5 A person of ordinary skill would take into consideration the entire disclosure of a reference,
6 including lipid effects other than LDL-C. In pointing only to LDL-C, Defendants ignore,
7 without explanation, the other effects of DHA that a person of ordinary skill would consider.
8 With respect to Kelley, These effects would teach a person of ordinary skill that DHA has a
9 favorable effect in hypertriglyceridemic patients.

10 Therefore, Geppert and/or Kelley fail to substantiate Defendants' assertion that it was
11 known that DHA was responsible for the increase in LDL-C levels. Further, Defendants ignore,
12 without explanation, other studies that demonstrate that DHA decreases or has little effect on
13 LDL-C levels.⁴²⁴⁶ Defendants identify no other basis upon which a person of ordinary skill
14 would have sought to combine the Lovaza PDR with Katayama, Satoh, Shinozaki, Contacos,
15 Geppert and/or Kelley.

16 (iv) A Person of Ordinary Skill Would Not Have
17 been Motivated to Find an Omega-3 Fatty
18 Acid "therapy that would reduce TG levels
19 in patients with TG levels ≥ 500 mg/dL
20 without negatively impacting LDL-C
21 levels."

22 Plaintiffs agree that although there was a *need* to find a therapy that would reduce TG
23 levels in patients with very-high TG levels, without negatively impacting LDL-C levels, there
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22 ⁴²⁴⁵ Kelley at 324 (providing that the objectives of the study were to determine "the effects of DHA supplementation
23 on the concentrations of apoproteins; large, medium, and small VLDL, LDL, and HDL particles; and the mean
24 diameters of these particles in fasting and postprandial plasma.").

⁴²⁴⁶ See e.g., Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

1 was no motivation to find an *omega-3 fatty acid* therapy, or to modify Lovaza/Omacor, to effect
2 a reduction in TG levels without increasing LDL-C levels for very-high TG patients at the time
3 of the invention. A person of ordinary skill in the art understood that the rise in LDL-C caused
4 by omega-3 fatty acids (or fibrates) and Lovaza/Omacor was a consequence of the TG-lowering
5 mechanism. The therapies that were available at the time of the invention to treat very-high TGs
6 were niacin, fibrates and prescription omega-3 fatty acids (Lovaza/Omacor). However, niacin
7 was associated with a highly undesirable side effects—including “flushing” (or reddening of the
8 face and other areas with a burning sensation) and dyspepsia—that limited their usefulness.⁴²⁴⁷
9 Fibrates were effective at reducing TGs, but they also caused an increase in LDL-C levels in
10 patients with very-high TG levels. To combat the rise of LDL-C, doctors often prescribed
11 fibrates in combination with an LDL-C lowering medication such as a statin.⁴²⁴⁸ However, the
12 risk of rhabdomyolysis increased five-fold if fibrates were administered with a statin.⁴²⁴⁹
13 Therefore, physicians were reluctant to recommend, and patients were hesitant embrace, a
14 combination fibrate/statin course of treatment.⁴²⁵⁰ Finally, Lovaza/Omacor were also effective at
15 reducing TG levels, but, similar to fibrates, could cause a substantial increase in LDL-C levels
16 for very-high TG patients. However, Lovaza/Omacor could be safely administered with statins
17 in order to mitigate increased LDL-C.

20 ⁴²⁴⁷ See *id.* at 991-92; McKenney 2007, at 718; ATP-III at 3315 (noting that patients often could not tolerate higher
21 doses of niacin due to side effects).

22 ⁴²⁴⁸ Bays May 16, 2011 Decl., ¶ 8; Topol, at 71 (noting that in high TG patients “the addition of a statin to a fibrate
is often required to achieve LDL-C and non-HDL-C goals”);

23 ⁴²⁴⁹ See *Id.*; McKenney 2007, at 719 (“[F]ibrates may cause rhabdomyolysis, especially when combined with
statins.”).

24 ⁴²⁵⁰ See *Id.*, ¶ 17

1 In any event, a person of ordinary skill in the art would have understood that omega 3-
2 fatty acids, including DHA and EPA, and fibrates cause an increase in LDL-C among very high
3 TG patients, as reflected in the prior art. Accordingly, a person of ordinary skill in the art would
4 not have been motivated to look to omega 3-fatty acids in order to obtain a reduction in TGs
5 without increasing LDL-C in very high TG patients:

	LDL-C Effect	
	Borderline-High or High TG Patients	Very-High TG Patients
Fibrate ⁴²⁵¹	-20%	+45%
Lovaza/Omacor ⁴²⁵²	-6%	+45%

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7
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9
10 That Epadel has been approved for decades but not approved for use in the very high TG
11 patient population prior to the invention of the asserted patents is a real-world reflection of the
12 lack of motivation. Research into the pharmaceutical uses of EPA started as early as the 1970s.
13 In 1990, Mochida Pharmaceutical, began to market Epadel, a high purity EPA drug. There have
14 been countless studies conducted which administer Epadel and report the effects observed.
15 Although a few studies administer Epadel to a patient population which included a few patients
16 with TG levels > 500 mg/dL, Defendants fail to identify a single reference directed to the
17 administration of Epadel to patients with very-high TG levels, reflecting the lack of motivation.

18 Defendants offer no “apparent reason” to administer EPA as claimed to patients with
19 fasting baseline TG levels of 500 mg/dl to about 1500 mg/dl. Defendants rely on
20 Lovaza/Omacor as the starting point to “find a therapy that would reduce TG levels in patients
21
22

23 ⁴²⁵¹ Tricor®, Physicians’ Desk Reference 502-505 (62d ed. 2008).

24 ⁴²⁵² Chan 2002 I at 2381 (Table 3).

1 with TG levels of at least 500 mg/dL without negatively impacting LDL-C levels.”⁴²⁵³

2 Ironically, Lovaza/Omacor significantly reduces TGs in patients with TG levels of at least 500
3 mg/dL but significantly increases LDL-C--an effect understood to be a consequence of TG
4 reduction and the increased conversion of VLDL to LDL particles.⁴²⁵⁴

5 It was well known at the time of the invention that omega-3 fatty acids, including both
6 EPA and DHA, caused significant decrease in the production of VLDL particles and a significant
7 increase in the conversion of VLDL to IDL and LDL, supporting the understanding that omega-3
8 fatty acids worked in part by inhibiting VLDL production and improving the conversion of
9 VLDL particles to LDL.⁴²⁵⁵ A person of ordinary skill in the art understood that EPA and DHA
10 had the *same* TG-lowering mechanism and did not differentiate between EPA and DHA when
11 discussing the TG-lowering mechanism of omega-3 fatty acids.⁴²⁵⁶ The discussion related to the
12 TG-lowering mechanism of omega-3 fatty acids is discussed above in Section III and
13 incorporated herein by reference.

14 In fact, it was well understood that the degree of LDL-C elevation observed with
15 prescription omega-3 therapy, such as Lovaza/Omacor, generally related to pretreatment TG
16 levels; that is, prescription omega-3 therapy, such as Lovaza/Omacor, increased LDL-C levels
17
18

19 ⁴²⁵³ Defendants’ Joint Invalidation Contentions at 576.

20 ⁴²⁵⁴ See Bays 2008 Rx Omega-3 p. 402; McKenny 2007 Role of Prescription Omega-3 at 720 (finding that “[t]hese
21 results illustrate that with prescription omega-3, fewer VLDL particles are secreted into the systemic circulation, and
secreted VLDL particles are rapidly converted to LDL particle, thus explaining why LDL levels may increase in
patients with very-high triglyceride levels when given prescription omega-3 therapy”); Chan 2003

22 ⁴²⁵⁵ Chan 202 at 2378-84; see also Westphal at 917 (stating “our data confirm the well-known and pronounced
decrease in VLDLs after n-3 fatty acid treatment”)

23 ⁴²⁵⁶ Bays I, at 398; Harold E. Bays, *Fish Oils in the Treatment of Dyslipidemia and Cardiovascular Disease*, in *The*
Johns Hopkins Textbook of Dyslipidemia 245, 247 (Peter O. Kwiterovich Jr. ed., 2009 (Bays III))

1 the most in patients with the highest pretreatment TG levels.⁴²⁵⁷ Therefore, a person of ordinary
2 skill in the art would have viewed increased LDL-C levels caused by Lovaza/Omacor as a direct
3 consequence of lowering triglycerides in patients with TG levels ≥ 500 mg/dL. The rise in LDL-
4 C was often offset by concurrent treatment with statins.⁴²⁵⁸ The safety and efficacy of using
5 prescription omega-3 in combination with a statin has been well-established.⁴²⁵⁹

6 Although an increase in LDL-C was generally observed when omega-3 fatty acids were
7 administered to patients with very-high TG levels, the increase in LDL-C was not necessarily a
8 cause for concern because LDL-C is often low in patients with severe hypertriglyceridemia.
9 Therefore, the final LDL-C concentration may still be in the normal range.⁴²⁶⁰ Furthermore, it
10 was understood that the overall lipid effect of Lovaza/Omacor was beneficial.⁴²⁶¹

11 In two pivotal studies in very-high TG patients, both of which used prospective,
12 randomized, double-blind, placebo-controlled study designs, Lovaza/Omacor increased HDL
13 levels from baseline 13% (p=0.014) and 5.9% (p=0.057).⁴²⁶² Correspondingly, prescription
14

15 ⁴²⁵⁷ See Bays 2008 Rx Omega-3 p. 402.

16 ⁴²⁵⁸ See Harris 2008 at 14, McKenney at 722.

17 ⁴²⁵⁹ McKenney at 722-23.

18 ⁴²⁶⁰ See Westphal at 918, Harris 1997 at 389.

19 ⁴²⁶¹ See Pownall at 295 (stating that “[t]reatment with ω -3 fatty acids appear to change the lipid profile of individuals
20 with elevated TG to one that may be less atherogenic by changing LDL structure; lowering serum [cholesteryl ester
21 transfer activity], serum TG and VLDL-C; and increasing serum HDL-C”); Harris 1997 at 389 (stating that “[t]he
22 increase in LDL, which was substantial on a percentage basis, has been a common finding in past studies in [very-
23 high TG] patients. It may not be as problematic as it appears, however,” and “the use of omega-3 fatty acids for the
24 treatment of severe hypertriglyceridemia may be beneficial not only for the short-term prevention of acute
pancreatitis, but also for the long-term prevention of CHD”); Bays III at 248 (“No clinical trial data exist that this
rise in LDL-C represents harm or potential “toxicity” to patients. In fact, most evidence supports that omega-3 fatty
acids reduce cardiovascular risk as do fibrates. Importantly, clinical trials mostly support that even with increases in
LDL-C, omega-3 fatty acids decrease the total cholesterol (TC) carried by atherogenic lipoproteins, as reflected by
decreased non-HDL-C levels (TC minus HDL-C”).

⁴²⁶² McKenney 2007 at 721 (citing Harris 1997 and Pownall).

1 | omega-3 fatty acids were known to have favorable effects on non-HDL-C levels.⁴²⁶³ Therefore,
2 | “[i]n patients with very-high triglyceride levels, prescription omega-3 fatty acids 4 g/day can
3 | substantially reduce triglycerides and VLDL levels and may increase LDL levels, but the net
4 | effect is a reduction in non-HDL levels. Modest increases in HDL level are also common in
5 | patients treated with prescription omega-3 fatty acids.” Prescription omega-3 therapy was also
6 | known to alter lipoprotein particle size and composition in a favorable manner by decreasing the
7 | number of small, dense LDL particles to larger LDL particles.⁴²⁶⁴ Lovaza/Omacor “adversely
8 | raise[d] LDL cholesterol concentration but the increase in LDL cholesterol concentration
9 | reflect[ed] a less atherogenic light LDL subfraction profile that may be favorable.”⁴²⁶⁵
10 | Therefore, one of ordinary skill in the art believed that the use of Lovaza/Omacor, and omega-3
11 | fatty acids generally, “for the treatment of severe hypertriglyceridemia may be beneficial not
12 | only for the short-term prevention of acute pancreatitis, but also for the longer-term prevention
13 | of [coronary heart disease].”⁴²⁶⁶

14 | Therefore, contrary to Defendants’ assertion that “a person of ordinary skill in the art at
15 | the time of the claimed inventions would have been motivated to find a therapy that would
16 | reduce TG levels in patients with TG levels of at least 500 mg/dL without negatively impacting
17 | LDL-C levels,”⁴²⁶⁷ one of ordinary skill in the art at the time of the invention understood that the
18 | rise in LDL-C caused by omega-3 fatty acids was a by-product of reducing TGs in patients with
19 | very-high TG levels. A person of ordinary skill in the art would have expected LDL-C to
20 |

21 | _____
22 | ⁴²⁶³ McKenney 2007 at 722 (*see* Fig. 1).

23 | ⁴²⁶⁴ McKenney 2007 at 722 (*citing* Calabresi and Stalenhoef).

24 | ⁴²⁶⁵ Stalenhoef at 134.

⁴²⁶⁶ Harris 1997 at 389.

⁴²⁶⁷ Defendants’ Joint Invalidity Contentions at 576.

1 increase in very-high TG patients, and in some instances the rise was not concerning because
2 LDL-C is often low in patients with severe hypertriglyceridemia and therefore final
3 concentration would still be in the normal range. When LDL-C levels increased beyond what
4 was recommended by the ATP-III, prescribers often relied on statins to safely and effectively
5 reduce LDL-C levels. Furthermore, it was well known that the overall lipid effect of
6 Lovaza/Omacor was beneficial because non-HDL-C levels often increased. Defendants fail to
7 identify any other basis upon which a person of ordinary skill would have been motivated to find
8 a therapy that would reduce TG levels in patients with very-high TG levels without negatively
9 impacting LDL-C levels. Further, a person of ordinary skill in the art would have understood
10 that EPA therapy would *not* reduce Apo-B⁴²⁶⁸ (which is a reflection of total atherogenic
11 lipoproteins)⁴²⁶⁹ in very high TG patients, and accordingly would not have been motivated to
12 administer the claimed EPA composition to the very high TG patient population.

13 Defendants make the conclusory allegation that “routine optimization” by a person of
14 ordinary skill would yield the claimed invention.⁴²⁷⁰ Defendants, however, have offered no
15 explanation to support that allegation and they further fail to establish any of the required criteria
16 of “routine optimization” or the prerequisites to this argument. They also fail to provide any
17 factual detail to support their allegation and they fail to link the allegation to any particular claim
18 or claim element. Defendants mere allegation constitute an improper placeholder to later
19 advance arguments not disclosed in their contentions as required by the Local Rules. In addition,
20 for the reasons discussed herein, a person of ordinary skill would not be motivated to make the

22 ⁴²⁶⁸ *see* Section V.O.

23 ⁴²⁶⁹ *see* Section III.

24 ⁴²⁷⁰ *See, e.g.*, Defendants’ Joint Invalidation Contentions at 572, 585, 602.

1 combinations alleged by Defendants and, for the same reasons, it would not be routine to
2 combine such references. Where, for example, defendants argue that it would be routine to go
3 from the high TG patient population to the very high TG patient population, they provide no
4 basis for that conclusory assertion and are incorrect. As discussed, a person of ordinary skill
5 would have understood these patient populations to be distinct with different impacts of lipid
6 therapy on blood-lipid chemistry for each group. Accordingly, a person of ordinary skill would
7 not have considered the dosage modification suggested by defendants to be routine; Defendants'
8 argument to the contrary represents hindsight bias.

9 In addition, a person of ordinary skill would have no motivation to combine these
10 references because EPA would have been expected to have same result as the mixture of EPA
11 and DHA used in Lovaza/Omacor.

12 (b) Defendants Have Not Shown It Would Have Been
13 Obvious to Administer Purified EPA in the Dosing
14 Regimen Recited in the Claims

14 (i) The '560 Patent is not Obvious Over WO
15 '118 or WO '900, in Combination with the
16 Lovaza PDR, and Further in View of Leigh-
17 Firbank and/or Mori 2000

16 With respect to the '560 patent, Defendants present a combination of five references:
17 "WO '118 or WO '900, in combination with treatment regimen of Lovaza as evidenced by the
18 Lovaza PDR, and further in view of Leigh-Firbank and/or Mori 2000."⁴²⁷¹ Defendants also
19 present charts arguing that an additional 61 references may be combined in order to render the
20 Claims obvious. Not only do Defendants ignore the improbability that a person of ordinary skill
21 would combine 61 separate references, they additionally do not identify any motivation for
22

23 _____
24 ⁴²⁷¹ Defendants' Joint Invalidation Contentions at 581.

1 combining these references.^{4272, 4273} Although Defendants need not point to an explicit statement
2 in the prior art motivating the combination of these references, any assertion of an “apparent
3 reason” to combine must find a basis in the factual record.⁴²⁷⁴ Defendants’ unsupported cobbling
4 of selective disclosures represents hindsight reconstruction.⁴²⁷⁵ Defendants’ contentions are no
5 more than an assertion that certain claim elements were known in the prior art. Throughout their
6 contentions, Defendants’ selectively cite to data points in a reference without considering other
7 disclosures or even the reference as a whole. Each reference, however, must be evaluated for all
8

9
10 ⁴²⁷² Defendants’ bare assertion that the asserted claims are obvious “in view of one or more the references cited in
11 Sections III and V.A and B, including, the ‘954 publication, WO ‘900, WO ‘118, Ando, Grimsgaard, Hayashi,
12 Katayama, Matsuzawa, Matak, Mori 2000, Nakamura, Nozaki, Okumura, Park, Saito 1998, Saito 2008 Satoh,
13 Shinozaki, Takaku, Yokoyama 2003, Yokoyama 2007, Calabresi, Chan 2002, Chan 2003, Contacos, Geppert,
Kelley, Leigh-Firbank, Maki, Mori 2006, Rambjør, Sanders or Theobold in combination with the knowledge of a
person of ordinary skill in the art in light of the dosing regimen employed with Lovaza/Omacor” similarly fails to
meet the disclosure requirements of the Nevada Local Patent Rules, and fails to provide any motivation to combine
these references. *See* Defendants’ Joint Invalidity Contentions at 580-81.

14 ⁴²⁷³ Defendants’ bare assertion that “the motivation or reason to combine or modify the prior art to create
15 invalidating combinations under 35 U.S.C. §103 can be found in the references identified above in Section III.C,”
16 and that “[c]ommon sense, design incentives. Market forces, and the background knowledge possessed by a person
having ordinary skill in the art provide the reasons or rationales for combining the teachings of multiple references
or modifying references to render obvious the claimed inventions of the asserted claims,” fails to meet the disclosure
requirements of the Nevada Local Patent Rules. *See* Defendants’ Joint Invalidity Contentions at 572.

17 ⁴²⁷⁴ *See, e.g., In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the
18 formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did
not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply
the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi*
19 *Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (stating that the assertion of a starting point
“must avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation
20 to select and then modify a lead compound to arrive at the claimed invention,” which turns on the known “properties
and limitations of the prior art compounds”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F.
21 Supp. 2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima*
facie obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and
22 concluding that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art
would have been motivated to resolve citalopram in June 1988”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

23 ⁴²⁷⁵ *See, e.g., Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under
24 KSR, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention
without any explanation as to how or why the references would be combined to produce the claimed invention”).

1 that it teaches.⁴²⁷⁶ Accordingly, Defendants fail to meet their burden to establish *prima facie*
2 obviousness.

3 WO '118 is directed at the composition containing EPA for the purpose of preventing the
4 occurrence of cardiovascular events in multiple risk patients. Further, the invention of WO '118
5 is directed, "in particular, [to] preventing occurrence of cardiovascular events in
6 hypercholesterolemia patients who have been treated with HMG-CoA RI but still suffer from the
7 risk of the cardiovascular events."⁴²⁷⁷ Contrary to Defendants' assertion that WO '118 discloses
8 "the administration of 4 g of pure EPA with no DHA,"⁴²⁷⁸ WO '118 fails to disclose the claimed
9 subject with the specified very high TG levels (500-1500 mg/dL) who does not receive
10 concurrent lipid altering therapy, the claimed pharmaceutical composition with the specified
11 fatty acid compositions or dosage, or the claimed method to effect the specified TG reduction
12 without substantially increasing LDL-C. WO '118 discloses a composition with a wide range of
13 possible EPA content, dosages, and teaches that DHA is a "preferable fatty acid" to include in
14 the disclosed composition.⁴²⁷⁹

15 WO '118 does not disclose administration of highly-purified ethyl-EPA to the target
16 population of the claimed invention. The asserted claims are directed to persons with severe
17 hypertriglyceridemia (i.e. TG level above 500 mg/dL). WO '118 on the other hand only
18 discloses administration of EPA to persons with triglyceride of at least 150 mg/dL.⁴²⁸⁰ WO
19 '118's emphasis on reducing cardiovascular events suggests that its disclosure is directed to

20 ⁴²⁷⁶ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

21 ⁴²⁷⁷ WO '118 at 9.

22 ⁴²⁷⁸ Defendants' Joint Invalidation Contentions at 581.

23 ⁴²⁷⁹ WO '118 at 22-23.

24 ⁴²⁸⁰ WO '118 at 8.

1 patients with borderline-high to high TG levels, since the primary goal for patients with very-
2 high TG is to prevent acute pancreatitis by decreasing TG levels.⁴²⁸¹

3 WO '118 also does not distinguish EPA from DHA in its disclosures regarding the
4 effectiveness of the substances for treating hypertriglyceridemia.⁴²⁸² WO '118 states that
5 “[a]nother preferable fatty acid . . . is DHA-E,” and that “the compositional ratio of EPA-
6 E/DHA-E, content of EPA-E and DHA-E . . . in the total fatty acid, and dosage of (EPA-E +
7 DHA-E) are not particularly limited as long as intended effects of the present invention are
8 attained.”⁴²⁸³ It further states that “the composition is preferably the one having a high purity of
9 EPA-E and DHA-E.”⁴²⁸⁴ Further, WO '118 does not disclose EPA’s effect on LDL-C, VLDL-C,
10 Apo-B, or Lp-PLA2.

11 WO '900 is directed to a process for producing purified EPA from a culture of micro-
12 organisms. WO '900 fails to disclose the claimed subject with the specified very high TG levels
13 (500-1500 mg/dL) who does not receive concurrent lipid altering therapy, the claimed
14 pharmaceutical composition with the specified dosage or administration period, or the claimed
15 method to effect the specified TG reduction without substantially increasing LDL-C. WO '900
16 only discloses the method of producing purified EPA for therapeutic use, it does not teach
17 *administration* of pure EPA. WO '900 has no discussion, for example, regarding claimed patient
18 population or method of treatment.

21 ⁴²⁸¹ See Section III.

22 ⁴²⁸² WO '118 at 11, 13, 16-21 (“the composition containing at least EPA-E and/or DHA-E as its effective
component”).

23 ⁴²⁸³ WO '118 at 22-23.

24 ⁴²⁸⁴ WO '118 at 23.

1 WO '900 does not teach administration of pure EPA to treat hypertriglyceridemia. It lists
2 more than 30 diseases that can be treated with pure EPA, but hypertriglyceridemia is not one of
3 them.⁴²⁸⁵ Moreover, WO '900 does not teach the desired effect of EPA other than commenting
4 generally that it “may promote health and ameliorate or even reverse the effects of a range of
5 common diseases.”⁴²⁸⁶ It has no discussion, for example, on any TG-lowering effect of EPA.
6 Although WO '900 identifies DHA as an “undesired molecule”, it does not identify the *specific*
7 undesired effect of DHA or other impurities it is trying to prevent other than commenting
8 generally that “the desired effects of EPA may be limited or reversed” by them.⁴²⁸⁷ It has no
9 discussion related to any LDL-C effects caused by DHA.

10 The proposed combination does not render the independent claims of the '560 patent
11 obvious and Defendants' burden to prove otherwise is especially difficult because the PTO
12 considered WO '118, WO '900, Mori 2000, and Lovaza (both generally and the Lovaza package
13 insert specifically) during prosecution.⁴²⁸⁸

14 The analysis of the independent claims of the '560 patent is incorporated into all asserted
15 claims that depend from those Claims.

16 (a) Leigh-Firbank and Mori 2000 Do
17 Not Disclose Purported Knowledge
18
19

20 ⁴²⁸⁵ See, e.g., '900 Pub. at 16-17.

21 ⁴²⁸⁶ '900 Pub. at 5.

22 ⁴²⁸⁷ '900 Pub. at 39.

23 ⁴²⁸⁸ See, e.g., *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012)(taking into account that “the
24 examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention.
Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear
and convincing standard came into play”).

1 that DHA was Responsible for the
2 Increase in LDL-C

3 Defendants contend that a “person of ordinary skill in the art would have been
4 motivated to administer pure EPA to severely hypertriglyceridemic patients according to
5 Lovaza’s known regimen, particularly in light of the knowledge that DHA is responsible for the
6 increase in LDL-C levels as evidenced by Leigh-Firbank or Mori 2000.”⁴²⁸⁹

7 Defendants fail to identify a specific motivation to combine WO ‘118 or WO ‘900 with
8 the treatment regimen of Lovaza, as evidenced by the Lovaza PDR. Although Defendants need
9 not point to an explicit statement in the prior art motivating the combination of these references,
10 any assertion of an “apparent reason” to combine must find a basis in the factual record.⁴²⁹⁰
11 Defendants’ unsupported cobbling of selective disclosures represents hindsight
12 reconstruction.⁴²⁹¹ Defendants’ contentions are no more than an assertion that certain claim
13 elements were known in the prior art. Accordingly, Defendants fail to meet their burden to
14 establish *prima facie* obviousness.

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16 _____
⁴²⁸⁹ Defendants’ Joint Invalidity Contentions at 581-82.

17 ⁴²⁹⁰ See, e.g., *In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the
18 formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did
19 not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply
20 the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi*
Sankyo Co. v. Matrix Labs., Ltd., 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must
21 avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to
22 select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and
elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp.
2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie*
obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding
that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been
motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

23 ⁴²⁹¹ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under
24 *KSR*, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention
without any explanation as to how or why the references would be combined to produce the claimed invention”).

1 Contrary to Defendants’ assertion, Leigh-Firbank and Mori 2000 do *not* disclose that
2 DHA is responsible for the increase in LDL-C level. The discussion regarding Leigh-Firbank
3 and Mori 2000 in Section V.I.3.c.1.a.i.a.iii is incorporated herein by reference. Leigh-Firbank
4 cannot comment on the effect of EPA and DHA alone because it did not administer EPA and
5 DHA separately. A person of ordinary skill would similarly understand that Leigh-Firbank does
6 not offer any disclosure regarding the effect of EPA and DHA separately or gain any
7 understanding of the separate impact of DHA or EPA on lipid parameters. Although Mori 2000
8 discloses an increase in LDL-C for patients administered DHA, it also teaches that DHA is
9 preferable to EPA—thus teaching away from the claimed invention and reflecting no motivation
10 to combine with WO ‘118 or WO ‘900. Engaging in hindsight bias, Defendants ignore, without
11 explanation, the other effects of DHA that a person of ordinary skill would consider. Defendants
12 fail to identify any other basis upon which a person of ordinary skill would have sought to
13 combine Mori 2000 with the Lovaza PDR.

14 Therefore, Leigh-Firbank and Mori 2000 fail to substantiate Defendants’ assertion that it
15 was known that DHA was responsible for the increase in LDL-C levels. Further, Defendants
16 ignore, without explanation, other studies that demonstrate that DHA decreases or has little
17 effect on LDL-C levels.⁴²⁹² Defendants identify no other basis upon which a person of ordinary
18 skill would have sought to combine WO ‘118, WO ‘900, the Lovaza PDR, Leigh-Firbank and/or
19 Mori.

- 20 (ii) The ‘560 Patent is not Obvious Over WO
21 ‘118, WO ‘900, Grimsgaard, Mori 2000
22 and/or Maki in Combination with the
23 Omacor PDR/Lovaza PDR, and Further in

24 ⁴²⁹² See *e.g.*, Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

With respect to the '560 patent, Defendants present a combination of nine references:

“WO '118, WO '900, Grimsgaard, Mori 2000 and/or Maki in combination with treatment regimen of Omacor/Lovaza as evidenced by the Omacor PDR/Lovaza PDR, and further in view of Katayama, Matsuzawa and/or Takaku.”⁴²⁹³ Defendants also present charts arguing that an additional 56 references may be combined in order to render the Claims obvious. Not only do Defendants ignore the improbability that a person of ordinary skill would combine 56 separate references, they additionally do not identify any motivation for combining these references. Although Defendants need not point to an explicit statement in the prior art motivating the combination of these references, any assertion of an “apparent reason” to combine must find a basis in the factual record.⁴²⁹⁴ Defendants’ unsupported cobbling of selective disclosures represents hindsight reconstruction.⁴²⁹⁵ Defendants’ contentions are no more than an assertion that certain claim elements were known in the prior art. Throughout their contentions,

⁴²⁹³ Defendants’ Joint Invalidity Contentions at 582.

⁴²⁹⁴ See, e.g., *In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp. 2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie* obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

⁴²⁹⁵ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under KSR, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention”).

1 Defendants’ selectively cite to data points in a reference without considering other disclosures or
2 even the reference as a whole. Each reference, however, must be evaluated for all that it
3 teaches.⁴²⁹⁶ Accordingly, Defendants fail to meet their burden to establish *prima facie*
4 obviousness.

5 The discussion related to WO ‘118 and WO ‘900 in Section V.I.3.c.1.b.i is incorporated
6 herein by reference. The discussion related to Grimsgaard, Mori 2000 and/or Maki in Section
7 V.I.3.c.1.a.ii.a.iii is incorporated herein by reference. Defendants contend that “Grimsgaard and
8 Mori 2000 also disclose the administration of 4 g per day of highly purified EPA with no DHA.”
9 However, neither Grimsgaard nor Mori 2000 discloses the administration of 4g/day EPA to the
10 *very high TG patient population*. Neither Grimsgaard nor Mori 2000 provides motivation to
11 administer 4g/day EPA to the *very high TG patient population*. Defendants identify no other
12 basis upon which a person of ordinary skill would have sought to combine the composition
13 disclosed in Grimsgaard or Mori 2000.

14 Defendants argue that it “would have been obvious to a person of ordinary skill in the art
15 to use EPA as described in WO ‘118, WO ‘900, Grimsgaard or Mori 2000 in the treatment
16 regimen used for Omacor/Lovaza as described in the Omacor PDR/Lovaza PDR,” but their
17 assertions fail to provide a motivation for combining the references.⁴²⁹⁷ Although Defendants
18 need not point to an explicit statement in the prior art motivating the combination of these
19 references, any assertion of an “apparent reason” to combine must find a basis in the factual
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23 ⁴²⁹⁶ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

24 ⁴²⁹⁷ Defendants’ Joint Invalidity Contentions at 582.

1 record.⁴²⁹⁸ Defendants’ assertions related to motivation are insufficient,⁴²⁹⁹ and accordingly
2 Defendants fail to meet their burden to establish *prima facie* obviousness.

3 Defendants formulate an obviousness argument that relies on Katayama, Matsuzawa, or
4 Takaku. However, they’ve failed to provide any factual or legal basis as to why each reference
5 discloses a claim element, an “apparent reason” or motivation to combine the elements in the
6 manner claimed.⁴³⁰⁰ Therefore, Defendants should be precluded from relying on this these
7 references.

8 As discussed above in Section V.I.3.c.1.a.i.a.i, Katayama and Matsuzawa were both only
9 designed to confirm the safety of long term treatment of Epadel and its ability to lower both
10 serum total cholesterol and triglyceride levels. They fail to provide motivation to administer
11 purified EPA to the very high TG patient population. As discussed above in Section

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14 ⁴²⁹⁸ See, e.g., *In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the
15 formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did
16 not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply
17 the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi*
18 *Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must
19 avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to
20 select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and
21 elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp.
22 2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie*
23 obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding
24 that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been
motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

⁴²⁹⁹ For example, Defendants’ assertion that “WO ’118 may be combined with other prior art in the field of treating
hypertriglyceridemia” is nothing more than a statement that a reference can be combined but fails to provide any
basis for that statement. While the paragraph associated with that statement makes assertions regarding the
disclosure of certain other references, it does not provide a basis for the assertion of motivation to combine with WO
’118. See Defendants’ Joint Invalidity Contentions at 582.

⁴³⁰⁰ *KSR*, 550 U.S. at 417–19; *TriMed, Inc. v. Stryker Corp.*, 608 F.3d 1333, 1341 (Fed. Cir. 2010). Hindsight may
not be employed to identify relevant prior art and relevant teachings therein: *Heidelberger Druckmaschinen AG v.*
Hantscho Comm. Prods., Inc., 21 F.3d 1068, 1071–72 (Fed. Cir. 1994); *Monarch Knitting Mach. Corp. v. Sulzer*
Morat GmbH, 139 F.3d 877, 881 (Fed. Cir. 1998).

1 V.I.3.c.1.a.ii.a.i, Takaku candidly acknowledges that “only a few subjects were examined” and
2 cautions against drawing a conclusion “only from the results of the present study.”⁴³⁰¹ Further,
3 the study did not include any placebo control, therefore, a person of ordinary skill in the art
4 would understand these reports do not provide the ability to conclude that the observed lipid
5 effects would have occurred independent of the drug that is administered. In addition, the study
6 was conducted exclusively in Japanese patients, and a person of ordinary skill would not have
7 expected the results to be applicable to the general population.⁴³⁰²

8 The proposed combination does not render the independent claims of the ’560 patent
9 obvious and Defendants’ burden to prove otherwise is especially difficult because the PTO
10 considered WO ’118, WO ’900, Grimsgaard, Mori 2000, Maki, Katayama, Matsuzawa and
11 Lovaza (both generally and the Lovaza package insert specifically) during prosecution.⁴³⁰³

12 The analysis of the independent claims of the ’560 patent is incorporated into all asserted
13 claims that depend from those Claims.

- 14 (a) Grimsgaard, Mori 2000 and/or Maki
15 Do Not Disclose Purported
16 Knowledge that DHA was
17 Responsible for the Increase in LDL-
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17 Defendants contend that a “person of ordinary skill in the art would have been motivated
18 to administer pure EPA to hypertriglyceridemic patients according to Omacor/Lovaza’s known
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20 ⁴³⁰¹ Takaku at ICOSAPENT_DFNDT00006897.

21 ⁴³⁰² Yokoyama 2007 at 1097 (“[b]ecause our population was exclusively Japanese, we cannot generalise our results
to other populations.”)

22 ⁴³⁰³ See, e.g., *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012) (taking into account that “the
23 examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention.
Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear
24 and convincing standard came into play”).

1 regimen, Katayama, Matsuzawa or Takaku, particularly in light of the knowledge that DHA is
2 responsible for the increase in LDL-C levels as evidenced by Grimsgaard, Mori 2000 or
3 Maki.”⁴³⁰⁴

4 Contrary to Defendants’ assertion, Grimsgaard, Mori 2000 and/or Maki do *not* disclose
5 that DHA is responsible for the increase in LDL-C level. The discussion related to Grimsgaard,
6 Mori 2000 and/or Maki in Section V.I.3.c.1.a.ii.a.iii is incorporated herein by reference. A
7 person of ordinary skill would understand that the results of Grimsgaard demonstrated that EPA
8 and DHA’s impact on LDL-C were the same as the effect of the placebo corn oil group; that is,
9 there was no difference between EPA, DHA, or placebo’s effect on LDL-C levels. Although
10 Mori 2000 discloses an increase in LDL-C for patients administered DHA, the reference does not
11 disclose administration of DHA to the requisite patient population and teaches that DHA is
12 preferable to EPA—thus teaching away from the claimed invention. Engaging in hindsight bias,
13 Defendants ignore, without explanation, the other effects of DHA that a person of ordinary skill
14 would consider. Most controlled studies in patients with normal to high baseline TG levels
15 indicated that DHA had little or no effect on LDL-C.⁴³⁰⁵ Therefore, a person of ordinary skill
16 would not have concluded that DHA increases LDL-C in patients with normal to high baseline
17 TG levels. Maki demonstrated that when 1.52 g/day DHA **and** 0.84 g/day palmitic acid is
18 administered to patients with below-average levels of HDL-C levels and borderline-high TG
19 levels, a significant increase in LDL-C is observed.⁴³⁰⁶ However, one of ordinary skill in the art
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⁴³⁰⁴ Defendants’ Joint Invalidity Contentions at 582.

22 ⁴³⁰⁵ Mori 2000 at 98. Moreover, Mori 2000, the only study which compared EPA versus DHA, and is placebo
23 controlled, found an increase in LDL-C after DHA administration.

24 ⁴³⁰⁶ Maki at 195.

1 knew that saturated fatty acids, such as palmitate, may contributed to the elevation in LDL-C.⁴³⁰⁷

2 Therefore, the results of Maki are inconclusive as to DHA's effect alone on LDL-C levels.

3 Therefore, Grimsgaard, Mori 2000 and/or Maki fail to substantiate Defendants' assertion
4 that it was known that DHA was responsible for the increase in LDL-C levels. Further,
5 Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or
6 has little effect on LDL-C levels.⁴³⁰⁸ Defendants identify no other basis upon which a person of
7 ordinary skill would have sought to combine WO '118, WO '900, Grimsgaard, Mori 2000, Maki,
8 the Omacor PDR/the Lovaza PDR, Katayama, Matsuzawa and/or Takaku.

9 (iii) A Person of Ordinary Skill Would Not Have
10 Been Motivated to Administer Purified EPA
11 in the Treatment Regimen Recited in the
12 Claims

12 For an invention to be obvious, there must have been an "apparent reason" to make it.
13 Defendants assert that a "person of ordinary skill in the art would have been motivated to
14 administer 4 grams of highly-purified EPA to patients with triglycerides greater than or equal to
15 500 mg/dL, with a reasonable expectation of success in lowering triglycerides."⁴³⁰⁹ However, as
16 set forth below, Defendants fail to address why a person of ordinary skill in the art would have
17 been motivated to administer 4 grams of highly-purified EPA to patients with triglycerides
18 greater than or equal to 500 mg/dL.

19 A person of ordinary skill in the art would have understood that omega 3-fatty
20 acids, including DHA and EPA, and fibrates cause an increase in LDL-C among very high TG

21 ⁴³⁰⁷ Maki at 197; Yu et al., *Plasma Cholesterol-Predictive Equations Demonstrate that Stearic Acid is Neutral and*
22 *Monounsaturated Fatty Acids are Hypocholesterlemic*, 61 AM J CLIN NUTR 1129, 1136 (1995); Weber 2000 ("A
number of the earlier-formulated (older) omega-3 fatty acid supplements contained significant amounts of saturated
fat and cholesterol, both of which are known to elevate LDL-C.").

23 ⁴³⁰⁸ See e.g., Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

24 ⁴³⁰⁹ Defendants' Joint Invalidity Contentions at 583.

1 patients, as reflected in the prior art. Accordingly, a person of ordinary skill in the art would not
2 have been motivated to look to omega 3-fatty acids in order to obtain a reduction in TGs without
3 increasing LDL-C in very high TG patients:

	LDL-C Effect	
	Borderline-High or High TG Patients	Very-High TG Patients
Fibrate ⁴³¹⁰	-20%	+45%
Lovaza/Omacor ⁴³¹¹	-6%	+45%

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8 That Epadel has been approved for decades but not approved for use in the very high TG
9 patient population prior to the invention of the asserted patents is a real-world reflection of the
10 lack of motivation. Research into the pharmaceutical uses of EPA started as early as the 1970s.
11 In 1990, Mochida Pharmaceutical, began to market Epadel, a high purity EPA drug. There have
12 been countless studies conducted which administer Epadel and report the effects observed.
13 Although a few studies administer Epadel to a patient population which included a few patients
14 with TG levels > 500 mg/dL, Defendants fail to identify a single reference directed to the
15 administration of Epadel to patients with very-high TG levels, reflecting a lack of motivation.

16 Defendants further argue that the disclosure in WO '118 would combine with the prior art
17 concerning Lovaza for at least two reasons; first, "products containing DHA were reported to
18 increase LDL-C levels while products containing only EPA did not," and second, "WO '118
19 reports a reduction in cardiovascular events in hypertriglyceridemic patients administered highly-
20 purified ethyl-EPA."⁴³¹² Both of the "reasons" identified by Defendants are false.

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22 ⁴³¹⁰ Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

23 ⁴³¹¹ Chan 2002 I at 2381 (Table 3).

24 ⁴³¹² Defendants' Joint Invalidity Contentions at 583.

1 Regarding Defendants’ first reason, that “products containing DHA were reported to
2 increase LDL-C levels while products containing only EPA did not,” most controlled studies in
3 patients with normal to high baseline TG levels indicated that DHA had little or no effect on
4 LDL-C.⁴³¹³ Therefore, a person of ordinary skill would not have concluded that DHA increases
5 LDL-C in patients with normal to high baseline TG levels. Specifically, Leigh-Firbank, Kelley,
6 and Theobald does *not* disclose that “DHA raises LDL-C, an effect associated with heart disease,
7 while EPA does not.”⁴³¹⁴ First, Leigh-Firbank cannot comment on the effect of EPA and DHA
8 alone because it did not administer EPA and DHA separately.⁴³¹⁵ A person of ordinary skill
9 would similarly understand that Leigh-Firbank does not offer any disclosure regarding the effect
10 of EPA and DHA separately or gain any understanding of the separate impact of DHA or EPA
11 on lipid parameters. Second, Kelley administered DHA-rich oil that was contaminated with
12 other saturated and polyunsaturated fatty acids.⁴³¹⁶ Therefore, a person of ordinary skill would
13 have known it is unsuitable for evaluating the independent effects of DHA because it is not clear
14 how much of the supplement’s effects can be attributed to DHA.⁴³¹⁷ Kelley does not show that
15 DHA is responsible for the increase in LDL-C. Kelley suggests that increase in LDL-C is a
16 general phenomenon associated with triglyceride-lowering drugs, stating that a similar increase
17 was induced by fibrate therapy.⁴³¹⁸ Kelley specifically teaches that the increase in LDL-C

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20 ⁴³¹³ Mori 2006 at 98. Moreover, Mori 2000, the only study which compared EPA versus DHA, and is placebo
controlled, found an increase in LDL-C after DHA administration.

21 ⁴³¹⁴ Defendants’ Joint Invalidation Contentions at 588.

22 ⁴³¹⁵ The discussion related to Leigh-Firbank in Section V.I.3.c.1.a.i.a.iii is incorporated herein by reference.

23 ⁴³¹⁶ The discussion related to Kelley in Section V.I.3.c.1.a.iii.a.ii is incorporated herein by reference.

24 ⁴³¹⁷ See Mori 2006 at 96.

⁴³¹⁸ Kelley at 329.

1 caused by DHA supplementation is unlikely to be “detrimental” because there was not a parallel
2 increase in overall LDL particle number. Rather than concluding that DHA was uniquely
3 responsible for a rise in LDL-C levels, a person of ordinary skill would understand Kelley to
4 disclose that DHA had uniquely beneficial cardioprotective effects.⁴³¹⁹ Finally, Theobald also
5 does not teach that DHA increases LDL-C. In Theobald, 0.7 g/day of DHA was administered for
6 3 months in patients with normal baseline TG levels. Theobald found that LDL-C increased by
7 7% when compared to placebo. However, the DHA composition that was administered in
8 Theobald contained significant amounts of other fatty acids, such as myristic acid, palmitic acid,
9 and oleic acid. Therefore, a person of ordinary skill would have known that the DHA
10 administered by Theobald is unsuitable for evaluating the independent effects of DHA because it
11 impossible to determine whether or how much of the supplement’s effects can be attributed to
12 DHA.⁴³²⁰ Contrary to Defendants’ assertion that there was “a reported advantage to using EPA
13 vs. DHA in hypertriglyceridemic subjects,”⁴³²¹ there was no known advantage to using EPA vs.
14 DHA. In fact, a number of the references Defendants cite in their contentions ultimately
15 conclude that DHA supplementation “may represent a more favorable lipid profile than after
16 EPA supplementation.”⁴³²² In addition, a person of ordinary skill would have recognized any
17 impact of DHA reported by the study to be applicable to EPA because they would have
18 understood these substances to function by the same mechanism. Furthermore, as discussed
19 above in Section III, a person of ordinary skill would not expect the same LDL-C effect in
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21 ⁴³¹⁹ Kelley at 324, 332 (Kelley’s ultimate conclusion is that “[o]verall, DHA supplementation reduced the
22 concentrations of atherogenic lipids and lipoproteins and increased concentrations of cardioprotective lipoproteins”
and that “DHA supplementation may improve cardiovascular health.”)

23 ⁴³²⁰ See Mori 2006 at 96.

24 ⁴³²¹ Defendants’ Joint Invalidation Contentions at 583.

⁴³²² Mori 2000 at 1092.

1 patients with lower baseline TG levels, including healthy patients, as in very-high TG patients
2 because patients with higher TG levels had different lipid responses compared to patients with
3 lower TG levels.

4 Regarding Defendants' second reason, that "WO '118 reports a reduction in
5 cardiovascular events in hypertriglyceridemic patients administered highly-purified ethyl-EPA,"
6 the cardioprotective effects of omega-3 fatty acids, including both EPA and DHA, have been
7 well documented.⁴³²³ Lovaza/Omacor has been shown to reduce the risk for cardiovascular
8 death plus nonfatal myocardial infarction and nonfatal stroke.⁴³²⁴ Omega-3 fatty acids have been
9 shown to exert cardioprotective effects in both primary and secondary coronary heart disease
10 prevention trials.⁴³²⁵ Omega-3 fatty acids were known to reduce TG concentration, have
11 antiarrhythmic effects, decrease platelet aggregation, stabilize plaque, reduce blood pressure
12 and/or reduce heart rate.⁴³²⁶

13 Defendants argue that a "person of ordinary skill in the art would have appreciated the
14 fact that highly-purified ethyl-EPA, and not Lovaza, had been demonstrated to reduce
15 cardiovascular events in high-risk hypertriglyceridemic patients, and understood the benefits of
16 replacing the EPA+DHA of Lovaza with the highly purified ethyl-EPA of WO '118."⁴³²⁷ As
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19 ⁴³²³ Harris et al., *Tissue n-3 and n-6 Fatty Acids and Risk for Coronary Heart Disease Events*, 193
20 *ATHEROSCLEROSIS*, 1, 8 (2007) ("Overall, these findings confirm the well-known relationship between the n-3 FA
and CHD risk.") ("Harris 2007"); Bays 2008 II at 229-230.

21 ⁴³²⁴ See Bays, *Clinical Overview of Omacor: A Concentrated Formulation of Omega-3 Polyunsaturated Fatty Acids*,
98 *AM. J. CARDIOL* 71i (2006) ("Bays 2006").

22 ⁴³²⁵ Harris et al., *Omega-3 Fatty Acids and Coronary Heart Disease Risk: Clinical and Mechanistic Perspectives*,
197 *ATHEROSCLEROSIS* 12, 13 (2008) ("Harris 2008").

23 ⁴³²⁶ Harris 2008 at 13.

24 ⁴³²⁷ Defendants' Joint Invalidity Contentions at 584.

1 discussed above, the cardioprotective effects of omega-3 fatty acids, including both EPA, DHA
2 and Lovaza/Omacor have been well documented.⁴³²⁸

3 In fact, a meta-analysis of twenty-five studies which examined the risk of coronary heart
4 disease endpoints as a function of tissue FA composition found that the evidence suggested that
5 DHA is *more* cardioprotective than EPA.⁴³²⁹ This study found that “depressed levels of long-
6 chain *n*-3 FA (especially DHA) in tissues is a consistent marker of increased risk for coronary
7 heart disease events.”⁴³³⁰ Further, the study found that DHA levels, with or without EPA, were
8 significantly lower in fatal endpoints.⁴³³¹ This study suggests that DHA is preferable to EPA—
9 thus teaching away from the claimed invention.⁴³³² Defendants rely on hindsight bias to argue
10 that a person of ordinary skill would have been motivated to use purified EPA, when both EPA
11 and DHA were known to have cardioprotective effects, and there were studies suggesting DHA
12 was *more* cardioprotective than EPA.

13 Defendants argue that the following claim elements were known: the administration of
14 highly-purified EPA-E to reduce TG levels in patients with normal to high TG levels, the
15 administration of purified EPA to patients with TG levels > 500 mg/dL, to administer EPA-E to

17 ⁴³²⁸ Harris et al., *Tissue n-3 and n-6 Fatty Acids and Risk for Coronary Heart Disease Events*, 193
18 *ATHEROSCLEROSIS*, 1, 8 (2007) (“Overall, these findings confirm the well-known relationship between the *n*-3 FA
and CHD risk.”) (“Harris 2007”).

19 ⁴³²⁹ Harris 2007 at 8.

20 ⁴³³⁰ *Id.*

21 ⁴³³¹ Harris 2007 at 7, Table 5; *see also* Harris 2007 at 8 (“Low DHA was the most common finding across all
22 studies, suggesting that this FA was perhaps more cardioprotective than EPA as others have suggested.”).

23 ⁴³³² *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994) (A reference may be said to teach away when a person of
24 ordinary skill, upon [examining] the reference, would be discouraged from following the path set out in the
reference, or would be led in a direction divergent from the path that was taken by the applicant.”); *see also*
Santarus, Inc. v. Par Pharm., Inc., 694 F.3d 1344, 1354 (Fed. Cir. 2012) (quoting Gurley); *W.L. Gore & Assocs.,
Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1552 (Fed. Cir. 1983) (“[P]roceed[ing] contrary to the accepted wisdom of the
prior art ... is strong evidence of nonobviousness.”).

1 patients with high and very high TG levels who were not receiving concurrent lipid altering
2 therapy, and the dose of 4g/day and 12-week regimen. Defendants then argue that the “only
3 question is whether one skilled in the art would have been motivated to use the DHA-free,
4 highly-purified EPA-E of the prior art for the treatment of patients with triglyceride levels of at
5 least 500 mg/dL as part of the claimed dosage regimen.”⁴³³³

6 Defendants’ contentions are no more than a recitation that certain claim elements were
7 known in the prior art. Defendants’ assertions to the contrary represent hindsight
8 reconstruction.⁴³³⁴ Notably, Defendants *do not* assert that a person of ordinary skill would have
9 known that purified EPA, when administered to patients with very-high TG levels (≥ 500 mg/dL),
10 *would not substantially increase LDL-C*. Further, Defendants point to three Japanese studies,⁴³³⁵
11 which included a small minority of patients with baseline TG levels > 500 mg/dL to argue that “a
12 number of prior art references disclosed the administration of purified EPA to patients with TG
13 levels > 500 mg/dL.”^{4336, 4337} The disclosures of Nakamura (one patient), Matsuzawa (disclosure
14 of three patients with TG between 400 and 1000 mg/dL, with no evidence or support for the
15 assertion that the patients had very high TGs), and Takaku (three patients) reflect that a person of
16 ordinary skill in the art would *not* understand these references to relate to the use of EPA in
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18 ⁴³³³ Defendants’ Joint Invalidation Contentions at 585.

19 ⁴³³⁴ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that even under
20 KSR, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention
without any explanation as to how or why the references would be combined to produce the claimed invention.”).

21 ⁴³³⁵ Nakamura, Matsuzawa, and Takaku.

22 ⁴³³⁶ Defendants’ Joint Invalidation Contentions at 585.

23 ⁴³³⁷ Okumura and Hayashi also fail to disclose administration of purified EPA to patients with TG levels > 500
24 mg/dL. Hayashi states that the baseline TG level was 300 ± 233 mg/dL. However, the standard error is unusually
high and there is no specific disclosure of a single subject with TG levels > 500 mg/dL. Okumura specifically
states that its hypertriglyceridemia patients had baseline TG levels between 150 and 500 mg/dL.

1 patients with very high TGs, nor would a person of ordinary skill in the art draw any conclusions
2 regarding these references in terms of the very high TG patient population. In Nakamura, one
3 patient had a baseline TG level > 500 mg/dL.⁴³³⁸ However, the mean baseline TG for all patients
4 was 2.07 mmol/l (183 mg/dL), indicating that the baseline TG values for the other patients was
5 well below 500 mg/dL.⁴³³⁹ In Matsuzawa, three patients had TG levels between 400 and 1000
6 mg/dL and one patient had TG levels > 1,000 mg/dL.⁴³⁴⁰ Based on this disclosure, only one
7 patient definitively had a baseline TG level \geq 500 mg/dL. Further, this one patient was excluded
8 when analyzing the lipid impact because he was a “heavy drinker” and the “effect of alcohol
9 made it impossible to assess triglyceride levels.”⁴³⁴¹ In Takaku, three patients had baseline TG
10 levels above 500 mg/dL.⁴³⁴² However, the mean baseline TG level for all patients was 245
11 mg/dL.⁴³⁴³ Indeed, the mean baseline TG level of the patients in all three studies was well below
12 500 mg/dL; therefore, a person of ordinary skill would not have expected the results to be
13 applicable to patients with triglycerides above 500 mg/dL. Further, in each of these studies,
14 patients with >500 mg/dL were most likely excluded from the LDL-C calculations because the
15 Friedewald’s Equation cannot be used for patients with triglyceride levels \geq 400 mg/dL.⁴³⁴⁴
16 Defendants have failed to identify all of the claimed elements and fail to provide motivation to
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19 ⁴³³⁸ Nakamura at 23, Table 1.

20 ⁴³³⁹ Nakamura at 23, Tables 1 and 2.

21 ⁴³⁴⁰ *Id.* at 23.

22 ⁴³⁴¹ *Id.* at 10.

23 ⁴³⁴² Takaku at ICOSAPENT_DFNDTS00006895.

24 ⁴³⁴³ Takaku at ICOSAPENT_DFNDTS00006875.

⁴³⁴⁴ *See* Matsuzawa at ICOSAPENT_DFNDTS00006450.

1 use the DHA-free, highly-purified EPA-E of the prior art for the treatment of patients with
2 triglyceride levels of at least 500 mg/dL as part of the claimed dosage regimen.

3 Defendants contend that a “person of ordinary skill in the art would have been motivated
4 to administer highly-purified EPA-E capsules, for at least 12 weeks . . . in order to achieve the
5 known TG-lowering effects of highly-purified EPA-E.”⁴³⁴⁵ This argument is flawed. The prior
6 art demonstrates a wide range of administration periods utilized in different clinical studies. For
7 example, EPA was administered for 4 weeks in Park, for 7 weeks in Grimsgaard, for 8 weeks in
8 Hayashi, for 1 year in Takaku, for 2 years in Katayama, and for 5 years in Yokoyama 2007.
9 Given the large number of choices of administration periods disclosed in prior art, Defendants
10 have not shown that a person of ordinary skill would not have been motivated to administer
11 highly-purified EPA-E capsules for 12 weeks and offer no basis for their assertions.

12 Moreover, a person of ordinary skill would not have been motivated to administer highly-
13 purified *EPA-E* capsules, as opposed to DHA or a combination of EPA and DHA (such as
14 Lovaza), for 12 weeks. It was well known that both EPA and DHA reduced blood
15 triglycerides.⁴³⁴⁶ In fact, Defendants acknowledge in their Joint Invalidation Contentions that
16 “DHA and EPA were both known to comparably reduce triglycerides, independently of one
17 another.”⁴³⁴⁷ Data from some studies even suggested that DHA or fish oil may reduce
18 triglyceride more effectively than EPA.⁴³⁴⁸ Therefore, a person of ordinary skill would not have
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⁴³⁴⁵ Defendants’ Joint Invalidation Contentions at 585.

21 ⁴³⁴⁶ Mori 2006 at 98.

22 ⁴³⁴⁷ Defendants’ Joint Invalidation Contentions at 590.

23 ⁴³⁴⁸ Mori 2000 (showing that EPA reduced triglyceride by 18% while DHA reduced triglyceride by 20%); Rambjor
24 (showing that fish oil reduced triglyceride more than EPA); Grimsgaard (showing that decrease in triglyceride was
grater with DHA supplementation than EPA supplementation).

1 | been motivated to administer highly-purified *EPA-E* capsules instead of DHA or a combination
2 | of EPA and DHA (such as Lovaza) for 12 weeks.

3 | Defendants argue that a “person of ordinary skill in the art also would have been
4 | motivated to administer 4 g/day highly-pure ethyl EPA . . . because of the observed significant
5 | reduction in TG that was achieved in six weeks of treatment,” citing Mori 2000.⁴³⁴⁹ This
6 | argument is incorrect. The administration of 4 g/day of highly-pure ethyl EPA to patients with
7 | *mild* hypertriglyceridemia for *six* weeks does not provide a person of ordinary skill motivation to
8 | administer the same dose to patients with *severe* hypertriglyceridemia for *twelve* weeks.

9 | Defendants also, once again, fail to demonstrate that a person of ordinary skill would have
10 | chosen to administer 4g/day EPA as opposed to DHA or a combination of EPA and DHA (such
11 | as Lovaza).

12 | Defendants further argue that “because Katayama and Saito 1998 teach that higher doses
13 | of highly-purified EPA-E reduce TG level to a greater extent than lower doses . . . a person of
14 | ordinary skill in the art would have been motivated to administer highly-purified EPA-E at a
15 | dose of 4 g/day rather than a lower dose.”⁴³⁵⁰ A person of ordinary skill would not have relied
16 | on either reference to determine the EPA dosage required to treat severe hypertriglyceridemia,
17 | because these studies were not designed to determine the effect of dose on the degree of TG
18 | reduction. Second, Katayama and Saito do not suggest that 4 g/day of EPA, rather than a lower
19 | dose or a higher dose, would be the right dosage to treat severe hypertriglyceridemia.

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21 |
22 | _____
23 | ⁴³⁴⁹ Defendants’ Joint Invalidation Contentions at 586.

24 | ⁴³⁵⁰ Defendants’ Joint Invalidation Contentions at 586.

1 Moreover, as discussed above, it was well known that both EPA and DHA reduced blood
2 triglycerides.⁴³⁵¹ Therefore, a person of ordinary skill would not have been motivated to
3 administer 4 g/day of highly-purified *EPA-E* capsules, as opposed to DHA or a combination of
4 EPA and DHA (such as Lovaza).

5 Defendants further argue that a “person of ordinary skill in the art would have also been
6 motivated to treat subjects having baseline TG levels of 500 mg/dl to about 1500 mg/dl with
7 highly-purified EPA-E, as suggested by Yokoyama’s teaching that TG was reduced to a much
8 greater extent in subjects having higher baseline TG levels . . . and because Katayama and Saito
9 treated subjects having baseline triglyceride levels greater than 500 mg/dl.”⁴³⁵² This argument is
10 incorrect. It was well known that any TG-reducing therapy will reduce TG to a greater extent in a
11 patient having higher baseline TG levels. Therefore, a person of ordinary skill would not have
12 been motivated to administer highly-purified *EPA-E* capsules as opposed to any other omega-3
13 fatty acid composition, fibrate, or other TG-lowering therapy, to treat subjects having baseline
14 TG levels above 500mg/dL. Further, a person of ordinary skill would have expected that a
15 greater decrease in TG levels, in the very high TG patient population, would lead to a greater
16 increase in LDL-C levels.

17 Defendants contend that a “person of ordinary skill in the art would have been motivated
18 to administer highly-purified EPA-E—either on its own or with statin therapy—to effect a
19 reduction in TG levels without affecting LDL-C if treatment was without statin therapy, or to
20 effect a reduction in TG and LDL-C, if treatment was with statin therapy.”⁴³⁵³ Defendants first
21

22 _____
⁴³⁵¹ See Section III.

23 ⁴³⁵² Defendants’ Joint Invalidation Contentions at 586.

24 ⁴³⁵³ Defendants’ Joint Invalidation Contentions at 587.

1 support this argument by asserting that a person of ordinary skill in the art would have known
2 that EPA could lower TG levels without increasing LDL-C in very high TG patients. That is
3 incorrect. As discussed above, a person of ordinary skill in the art would not have expected EPA
4 to raise LDL-C levels in very high TG patients. Defendants’ broadly cite to “Yokoyama 2003,
5 Yokoyama 2007, Mori 2000, Mori 2006, Saito 1998, and the other references discussed in
6 V.B.4. and 5” to support this proposition,⁴³⁵⁴ however these references do not disclose or suggest
7 to a person of ordinary skill that EPA could lower TG levels without increasing LDL-C in very
8 high TG patients.⁴³⁵⁵

9 Defendants next argue again that DHA was known to be responsible for the increase in
10 LDL-C levels in very high TG patients, but as discussed above, *see* Section III, a person of
11 ordinary skill would understand that both EPA and DHA function similarly, and that both would
12 have little to no impact on borderline-high TG patients in terms of LDL-C levels and would
13 increase LDL-C levels in patients with very high TGs.

14 Defendants argue that a person of ordinary skill in the art “would have known that an
15 increase in LDL-C was an adverse health effect to be avoided.”⁴³⁵⁶ While an increase in LDL-C
16 was seen as a *possible* adverse health effect, a person of ordinary skill in the art understood that
17 the increase in LDL-C seen in the very-high TG patient population with Lovaza, and omega-3
18 fatty acids generally, was related to increased conversion of VLDL to LDL particles.⁴³⁵⁷

19 _____
20 ⁴³⁵⁴ Defendants’ Joint Invalidity Contentions at 587.

21 ⁴³⁵⁵ *See* Section IV.

22 ⁴³⁵⁶ Defendants’ Joint Invalidity Contentions at 589.

23 ⁴³⁵⁷ *See* Bays 2008 I at 402; McKenny 2007 at 720 (finding that “[t]hese results illustrate that with prescription
24 omega-3, fewer VLDL particles are secreted into the systemic circulation, and secreted VLDL particles are rapidly
converted to LDL particle, thus explaining why LDL levels may increase in patients with very-high triglyceride
levels when given prescription omega-3 therapy”); Chan 2003.

1 Defendants rely on Kelley and the Lovaza label to argue that “one of ordinary skill in the
2 art would have been motivated, with a reasonable expectation of success, to administer a highly-
3 purified EPA-E dosage form, with little to no DHA, in order to avoid the expected increase in
4 LDL-C with DHA.”⁴³⁵⁸ However, a person of ordinary skill in the art expected an increase in
5 LDL-C in the very high TG population, with both EPA and DHA. It was well known at the time
6 of the invention that omega-3 fatty acids, including both EPA and DHA, caused significant
7 decrease in the production of VLDL particles and a significant increase in the conversion of
8 VLDL to IDL and LDL, supporting the theory that omega-3 fatty acids worked in part by
9 inhibiting VLDL production and improving the conversion of VLDL particles to LDL.⁴³⁵⁹ A
10 person of ordinary skill in the art understood that EPA and DHA had the *same* TG-lowering
11 mechanism and did not differentiate between EPA and DHA when discussing the TG-lowering
12 mechanism of omega-3 fatty acids.⁴³⁶⁰ The discussion related to the TG-lowering mechanism of
13 omega-3 fatty acids is discussed above in Section III and incorporated herein by reference.
14 Further, a person of ordinary skill in the art would have understood that EPA therapy would *not*
15 reduce Apo-B⁴³⁶¹ (which is a reflection of total atherogenic lipoproteins)⁴³⁶² in very high TG
16 patients, and accordingly would not have been motivated to administer the claimed EPA
17 composition to the very high TG patient population.

18 Defendants contend that it would have been obvious to “administer 4 capsules per day,
19 each capsule containing about 900 mg to about 1 g or ethyl eicosapentaenoate, totaling about

20 ⁴³⁵⁸ Defendants’ Joint Invalidation Contentions at 589-90.

21 ⁴³⁵⁹ Chan 202 at 2378-84; *see also* Westphal at 917 (stating “our data confirm the well-known and pronounced
22 decrease in VLDLs after n-3 fatty acid treatment”).

23 ⁴³⁶⁰ Bays 2008 I, at 398; Bay *in* Kwiterovich at 247.

24 ⁴³⁶¹ *see* Section V.O.

⁴³⁶² *see* Section III.

1 3600 mg to 4g of EPA a day.” These contentions: 1) do not assert what the prior art discloses to
2 a person of ordinary skill in the art; 2) are irrelevant to an obvious analysis; 3) fail to address
3 whether the specific combination of claim elements were all present in the prior art references
4 that would have been combined by a person of ordinary skill in the art to produce the claimed
5 invention with a reasonable expectation of success; and 4) fail to establish *prima facie*
6 obviousness. Defendants do not offer an obvious analysis, but trivialize the claim element to the
7 point of reading the element out of the claim. Although convenient and expedient, Defendants’
8 approach does not conform with the Local Patent Rules of this District, the law of claim
9 construction, or the law of obviousness.

10 Defendants do not identify any combination of references. Because Defendants do not
11 identify any combination of references, they necessarily fail to offer any evidence that a person
12 of skill in the art would be motivated to combine those references in order to achieve the
13 invention of the claim as a whole. Defendants’ conclusory statement fails to provide a reason
14 that would have prompted a person of ordinary skill to reduce triglycerides by the recited
15 amount.⁴³⁶³ Defendants have not met the burden with the naked assertion that the claim is
16 obvious. Similarly, without the disclosure of a combination of references and a
17 motivation/reason to combine or modify the references, Defendants necessarily fail to offer any
18
19

20 ⁴³⁶³ *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (“Rejections on obviousness grounds cannot be
21 sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational
22 underpinning to support the legal conclusion of obviousness.”) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir.
23 2006)) (internal quotation marks omitted); *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350,
24 1356-57 (Fed. Cir. 2007) (“While the *KSR* Court rejected a rigid application of the teaching, suggestion, or
motivation (‘TSM’) test in an obviousness inquiry, the Court acknowledged the importance of identifying ‘a reason
that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the
claimed new invention does’ in an obviousness determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S.
398, 418 (2007)).

1 evidence that a person of ordinary skill in the art would have had a reasonable expectation of
2 success in achieving the claimed invention.

3 Accordingly, a person of ordinary skill would not have been motivated to combine WO
4 '118, WO '900, Grimsgaard, Mori 2000 and/or Maki in with the Omacor PDR/Lovaza PDR, and
5 Katayama, Matsuzawa and/or Takaku. A person of ordinary skill in the art further would not
6 have been motivated to combine WO '118 or WO '900, with the Lovaza PDR, or with Leigh-
7 Firbank and/or Mori 2000.

8 (2) Dependent Claims

9 (a) Defendants Have Not Shown that Claims 2 and 12
10 of the '560 Patent Would Have Been Obvious

11 Plaintiffs incorporate by reference the discussion related to the Independent Claims in
12 Section V.I.3. Because Defendants have not shown the obviousness of the Independent Claims
13 by clear and convincing evidence, they also have not adequately proven the obviousness of
14 Claims 2 and 12.

15 Defendants contend that it would be obvious that a person receiving the claimed EPA
16 compositions would have a fasting baseline LDL-C from 50 mg/dL to about 300 mg/dL because
17 hypertriglyceridemic patients in the Lovaza label had a mean LDL-C level of 100 mg/dL. These
18 contentions: 1) fail to address whether the specific combination of claim elements were all
19 present in the prior art references that would have been combined by a person of ordinary skill in
20 the art to produce the claimed invention with a reasonable expectation of success; and 2) fail to
21 establish *prima facie* obviousness. Defendants do not offer an obvious analysis, but trivialize the
22 claim element to the point of reading the element out of the claim. Although convenient and
23 expedient, Defendants' approach does not conform with the Local Patent Rules of this District,
24 the law of claim construction, or the law of obviousness.

1 Defendants do not identify any combination of references. Because Defendants do not
2 identify any combination of references, they necessarily fail to offer any evidence that a person
3 of skill in the art would be motivated to combine those references in order to achieve the
4 invention of the claim as a whole. Further, Defendants do not discuss at all whether a person of
5 ordinary skill would have been motivated to combine the elements, other than stating that a
6 patient with LDL-C levels of 50 mg/dL to about 300 mg/dL would benefit from receiving the
7 claimed fish oil treatment. Defendants also state erroneously that a patient with LDL-C levels of
8 50 mg/dL to about 300 mg/dL would be considered hypertriglyceridemic. Defendants do not
9 establish that a person of ordinary skill would have been motivated to combine the elements to
10 achieve the claimed invention.⁴³⁶⁴

11 Similarly, without the disclosure of a combination of references and a motivation/reason
12 to combine or modify the references, Defendants necessarily fail to offer any evidence that a
13 person of ordinary skill in the art would have had a reasonable expectation of success in
14 achieving the claimed invention. Defendants do not even discuss whether a person of ordinary
15 skill would have expected that the combination to work for its intended purpose for treating the
16 recited patient population.⁴³⁶⁵ As such, Defendants fail to demonstrate reasonable expectation of
17 success of the claimed invention.

20 ⁴³⁶⁴ *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the *KSR*
21 Court rejected a rigid application of the teaching, suggestion, or motivation (‘TSM’) test in an obviousness inquiry,
22 the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill
in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness
determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

23 ⁴³⁶⁵ *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable
24 result’ discussed in *KSR* refers not only to the expectation that prior art elements are capable of being physically
combined, but also that the combination would have worked for its intended purpose.”)

(b) Defendants Have Not Shown that Claims 3 and 13 of the '560 Patent Would Have Been Obvious

Plaintiffs incorporate by reference the discussion related to the Independent Claims in Section V.I.3. Because Defendants have not shown the obviousness of the Independent Claims by clear and convincing evidence, they also have not adequately proven the obviousness of Claims 3 and 13.

Defendants do not identify any combination of references and simply provide a laundry list of references without explaining how each reference relates to the claimed invention. Defendants further contend, without any support, that a person of ordinary skill would have been able to determine the patient population in need of the claimed methods of treatment, would seek to measure the HDL-C, VLDL-C and cholesterol baselines of a patient, and would seek to treat those patients having very high triglycerides regardless of the baseline values of these lipids.⁴³⁶⁶ These contentions: 1) do not assert what the prior art discloses to a person of ordinary skill in the art; 2) are irrelevant to an obvious analysis; 3) fail to address whether the specific combination of claim elements were all present in the prior art references that would have been combined by a person of ordinary skill in the art to produce the claimed invention with a reasonable expectation of success; and 4) fail to establish *prima facie* obviousness. Defendants do not offer an obvious analysis, but trivialize the claim element to the point of reading the element out of the claim. Although convenient and expedient, Defendants' approach does not conform with the Local Patent Rules of this District, the law of claim construction, or the law of obviousness.

⁴³⁶⁶ *Id.*

1 Defendants fail to show a specific combination of references that discloses each element
2 of the claimed invention. Defendants merely list references, without reference to a specific page
3 or section, that purportedly disclose disparate elements without explaining how they can be
4 combined.⁴³⁶⁷ As such, Defendants discuss the claim elements in isolation, and fail to address
5 the claimed invention as a whole.⁴³⁶⁸ Moreover, by simply identifying prior art references
6 without discussing the specific teachings of each reference, Defendants fail to consider each
7 prior art reference as a whole.⁴³⁶⁹ Each reference must be evaluated for all that it teaches.
8 Defendants' unsupported cobbling of selective disclosures represents hindsight
9 reconstruction.⁴³⁷⁰

10 Because Defendants do not identify any combination of references, they necessarily fail
11 to offer any evidence that a person of skill in the art would be motivated to combine those
12 references in order to achieve the invention of the claim as a whole. Defendants make a
13 conclusory statement that a person of ordinary skill "would indeed seek" to perform the claimed
14 methods of treatment, without providing a reason that would have prompted a person of ordinary
15 skill to combine the elements.⁴³⁷¹ Such a naked assertion does not show why a person of
16

17 ⁴³⁶⁷ *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int'l Co. v.*
18 *Teleflex Inc.*, 550 U.S. 398, 418 (2007)) ("[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").

19 ⁴³⁶⁸ *Sanofi Syntheolabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008) ("The determination of obviousness is
made with respect to the subject matter as a whole, not separate pieces of the claim").

20 ⁴³⁶⁹ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011) ("A prior
21 patent must be considered in its entirety, i.e., as a whole, including portions that would lead away from the invention
in suit.") (internal citation and quotation marks omitted).

22 ⁴³⁷⁰ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under
KSR, "[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention
without any explanation as to how or why the references would be combined to produce the claimed invention").

23 ⁴³⁷¹ *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) ("Rejections on obviousness grounds cannot be
24 sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational

1 ordinary skill would have been motivated to treat the recited patient population using the claimed
2 methods of treatment.⁴³⁷²

3 Similarly, without the disclosure of a combination of references and a motivation/reason
4 to combine or modify the references, Defendants necessarily fail to offer any evidence that a
5 person of ordinary skill in the art would have had a reasonable expectation of success in
6 achieving the claimed invention. In fact, other than simply identifying prior art references that
7 purportedly disclose disparate elements, Defendants do not even discuss whether a person of
8 ordinary skill would have expected that the combination to work for its intended purpose for
9 treating the recited patient population.⁴³⁷³ As such, Defendants fail to demonstrate reasonable
10 expectation of success of the claimed invention.

11 (c) Defendants Have Not Shown that Claims 4, 7, 14
12 and 17 of the '560 Patent Would Have Been
Obvious

13 Plaintiffs incorporate by reference the discussion related to the Independent Claims in
14 Section V.I.3. Because Defendants have not shown the obviousness of the Independent Claims
15 by clear and convincing evidence, they also have not adequately proven the obviousness of
16 Claims 4, 7, 14 and 17.

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19 _____
underpinning to support the legal conclusion of obviousness.”) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir.
2006)) (internal quotation marks omitted)

20 ⁴³⁷² *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the *KSR*
21 Court rejected a rigid application of the teaching, suggestion, or motivation (‘TSM’) test in an obviousness inquiry,
the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill
22 in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness
determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

23 ⁴³⁷³ *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable
24 result’ discussed in *KSR* refers not only to the expectation that prior art elements are capable of being physically
combined, but also that the combination would have worked for its intended purpose.”)

1 Defendants' contentions fail to disclose each and every element of the claims of the '560
2 patent. Specifically, Defendants do not contend that the relied upon references disclose the
3 following elements of Claims 4 and 14: *administering the claimed pharmaceutical composition*
4 *to the recited subject to effect the recited reduction in triglycerides without increasing LDL-C by*
5 *more than 5%*. Therefore, Defendants' prior art combinations cannot render the claims *prima*
6 *facie* obvious.

7 Defendants contend, without support, that the recited reduction in TG represents
8 therapeutic efficacy, and that a person of ordinary skill would naturally seek to reduce TG to
9 therapeutic efficacy. Defendants further contend that it would have been obvious to a person of
10 ordinary skill to seek to reduce TG by the recited amount because there is no significance
11 attached to the amount. Defendants conclude, without support, that there was a reasonable
12 expectation of success without identifying any combination of references and without explaining
13 how each reference relates to the claimed invention.⁴³⁷⁴ These contentions: 1) do not assert
14 what the prior art discloses to a person of ordinary skill in the art; 2) are irrelevant to an obvious
15 analysis; 3) fail to address whether the specific combination of claim elements were all present in
16 the prior art references that would have been combined by a person of ordinary skill in the art to
17 produce the claimed invention with a reasonable expectation of success; and 4) fail to establish
18 *prima facie* obviousness. Defendants do not offer an obvious analysis, but trivialize the claim
19 element to the point of reading the element out of the claim. Although convenient and expedient,
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22 _____
23 ⁴³⁷⁴ Ando, Calabresi, Contacos, Grimsgaard, Harris, Hayashi, Katayama, Kris_Etherton 2002, Kurabayashi, Leigh-
24 Firbank, Lovaza 2007 Label, Lovaza PDR, Omacor 2004 Label, Omacor PDR, Lovegrove, Matsuzawa, McKenney
2003, McKenney 2007, Mori 2000, Mori 2006, Nakamura, Nestel, Nozaki, Pownall, Sanders, Shinozaki, Takaku,
von Schacky, Wojenski, Yokoyama 2003, and/or Yokoyama 2007.

1 Defendants' approach does not conform with the Local Patent Rules of this District, the law of
2 claim construction, or the law of obviousness.

3 Defendants further contend, without support, that a person of ordinary skill would
4 "reasonably expect to see the same hypotriglyceridemic effect from a pure EPA formulation
5 containing no DHA," as a formulation containing both EPA and DHA. Defendants conclude,
6 without support, that it would have been obvious to administer a composition containing EPA,
7 but containing no DHA, with a reasonable expectation of success in reducing triglycerides while
8 avoiding an increase in LDL. These contentions: 1) do not assert what the prior art discloses to
9 a person of ordinary skill in the art; 2) fail to address whether the specific combination of claim
10 elements were all present in the prior art references that would have been combined by a person
11 of ordinary skill in the art to produce the claimed invention with a reasonable expectation of
12 success; and 3) fail to establish *prima facie* obviousness. Defendants do not offer an obvious
13 analysis, but trivialize the claim element to the point of reading the element out of the claim.
14 Although convenient and expedient, Defendants' approach does not conform with the Local
15 Patent Rules of this District, the law of claim construction, or the law of obviousness.

16 Defendants do not identify any combination of references and simply provide a laundry
17 list of references that purportedly disclose disparate elements without explaining how they can
18 be combined.⁴³⁷⁵ As such, Defendants discuss the claim elements in isolation, and fail to address
19 the claimed invention as a whole.⁴³⁷⁶ Defendants selectively cite to an unspecified isolated
20

21 ⁴³⁷⁵ *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int'l Co. v.*
22 *Teleflex Inc.*, 550 U.S. 398, 418 (2007)) ("[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").

23 ⁴³⁷⁶ *Sanofi Syntheolabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008) ("The determination of obviousness is
24 made with respect to the subject matter as a whole, not separate pieces of the claim").

1 disclosure within a reference without considering other disclosures or even the reference as a
2 whole. Each reference, however, must be evaluated for all that it teaches.⁴³⁷⁷ Defendants’
3 unsupported cobbling of selective disclosures represents hindsight reconstruction.⁴³⁷⁸

4 Because Defendants do not identify any combination of references, they necessarily fail
5 to offer any evidence that a person of skill in the art would be motivated to combine those
6 references in order to achieve the invention of the claim as a whole. Defendants make a
7 conclusory statement that “it would have been obvious to the ordinarily skilled artisan to seek to
8 reduce triglycerides by 5% to 25%,” without providing a reason that would have prompted a
9 person of ordinary skill to reduce triglycerides by the recited amount.⁴³⁷⁹ Defendants’ burden to
10 establish *prima facie* obviousness is not discharged because there is allegedly “no significance”
11 attached to the recited TG reduction amount.⁴³⁸⁰ Defendants have not met the burden with the
12 naked assertion that it would have been obvious to seek the claim element.

13 Similarly, without the disclosure of a combination of references and a motivation/reason
14 to combine or modify the references, Defendants necessarily fail to offer any evidence that a

15 ⁴³⁷⁷ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

16 ⁴³⁷⁸ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under
17 KSR, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention
without any explanation as to how or why the references would be combined to produce the claimed invention”).

18 ⁴³⁷⁹ *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (“Rejections on obviousness grounds cannot be
19 sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational
underpinning to support the legal conclusion of obviousness.”) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir.
2006)) (internal quotation marks omitted); *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350,
20 1356-57 (Fed. Cir. 2007) (“While the KSR Court rejected a rigid application of the teaching, suggestion, or
motivation (“TSM”) test in an obviousness inquiry, the Court acknowledged the importance of identifying ‘a reason
21 that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the
claimed new invention does’ in an obviousness determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S.
22 398, 418 (2007)).

23 ⁴³⁸⁰ Plaintiffs do not have to show that a claimed range is critical unless a *prima facie* case of obviousness has been
established. See *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003) (“An applicant may overcome a *prima facie*
24 case of obviousness by establishing that the claimed range is critical . . .”) (internal quotation marks omitted).

1 person of ordinary skill in the art would have had a reasonable expectation of success in
2 achieving the claimed invention. Defendants make a conclusory statement that there was a
3 reasonable expectation of success, without providing a support other than merely identifying
4 prior art references that purportedly disclose disparate elements.⁴³⁸¹ The mere fact that elements
5 are capable of being physically combined does not establish reasonable expectation of
6 success.⁴³⁸²

7 (i) A Person of Ordinary Skill Would Not Have
8 Had a Reasonable Expectation of Success in
9 Replacing the Mixed Fish Oil Active
Ingredient in Lovaza with Pure EPA

10 Defendants provide no evidence that a person of ordinary skill would have had a
11 reasonable expectation of successfully obtaining the claimed invention—a method of reducing
12 triglycerides in a subject having very-high triglyceride levels by administering EPA of the
13 recited purity to effect a reduction in triglycerides *with the claimed LDL-C effect*—by combining
14 the references cited by defendants. For a particular combination of references, there must be a
15 reasonable expectation that the combination will produce the claimed invention. In this case, the
16 art taught that DHA and EPA have similar effects on LDL-C levels in patients with very-high
17 TG levels.⁴³⁸³ A person of ordinary skill would have expected EPA, like Lovaza/Omacor, to

18 ⁴³⁸¹ *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (“Rejections on obviousness grounds cannot be
19 sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational
20 underpinning to support the legal conclusion of obviousness.”) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir.
2006)) (internal quotation marks omitted).

21 ⁴³⁸² *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable
22 result’ discussed in *KSR* refers not only to the expectation that prior art elements are capable of being physically
23 combined, but also that the combination would have worked for its intended purpose.”).

24 ⁴³⁸³ As discussed above, see *supra* section III, a person of ordinary skill would have understood EPA and DHA to
have the same TG lowering mechanism and would have further understood that the increase in LDL-C
accompanying the TG-lowering effects of Lovaza was a product of that same mechanism. Accordingly, a person of
ordinary skill would have expected EPA to increase LDL-C levels in patients with very-high TG levels in similar
fashion to Lovaza or DHA alone.

1 raise LDL-C levels when administered to patients in the very-high TG patient population. As
 2 discussed in Section III and above, it was well known that TG-lowering agents, specifically
 3 fibrates and Lovaza/Omacor, and little or no effect on LDL-C levels for normal to high TG
 4 patients, but caused significant increases in LDL-C levels for patients with very-high
 5 triglycerides. The art cited by Defendants provides no basis for a person of ordinary skill to
 6 expect anything to the contrary. A person of ordinary skill would have understood that omega 3-
 7 fatty acids, including DHA and EPA, and fibrates cause an increase in LDL-C among very high
 8 TG patients, as reflected in the prior art:

	LDL-C Effect	
	Borderline-High or High TG Patients	Very-High TG Patients
Fibrate ⁴³⁸⁴	-20%	+45%
Lovaza/Omacor ⁴³⁸⁵	-6%	+45%

12 Accordingly, a person of ordinary skill would *not* have a reasonable expectation of
 13 success in achieving a reduction in TG levels *with the claimed LDL-C effect* in patients with
 14 very-high TG levels.⁴³⁸⁶

15 Defendants' position that a person of ordinary skill would have had a reasonable
 16 expectation of success in administering purified EPA to patients with very high triglyceride
 17 levels to achieve TG lowering *with the claimed LDL-C effect* is belied by the fact that
 18 Defendants' provide no evidence that anyone thought to administer Epadel.⁴³⁸⁷ Epadel was
 19 available for many years prior to the invention of the '560 patent, to patients with very-high TGs

21 ⁴³⁸⁴ Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

22 ⁴³⁸⁵ Chan 2002 I at 2381 (Table 3).

23 ⁴³⁸⁶ Indeed, as discussed above, a person of ordinary skill would have understood that DHA had a better overall
 effect on lipid parameters, teaching away from this combination.

24 ⁴³⁸⁷ Although Epadel was available at different levels of purity, the fact that Epadel—at any level of purity—was not
 examined in any study directed to the very-high TG patient population supports Amarin's position.

1 as a treatment. A person of ordinary skill did not expect Epadel, which consisted of mostly EPA,
2 to have superior qualities over a drug such as Lovaza/Omacor, which comprised a mixture of
3 EPA and DHA, in patients with very-high triglycerides. Indeed, none of clinical studies cited by
4 Defendants are directed to the use of purified EPA in the very-high TG population.

5 Research into the pharmaceutical uses of EPA started as early as the 1970s. In 1990,
6 Mochida Pharmaceutical, began to market Epadel, a high purity EPA drug. There have been
7 countless studies conducted which administer Epadel and report the effects observed. Although
8 a few studies administer Epadel to a patient population which included a few patients with TG
9 levels > 500 mg/dL, Defendants fail to identify a single reference directed to the administration
10 of Epadel to patients with very-high TG levels. The fact is, a person of ordinary skill did not
11 expect Epadel, which consisted of mostly EPA, to have superior qualities over a drug such as
12 Lovaza/Omacor, which comprised a mixture of EPA and DHA, in patients with very-high
13 triglycerides.

14 Defendants argue that because Grimsgaard administered purified ethyl EPA to patients
15 with borderline-high/high TG, it would have been obvious to try administering purified ethyl
16 EPA to patients with very-high TG levels with a reasonable expectation of success. Defendants
17 base this unsupported conclusion on Grimsgaard, Lovaza/Omacor, the known administration of
18 2.7 grams of purified EPA to patients with greater than 500 mg/dL TG by Matsuzawa.

19 Defendants' contentions are no more than a demonstration that certain claim elements was
20 known in the prior art and demonstrates impermissible hindsight reconstruction.⁴³⁸⁸ As is
21 reflected in Table 4 of Grimsgaard, the study authors found no difference between the DHA,

22
23 ⁴³⁸⁸ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that even under
24 KSR, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention
without any explanation as to how or why the references would be combined to produce the claimed invention.”).

EPA, and control in terms of LDL-C levels. Defendants use hindsight to argue that, despite EPA and DHA showing the same effect on LDL-C, one would have chosen EPA and expected that administration to very-high TG would have resulted in little or no impact on LDL-C. Notably, none of these references would provide a person of ordinary skill in the art with a reasonable expectation of successfully obtaining the claimed invention even if there were reasons to combine disparate, independent elements found in the prior art, which there were not.

TABLE 4
Serum lipids and apolipoproteins at baseline and change after 7 wk of supplementation with docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), or corn oil

	DHA (n = 72)		EPA (n = 75)		Corn oil (n = 77)		F test: P ¹	Contrasts between groups: P		
	Baseline	Change	Baseline	Change	Baseline	Change		DHA vs EPA	DHA vs corn oil	EPA vs corn oil
Triacylglycerols (mmol/L)	1.24 ± 0.58 ²	-0.22 ± 0.31 ²	1.23 ± 0.57	-0.15 ± 0.40 ⁴	1.22 ± 0.55	0.11 ± 0.34 ⁴	0.0001	0.14	0.0001	0.0001
Total cholesterol (mmol/L)	6.00 ± 0.95	0.03 ± 0.49	5.98 ± 0.94	-0.15 ± 0.55 ²	6.02 ± 1.08	0.10 ± 0.55	0.01	0.04	0.4	0.004
LDL cholesterol (mmol/L)	4.06 ± 0.86	0.07 ± 0.46	4.06 ± 0.83	-0.08 ± 0.48	4.04 ± 0.98	0.06 ± 0.48	0.10	—	—	—
HDL cholesterol (mmol/L)	1.36 ± 0.30	0.06 ± 0.13 ²	1.33 ± 0.31	0.01 ± 0.12	1.41 ± 0.28	-0.01 ± 0.11	0.001	0.009	0.0005	0.4
Apolipoprotein A-I (g/L)	1.38 ± 0.21	0.02 ± 0.13	1.38 ± 0.20	-0.04 ± 0.10 ²	1.46 ± 0.23	0.00 ± 0.12	0.003	0.0008	0.3	0.02
Apolipoprotein B (g/L)	1.00 ± 0.21	-0.01 ± 0.11	1.01 ± 0.23	-0.03 ± 0.11 ²	1.02 ± 0.28	0.02 ± 0.11	0.05	—	—	—
HDL-apolipoprotein A-I	0.97 ± 0.14	0.04 ± 0.07 ²	0.96 ± 0.13	0.04 ± 0.08 ²	0.97 ± 0.12	-0.01 ± 0.06	0.0001	0.8	0.0003	0.0001
Total:HDL cholesterol	4.62 ± 1.19	-0.19 ± 0.52 ⁴	4.70 ± 1.24	-0.13 ± 0.47 ²	4.43 ± 1.19	0.11 ± 0.62	0.002	0.4	0.0006	0.007

¹ ANOVA for between-group comparisons of change.

² $\bar{x} \pm$ SD.

³⁻⁵ One-sample t test of difference between baseline and 7 wk: ³ P < 0.001, ⁴ P < 0.01, ⁵ P < 0.05.

In addition, Grimsgaard was conducted in patients with normal TG levels, so a person of ordinary skill would have expected no difference between EPA and DHA in terms of LDL-C level change and would have expected no significant increase (or decrease) in LDL-C, as reported by that publication. A person of ordinary skill would further have understood that the data reported by Grimsgaard to be consistent with the understanding that while LDL-C levels are not significantly impacted in normal to high TG patient populations, LDL-C levels would increase significantly in very-high TG patients.

Matsuzawa similarly provides no basis for a reasonable expectation of success in achieving the claimed invention. The subjects of Matsuzawa had a wide range of baseline TG levels and the study was not directed to the very-high TG patient population. Accordingly, just as with Grimsgaard, Matsuzawa would not provide a reasonable expectation of success as a person of ordinary skill would understand patients with very-high TG levels to be different in terms of LDL-C effect than patients with lower TG levels.

1 To the extent that Defendants’ arguments are based on results that are not statistically
2 significant and not reported by Grimsgaard as significant, a person of ordinary skill would not
3 draw conclusions from these statistically insignificant differences. Indeed, the standard
4 deviation for the changes reported is greater than the value of the change itself.

5 Defendants argue that it would have been obvious to try administering purified ethyl EPA
6 to patients with very-high TG levels with a reasonable expectation of success. However, the
7 Federal Circuit has often rejected the notion that showing something may have been “obvious-to-
8 try” proves that the claimed invention was obvious where the prior art did not suggest what to
9 try.⁴³⁸⁹ Rather than there being a limited number of options, the state of the art provided a
10 plethora of compositions and administration protocols associated with multiple kinds of TG-
11 lowering therapies.⁴³⁹⁰ There were not a finite number of options for a person of ordinary skill
12 seeking to reduce TG levels without increasing LDL-C among the very-high TG patient
13 population.

14 Defendants argue that a person of ordinary skill at the time of the invention, based on
15 studies in normal, borderline-high and high TG patients, knew that administration of DHA alone
16 resulted in undesirable increased LDL-C levels while administration of EPA alone had little to
17 no impact on LDL-C levels. However, that statement does not conform with what was known
18 regarding the effect of Epadel and Lovaza/Omacor in normal, borderline-high and high TG
19 patients. Instead as Defendants’ own prior art demonstrates, Epadel and Lovaza/Omacor were
20 both known to have little or no effect on LDL-C in patients with borderline-high/high TG levels.

23 ⁴³⁸⁹ See *Sanofi*, 748 F.3d at 1360–61.

24 ⁴³⁹⁰ See *supra* Section III.

1 With the lack of any reasonable expectation of success, Defendants argue that their
2 proposed combination amounts to a simple substitution of one known element for another, and
3 that that these changes yield predictable results. Such an argument, however, represents pure
4 and impermissible hindsight bias and further does not consider that reasons for which a person of
5 ordinary skill would not be motivated to combine these references and affirmatives ways in
6 which the art taught away from these combinations.

7 (ii) A Person of Ordinary Skill Would Not Have
8 Had a Reasonable Expectation of Success in
9 Administering the Purified EPA in the
10 Dosing Regimen Recited in the Claims

10 Defendants contend that a “person of ordinary skill in the art would have been motivated
11 to administer 4 grams of highly-purified EPA to patients with triglycerides greater than or equal
12 to 500 mg/dL, with a reasonable expectation of success in lowering triglycerides.” Defendants
13 also argue that “[a]t least Katayama, Saito 1998, Yokoyama 2007, and Mori 2000 . . . would
14 have given a person of ordinary skill in the art a reasonable expectation of successfully
15 administering 4 g/day of highly-purified EPA-E for at least 12 weeks to lower triglycerides in
16 these subjects relative to baseline or placebo.” However, Defendants provide no evidence that a
17 person of ordinary skill would have had a reasonable expectation of success in a method of
18 reducing triglycerides in a subject having very-high triglyceride levels by administering purified
19 EPA to effect a reduction in triglycerides *with the claimed LDL-C effect*. Therefore, Defendants
20 fail to provide a reasonable expectation of success for the claimed invention.

21 Defendants further argue, that “because it was known that DHA and EPA were
22 comparably efficacious in reducing triglycerides . . . one of ordinary skill in the art would have
23 reasonably expected to see the same hypotriglyceridemic effect from a 4 g/day dose of purified
24 EPA-E as seen with 4 g/day of a combination of both EPA and DHA. Thus, it would have been

1 obvious to one of ordinary skill in the art to administer a highly-purified EPA-E composition
 2 with a reasonable expectation of success that such administration would result in reducing
 3 triglycerides while avoiding an increase in LDL.” Defendants argument is without any basis. To
 4 the contrary, because a person of ordinary skill in the art would have understood DHA and EPA
 5 to lower TGs via the same mechanism, the person of ordinary skill in the art would have
 6 expected DHA and EPA to have the same impact on LDL-C levels. Defendants provide no
 7 explanation and cite to no article to support their argument that the similar effects on TG levels is
 8 a basis to differentiate the efficacy of DHA and EPA with respect to LDL-C impact. Based on
 9 the hypotriglyceridemic effect alone, a person of ordinary skill would have reasonably expected
 10 both EPA and DHA, whether administered alone or in combination, would cause an increase in
 11 LDL-C when administered to the very high TG patient population.

12 The prior art taught that DHA and EPA have similar effects on LDL-C levels in patients
 13 with very-high TG. A person of ordinary skill would have thus expected EPA, like
 14 Lovaza/Omacor, to raise LDL-C levels when administered to the very-high TG patient
 15 population. It was well known that TG-lowering agents, specifically fibrates and
 16 Lovaza/Omacor, and little or no effect on LDL-C levels for normal to high TG patients, but
 17 caused significant increases in LDL-C levels for patients with very-high triglycerides. The art
 18 cited by Defendants provides no basis for a person of ordinary skill to expect anything to the
 19 contrary. A person of ordinary skill would have understood that omega 3-fatty acids, including
 20 DHA and EPA, and fibrates cause an increase in LDL-C among very high TG patients, as
 21 reflected in the prior art:

	LDL-C Effect	
	Borderline-High or High TG Patients	Very-High TG Patients

Fibrate ⁴³⁹¹	-20%	+45%
Lovaza/Omacor ⁴³⁹²	-6%	+45%

Accordingly, a person of ordinary skill would not have a reasonable expectation of success in achieving a reduction in TG levels *with the claimed LDL-C effect* in patients with very-high TG levels using EPA.

Defendants' position that a person of ordinary skill would have had a reasonable expectation of success in administering purified EPA to the requisite patient population to achieve a lowering in TG levels *with the claimed LDL-C effect* is belied by the fact that Defendants' provide no evidence that anyone thought to administer Epadel, which was available for many years prior to the invention of the '560 patent, to patients with very-high TGs as a treatment. Indeed, none of clinical studies cited by Defendants are directed to the use of purified EPA in the very-high TG population.

Research into the pharmaceutical uses of EPA started as early as the 1970s. In 1990, Mochida Pharmaceutical, began to market Epadel, a high purity EPA drug. There have been countless studies conducted which administer Epadel and report the effects observed. Although a few studies administer Epadel to a patient population which included a few patients with TG levels > 500 mg/dL, Defendants fail to identify a single reference directed to the administration of Epadel to patients with very-high TG levels. The fact is, a person of ordinary skill did not expect Epadel, which consisted of mostly EPA, to have superior qualities over a drug such as Lovaza/Omacor, which comprised a mixture of EPA and DHA, in patients with very-high triglycerides.

⁴³⁹¹ Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

⁴³⁹² Chan 2002 I at 2381 (Table 3).

1 Accordingly, a person of ordinary skill would not have a reasonable expectation of
2 success in achieving the claimed invention.

3 (d) Defendants Have Not Shown that Claims 5 and 15
4 of the '560 Patent Would Have Been Obvious

5 Plaintiffs incorporate by reference the discussion related to the Independent Claims in
6 Section V.I.3. Because Defendants have not shown the obviousness of the Independent Claims
7 by clear and convincing evidence, they also have not adequately proven the obviousness of
8 Claims 5 and 15.

9 Defendants offer no reference in support of their contention that these claims are obvious.
10 Defendants contend, without providing any support, that it would be obvious to one of skill in
11 the art to administer a composition containing EPA, but containing no DHA, with a reasonable
12 expectation of success in reducing Apo-B levels and thus also reduce LDL-C levels. These
13 contentions: 1) do not assert what the prior art discloses to a person of ordinary skill in the art;
14 2) are irrelevant to an obvious analysis; 3) fail to address whether the specific combination of
15 claim elements were all present in the prior art references that would have been combined by a
16 person of ordinary skill in the art to produce the claimed invention with a reasonable expectation
17 of success; and 4) fail to establish *prima facie* obviousness. Defendants do not offer an obvious
18 analysis, but trivialize the claim element to the point of reading the element out of the claim.
19 Although convenient and expedient, Defendants' approach does not conform with the Local
20 Patent Rules of this District, the law of claim construction, or the law of obviousness.

21 Defendants fail to show a specific combination of references that discloses each element
22 of the claimed invention. None of the cited references discloses administration of the claimed
23 EPA to very high TG patients. Defendants further fail to explain how the cited references can be
24

1 combined to teach the administration of the claimed EPA to very high TG patients.⁴³⁹³
2 Defendants selectively cite to an unspecified, isolated disclosure within a reference without
3 considering other disclosures or even the reference as a whole. Each reference, however, must
4 be evaluated for all that it teaches.⁴³⁹⁴ Defendants’ unsupported cobbling of selective disclosures
5 represents hindsight reconstruction.⁴³⁹⁵

6 Defendants fail to show a motivation or reason to combine or modify the references
7 recited above. Defendants make a conclusory statement that the claimed methods of treatment
8 would have been obvious but such a naked assertion does not show why a person of ordinary
9 skill would have been motivated to combine the references to achieve the claimed invention.⁴³⁹⁶

10 Defendants fail to show a reasonable expectation that a person of ordinary skill would
11 have successfully achieved the claimed invention. In fact, Defendants do not even discuss
12 whether a person of ordinary skill would have expected that the combination to work for its
13 intended purpose.⁴³⁹⁷ As such, Defendants fail to demonstrate reasonable expectation of success
14 of the claimed invention.

16 ⁴³⁹³ *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)) (“[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”).

18 ⁴³⁹⁴ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

19 ⁴³⁹⁵ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under KSR, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention”).

20 ⁴³⁹⁶ *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the KSR Court rejected a rigid application of the teaching, suggestion, or motivation (‘TSM’) test in an obviousness inquiry, the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

22 ⁴³⁹⁷ *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable result’ discussed in KSR refers not only to the expectation that prior art elements are capable of being physically combined, but also that the combination would have worked for its intended purpose.”)

1 Defendants cite only one reference in their invalidity contentions with respect to this
2 claim, Theobald, and *not* for the proposition that the asserted claim is obvious. Instead,
3 Defendants cite Theobald for the proposition that “it was known that Apo-B is a component of
4 LDL-C.” Defendants cite to no passage or page of Theobald in connection with that argument
5 and no support for their argument that Theobald makes such a disclosure. Defendants appear to
6 suggest a correlation between Apo-B and LDL-C but ignore that Apo-B is present on all
7 atherogenic lipoproteins.⁴³⁹⁸

8 Defendants then make the unsupported assertion that “one of ordinary skill in the art
9 would reasonably expect that a pure EPA composition would reduce Apo-B, as it is known to
10 reduce VLDL syntheses.” They are incorrect. Neither Defendants’ characterization of Theobald
11 nor the disclosures of that reference teach that EPA compositions would reduce Apo-B or render
12 this claim obvious. Defendants’ assertion that EPA was known to reduce VLDL synthesis
13 ignores that, as discussed above, *see* Section III, DHA was also understood to reduce VLDL
14 synthesis. Nor do defendants explain the relevance of VLDL synthesis to their arguments with
15 respect to these claims or Apo-B levels.

16 As discussed above, *see* Section IV, Theobald discloses the administration of a
17 triacylglycerol composition derived from *Cryptocodinium cohnii* to healthy subjects. While
18 Defendants make an unexplained citation to Theobald regarding the proposition that Apo-B is a
19 component of LDL-C, they fail to discuss the reference’s disclosures regarding the impact of
20 administration of the triacylglycerol composition on Apo-B levels. In doing so, they fail to
21
22

23 ⁴³⁹⁸ June 26, 2012 Bays Declaration; *see also* Section III.
24

consider the reference for all that it teaches. Theobald discloses an *increase* in Apo-B following administration of the triacylglycerol composition of that reference.⁴³⁹⁹

TABLE 3
Serum lipoproteins before treatment and after 3 mo of docosahexaenoic acid (DHA) and placebo treatment in all subjects

	DHA		Placebo		Treatment effect ¹
	Before treatment	After treatment	Before treatment	After treatment	
Total cholesterol (mmol/L)	5.15 ± 0.145 ²	5.44 ± 0.174	5.08 ± 0.168	5.22 ± 0.155	0.22 (0.01, 0.42) ³
LDL cholesterol (mmol/L)	3.16 ± 0.129	3.48 ± 0.152	3.16 ± 0.146	3.25 ± 0.131	0.23 (0.08, 0.38) ⁴
HDL cholesterol (mmol/L) ⁵	1.47 ± 0.052	1.55 ± 0.064	1.46 ± 0.062	1.48 ± 0.056	0.07 (0.005, 0.14)
Triacylglycerol (mmol/L) ⁶	1.03 ± 0.094	1.01 ± 0.089	1.06 ± 0.106	1.19 ± 0.103	-0.18 (-0.37, 0.05)
Apolipoprotein B (g/L)	0.84 ± 0.027	0.87 ± 0.026	0.83 ± 0.028	0.84 ± 0.028	0.03 (0.002, 0.055) ⁷
LDL cholesterol:apo B (mmol/g)	3.75 ± 0.376	3.96 ± 0.462	3.74 ± 0.521	3.84 ± 0.409	0.12 (0.004, 0.24) ³
Weight (kg) ⁸	70.1 ± 2.04	70.6 ± 2.06	70.5 ± 2.01	70.6 ± 2.01	0 (-0.85, 0.24)

¹ Mean difference between active treatment and placebo; 95% CI in parentheses.

² $\bar{x} \pm \text{SEM}$ (all such values); $n = 38$.

^{3,4,7} Paired t test: ³ $P = 0.04$, ⁴ $P = 0.004$, ⁷ $P = 0.03$.

⁵ HDL increased in subjects receiving DHA first. Significant treatment \times order effect, $P = 0.005$.

⁶ $n = 37$; data were log transformed before analysis by paired t test.

⁸ Weight increased over the entire study period. Significant order \times time effect, $P = 0.001$.

As discussed above, *see* Section III, a person of skill in the art would not have distinguished between the lipid effects of EPA and DHA therapy. To the extent, then that a person of ordinary skill would have considered Theobald, they would not conclude from the reference that EPA therapy decreases Apo-B levels in very high TG patients.

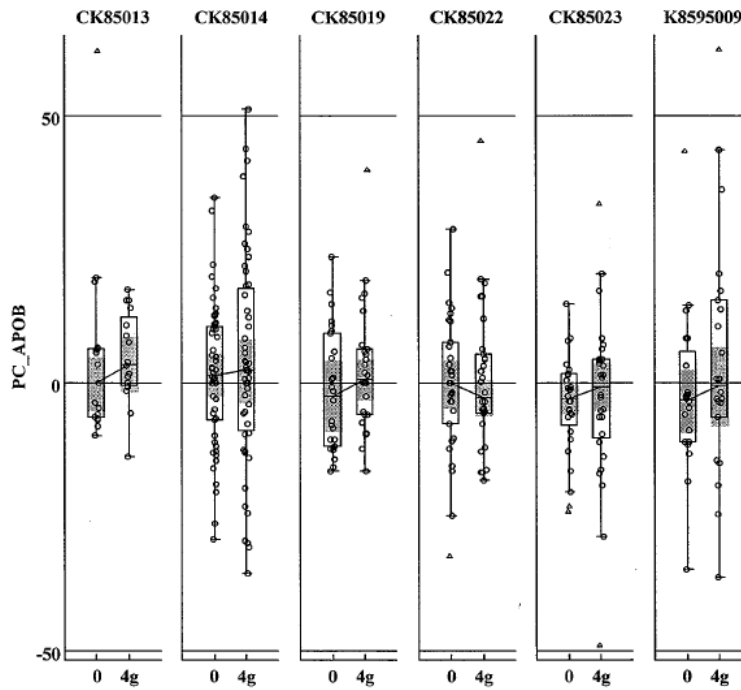
A person of skill in the art would *not* have understood that EPA therapy in very high TG patients would yield a reduction in Apo-B levels. A person of ordinary skill would have looked to the Lovaza clinical trials—the only clinical trial to study the effects of omega-3 fatty acids on Apo-B levels in patients with very high TG levels.⁴⁴⁰⁰ The Lovaza clinical trial, which was a large study conducted on patients with very high TG levels, shows no difference between a placebo-control group and the treatment group with respect to Apo-B levels.⁴⁴⁰¹

⁴³⁹⁹ Theobald at 561, table 3.

⁴⁴⁰⁰ May 8, 2012 Bays Declaration.

⁴⁴⁰¹ Lovaza Approval Package at Table 14.

14. Box plot of individual Category I studies -% change of APOB

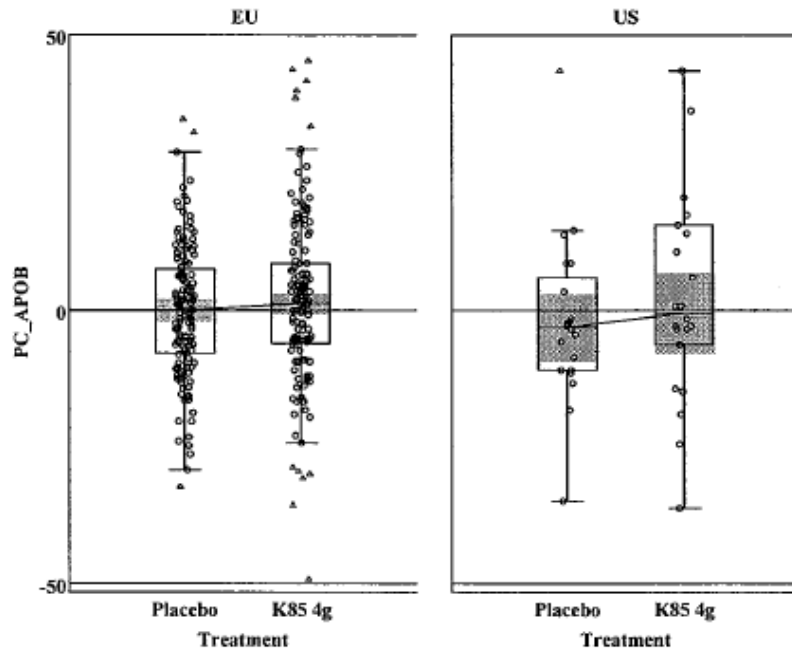


In each of these studies, including K8595009, where subjects had a median baseline TG level of 818 mg/dL,⁴⁴⁰² there was no change in Apo-B between the control and treatment groups. Likewise, pooling the data from the different studies of Lovaza in the EU and US also reflected that treatment with Lovaza did not impact Apo-B compared to placebo.⁴⁴⁰³

⁴⁴⁰² The parameters for each study reports can be located at page 4 of the Lovaza Approval Package.

⁴⁴⁰³ Lovaza Approval Package at Table 7.

7. Box plot of pooled Category I studies -% change of APOB



Indeed, none of the data reported in the Lovaza clinical trials reflects a decrease in Apo-B. In addition to the Lovaza studies, a person of ordinary skill would have understood that the literature reported, in a variety of clinical studies, that omega-3s do not impact Apo-B levels.⁴⁴⁰⁴ While Theobald does not even support Defendants' obviousness arguments, their selective citation of that reference represents impermissible hindsight bias. The examiner had before him a large number of prior art references reporting Apo-B effects and, even as defendants concede, agreed that the Apo-B effects reported by the claimed inventions were unexpected in light of

⁴⁴⁰⁴ See Grimsgaard, Okumura, Hayashi, Hayasaka 1995, and Aoki 1993.

1 those references, also reflecting a lack of motivation and no reasonable expectation of
2 success.⁴⁴⁰⁵

3 Further, a person of skill in the art would have understood Apo-B to be a surrogate for the
4 number of atherogenic lipoproteins (VLDL, IDL, LDL) present in the body.⁴⁴⁰⁶ The person of
5 skill in the art would also have recognized that, as TG levels in patients with very high TG levels
6 rose, an increasing amount of TGs in those patients were contained within chylomicrons. As
7 discussed above, *see* Section III, the processing of chylomicrons would not yield atherogenic
8 lipoproteins, but instead smaller, denser particles referred to as remnant.⁴⁴⁰⁷ Accordingly,
9 because very high TG patients had increasing levels of TGs stored in chylomicrons and because
10 chylomicron processing would not have been understood to yield changes in Apo-B, a person of
11 skill in the art would have believed that TG-lowering therapies directed to very high TG patients
12 would not significantly impact Apo-B.

13 Accordingly, a person of ordinary skill in the art would not have been motivated to
14 replace EPA with the composition of Lovaza, nor would the person of ordinary skill in the art
15 have been motivated to administer the EPA composition of the claimed invention to very high
16 TG patients. For the same reasons, a person of ordinary skill in the art would not have a
17 reasonable expectation of success in achieving the claimed invention.

18
19
20
21
22 _____
⁴⁴⁰⁵ Defendants' Contentions at 236.

23 ⁴⁴⁰⁶ ATP-III at 3170; Bays 2008 I at 395.

24 ⁴⁴⁰⁷ Kwiterovich in Kwiterovich at 4.

(e) Defendants Have Not Shown that Claims 6 and 16 of the '560 Patent Would Have Been Obvious

Plaintiffs incorporate by reference the discussion related to the Independent Claims in Section V.I.3. Because Defendants have not shown the obviousness of the Independent Claims by clear and convincing evidence, they also have not adequately proven the obviousness of Claims 6 and 16.

Defendants contend that it would have been obvious to use the claimed composition to reduce VLDL-C levels, and that the recited VLDL-C reduction represents therapeutic efficacy. These contentions: 1) do not assert what the prior art discloses to a person of ordinary skill in the art; 2) are irrelevant to an obvious analysis; 3) fail to address whether the specific combination of claim elements were all present in the prior art references that would have been combined by a person of ordinary skill in the art to produce the claimed invention with a reasonable expectation of success; and 4) fail to establish *prima facie* obviousness. Defendants do not offer an obvious analysis, but trivialize the claim element to the point of reading the element out of the claim. Although convenient and expedient, Defendants' approach does not conform with the Local Patent Rules of this District, the law of claim construction, or the law of obviousness.

Defendants do not identify any combination of references. Because Defendants do not identify any combination of references, they necessarily fail to offer any evidence that a person of skill in the art would be motivated to combine those references in order to achieve the invention of the claim as a whole. In fact, Defendants do not discuss at all whether a person of ordinary skill would have been motivated to combine the elements.⁴⁴⁰⁸ As such, Defendants fail

⁴⁴⁰⁸ *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the *KSR* Court rejected a rigid application of the teaching, suggestion, or motivation (‘TSM’) test in an obviousness inquiry,

1 to demonstrate that there was no motivation to combine the references to achieve the claimed
2 invention.

3 Similarly, without the disclosure of a combination of references and a motivation/reason
4 to combine or modify the references, Defendants necessarily fail to offer any evidence that a
5 person of ordinary skill in the art would have had a reasonable expectation of success in
6 achieving the claimed invention. Defendants make conclusory statements without providing any
7 support. What is more, Defendants do not even discuss the reasonable expectation of reducing
8 VLDL-C levels. As such, Defendants fail to demonstrate reasonable expectation of success of
9 reducing VLDL-C levels using the claimed methods.

10 (f) Defendants Have Not Shown that Claims 8, 18, 19
11 and 20 of the '560 Patent Would Have Been
Obvious

12 Plaintiffs incorporate by reference the discussion related to the Independent Claims in
13 Section V.I.3. Because Defendants have not shown the obviousness of the Independent Claims
14 by clear and convincing evidence, they also have not adequately proven the obviousness of
15 Claims 8 and 18-20.

16 Defendants contend that WO '900, the Lovaza label, Grimsgaard and Mori 2000 teach
17 the additional claim elements of dependent Claims 8 and 18-20. Defendants contend, without
18 providing any support, that the claim elements are the results of simply optimizing the conditions
19 described in the prior art and within the purview of the skilled physicians. These contentions: 1)
20 do not assert what the prior art discloses to a person of ordinary skill in the art; 2) are irrelevant
21 to an obvious analysis; 3) fail to address whether the specific combination of claim elements

22
23 the Court acknowledged the importance of identifying 'a reason that would have prompted a person of ordinary skill
24 in the relevant field to combine the elements in the way the claimed new invention does' in an obviousness
determination.") (quoting *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

1 were all present in the prior art references that would have been combined by a person of
2 ordinary skill in the art to produce the claimed invention with a reasonable expectation of
3 success; and 4) fail to establish *prima facie* obviousness. Defendants do not offer an obvious
4 analysis, but trivialize the claim element to the point of reading the element out of the claim.
5 Although convenient and expedient, Defendants’ approach does not conform with the Local
6 Patent Rules of this District, the law of claim construction, or the law of obviousness.

7 Defendants fail to show a specific combination of references that discloses each element
8 of the claimed invention. None of the cited references discloses administration of the claimed
9 EPA to very high TG patients. Defendants further fail to explain how the cited references can be
10 combined to teach the administration of the claimed EPA to very high TG patients.⁴⁴⁰⁹

11 Defendants selectively cite to an unspecified, isolated disclosure within a reference without
12 considering other disclosures or even the reference as a whole. Each reference, however, must
13 be evaluated for all that it teaches.⁴⁴¹⁰ Defendants’ unsupported cobbling of selective disclosures
14 represents hindsight reconstruction.⁴⁴¹¹

15 Defendants fail to show a motivation or reason to combine or modify the references
16 recited above. Defendants make a conclusory statement that the claimed methods of treatment
17 “would have been obvious to one of ordinary skill in the art,” but such a naked assertion does not
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20 ⁴⁴⁰⁹ *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int’l Co. v.*
21 *Teleflex Inc.*, 550 U.S. 398, 418 (2007)) (“[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”).

22 ⁴⁴¹⁰ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

23 ⁴⁴¹¹ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under
24 *KSR*, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention
without any explanation as to how or why the references would be combined to produce the claimed invention”).

1 show why a person of ordinary skill would have been motivated to combine the references to
2 achieve the claimed invention.⁴⁴¹²

3 Defendants fail to show a reasonable expectation that a person of ordinary skill would
4 have successfully achieved the claimed invention. In fact, other than simply identifying prior art
5 references that purportedly disclose disparate elements, Defendants do not even discuss whether
6 a person of ordinary skill would have expected that the combination to work for its intended
7 purpose.⁴⁴¹³ As such, Defendants fail to demonstrate reasonable expectation of success of the
8 claimed invention.

9 **4. The '560 Patent is Not Invalid Under § 112**

10 a) Defendants Have Not Demonstrated that the Claims of the '560
11 patent Are Invalid for Indefiniteness

12 35 U.S.C. ¶ 112(b) requires that a patentee “particularly point[] out and distinctly claim[]
13 the subject matter which the applicant regards as his invention.”⁴⁴¹⁴ Patent claims are valid in
14 light of an indefiniteness challenge if they “inform, with reasonable certainty, those skilled in the
15 art about the scope of the invention” in light of the specification and the prosecution history.⁴⁴¹⁵

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17 ⁴⁴¹²*Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the *KSR*
18 Court rejected a rigid application of the teaching, suggestion, or motivation (‘TSM’) test in an obviousness inquiry,
the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill
in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness
determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

19 ⁴⁴¹³*DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable
20 result’ discussed in *KSR* refers not only to the expectation that prior art elements are capable of being physically
combined, but also that the combination would have worked for its intended purpose.”)

21 ⁴⁴¹⁴ Defendants were required to disclose the basis for their assertion of indefiniteness with respect to each term, and
they have not met that requirement. They simply make conclusory assertions regarding indefiniteness despite
22 bearing the burden of proof. Moreover, Defendants’ failure prevents Plaintiffs from responding to their assertions
other than by making conclusory assertions in return. Therefore, Defendants should be precluded from
23 supplementing their naked assertions with new basis in the course of the litigation.

24 ⁴⁴¹⁵*Nautilus, Inc. v. Biosig Instruments, Inc.*, 134 S. Ct. 2120, 2124 (2014).

1 The Supreme Court has recognized that “absolute precision is unattainable” in claim language
2 and “the certainty which the law requires in patents is not greater than is reasonable.”⁴⁴¹⁶

3 Defendants allege that a number of terms containing the phrases “about” and
4 “substantially” are indefinite. Defendants do not provide any reason why these terms are
5 indefinite other than that they contain the phrases “about” and “substantially.” But, of course,
6 these terms are routinely used in patent claims, and are not *per se* indefinite.⁴⁴¹⁷ In particular,
7 courts have held repeatedly that claims that contain the words “about” and “substantially” are not
8 indefinite.⁴⁴¹⁸ Here, a person of ordinary skill would understand with reasonable certainty what
9 is claimed when the claims are read in light of the specification and prosecution history.⁴⁴¹⁹
10 Therefore, the terms that contain the words “about” and “substantially” are not invalid for being
11 indefinite.

12 Defendants further allege that the terms “a pharmaceutical composition comprising ...
13 not more than about 3% docosahexaenoic acid ... by weight of all fatty acids present” are

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15 ⁴⁴¹⁶ *Id.* at 2129.

16 ⁴⁴¹⁷ *Interval Licensing LLC v. AOL, Inc.*, 766 F.3d 1364, 1370 (Fed. Cir. 2014) (“Claim language employing terms
17 of degree has long been found definite where it provided enough certainty to one of skill in the art when read in the
18 context of the invention.”); *see also BJ Servs. Co. v. Halliburton Energy Servs., Inc.*, 338 F.3d 1368, 1372 (Fed. Cir.
19 2003) (“The question becomes whether one of ordinary skill in the art would understand what is claimed when the
20 claim is read in light of the specification.”) (discussing the term “about”); *Verve, LLC v. Crane Cams, Inc.*, 311 F.3d
21 1116, 1120 (Fed. Cir. 2002) (“It is well established that when the term ‘substantially’ serves reasonably to describe
22 the subject matter so that its scope would be understood by persons in the field of the invention, and to distinguish
23 the claimed subject matter from the prior art, it is not indefinite.”).

20 ⁴⁴¹⁸ *See, e.g., Deere & Co. v. Bush Hog, LLC*, 703 F.3d 1349, 1359 (Fed. Cir. 2012) (rejecting contention that claim
21 term “substantially planar” is indefinite); *Enzo Biochem, Inc. v. Applera Corp.*, 599 F.3d 1325, 1335 (Fed. Cir.
22 2010) (holding that the claim phrase “not interfering substantially” was not indefinite even though the construction
23 “define[d] the term without reference to a precise numerical measurement”); *BJ Services Co. v. Halliburton Energy
24 Services, Inc.*, 338 F.3d 1368, 1372–73 (Fed. Cir. 2003) (affirming jury’s verdict that claims reciting a concentration
as “about 0.06” were not invalid for being indefinite); *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540,
1557 (Fed. Cir. 1983) (ruling that the claim term “stretching ... at a rate exceeding about 10% per second” is not
indefinite).

⁴⁴¹⁹ *See generally* the ’560 patent and its prosecution history.

1 indefinite. They contend that, because there is no indication of how much of the pharmaceutical
2 composition is composed of fatty acids, by extension it is indefinite how much of each fatty acid
3 is present in the composition. This is incorrect. A claim can use a ratio to define amounts of
4 components in a product, using terms such as “percent by weight.”⁴⁴²⁰ In light of the
5 specification and prosecution history, a person of ordinary skill would understand with
6 reasonable certainty the range of relative quantities of EPA, DHA and/or other fatty acids in the
7 recited pharmaceutical composition in relation to all fatty acids present.⁴⁴²¹ Therefore, these
8 terms are not indefinite and do not render the claims indefinite.

9 Defendants also allege that it is impossible to ascertain the metes and bounds of “subject
10 compared to placebo control” A person of ordinary skill, however, would understand the metes
11 and bounds of the term in light of the specification and the prosecution history.⁴⁴²² Moreover,
12 the method of comparing a subject to a second subject, such as a placebo controlled, randomized,
13 double blind study, would have been known to a person of ordinary skill at the time of the
14 invention. Therefore, the term does not render the claims indefinite.

15 Finally, Defendants contend that the asserted claims improperly mix methods and
16 formulations because Plaintiffs’ assertion of contributory infringement apparently suggests that
17 the scope of the claims includes formulations. This is a mistaken interpretation. Indefiniteness
18 analysis is based on what the claim language informs a person of ordinary skill in the art in light
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20 ⁴⁴²⁰ *T.F.H. Publications, Inc. v. Doskocil Mfg. Co.*, No. CIV.A. 08-4805 FLW, 2012 WL 715628, at *5–6 (D.N.J.
21 Mar. 5, 2012) (construing “by weight” to mean the weight of a first component was in a ratio to the weight of a
22 second component); *Allergan, Inc. v. Sandoz Inc.*, No. 2:09-CV-182, 2011 WL 1599049, at *10 (E.D. Tex. Apr. 27,
2011) (construing percent by weight to mean “ratio of the weight of the ingredient in question divided by the total
volume of the solution, with this ratio expressed as a percentage”).

23 ⁴⁴²¹ See generally the ’560 patent and its prosecution history.

24 ⁴⁴²² See generally the ’560 patent and its prosecution history.

1 of the specification and the prosecution history. Defendants do not identify any actual claim
2 language that mixes methods and formulations. Moreover, contributory infringement may be
3 asserted and proven when a party sells “a material or apparatus for use in *practicing a patented*
4 *process . . . knowing the same to be especially made or especially adapted for use in an*
5 *infringement of such patent.*”⁴⁴²³ Plaintiffs assert that Defendants’ ANDA products will be used
6 in practicing the claimed methods. Plaintiffs do not assert that the pharmaceutical compound
7 itself directly infringes. Therefore, Defendants’ interpretations of Plaintiffs’ assertions are
8 mistaken and the ’560 patent claims are not indefinite for improperly mixing methods and
9 formulations.

10 b) Defendants Have Not Demonstrated that the Claims of the ’560
11 patent Are Invalid for Insufficient Written Description

12 The first paragraph of 35 U.S.C. § 112 requires that a patent specification “contain a
13 written description of the invention.” This requires that the specification “reasonably convey”
14 that the applicant “invented” or “had possession” of the claimed subject matter when the
15 application was filed.⁴⁴²⁴ Support need not be literal⁴⁴²⁵—it may be implicit⁴⁴²⁶ or inherent⁴⁴²⁷ in
16 the disclosure. In addition, it is unnecessary to include information that is already known or
17 available to persons of ordinary skill.⁴⁴²⁸

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⁴⁴²³ 35 U.S.C. § 271(c) (emphasis added).

19 ⁴⁴²⁴ *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010).

20 ⁴⁴²⁵ *Id.* at 1352; *Cordis Corp. v. Medtronic AVE, Inc.*, 339 F.3d 1352, 1365 (Fed. Cir. 2003); *In re Wright*, 866 F.2d
422, 425 (Fed. Cir. 1989); *In re Smith*, 481 F.2d 910, 914 (C.C.P.A. 1973).

21 ⁴⁴²⁶ *All Dental Prodx, LLC v. Advantage Dental Prods. Inc.*, 309 F.3d 774, 779 (Fed. Cir. 2002); *In re Wright*, 866
F.2d at 424–25.

22 ⁴⁴²⁷ *In re Gay*, 309 F.2d 769, 771 (C.C.P.A. 1962).

23 ⁴⁴²⁸ *Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1367–68 (Fed. Cir. 2006); *Capon v. Eshhar*, 418 F.3d 1349,
1357 (Fed. Cir. 2005); *In re Gay*, 309 F.2d at 774.

1 Defendants make three arguments regarding the written description requirement. First,
2 Defendants contend that elements reciting the baseline TG levels of the asserted claims lack
3 written description. This is incorrect. The specification of asserted patents literally discloses the
4 claimed invention.⁴⁴²⁹ Moreover, the recited baseline TG levels of the claimed invention appear
5 in the original claims of the application to which the asserted patent claims priority. Thus, there
6 is a strong presumption that the claimed invention is adequately described.⁴⁴³⁰ Defendants do
7 not and cannot rebut this presumption. Specifically, the patient population is originally claimed
8 as “a subject having a fasting baseline triglyceride level of about 500 mg/dl to about 1500
9 mg/dl.”⁴⁴³¹ The asserted claims recite the same patient population. Defendants do not contend
10 that the patient population of the asserted claims is not literally described by the specification
11 and in the original claims of the application to which the asserted patent claims priority. In fact,
12 the specification and the provisional patent application claims at the time of filing described
13 these limitations. Therefore, Defendants have failed to explain whether and how an aspect of the
14 claimed invention has not been described with sufficient particularity such that one skilled in the
15 art would recognize that the applicant had possession of the claimed invention.

16 Second, Defendants contend that “a person of skill in the art would not understand that
17 the inventor was in possession of a method incorporating [] specific dosages and quantities.”
18 Defendants’ assertion is incorrect. The specification of the asserted patents literally discloses the

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20 ⁴⁴²⁹ *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (“[T]he test requires an objective
21 inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art.”);
Snitzer v. Etzel, 465 F.2d 899, 902 (C.C.P.A. 1972) (“[T]he literal description of a species provides the requisite
22 legal foundation for claiming that species.”).

23 ⁴⁴³⁰ *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976) (“we are of the opinion that the PTO has the
24 initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure
a description of the invention defined by the claims”).

⁴⁴³¹ See U.S. Application No. 12/702,889.

1 dosages and quantities of the claimed methods.⁴⁴³² Moreover, the dosages and quantities of the
2 method appear in the claims, as originally filed. Thus, there is a strong presumption that the
3 claimed invention is adequately described.⁴⁴³³ Defendants do not and cannot rebut this
4 presumption. For example, the dosage of the composition was originally claimed as “about 1 g
5 to about 4g.”⁴⁴³⁴ Defendants do not contend that dosages and quantities of the asserted claims
6 are not literally described by the specification and in the original claims. In fact, the
7 specification and the provisional patent application claims, at the time of filing, described these
8 limitations. Therefore, Defendants have failed to explain whether and how an aspect of the
9 claimed invention has not been described with sufficient particularity such that one skilled in the
10 art would recognize that the applicant had possession of the claimed invention.

11 Third, Defendants contend that “a person of skill in the art would not understand that the
12 inventor was in possession of a method comprising a comparison against a placebo control.”
13 Although this allegation does not appear to implicate written description, the specification
14 describes such a comparison. Therefore, a person of ordinary skill would have understood that
15 the inventor was in possession of a method comprising administration of a composition with the
16 recited properties, based on a specific comparison of a subject or a population against a second
17 subject, a placebo control, or a second population.

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20 ⁴⁴³² *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (“[T]he test requires an objective
21 inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art.”);
22 *Snitzer v. Etzel*, 465 F.2d 899, 902 (C.C.P.A. 1972) (“[T]he literal description of a species provides the requisite
23 legal foundation for claiming that species.”).

24 ⁴⁴³³ *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976) (“we are of the opinion that the PTO has the
initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure
a description of the invention defined by the claims”).

⁴⁴³⁴ See U.S. Application No. 12/702,889.

1 In its 2010 *en banc* decision in *Ariad Pharmaceuticals, Inc. v. Eli Lilly Co.*,⁴⁴³⁵ the court
2 elaborated that “possession” means possession as evidenced by disclosure. In this case, the
3 specification of asserted patents literally disclose the claimed invention in the specification and
4 the claims as originally filed. Thus, an examination of the four corners of the specification from
5 the perspective of a person of ordinary skill in the art demonstrates that the inventors of the
6 asserted patents were in possession of the claimed invention.

7 Defendants conclude by alleging that the specification does not describe anything more
8 than what is obvious, and thus does not provide adequate support for any nonobvious claim.
9 That is incorrect and irrelevant. Nonobviousness does not have to be supported solely by the
10 specification; nonobviousness can be supported by post-filing date evidence for example.⁴⁴³⁶
11 Written description requires only that the specification reasonably conveys that the applicant had
12 possession of the claimed subject matter when the application was filed. Therefore, whether the
13 claims are obvious has no bearing on the adequacy of written description.

14 c) Defendants Have Not Demonstrated that the Claims of the ‘560
15 patent Are Invalid for Lack of Enablement

16 The first paragraph of 35 U.S.C. § 112 requires that the specification “enable any person
17 skilled in the art . . . to make and use [the claimed invention].” A claim is not enabled if it would
18 require undue experimentation for a person of ordinary skill to make or use the invention.

19 ⁴⁴³⁵ *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1343-48 (Fed. Cir. 2010).

20 ⁴⁴³⁶ See *Sanofi–Aventis Deutschland GmbH v. Glenmark Pharm., Inc.*, 748 F.3d 1354, 1360 (Fed. Cir. 2014)
21 (“Glenmark also argues that later-discovered benefits cannot be considered in an obviousness analysis.... That is
22 incorrect; patentability may consider all of the characteristics possessed by the claimed invention, whenever those
23 characteristics become manifest.”); *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291,
24 1307 (Fed. Cir. 2011) (“[E]vidence of unexpected results may be [considered] ... even if that evidence was obtained
after the patent's filing or issue date.”); *Knoll Pharm. Co. v. Teva Pharm. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir.
2004) (“Evidence developed after the patent grant is not excluded from consideration, for understanding of the full
range of an invention is not always achieved at the time of filing the patent application.”).

1 Factors that may be considered include the quantity of experimentation necessary, the amount of
2 direction or guidance presented, the presence or absence of working examples, the nature of the
3 invention, the state of the prior art, the relative skill of those in the art, the predictability or
4 unpredictability of the art, and the breadth of the claims.⁴⁴³⁷ The enablement requirement is
5 separate and distinct from the written description requirement,⁴⁴³⁸ and as such a claim does not
6 require descriptive support in the disclosure as originally filed for it to be enabled.⁴⁴³⁹

7 Defendants make two specific arguments regarding the enablement requirement. First,
8 Defendants contend that “[i]t would take undue experimentation to obtain the actual amounts of
9 the composition found in the ultimate claims.” This is incorrect. As Defendants admit, the
10 claims disclose amounts of the composition to be administered. Therefore, a person of ordinary
11 skill would be able to determine the amounts of the components in the pharmaceutical
12 composition without any experimentation, much less undue experimentation.

13 Second, Defendants contend that it would take undue experimentation to obtain the
14 claimed required results listed in the full scope of the patent claims, including the claimed lipid
15 effects. This is incorrect. The asserted claims require no experimentation to practice the claimed
16 method and certainly not undue experimentation. Administration of a recited amount of a recited
17 composition, for a recited duration, to a specific, recited patient population produces the recited
18 results. No additional experimentation is required, and Defendants do not explain their
19 allegation that undue experimentation would be required. Defendants also do not contend that
20 following the claimed method (each recited element) does not produce the recited results. The
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⁴⁴³⁷ See, e.g., *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

23 ⁴⁴³⁸ *Vas-. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991)

24 ⁴⁴³⁹ MPEP § 2164.

1 clinical studies included in the VASCEPA® label and submitted to the USPTO clearly
2 demonstrate that administration of EPA of the recited composition, when administered to
3 patients with very high TG levels for at least 12 weeks, as specified, produces the recited
4 results.⁴⁴⁴⁰ Therefore, the claims are not invalid for lack of enablement.

5 Defendants conclude by alleging that the specification does not enable anything more
6 than what is obvious over the prior art or was known to a person of skill in the art. First,
7 Defendants do not cite any case or present a legal theory to support this assertion. As such, they
8 do not allow Plaintiffs to adequately respond to the assertion. Therefore, Defendants should be
9 precluded in the future from raising any new legal theory to support this assertion. Moreover,
10 while the '560 patent's specification enables a person of ordinary skill to obtain the claimed
11 limitations without undue experiment, the claimed limitations would not have been obvious to a
12 person of ordinary skill, as discussed in Section V.I.3. Furthermore, Plaintiffs have initiated
13 human clinical trials and submitted the trial results to the USPTO to substantiate the utility of its
14 claimed methods.^{4441, 4442} Therefore, a person of ordinary skill would have concluded that the
15 claims possessed credible therapeutic utility, and the full scope of the claims was enabled.

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⁴⁴⁴⁰ See VASCEPA® Prescribing Information at Table 2.

21 ⁴⁴⁴¹ *In re Brana*, 51 F.3d 1560, 1567 n.19 (Fed. Cir. 1995) (Post-filing evidence “can be used to substantiate any
22 doubts as to the asserted utility.”); MPEP § 2107.03 (“[A]s a general rule, if an applicant has initiated human clinical
23 trials for a therapeutic product or process, Office personnel should presume that the applicant has established that
the subject matter of that trial is reasonably predictive of having the asserted therapeutic utility.”).

24 ⁴⁴⁴² See May 16, 2011 Bays Declaration at Appendix B.

1 **J. The ‘650 Patent**

2 **1. The ‘650 Patent Claims Eligible Subject Matter Under § 101**

3 Defendants’ allegation that the asserted claims of the ‘650 patent relate to ineligible
4 subject matter under Section 101 is without merit. Defendants do not establish a *prima facie*
5 case under Section 101 or provide a legal or factual basis to support their allegations.

6 As an initial matter, Defendants’ disclosure is also insufficient under the Nevada Local
7 Patent Rules as the grounds for any allegation of invalidity under Section 101 must be
8 provided.⁴⁴⁴³ The bare assertion of invalidity under Section 101 without providing the grounds
9 for such an allegation and examining the elements of the asserted claims of the ‘650 patent does
10 not meet this requirement and thwarts the purpose of the Rules.⁴⁴⁴⁴

11 The inquiry under Section 101 involves a two-step test: first, a court must determine
12 whether the claim at issue is directed to a patent-ineligible concept: a law of nature, physical
13 phenomenon, or abstract idea.⁴⁴⁴⁵ Second, even if the claim is directed to one of these concepts,
14 it still may be patent eligible and the court must determine what else is part of the claim.⁴⁴⁴⁶

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17 ⁴⁴⁴³ See Nevada Local Patent Rule 1.8(e) (“[E]ach party opposing a claim of patent infringement, shall serve on all
18 other parties Non-Infringement, Invalidity, and Unenforceability Contentions that must include . . . A detailed
statement of any grounds of invalidity based on 35 U.S.C. § 101.”).

19 ⁴⁴⁴⁴ Nor does the preceding paragraph, which provides only a purported summary of the claims of the ‘650 patent, or
20 subsequent paragraph, which makes what appears to be an argument entirely unrelated to Section 101, provide the
21 grounds for Defendants’ allegation of invalidity under 35 U.S.C. § 101. See, e.g., *Silver State Intellectual Techs.,
Inc. v. Garmin Int’l, Inc.*, 32 F. Supp. 3d 1155, 1161–62 (D. Nev. 2014) (“The District of Nevada’s Local Patent
Rules, like the local patent rules for the Northern District of California, are designed to require the parties to provide
early notice of their infringement and invalidity contentions, and to proceed with diligence in amending those
contentions when new information comes to light in the course of discovery”) (internal quotation marks omitted).

22 ⁴⁴⁴⁵ *Alice Corp. Pty. v. CLS Bank Int’l*, 134 S. Ct. 2347, 2355 (2014) (“First, we determine whether the claims at
23 issue are directed to one of those patent-ineligible concepts.”).

24 ⁴⁴⁴⁶ *Id.* (quoting *Mayo*, 132 S. Ct. at 1294) (“If so, we then ask, ‘[w]hat else is there in the claims before us?’”).

1 The sole Section 101 case identified by Defendants, *Mayo Collaborative Services v.*
2 *Prometheus Laboratories, Inc.*, 132 S. Ct. 1289 (2012), is inapplicable to the asserted claims of
3 the '650 patent. In *Mayo*, the claims were directed to “well-understood, routine, [and]
4 conventional” steps, and the only novel element related to administering the proper dosage based
5 on a natural law observation.⁴⁴⁴⁷ However, the claims merely recited this natural law without
6 reciting any novel application of it.⁴⁴⁴⁸ The Court found that providing protection to such
7 claims would result in pre-empting “a broad range of potential uses” and excluding others from
8 using “the basic tools of scientific and technical work.”⁴⁴⁴⁹ A method of treatment claim,
9 specifying the subjects, dosage levels, composition, and time course does not raise the concerns
10 of *Mayo* and instead is akin to the typical claims which *Mayo* acknowledges are entitled to patent
11 protection.⁴⁴⁵⁰

12 Defendants suggest that the recited EPA composition of each asserted claim is a naturally
13 occurring substance. It is not. Even references contained within Defendants’ own contentions
14 make clear that EPA of the requisite purity and characteristics is not found in nature.⁴⁴⁵¹ As
15 expressed by the patents cited in Defendants’ contentions and well-established precedent, for
16 decades it has been accepted that compositions isolated from nature or purified beyond their

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18 ⁴⁴⁴⁷ *Mayo*, 132 S. Ct. at 1294.

19 ⁴⁴⁴⁸ *Id.* at 1301.

20 ⁴⁴⁴⁹ *Id.*

21 ⁴⁴⁵⁰ *Id.* at 1302 (contrasting the patent-ineligible claims of that case to “a typical patent on a new drug or a new way
22 of using an existing drug); *see also Diamond v. Diehr*, 450 U.S. 175, 177 , 191-193 (1981) (upholding patentability
23 for “a process for curing synthetic rubber which includes in several of its steps the use of a mathematical formula
24 and a programmed digital computer” under Section 101); *Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc.*, 827 F.3d
1042, 1048-49 (Fed. Cir. 2016) (finding claims patent eligible because by holding otherwise, a host of other patent
eligible claims, such as method of treatment claims, would also be necessarily ineligible).

⁴⁴⁵¹ *See, e.g.*, U.S. Patent No. 5,215,630, “Method of Purifying Eicosapentaenoic Acid or the Ester Derivative
Thereof by Fractional Distillation” (cited in Defendants’ Joint Invalidity Contentions, *e.g.*, at 26–27).

1 natural state are patent-eligible.⁴⁴⁵² Moreover, Defendants’ assertions are immaterial to a Section
2 101 defense because method of treatment claims like the ones asserted in this case are patent
3 eligible even if they are directed to administration of a naturally occurring substance.⁴⁴⁵³

4 To the extent Defendants are arguing that a law of nature both underlies the claims and
5 renders them ineligible, that argument is unsupported and incorrect. Defendants allege that “the
6 claimed effects are the natural result of ingesting a naturally-occurring substance.”⁴⁴⁵⁴ Since the
7 composition that is the subject of the claims is not naturally occurring, Defendants appear to
8 suggest that all method of treatment claims involve a law of nature. That is not what *Mayo* states
9 or even suggests, and indeed the Federal Circuit has refused to adopt Defendants’ overbroad
10 characterization of laws of nature.⁴⁴⁵⁵ To say that the claims of the ’650 patent claim a law of
11 nature is to suggest that all patents claim such laws and engage in an infinitely regressive mode
12 of analysis that the Supreme Court did not adopt in which “all inventions can be reduced to
13 underlying principles of nature” that would “make all inventions unpatentable.”⁴⁴⁵⁶ Indeed, even
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18 ⁴⁴⁵² See, e.g., *In re Bergy*, 596 F.2d 952; *In re Kratz*, 592 F.2d 1169 (CCPA 1979); *In re Bergstrom*, 427 F.2d 1394
(CCPA 1970); *Parke-Davis & Co. v. H.K. Mulford Co.*, 189 F.95 (S.D.N.Y. 1911).

19 ⁴⁴⁵³ *Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc.*, 827 F.3d 1042, 1048-49 (Fed. Cir. 2016).

20 ⁴⁴⁵⁴ See Defendants’ Joint Invalidation Contentions at .

21 ⁴⁴⁵⁵ See *CellzDirect*, 827 F.3d at 1048-49 (“The [asserted] claims are like thousands of others that recite processes
22 to achieve a desired outcome That one way of describing the process is to describe the natural ability of the
subject matter to *undergo* the process does not make the claim ‘directed to’ that natural ability. If that were so, we
would find patent-ineligible methods of . . . treating cancer with chemotherapy (as directed to cancer cells’ inability
to survive chemotherapy), or treating headaches with aspirin (as directed to the human body’s natural response to
aspirin).”).

23 ⁴⁴⁵⁶ See *Mayo*, 132 S. Ct. at 1034 (quoting *Diamond v. Diehr*, 450 U.S. 175, 188 (1981)).
24

1 those concerned about the implications of *Mayo* on future patents were focused on diagnostic
2 claims not treatment claims of the type that *Mayo* stated were typical and patentable.⁴⁴⁵⁷

3 Even if there is some underlying law of nature in the asserted claims, the subject matter
4 of the '650 patent remains eligible for protection under Section 101. As articulated by *Mayo* and
5 *Diehr*, patents claiming a law of nature, such as a mathematical equation, are entitled to
6 protection where claims “did not ‘seek to pre-empt the use of [the] equation,’ but sought ‘only to
7 foreclose from others the use of that equation in conjunction with all of the other steps in their
8 claimed process.’”⁴⁴⁵⁸ As discussed above, the asserted claims of the '650 patent contain a
9 novel, unconventional, and specific method of treatment comprising a particularized application
10 of a nonnaturally occurring substance and does not preempt the use of a law of nature.⁴⁴⁵⁹

11 Defendants also argue that any argument by Amarin in response to Defendants’ § 112
12 arguments are further evidence of invalidity under § 101. This argument is without merit. The
13 claims are enabled and written description is satisfied for the reasons discussed below. In
14 addition, as discussed above, the asserted claims are not merely a naturally-occurring
15 phenomena, and thus satisfy the requirements of § 101.

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20 ⁴⁴⁵⁷ See *Mayo*, 132 S. Ct. at 1034 (“Prometheus, supported by several *amici*, argues that a principle of law denying
21 patent coverage here will interfere significantly with the ability of medical researchers to make valuable discoveries,
particularly in the area of diagnostic research.”).

22 ⁴⁴⁵⁸ See *Mayo*, 132 S. Ct. at 1299 (quoting *Diehr*, 450 U.S. at 187).

23 ⁴⁴⁵⁹ See, e.g., *Tannas Electronics v. Luxell Technologies, Inc.*, 2012 WL 3800822, at *4 (C.D. Cal. July 24, 2012)
24 (rejecting a challenge to the patentability of a claim under Section 101 where the alleged natural phenomenon was
“just one step in the whole process” claimed by the invention).

1 **2. The Asserted Claims of the ‘650 Patent Are Not Anticipated by WO**
2 **‘118**

3 To anticipate, a single prior art reference must sufficiently describe a claimed invention
4 so that the public is in “possession” of that invention.⁴⁴⁶⁰ Therefore, to anticipate, a reference
5 must set forth every element of the claim, either expressly or inherently, in as complete detail as
6 is contained in the claim.⁴⁴⁶¹ The claim elements must also be “arranged” in the prior art
7 reference, just as they are in the claim,⁴⁴⁶² rather than as “multiple, distinct teachings that the
8 artisan might somehow combine to achieve the claimed invention.”⁴⁴⁶³ In addition, public
9 “possession” requires that the prior art enable a person of ordinary skill to make and use the
10 invention without undue experimentation.⁴⁴⁶⁴ Factors that may be included in this analysis
11 include the quantity of experimentation necessary, the amount of direction or guidance
12 presented, the presence or absence of working examples, the nature of the invention, the state of
13 the prior art, the relative skill of those in the art, the predictability or unpredictability of the art,
14 and the breadth of the claims.⁴⁴⁶⁵ This inquiry is objective, and thus evidence of undue
15 experimentation need not be prior art.⁴⁴⁶⁶

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⁴⁴⁶⁰ *Akzo N.V. v. U.S. Int’l Trade Com’n*, 808 F.2d 1471, 1479 (Fed. Cir. 1986).

17 ⁴⁴⁶¹ *Id.*; *In re Bond*, 910 F.2d 831, 832 (Fed. Cir. 1990); *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed.
18 Cir. 1989).

⁴⁴⁶² *Bond*, 910 F.2d at 833; *Akzo*, 808 F.2d at 1479.

19 ⁴⁴⁶³ *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369–71 (Fed. Cir. 2008); *In re Arkley*, 455 F.2d 586, 587
(C.C.P.A. 1972); *In re Ruschig*, 343 F.2d 965, 974 (C.C.P.A. 1965).

20 ⁴⁴⁶⁴ *Akzo*, 808 F.2d at 1479; *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1085 (Fed. Cir. 2008); *Forest Labs.,*
Inc. v. Ivax Pharms., Inc., 501 F.3d 1263, 1268–69 (Fed. Cir. 2007).

21 ⁴⁴⁶⁵ *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

22 ⁴⁴⁶⁶ *Plant Genetic Sys., N.V. v. DeKalb Genetics Corp.*, 315 F.3d 1335, 1344 (Fed. Cir. 2003); *In re Wright*, 999
23 F.2d 1557, 1562 (Fed. Cir. 1993); *Liquid Dynamics Corp. v. Vaughan Co., Inc.*, 449 F.3d 1209, 1224–25 (Fed. Cir.
2006); *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1336 (Fed. Cir. 2003); *Gould v. Quigg*, 822
24 F.2d 1074, 1078 (Fed. Cir. 1987).

1 Defendants assert that Claims 1-14 of the '650 Patent are anticipated by the WO '118
2 reference.⁴⁴⁶⁷

3 A element-by-element analysis, identifying each element of each asserted claim that is
4 absent from WO '118, is provided below. The contentions below are incorporated by reference
5 into Exhibit J, and vice-versa. WO '118 does not anticipate the claims of the '650 patent
6 because it does not describe, properly arrange, or enable the '650 patent claims.

7 a) WO '118 Does Not Teach Every Element of the Claims of the
8 '650 Patent

9 (1) WO '118 Does Not Describe the Claimed Lipid Effects

10 It is well established that, for a prior art reference to anticipate, "every element of the
11 claimed invention must be identically shown in a single reference."⁴⁴⁶⁸ Moreover, the elements
12 of the claimed invention must have "strict identity" with the elements of the reference; "minimal
13 and obvious" differences are sufficient to prevent anticipation.⁴⁴⁶⁹ Here, WO '118 entirely fails
14 to disclose the following elements of Claim 1 of the '650 Patent: *a method of reducing*
15 *triglycerides*. WO '118 also entirely fails to disclose the following elements of Claim 8 of the
16 '650 Patent: *to effect a reduction in triglycerides in the subject compared to placebo control*.
17 Defendants appear to concede that WO '118 does not expressly teach these elements, as they fail
18 to set forth any basis for concluding that WO '118 teaches this element.⁴⁴⁷⁰ Indeed, Defendants
19 could not set forth any basis for concluding that WO '118 teaches this element because WO '118

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21 ⁴⁴⁶⁷ References to "WO '118" are to the English translation that was filed with the European application. Plaintiffs
reserve their right to obtain a certified translation of WO '118.

22 ⁴⁴⁶⁸ *Diversitech Corp. v. Century Steps, Inc.*, 850 F.2d 675, 677 (Fed. Cir. 1988); *see also Hybritech Inc. v.*
Monoclonal Antibodies, Inc., 802 F.2d 1367 (Fed. Cir. 1986).

23 ⁴⁴⁶⁹ *Trintech Industries, Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1296 (Fed. Cir. 2002).

24 ⁴⁴⁷⁰ Defendants' Invalidation Contentions at 202-204.

1 does not.

2 Instead, Defendants argue that these elements express the intended result of a method that
3 is positively recited, and therefore is inherently anticipated. However, for the reasons set forth
4 below, WO ‘118 fails to disclose each element of the independent claims of the ‘650 Patent,
5 either expressly or inherently. Therefore, WO ‘118 cannot anticipate the claimed method.
6 Defendants also argue that these elements represent inherent, natural properties of EPA, and are
7 entitled to no patentable weight. This conclusion is incorrect and inconsistent with the law of
8 anticipation and claim construction. Further, while Defendants argue that the inherent properties
9 are exemplified in the prior art, they fail to identify even a single prior art reference that makes
10 such a disclosure. Defendants cannot point to a single, specific prior art reference because the
11 claimed pharmaceutical composition has never been administered in the manner claimed to the
12 claimed patient population. Also, these elements are positively recited in the body of the claim
13 and therefore cannot be construed as a non-limiting preamble and must be given patentable
14 weight.

15 Further, Defendants entirely fail to prove that inherently discloses the claimed lipid
16 effects. A prior art reference that “only ‘probably’ or ‘possibly’ meets the claims cannot
17 inherently anticipate as a matter of law.”⁴⁴⁷¹ I “[A]nticipation by inherent disclosure is
18 appropriate only when the reference discloses prior art that must *necessarily* include the unstated
19 limitation.”⁴⁴⁷² “It is not sufficient if a material element or limitation is ‘merely probably or
20 possibly present’ in the prior art.”⁴⁴⁷³ WO ‘118 fails to provide any data related to the lipid
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⁴⁴⁷¹ *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

23 ⁴⁴⁷² *Transclean Corp. v. Bridgewood Servs., Inc.*, 290 F.3d 1364, 1373 (Fed. Cir. 2002) (emphasis in original).

24 ⁴⁴⁷³ *In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1378 (Fed. Cir. 2007).

1 effects of the disclosed invention on patients described in the publication. Therefore, Defendants
2 fail to prove by clear and convincing evidence that the composition disclosed by WO '118 meets
3 the elements of the independent claims every time it is administered.

4 Defendants fail to demonstrate that administration of the claimed EPA compositions
5 “necessarily” yields the claimed lipid effects. For example, one study cited by Defendants
6 suggests that EPA administration may increase LDL-C.⁴⁴⁷⁴ Rambjor is a clinical study which
7 administered EPA, DHA, fish oil or placebo to human subjects. Rambjor showed that both EPA
8 and fish oil caused a significant increase in LDL-C. On the other hand, DHA effected only a
9 non-significant increase in LDL-C. As reflected by the disclosure of Rambjor, EPA does *not*
10 decrease TG without increasing LDL-C *every time it is administered*.

11 Therefore, WO '118 cannot anticipate the independent claims of the '650 patent.
12 Because the dependent claims include all of the claim elements of the independent claims, WO'
13 118 cannot anticipate any of the dependent claims as well.

14 (2) WO '118 Does Not Disclose Methods of Treating The
15 Claimed Patient Population

16 In addition, WO '118 fails to disclose or suggest the claimed pharmaceutical composition
17 be administered in the manner claimed to the claimed patient population. Defendants attempt to
18 eliminate these important elements by arguing that the preamble is non-limiting. A preamble is
19 the introductory clause of a patent claim and includes everything from the beginning of the claim
20 until a transitional phrase, such as “comprising.” Defendants improperly attempt to truncate the
21 preamble.

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23 _____
24 ⁴⁴⁷⁴ See, e.g., Rambjor.

1 A claim preamble has patentable weight if, “when read in the context of the entire claim,
2 [it] recites limitations of the claim, or, if the claim preamble is ‘necessary to give life, meaning,
3 and vitality’ to the claim.”⁴⁴⁷⁵ Additionally, the preamble constitutes a claim element when the
4 claim depends on it for antecedent basis because “it indicates reliance on both the preamble and
5 claim body to define the claimed limitation.”⁴⁴⁷⁶

6 The preamble of the asserted claims is limiting for several reasons. The term “subject” in
7 the preamble of the independent claims defines and provides antecedent basis for the “subject”
8 recited in the body of the claims. When reading the claim, one must rely on both the preamble
9 and the claim body to define the claimed invention.

10 If the preamble states “a fundamental characteristic of the claimed invention,” then it “is
11 properly construed as a limitation of the claim itself.”⁴⁴⁷⁷ The recitation of a “method of
12 reducing triglycerides” in the preamble provides antecedent basis for the effect of reducing
13 triglycerides in the body of the claim and emphasizes the intentional purpose for which the
14 method must be performed - to reduce triglycerides.

15 It is clear that “the claim drafter chose to use both the preamble and the body of the claim
16 to define the subject matter of the claimed invention.”⁴⁴⁷⁸ Thus, the entire preamble in the
17 independent claims of the ‘650 must contain patentable weight.

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20 ⁴⁴⁷⁵ *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305 (Fed. Cir. 1999) (citation omitted).

21 ⁴⁴⁷⁶ *Catalina Marketing Int’l v. Coolsavings.com, Inc.*, 289 F.3d 801, 808 (Fed. Cir. 2002) (citation omitted).

22 ⁴⁴⁷⁷ *Poly-Am. L.P. v. GSE Lining Tech., Inc.*, 383 F.3d 1303, 1309 (Fed. Cir. 2004); *see also e.g., Computer*
23 *Docking Station Corp. v. Dell, Inc.*, 519 F.3d 1366, 1375 (Fed. Cir. 2008) (concluding the preamble phrases
“portable computer” and “portable computer microprocessing system” limit the claims because they “clearly recite a
necessary and defining aspect of the invention, specifically its portability,” and because the specification and
prosecution history “emphasize this feature of the invention”).

24 ⁴⁴⁷⁸ *Bicon, Inc. v. Straumann Co.*, 441 F.3d 945, 953 (Fed. Cir. 2006).

1 WO '118 fails to disclose the patentable elements of the preamble of the asserted claims.
2 WO '118 does not describe or suggest that the claimed pharmaceutical composition be
3 administered in the manner claimed to the claimed patient population.

4 First, WO '118 fails to expressly disclose “a method of reducing triglycerides.” In fact,
5 the invention disclosed by WO '118 relates to a composition for **preventing occurrence of**
6 **cardiovascular events**, as evidenced by the title which reads “Composition for Preventing the
7 Occurrence of Cardiovascular Event in Multiple Risk Patient.” The prevention of the occurrence
8 of cardiovascular events is defined in WO '118 as “all cases of primary prevention, and
9 exemplary cases include prevention of cardiovascular death, fatal myocardial infarction, sudden
10 cardiac death, nonfatal myocardial infarction, cardiovascular angioplasty, new occurrence of rest
11 angina and exercise-induced angina, and destabilization of the angina.”⁴⁴⁷⁹ The invention of WO
12 '118 is intended to be administered to any person in need of prevention of the occurrence of
13 cardiovascular events, who are typically hypercholesterolemia patients.⁴⁴⁸⁰ WO '118 does not
14 expressly describe its invention as a “method of reducing triglycerides,” therefore it cannot
15 anticipate the independent claims.

16 Second, WO '118 fails to disclose the subject as described in the claims. Defendants fail
17 to prove that these elements of the claimed invention have “strict identity” with the elements of
18 the reference.⁴⁴⁸¹ WO '118 fails to anticipate this claim element because the broad disclosure
19 fails to anticipate the narrow claimed range, and the specific patient population defined in the
20 claims is an essential part of the claimed invention.

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⁴⁴⁷⁹ WO '118 at 12.

23 ⁴⁴⁸⁰ *Id.*

24 ⁴⁴⁸¹ *Trintech Industries, Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1296 (Fed. Cir. 2002).

1 There is no evidence in that subject as described in the claims were ever treated. In fact,
2 WO '118 fails to disclose baseline lipid levels of a single subject. Defendants rely on the
3 definition of "hypertriglyceridemia" in WO '118 to argue that WO '118 discloses treatment of
4 the subject as described in the claims. It does not. Defendants' argument rests on the definition
5 in WO '118 of "hypertriglyceridemia" as "fasting serum triglyceride levels of at least 150
6 mg/dL." WO '118's definition is not tied to a specific subject and there are no working
7 examples, data or other reference in WO '118 indicating that any subject with fasting TG levels
8 of at least 500 mg/dL received an EPA composition as claimed in the asserted patents, or any
9 EPA at all. In addition, Defendants rely on a reference to "Omacor" in WO '118 (at 32) as
10 evidence that a "person of ordinary skill in the art would have understood that the term
11 'hypertriglyceridemia' when used in the WO '118 includes patients with triglyceride levels of
12 500 mg/dL to about 1500 mg/dL." The cited section states that "soft capsules" are preferable
13 and then merely provides examples of commercially available "soft capsules," such as Omacor.
14 The passage does not define "hypertriglyceridemia" as used in WO '118 as referring to patients
15 with triglyceride levels over 500 mg/dL. Nor does it suggest that the claimed EPA should be
16 used in the over 500 mg/dL TG patient population. A prior art reference that "only 'probably'
17 or 'possibly' meets the claims cannot inherently anticipate as a matter of law."⁴⁴⁸² Therefore,
18 Defendants fail to prove by clear and convincing evidence that the composition disclosed by WO
19 '118 meets the claim elements of the independent claims every time it is administered.

20 Further, the broad range disclosed by WO '118 is insufficient to anticipate the ranges
21 claimed by the '650 patent. In *Atofina*, the prior art disclosed a temperature range of 100 to 500
22 degrees and a preferred range of 150 to 350 degrees; the patent at issue claimed a range between
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24 ⁴⁴⁸² *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

1 330 and 450 degrees. The court found that the broader prior art range could not anticipate the
2 claimed temperature range, “[g]iven the considerable difference between the claimed range and
3 the range in the prior art, no reasonable fact finder could conclude that the prior art describes the
4 claimed range with sufficient specificity to anticipate this element of the claim.”⁴⁴⁸³ A prior art’s
5 teaching of a broad genus does not necessarily disclose every species within that genus. The
6 court explained the slightly overlapping range between the preferred range and claimed range “is
7 not disclosed as . . . a species of the claimed generic range of 330 to 450 °C,”⁴⁴⁸⁴ and therefore
8 failed to anticipate the claimed range. Likewise, WO ‘118’s broad disclosure of
9 hypertriglyceridemia as a “fasting serum triglyceride levels of at least 150 mg/dL” does not
10 anticipate the subject as described in the claims because it fails to described the claimed TG
11 range with sufficient specificity.

12 The court in *Atofina* ruled on an additional question of anticipation that also involved a
13 range of numbers. A prior art reference had disclosed a range of 0.001 to 1.0 percent, as
14 compared to the patent’s claimed range of 0.1 to 5.0 percent.⁴⁴⁸⁵ The court explained that
15 “although there is a slight overlap, no reasonable fact finder could determine that this overlap
16 describes the entire claimed range with sufficient specificity to anticipate this limitation of the
17 claim. The ranges are different, not the same. . . . Thus, there is no anticipation.”⁴⁴⁸⁶ Similarly,
18 although there may be overlap between the definition of hypertriglyceridemia taught by WO
19 ‘118 and the TG range recited by the claims of the asserted patents, WO ‘118 does not
20 specifically discuss, highlight or otherwise suggest treating patients with TG values above 500

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22 ⁴⁴⁸³ *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006).

23 ⁴⁴⁸⁴ *Atofina*, 441 F.3d at 1000.

24 ⁴⁴⁸⁵ *Id.*

⁴⁴⁸⁶ *Id.*

1 mg/dL. In fact, WO '118 is directed to compositions and methods for preventing occurrence of
2 cardiovascular events, suggesting that the treatment was envisioned for patients with TG levels
3 below 500 mg/dL (the patient population the ATP III identifies the prevention of atherogenic
4 events as the primary clinical objective),⁴⁴⁸⁷ WO '118, therefore, does not expressly disclose the
5 specific patient population that is an essential element of the claims of the asserted patents.
6 Therefore, WO '118 cannot anticipate the claims of the asserted patents.

7 The treatment of a patient with elevated TG levels varies depending on their serum
8 triglyceride levels. Identification of the patient population with very high TG levels (at least 500
9 mg/dL) is central to the claimed invention. In the 2000s, physicians treating lipid disorders,
10 including hypertriglyceridemia, relied on the ATP-III for authoritative guidance on the treatment
11 of lipid disorders.⁴⁴⁸⁸ The ATP-III divided hypertriglyceridemia patients into three classes based
12 on the levels of TG in their blood—borderline-high (150-199 mg/dL), high (200-499 mg/dL),
13 and very-high TGs (\geq 500 mg/dL)—and recommended substantially different treatment
14 strategies for patients depending on classification.⁴⁴⁸⁹ For the borderline-high and high TG
15 groups (150-499 mg/dL), the primary goal was to reduce risk of coronary heart disease.⁴⁴⁹⁰
16 Accordingly, in these populations, physicians focused on lowering LDL-C.⁴⁴⁹¹ In this patient
17 population, lowering of TG and non-HDL-C levels were considered secondary treatment goals.
18 In contrast, the primary goal for very-high TG patients (\geq 500 mg/dL) was to reduce the risk of
19 pancreatitis—a potentially life threatening condition expected to be precipitated by elevated

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21 ⁴⁴⁸⁷ See Section III.

22 ⁴⁴⁸⁸ *Id.*

23 ⁴⁴⁸⁹ ATP III at 3335; *See also* Section III.

24 ⁴⁴⁹⁰ *Id.*

⁴⁴⁹¹ *Id.*

1 TGs— by lowering TG levels. In very high TG patients, lowering LDL-C is a secondary
2 treatment goal.⁴⁴⁹² Therefore, as evidenced by the ATP-III, patients with very-high TG levels
3 were considered fundamentally different from patients with borderline-high or high TGs from a
4 lipid chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint.

5 Therefore, WO ‘118’s definition of “hypertriglyceridemia” as “fasting serum triglyceride
6 levels of at least 150 mg/dL” fails to anticipate the claimed subject with very high TG levels. In
7 fact, as described above, WO ‘118 is not directed toward patients with the claimed TG levels at
8 all. WO 118’s disclosure is clearly directed towards preventing the occurrence of cardiovascular
9 risk, which is the primary aim for treatment of patients with high triglycerides (200-499 mg/dL).
10 Thus, WO ‘118’s disclosure is *not* directed towards patients with very high triglyceride levels
11 (where the primary goal is to prevent acute pancreatitis and damage to the pancreas by
12 decreasing triglycerides), as required by the independent claims of the asserted patents, and
13 therefore cannot anticipate the independent claims of the ‘650 Patent.

14 (3) WO ‘118 Does Not Describe the Claimed Pharmaceutical
15 Composition or its Specific Administration

16 WO ‘118 further does not anticipate the claims of the ‘650 patent because it does not
17 disclose “administering orally to the subject.” As WO ‘118 fails to disclose the subject as
18 claimed, it cannot anticipate oral administration to the claimed “subject.”

19 WO ‘118 additionally cannot anticipate the claims of the ‘650 patent because it does not
20 disclose administering the pharmaceutical composition at a dose of about 4g per day.

21 Defendants argue that this element is disclosed by WO ‘118’s teaching that the daily dose is
22 “typically 0.3 to 6 g/day.” Defendants fail to provide the entire disclosure of WO ‘118, which
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24 ⁴⁴⁹² *Id.*

1 states that the daily dose is “typically 0.3 to 6 g/day, preferably 0.9 to 3.6 g/day, and still more
2 preferably 1.8 to 2.7 g/day. Another preferable daily dose is 0.3 to 2.7 g/day, and 0.3 to 1.8
3 g.day. Another preferable fatty acid included is DHA-E.” WO ‘118 teaches that the dosage is
4 not particularly limited as long as the intended effect, preventing the occurrence of
5 cardiovascular events, is attained. However, Defendants fail to provide any evidence that a dose
6 that is effective to prevent the occurrence of cardiovascular event, is also a dose that would be
7 effective to reduce triglycerides in the claimed patient population. Furthermore, there are no
8 working examples, data or other reference in WO ‘118 indicating that any subject (much less
9 one with fasting TG levels of at least 500 mg/dL) received an EPA composition as claimed in the
10 asserted patents or any EPA at all, much less at the claimed dose of 4 grams/day.

11 As discussed above, in *Atofina*, the prior art disclosed a preferred temperature range of
12 150 to 350 degrees, and the patent at issue claimed a range between 330 and 450 degrees. The
13 court explained that this slight overlap “is not disclosed as . . . a species of the claimed generic
14 range of 330 to 450 °C,”⁴⁴⁹³ and therefore failed to anticipate the claimed range. The court in
15 *Atofina* also found that a prior art disclosure of a range of 0.001 to 1.0 percent failed to anticipate
16 the patent’s claimed range of 0.1 to 5.0 percent.⁴⁴⁹⁴ The court explained that “although there is a
17 slight overlap, no reasonable fact finder could determine that this overlap describes the entire
18 claimed range with sufficient specificity to anticipate this limitation of the claim. The ranges are
19 different, not the same. . . . Thus, there is no anticipation.”⁴⁴⁹⁵ Similarly, although there may be
20 some overlap between the daily dose disclosed by WO ‘118 and the dose claimed by the ‘650

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⁴⁴⁹³ *Atofina*, 441 F.3d at 1000.

23 ⁴⁴⁹⁴ *Id.*

24 ⁴⁴⁹⁵ *Id.*

1 patent, WO '118 does not specifically highlight the overlapping area and, moreover, the range
2 claimed by the '650 patent does not fall within WO '118's preferred range. Defendants
3 conveniently omit the preferred range and mischaracterize the teaching of WO '118. Notably,
4 the example indicates that up to 900 mg of the EPA composition could be used three times per
5 day (2.7 g). Thus, WO '118 does not expressly disclose the 4 g per day dose claimed by the '650
6 patent and cannot anticipate the independent claims of the '650 Patent.

7 WO '118 further does not anticipate the claims of the '650 patent because it does not
8 disclose the claimed EPA pharmaceutical composition. Defendants once again cite only a
9 portion of the disclosure and exclude sections that show the breadth of WO '118's teachings.
10 WO '118's full disclosure recites that "the EPA-E used is preferably the one having a high
11 purity, for example, the one having the proportion of the EPA-E in the total fatty acid and
12 derivatives thereof of preferably 40% by weight or higher, more preferably 90% by weight or
13 higher, and still more preferably 96.5% by weight or higher."⁴⁴⁹⁶ Therefore, WO '118 discloses
14 EPA-E with "high purity" is a composition which contains EPA-E of 40% by weight, of total
15 fatty acid and derivatives, or higher. This non-specific disclosure is not a species of the claimed
16 generic range for the EPA composition in the claimed pharmaceutical composition.

17 The Federal Circuit has explained that "a preferred . . . range . . . that slightly overlaps the
18 . . . range claimed in the" patent is insufficient for anticipation.⁴⁴⁹⁷ In *Atofina*, the prior art
19 disclosed a preferred temperature range of 150 to 350 degrees, and the patent at issue claimed a
20 range between 330 and 450 degrees. The court explained that this slight overlap "is not
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23 ⁴⁴⁹⁶ WO '118 at 22.

24 ⁴⁴⁹⁷ *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 1000 (Fed. Cir. 2006).

1 disclosed as . . . a species of the claimed generic range of 330 to 450 °C,⁴⁴⁹⁸ and therefore failed
2 to anticipate the claimed range.⁴⁴⁹⁹ The court in *Atofina* also found that a prior art disclosure of a
3 range of 0.001 to 1.0 percent failed to anticipate the patent’s claimed range of 0.1 to 5.0
4 percent.⁴⁵⁰⁰ The court explained that “although there is a slight overlap, no reasonable fact finder
5 could determine that this overlap describes the entire claimed range with sufficient specificity to
6 anticipate this element of the claim. The ranges are different, not the same. . . . Thus, there is no
7 anticipation.”⁴⁵⁰¹

8 Similarly, although there may be some overlap between the E-EPA content disclosed by
9 WO ‘118 and the ranges claimed by the ‘650 patent, WO ‘118 does not specifically highlight the
10 overlapping area. The high content of E-EPA in the claimed pharmaceutical composition is a
11 critical factor of the invention disclosed in the ‘650 patent. Therefore, WO ‘118’s broad
12 disclosure of the E-EPA content in its invention does not describe the claimed range with
13 sufficient specificity and cannot anticipate the independent claims of the ‘650 patent.

14 WO ‘118 is additionally insufficient for anticipation because it does not expressly
15 disclose the recited DHA content of the claimed pharmaceutical composition. In fact, WO ‘118
16 makes no distinction between EPA and DHA, stating that “[a]nother preferable fatty acid is
17 DHA-E.”⁴⁵⁰² The disclosure goes on to state that the composition of the invention is preferably
18 one having high purity of EPA-E and DHA-E. The recited DHA content of the claimed
19 pharmaceutical composition is a critical factor of the invention disclosed in the ‘650 patent.
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21 ⁴⁴⁹⁸ *Atofina*, 441 F.3d at 1000.

22 ⁴⁴⁹⁹ *Atofina*, 441 F.3d at 1000.

23 ⁴⁵⁰⁰ *Id.*

23 ⁴⁵⁰¹ *Id.*

24 ⁴⁵⁰² WO ‘118 at 22.

1 The disclosure of WO '118 treats DHA and EPA interchangeably. The disclosed
2 concentrations of EPA and DHA may range from 0 to 100% and every concentration in between.
3 There is no express teaching or guidance directing the person of ordinary skill in the art to the
4 claimed EPA compositions, Therefore, WO '118's broad disclosure, which indicates no
5 difference between the use of EPA or DHA in its invention, cannot anticipate the independent
6 claims of the '650 patent.

7 Defendants contend that Plaintiffs are estopped from arguing there is any material
8 difference between "not more than about 4% DHA" and "substantially no DHA." Defendants
9 provide no legal basis for their argument of estoppel. Defendants appear to suggest that testing
10 data obtained by Plaintiffs constitutes the basis for their assertion of estoppel. That argument is
11 without merit. Plaintiffs' clinical data cannot form the basis for an estoppel argument and
12 Defendants have cited no authority to support their position suggesting the contrary. The
13 language of "not more than about 4% DHA" and "substantially no DHA" are different phrases
14 and are not co-extensive. Accordingly, plaintiffs are not estopped.

15 In the same paragraph containing their allegation of estoppel, Defendants also quote from
16 Amarin's 2011 10-K. It is unclear whether these quotations are associated with their
17 unexplained estoppel arguments. To the extent that they are, Plaintiffs disagree that these
18 statements form the basis for any theory of estoppel. To the extent that Defendants quote
19 Amarin's post-invention 10-K to make any invalidity argument, that is also unavailing. The
20 quoted statements do not identify any recited claim element, including the specific
21 pharmaceutical composition, the recited patient population, administration in the manner
22 claimed, and recited lipid effects. Nor can these elements of the asserted claims be inferred from
23 the quoted statements.
24

1 (4) WO '118 Does Not Describe the Dependent Claims

2 Defendants fail to address any of the claim elements of the dependent claims.

3 Defendants appear to concede that WO '118 does not expressly teach these elements, as they fail
4 to set forth any meaningful basis for concluding that WO '118 teaches these elements.

5 Defendants further argue that “aspects of the claims relating to effects that are to be achieved by
6 practicing the claimed method represent inherent, natural properties of EPA, and are entitled to
7 no patentable weight.” To the extent the recited claim elements relate to the administration step,
8 the dosage form or characteristics of the treated subject and the specific effect produced by the
9 claimed method, Defendants’ contentions that the claim limitations are inherent properties of
10 EPA are unavailing. While Defendants assert that the inherent properties are exemplified in WO
11 '118, they fail to identify any basis, explanation, or even supporting argument for that assertion.
12 Defendants have not met the burden to establish anticipation with the naked assertion that the
13 effects are inherent, natural properties of EPA.

14 Further, Defendants entirely fail to prove that inherently discloses the recited claim
15 limitations. A prior art reference that “only ‘probably’ or ‘possibly’ meets the claims cannot
16 inherently anticipate as a matter of law.”⁴⁵⁰³ “[A]nticipation by inherent disclosure is appropriate
17 only when the reference discloses prior art that must *necessarily* include the unstated
18 limitation.”⁴⁵⁰⁴ “It is not sufficient if a material element or limitation is ‘merely probably or
19 possibly present’ in the prior art.”⁴⁵⁰⁵ Defendants fail to show that WO '118 “*necessarily*” meets
20 the recited claim elements relating to the administration step, the dosage form or characteristics

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22 _____
⁴⁵⁰³ *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

23 ⁴⁵⁰⁴ *Transclean Corp. v. Bridgewood Servs., Inc.*, 290 F.3d 1364, 1373 (Fed. Cir. 2002) (emphasis in original).

24 ⁴⁵⁰⁵ *In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1378 (Fed. Cir. 2007).

1 of the treated subject and the specific effect produced by the claimed method *every time*. WO
2 '118 fails to provide any data related to the TG, LDL-C, VLDL-C, non-HDL-C, Lp-PLA2, total
3 cholesterol, Apo-B, or any other lipid effect of the disclosed invention on patients described in
4 the publication. Further, WO '118 is a translated Japanese disclosure that makes no reference to,
5 let alone a disclosure of, a Western diet. Therefore, Defendants fail to prove by clear and
6 convincing evidence that the composition disclosed by WO '118 meets any dependent claim
7 elements.

8 **3. The Claims of the '650 Patent Would Not Have Been Obvious In**
9 **Light of the Asserted References**

10 Defendants identify 77 separate references that it asserts somehow render the claims of
11 the '650 patent obvious.⁴⁵⁰⁶ Defendants fail to demonstrate by clear and convincing evidence
12 that any of these references, alone or in combination, would render obvious any claims of the
13 '650 patent. Defendants' arguments rely on hindsight by impermissibly using the blueprint of
14 the '650 patent itself to guide its combination of references.⁴⁵⁰⁷ Defendants chart a laundry list
15 of 77 separate references, without explanation. Defendants' disclosures do not comply with
16 Local Patent Rule 1-8(d) and fail to put Plaintiffs on notice of how these references allegedly
17 establish that the asserted claims are allegedly *prima facie* obviousness. Consequently, Plaintiffs
18 cannot respond to undisclosed combinations and arguments.⁴⁵⁰⁸

19 ⁴⁵⁰⁶ Defendants' Joint Invalidation Contentions at 13-25.

20 ⁴⁵⁰⁷ *In re Suong-Hyu Hyon*, 679 F.3d 1363, 1371 (Fed. Cir. 2012) ("It is impermissible to use the claimed invention
21 as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is
22 obvious." (citing *In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992))).

23 ⁴⁵⁰⁸ This includes Defendants' improper attempt to incorporate by reference any alleged prior art or argument,
24 including Defendants' attempt to incorporate by reference "the reasons set forth in the opposition proceedings for
EP 2 395 991 B1" in the European Patent Office. Such wholesale incorporation by reference does not satisfy the
Defendants' obligations or burden of proof and is contrary to the Nevada Local Patent Rules, which require that
each prior art be identified specifically. *See* Local Pat. R. 1-8. Plaintiffs reserve the right to strike any attempt to
rely on undisclosed or insufficiently disclosed references or argument.

1 Despite the general, non-limiting nature of Defendants’ Joint Invalidity Contentions,
2 Plaintiffs have discerned and will specifically respond to the following alleged prior art
3 combinations:

- 4 • 1) “. . .the asserted claims of the ’650 patent would have been obvious over the
5 Omacor PDR/Lovaza PDR in combination with the known clinical benefits of
6 administering pure EPA as evidenced by Katayama and/or Matsuzawa, further in
7 view of Nozaki and/or Hayashi, and further in view of Leigh-Firbank and/or Mori
8 2000.”
- 9 • 2) “. . .the asserted claims of the ’650 patent would have been obvious over the
10 Omacor PDR/Lovaza PDR in combination with the known clinical benefits of
11 administering purified EPA as evidenced by Katayama, Matsuzawa and/or Takaku,
12 further in view of Nozaki and/or Hayashi, and further in view of Grimsgaard, Mori
13 2000 and/or Maki.”
- 14 • 3) “. . .the asserted claims of the ’650 patent would have been obvious over the
15 Omacor PDR/Lovaza PDR in combination with the known clinical benefits of
16 administering pure EPA as evidenced by Katayama in view of Satoh and/or in view
17 of Satoh or Shinozaki in further view of Contacos.”
- 18 • 4) “. . . the asserted claims of the ’650 patent would have been obvious over WO ’118
19 or WO ’900 in combination with treatment regimen of Lovaza as evidenced by the
20 Lovaza PDR, and further in view of Leigh-Firbank and/or Mori 2000.”
- 21 • 5) “. . . the asserted claims of the ’650 patent would have been obvious over WO
22 ’118, WO ’900, Grimsgaard, Mori 2000 and/or Maki in combination with treatment
23 regimen of Omacor/Lovaza as evidenced by the Omacor PDR/Lovaza PDR, and
24 further in view of Katayama, Matsuzawa and/or Takaku.”

18 A patent claim is invalid “if the differences between the subject matter sought to be
19 patented and the prior art are such that the subject matter as a whole would have been obvious at
20 the time the invention was made to a person having ordinary skill in the art.”⁴⁵⁰⁹ Obviousness is
21 a legal determination, but it turns on factual inquiries into (1) the level of ordinary skill in the art,

23 ⁴⁵⁰⁹ 35 U.S.C. § 103(a).

1 (2) the scope and content of the prior art, and (3) the differences between the prior art and the
2 claims at issue.⁴⁵¹⁰

3 In evaluating obviousness, each prior art reference must be evaluated for all that it
4 teaches, including the portions that would lead away from the claimed invention.⁴⁵¹¹ Indeed, any
5 teaching in the art that points away from the claimed invention must be considered.⁴⁵¹² A
6 reference teaches away if a person of ordinary skill, upon reading the reference, would be
7 discouraged from following the path set out in the reference, or would be led in a direction
8 divergent from the path that was taken by the applicant.⁴⁵¹³ For instance, a reference teaches
9 away if it suggests that the line of development flowing from the reference’s disclosure is
10 unlikely to be productive of the result sought by the applicant.⁴⁵¹⁴

11 In order to find obviousness based on a combination of references, there must be some
12 rationale for combining the references in the way claimed that is separate and apart from the
13 hindsight provided by the patented invention itself.⁴⁵¹⁵ The law prohibits an obviousness
14 challenge based on a hindsight reconstruction of the claimed invention from isolated prior art
15 references. It is improper for “the claims [to be] used as a frame, and individual, naked parts of
16 separate prior art references [to be] employed as a mosaic to recreate a facsimile of the claimed
17 invention.”⁴⁵¹⁶ “The invention must be viewed not after the blueprint has been drawn by the
18

19 ⁴⁵¹⁰ *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966); *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007).

20 ⁴⁵¹¹ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

21 ⁴⁵¹² *Tec Air, Inc. v. Denso Mfg. Mich. Inc.*, 192 F.3d 1353, 1359-60 (Fed. Cir. 1999)

22 ⁴⁵¹³ *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994)

23 ⁴⁵¹⁴ *Id.*

24 ⁴⁵¹⁵ *Immogenetics, N.V. v. Abbott Labs*, 512 F.3d 1363, 1373–74 (Fed. Cir. 2008)

⁴⁵¹⁶ *See W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1552 (Fed. Cir. 1983)

1 inventor, but as it would have been perceived in the state of the art that existed at the time the
2 invention was made.”⁴⁵¹⁷

3 “The determination of obviousness is made with respect to the subject matter as a whole,
4 not separate pieces of the claim.”⁴⁵¹⁸ “[A] patent composed of several elements is not proved
5 obvious merely by demonstrating that each of its elements was, independently, known in the
6 prior art.”⁴⁵¹⁹ “This is so because inventions in most, if not all, instances rely upon building
7 blocks long since uncovered, and claimed discoveries almost of necessity will be combinations
8 of what, in some sense, is already known.”⁴⁵²⁰

9 Accordingly, it is improper to pick and choose isolated elements from the prior art and
10 combine them so as to yield the invention⁴⁵²¹ or to modify a prior art reference in a way that
11 “would destroy the fundamental characteristics of that reference.”⁴⁵²² Moreover, a combination
12 is not obvious where “it would be impossible to apply these teachings [of the secondary
13 reference] to the [primary reference] without entirely changing the basic mechanism and
14 procedure thereof,”⁴⁵²³ or where the proposed combination requires “material and radical
15 modification in order to conform to [the patentee’s] claims” or a “total reconstruction” of the
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19 ⁴⁵¹⁷ *Sensonics, Inc. v. Aerosonic Corp.*, 81 F.3d 1566, 1570 (Fed. Cir. 1996)

20 ⁴⁵¹⁸ *Sanofi Syntheolabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008)

21 ⁴⁵¹⁹ *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007))

22 ⁴⁵²⁰ *KSR*, 550 U.S. at 418-419.

23 ⁴⁵²¹ *Abbott Labs v. Sandoz, Inc.*, 544 F.3d 1341, 1348 (Fed. Cir. 2008)

24 ⁴⁵²² *Apple, Inc. v. Samsung Elec. Co., Ltd.*, 678 F.3d 1314, 1331 (Fed. Cir. 2012)

⁴⁵²³ *In re Irmischer*, 262 F.2d 85, 87 (CCPA 1958)

1 prior art device.⁴⁵²⁴ Furthermore, it is improper “to modify the secondary reference before it is
2 employed to modify the primary reference” in assessing obviousness.⁴⁵²⁵

3 Further, a party asserting obviousness in view of a combination of prior art disclosures
4 must show that a person of ordinary skill in the relevant field had an “apparent reason” to
5 combine the elements in the manner claimed⁴⁵²⁶ and “a reasonable expectation of success.”⁴⁵²⁷

6 For chemical compounds, there must have been a reason both to select the prior art
7 compound “most promising to modify” and to make the necessary changes to arrive at the
8 claimed compound.⁴⁵²⁸ This protects against the use of hindsight to pick through the prior art
9 based solely on structural similarity to the claimed compound.⁴⁵²⁹ Any assertion of an “apparent
10 reason” must find a basis in the factual record.⁴⁵³⁰

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12 ⁴⁵²⁴ *Id.* at 88.

13 ⁴⁵²⁵ *In re Hummer*, 241 F.2d 742, 745 (CCPA 1957)

14 ⁴⁵²⁶ *KSR*, 550 U.S. at 417–19; *TriMed, Inc. v. Stryker Corp.*, 608 F.3d 1333, 1341 (Fed. Cir. 2010). Hindsight may
15 not be employed to identify relevant prior art and relevant teachings therein: *Heidelberger Druckmaschinen AG v.*
Hantscho Comm. Prods., Inc., 21 F.3d 1068, 1071–72 (Fed. Cir. 1994); *Monarch Knitting Mach. Corp. v. Sulzer*
Morat GmbH, 139 F.3d 877, 881 (Fed. Cir. 1998).

16 ⁴⁵²⁷ *Proctor & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (henceforth, “P&G”);
Takeda Chem. Indus. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1361 (Fed. Cir. 2007); *KSR*, 550 U.S. at 416 (a
17 combination of elements “must do more than yield a predictable result;” combining elements that work together “in
an unexpected and fruitful manner” would not have been obvious).

18 ⁴⁵²⁸ *Daiichi Sankyo Co. v. Matrix Labs. Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010); *Takeda*, 492 F.3d at 1355, 1359–
60; P&G, 566 F.3d at 994–95; *Eisai Co. Ltd. v. Dr. Reddy’s Labs., Ltd.*, 533 F.3d 1533, 1358 (Fed. Cir. 2008); *Eli*
Lilly & Co. v. Zenith Goldline Pharms., Inc., 471 F.3d 1369, 1378–80 (Fed. Cir. 2006).

19 ⁴⁵²⁹ *Daiichi Sankyo*, 619 F.3d at 1354; *Pfizer*, 2010 WL 339042, at *14. *Accord In re Vaidyanathan*, 381. 985, 994
20 (Fed. Cir. 2010) (nonprecedential); *Processing Corp. v. Am. Maize-Products Co.*, 840 F.2d 902, 907 (Fed. Cir.
1988); *Power-One*, 599 F.3d at 1351–52; *Crown Ops. Int’l, Ltd. v. Solutia, Inc.*, 289 F.3d 1367, 1376 (Fed. Cir.
2002).

21 ⁴⁵³⁰ *See, e.g., Vaidyanathan*, 381. at 993–94 (“[W]hile *KSR* relaxed some of the formalism of earlier decisions
22 requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did not remove the need to
anchor the analysis in explanation of how a person of ordinary skill would select and apply the teachings of the
23 references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi Sankyo*, 619 F.3d at
1354 (The assertion of a starting point “must avoid hindsight bias; it must look at the state of the art *at the time the*
24 *invention was made* to find a motivation to select and then modify a lead compound to arrive at the claimed

1 The “reasonable expectation of success” for a chemical compound must be of all of a
2 claimed compound’s relevant properties,⁴⁵³¹ including those discovered after the patent was filed
3 or even issued.⁴⁵³² “The basic principle behind this rule is straight-forward—that which would
4 have been surprising to a person of ordinary skill in a particular art would not have been
5 obvious.”⁴⁵³³ Any assertion of a “reasonable expectation of success” must find a basis in the
6 factual record.⁴⁵³⁴

7 In an obviousness determination, any objective indicia of nonobviousness must be taken
8 into account.⁴⁵³⁵ An objective indicium is any “event[] proved to have actually happened in the
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11 invention.” This turns on the known “properties and elements of the prior art compounds.”; *Forest Labs.*, 438
12 F.Supp.2d at 492–93 (rejecting defendants’ contention that claims to (+)-citalopram were “prima facie obvious in
13 light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding that
14 defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been
15 motivated to resolve citalopram in June 1988”).

16 ⁴⁵³¹ *Yamanouchi Pharm. Co., Ltd. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1345 (Fed. Cir. 2000) (“The success
17 of discovering famotidine . . . was finding a compound that had high activity, few side effects, and lacked toxicity. . .
18 . [T]he ordinary medicinal chemist would not have expected famotidine to have the ‘most desirable combination of
19 pharmacological properties’ that it possesses.”); *Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 364 F.Supp.2d
20 820, 908 (S.D. Ind. 2005) (“[S]uccess was not simply finding a compound as active as clozapine . . . Here, the
21 ordinary medicinal chemist . . . would not have expected olanzapine to have the highly desirable combination of
22 pharmacological properties that it possesses.”).

23 ⁴⁵³² *Knoll Pharm. Inc. v. Teva Pharms. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004); *Eli Lilly*, 364 F.Supp.2d at
24 908.

⁴⁵³³ *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995) (“The principle applies most often to the less predictable fields,
such as chemistry, where minor changes in a product or process may yield substantially different results.”).

⁴⁵³⁴ See, e.g., *Sanofi-Synthelabo*, 550 F.3d at 1089 (“Apotex argues that the district court applied an incorrect
inquiry, and that the correct inquiry is not whether the results obtained with the separated enantiomer were
unexpected, but whether it would have been obvious to separate and test the enantiomers, based on the general
knowledge that enantiomers can exhibit different properties. Apotex refers to *In re Adamson*, 275 F.2d [952,] 955
[(C.C.P.A. 1960)], where the CCPA held that an enantiomer would have been obvious in view of its racemate.
However, the scientific facts differed from these herein, for in *Adamson* the court found that it was ‘particularly
expected’ that the specific enantiomer would have the observed properties. In contrast, as Sanofi points out, in *In re
May*, 574 F.2d at 1095, the CCPA held, as to the enantiomer claimed therein, that the appellant ‘established a
substantial record of unpredictability vis-à-vis a highly significant combination of properties.’”).

⁴⁵³⁵ *Graham*, 383 U.S. at 17–18; *KSR*, 550 U.S. at 406; *Jones v. Hardy*, 727 F.2d 1524, 1530–31 (Fed. Cir. 1984).

1 real world” that evidences the nonobvious nature of the invention.⁴⁵³⁶ The existence of an
2 enduring, unmet need, difficulties encountered by those skilled in the field, unexpected or
3 surprising results, expressions of skepticism, industry praise, commercial success, and copying
4 are classical indicia of nonobviousness.⁴⁵³⁷ These factual inquiries “guard against slipping into
5 use of hindsight,”⁴⁵³⁸ and “may often be the most probative and cogent evidence of
6 nonobviousness.”⁴⁵³⁹

7 Also, as with assertions of anticipation, in order for an invention to be obvious, it must
8 have been fully “in possession” of the public—which requires that the claimed invention have
9 been enabled.⁴⁵⁴⁰

10 A element-by-element analysis, identifying each limitation of each asserted claim that is
11 absent from the prior art, is provided below, and also provided at Exhibit J. The contentions
12 below are incorporated by reference into Exhibit J, and vice-versa.

13 a) General Overview

14 Defendants fail to provide a single prior art reference that discloses administration of the
15 recited composition of EPA ethyl (in the recited purity) to the very-high TG patient population
16 (≥ 500 mg/dL) and the resulting lipid effects. Instead, they rely on a large number of studies,

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18 ⁴⁵³⁶ *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1569 (Fed. Cir. 1987).

19 ⁴⁵³⁷ *Graham*, 383 U.S. at 17–18; *KSR*, 550 U.S. at 406; *U.S. v. Adams*, 383 U.S. 39, 52 (1966); *Merck & Co. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1376 (Fed. Cir. 2005); *Panduit*, 810 F.2d at 1569; *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995); *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988); *Janissen*, 456 F.Supp.2d at 669–72.

20 ⁴⁵³⁸ *Graham*, 383 U.S. at 36.

21 ⁴⁵³⁹ *Ortho-McNeil Pharm. Inc. v. Mylan Labs. Inc.*, 520 F.3d 1358, 1365 (Fed. Cir. 2008) (quoting *Catalina Lighting Inc. v. Lamps Plus, Inc.*, 295 F.3d 1277, 1288 (Fed. Cir. 2002)).

22 ⁴⁵⁴⁰ *In re Kumar*, 418 F.3d 1361, 1368 (Fed. Cir. 2005) (“[I]n order to render an invention unpatentable for
23 obviousness, the prior art must enable a person of ordinary skill to make and use the invention.”); *In re Hoeksema*,
24 399 F.2d 269, 274 (C.C.P.A. 1968) (“[I]f the prior art of record fails to disclose or render obvious a method for
making a claimed compound, at the time the invention was made, it may not be legally concluded that the compound
itself is in the possession of the public.”).

1 many of which are not placebo controlled, which administer EPA, DHA, or both, in varying
2 degrees of purity, in a wide range of doses and administration periods, to subjects who have
3 baseline TG levels lower than 500 mg/dL and in many cases significantly lower. The importance
4 of a placebo-controlled study cannot be overstated. Randomized, double-blind placebo
5 controlled studies are considered the “gold standard” of clinical studies. Studies involving the
6 administration of fish oils or omega-3 fatty acids which are not placebo controlled cannot
7 distinguish between the effect of the placebo from that of the active agent. Studies which
8 administer mixtures enriched for either EPA or DHA are not suitable for evaluating the
9 independent effects of EPA and DHA.⁴⁵⁴¹ Inconsistency in dosages and administration periods
10 and variations in the administered fatty acid compositions also complicate the interpretation of
11 the results and limit the application of these studies.

12 Defendants also rely on the ANCHOR study to argue that Amarin’s use of “patients with
13 very high TGs together with patients with high and borderline high TGs indicates that there is no
14 medical difference in responsiveness to treatment among the groups of people.”⁴⁵⁴² Defendants
15 mischaracterize the ANCHOR study. The ANCHOR study was a multi-center, placebo-
16 controlled, randomized, double-blind, 12-week pivotal Phase 3 study on the effects of Vascepa in
17 patients with high triglycerides (≥ 200 mg/dL and < 500 mg/dL) who were also on statin therapy.
18 Defendants point to the reported “Min-max” TG levels, 157-782 mg/dL, for the AMR101 4g
19 daily group to argue that Amarin used very-high TG patients with high and borderline-high TG
20 patients. However, the mean TG level for this same group, 281.1 mg/dL, makes it clear that

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23 ⁴⁵⁴¹ Mori 2006 at 96.

24 ⁴⁵⁴² Defendants’ Joint Invalidation Contentions at 623 (see FN 116).

1 almost all of the 233 patients in this group had baseline TG values well below 500 mg/dL.⁴⁵⁴³ In
2 addition, the mean baseline TG values for the Placebo and AMR101 2g daily groups were
3 reported as 270.6 mg/dL and 270.2 mg/dL, respectively. Further, Amarin did *not* attempt to use
4 the results of ANCHOR to predict lipid effects in the very high TG patient population. Neither a
5 person of ordinary skill, nor the FDA, would attempt to draw conclusions or gain insight into the
6 very high TG patient population from the ANCHOR trial. In fact, Amarin simultaneously (to
7 ANCHOR) conducted an independent study with Vascepa in patients with very high TG levels.
8 Contrary to Defendants' assertion, the ANCHOR study does *not* indicate that there is no medical
9 difference in responsiveness to treatment between the very-high TG patient population and lower
10 TG patient populations merely because there was possibly one patient with baseline TG levels of
11 at least 500 mg/dL.

12 As discussed above in Section III, patients with very-high TG levels were considered
13 fundamentally different from patients with borderline-high or high TGs from a clinical,
14 regulatory, and therapeutic perspective.⁴⁵⁴⁴ Clinically, the authoritative guidance to physicians
15 on the treatment of lipid disorders throughout the last decade, the Adult Treatment Panel III
16 (ATP-III) divided hypertriglyceridemic patients into three groups: normal/borderline high TG;
17 high TG; and very high TG. The primary risk faced by borderline-high and high TG patients
18 was atherosclerosis, while the primary risk faced by very-high TG patients was acute
19 pancreatitis. Therefore, the primary focus of treatment, as described by the ATP III, for
20 borderline-high and high TG patients was to lower LDL-C levels. In contrast, the priority for

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22 ⁴⁵⁴³ FDA Briefing Document, Oct. 16, 2013 at pg. 26 (The mean baseline TG value for the placebo group was 270.6
23 mg/dL, AMR101 2g group was 270.2 mg/dL, and AMR101 4g group was 281.1 mg/dL. While there may have been
a few patients with TG > 500mg/dL in the AMR101 4g group, it is clear that the overwhelming majority had baseline
TG values < 500 mg/dL).

24 ⁴⁵⁴⁴ See Bays Jan. 8, 2012 Decl., ¶ 20.

1 very-high TG patients was TG reduction. This distinction between patients with borderline-
2 high/high TG levels and patients with very high TG levels is also observed on the regulatory
3 level. The FDA recognized the different clinical status of the very-high TG population by
4 approving some drugs specifically for the very-high TG group without granting treatment
5 indications for the borderline-high or high TG populations (i.e. Lovaza/Omacor).⁴⁵⁴⁵

6 Finally, from a therapeutic standpoint, a person of ordinary skill understood that the
7 effects of lipid-lowering therapies on lipid parameters, such as LDL-C, varied depending on the
8 patient's baseline TG level. Fibrates and prescription omega-3 therapies (two well-known
9 classes of drugs used to treat patient with very-high TGs to lower TG levels at the time of the
10 invention), for example, exhibit different effects on LDL-C levels, depending on the baseline TG
11 level of the patient receiving treatment.

12 Fibrates lower both TGs and LDL-C in normal and borderline-high TG patients, but
13 *increase* LDL-C in very-high TG patients.⁴⁵⁴⁶ The fibrate, Tricor (fenofibrate), for example,
14 decreased LDL-C significantly in both patients with normal baseline TG values (about 31%)⁴⁵⁴⁷
15 and high baseline TG values (mean baseline TG value of 231.9 mg/dL) (about 20%).⁴⁵⁴⁸ In
16 patients approaching very-high TGs levels (mean baseline TG value of 432 mg/dL), a non-
17 significant increase in LDL-C was observed.⁴⁵⁴⁹ In patients with very-high TGs (mean baseline
18 TG = 726 mg/dL), a significant increase in LDL-C was observed (about 45%).⁴⁵⁵⁰ Similar

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20 ⁴⁵⁴⁵ See Bays Jan. 8, 2012 Decl., ¶ 22.

21 ⁴⁵⁴⁶ See Bays 2008 II, at 214-15 (noting that a fibrate caused LDL-C to go down in borderline-high group, remain
22 roughly the same in high TG group, and increase by around 50% in the very-high TG group).

23 ⁴⁵⁴⁷ Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

24 ⁴⁵⁴⁸ *Id.*

⁴⁵⁴⁹ *Id.* See also, Trilipix Label at 27.

⁴⁵⁵⁰ *Id.* See also, Trilipix Label at 27.

1 results were seen with the administration of Lopid (gemfibrozil).⁴⁵⁵¹ The differing effects of
 2 fibrates, such as Tricor, on TG, LDL-C , HDL-C and Total-C based on baseline TG values
 3 demonstrates how a person of ordinary skill at the time of the invention would have understood
 4 that one could not simply assume that an observed effect of a TG-lowering agent on lipid
 5 parameters in patients with normal, borderline-high or high TG levels would be the same in
 6 patients with very-high TG levels (at least 500 mg/dL) compared to a patient with high or
 7 borderline-high TG levels (150-499 mg/dL). As illustrated in the table, below, patients with
 8 normal or high baseline TG levels experience reduced LDL-C levels upon treatment with a TG-
 9 reducing agent such as the fibrate, Tricor. Patients approaching very high TG levels (mean
 10 baseline TG level of 432 mg/dL) and patients with very high TG levels (mean baseline TG level
 11 of 726 mg/dL) experience significantly increased LDL-C levels.

Fibrate	Mean Baseline TG Value	TG	LDL-C	HDL-C	Total-C
Tricor (fenofibrate) ⁴⁵⁵²	101.7 mg/dL	-23.5%*	-31.4%*	+9.8%*	-22.4%*
	231.9 mg/dL	-35.9%*	-20.1%*	+14.6%*	-16.8%*
	432 mg/dL	-46.2*	+14.5	+19.6*	-9.1*
	726 mg/dL	-54.5*	+45.0*	+22.9*	-13.8*

* = p < 0.05 vs. Placebo

17 Lovaza/Omacor was (and is) a prescription omega-3 therapy known to have differing
 18 lipid effects depending on the patient's baseline TG level. When administered to patients with
 19 borderline-high baseline TG levels, Lovaza/Omacor significantly reduced TGs and raised HDL-
 20

21 ⁴⁵⁵¹ See Otvos at 1558 (showing administration of Gemfibrozil to patients with borderline-high baseline TG levels
 22 had no impact on LDL-C levels); Manttari at 14 and 16 (stating that the effect of gemfibrozil on LDL-C was
 23 dependent on initial TG levels, no change was observed for LDL-C in subjects with high baseline TG levels while
 24 subjects with normal or borderline-high baseline TG levels showed significant decreases in LDL-C).

⁴⁵⁵² Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

1 C.⁴⁵⁵³ It had no significant effect on other lipid-related variable, including LDL-C and Apo-
2 B.⁴⁵⁵⁴ However, when administered to patients with very-high baseline TG levels, TGs were
3 reduced significantly by nearly 50% while LDL-C increased sharply by nearly 50%.⁴⁵⁵⁵
4 Although the increase in LDL-C was concerning, it was understood that the overall lipid effect of
5 Lovaza/Omacor was beneficial.⁴⁵⁵⁶

6 Fibrates and prescription Omega-3 therapies demonstrate that one could not simply
7 assume that a lipid lowering agent would have the same effect in a patient with very-high TG
8 levels (≥ 500 mg/dL) as a patient with borderline-high or high TG levels (150-499 mg/dL). They
9 also demonstrate that one of ordinary skill would not expect to see an increase in LDL-C when
10 the normal, borderline-high or high TG patient populations were administered omega-3 fatty
11 acids. As discussed in Section III, the increase in LDL-C for very-high TG patients was
12 expected as a natural consequence of lowering TGs. A person of ordinary skill would have
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14 ⁴⁵⁵³ Chan 2002 I at 2379-81.

15 ⁴⁵⁵⁴ *Id.*; See also, Westphal at 918.

16 ⁴⁵⁵⁵ See Weintraub Sept. 7, 2011 Decl., ¶ 23 (citing Lovaza package insert); Bays May 16, 2011 Decl., ¶ 10; see also, Lovaza PDR and Omacor PDR.

17 ⁴⁵⁵⁶ See Pownall *et al.*, *Correlation of serum triglyceride and its reduction by ω -3 fatty acids with lipid transfer activity and the neutral lipid compositions of high-density and low-density lipoproteins*, 143 *Atherosclerosis* 285, 295 (1999) (“Treatment with ω -3 fatty acids appear to change the lipid profile of individuals with elevated TG to one that may be less atherogenic by changing LDL structure; lowering serum [cholesterol ester transfer activity], serum TG and VLDL-C; and increasing serum HDL-C.”); Stalenhoef at 134 (stating that “Omacor . . . adversely raise LDL cholesterol concentration but the increase in LDL cholesterol concentration reflects a less atherogenic light LDL subfraction profile that may be favorable”); Harris 1997 at 389 (“The increase in LDL, which was substantial on a percentage basis, has been a common finding in past studies in [very-high TG] patients. It may not be as problematic as it appears, however.” And “the use of omega-3 fatty acids for the treatment of severe hypertriglyceridemia may be beneficial not only for the short-term prevention of acute pancreatitis, but also for the long-term prevention of CHD”); Bays III at 248 (“No clinical trial data exist that this rise in LDL-C represents harm or potential “toxicity” to patients. In fact, most evidence supports that omega-3 fatty acids reduce cardiovascular risk as do fibrates. Importantly, clinical trials mostly support that even with increases in LDL-C, omega-3 fatty acids decrease the total cholesterol (TC) carried by atherogenic lipoproteins, as reflected by decreased non-HDL-C levels (TC minus HDL-C.)”)

1 considered the rise in LDL-C to be a direct consequence of TG lowering through increased
2 VLDL particle conversion.⁴⁵⁵⁷ Because normal to high TG patients did not have the large
3 backlog of VLDL particles that very high TG patients have, a person of ordinary skill did not
4 expect LDL-C to increase in normal to high TG patients. It was also well known that the degree
5 of LDL-C elevation observed with prescription omega-3 fatty acids, such as Lovaza/Omacor,
6 was linked to baseline TG levels; that LDL-C levels increased the most in patients with the
7 highest baseline TG levels⁴⁵⁵⁸ and did not increase for patients with lower TG levels. Therefore,
8 the prior art defendants rely upon to show that EPA did *not* increase LDL-C levels in normal,
9 borderline-high or high TG patients was *expected*.

10 Defendants contend that “a composition and its properties are inseparable, and therefore
11 do not impart any additional patentability,” and that “all of the limitations regarding the
12 properties of the ethyl EPA compound identified in the claims of the ‘650 patent are inherent to
13 the compound when administered to a human subject.”⁴⁵⁵⁹ Inherency may not supply a missing
14 claim limitation in an obviousness analysis unless the inherency would have been obvious to one
15 of ordinary skill in the art.⁴⁵⁶⁰ Obviousness is based on what is *known* in the art at the time of the

16
17 ⁴⁵⁵⁷ Bays May 16, 2011 Decl., ¶ 11 (noting the “general knowledge in the art that omega-3 fatty acids as a class
18 increase LDL-C” in very-high TG patients); McKenney 2007, at 724 (“Because of the increase in LDL levels
19 observed in some patients treated with prescription omega-3, LDL levels also should be periodically assessed during
20 treatment.”); Bays in Kwiterovich at 247 (noting that increased LPL activity caused by fish oil “helps explain some
21 of the seemingly paradoxical lipid effects found with their clinical use, for example, the rise in LDL-C with the
22 decrease in VLDL.”).

23 ⁴⁵⁵⁸ Bays 2008 I at 400-402.

24 ⁴⁵⁵⁹ Defendants’ Joint Invalidity Contentions at 624.

⁴⁵⁶⁰ See, e.g., *PAR Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1195–96 (Fed. Cir. 2014) (“A party must . . .
meet a high standard in order to rely on inherency to establish the existence of a claim limitation in the prior art in an
obviousness analysis—the limitation at issue necessarily must be present, or the natural result of the combination of
elements explicitly disclosed by the prior art.”); *In re Rijckaert*, 9 F.3d 1531, 1533–34 (Fed. Cir. 1993) (“The mere
fact that a certain thing may result from a given set of circumstances is not sufficient [to establish inherency].”) (internal quotation omitted).

1 invention.⁴⁵⁶¹ It was not known or reasonably expected at the time of the claimed invention that
2 purified EPA, when administered to patients with very-high TG levels (≥ 500 mg/dL), would not
3 substantially increase LDL-C or would reduce Apo-B. Nor was EPA's effect on LDL-C and
4 Apo-B necessarily present, or the natural result of the combination of elements explicitly
5 disclosed by the prior art.⁴⁵⁶² Therefore, inherency does not supply the missing claim elements
6 in the prior art cited by Defendants.

7 Defendants argue that the claims of the '650 patent which contain "a limiting clause, such
8 as 'to effect' or 'is effective to,'" simply express the intended result of a process step positively
9 recited and therefore are not elements.⁴⁵⁶³ This is incorrect. "There is nothing inherently wrong
10 with defining some part of an invention in functional terms."⁴⁵⁶⁴ When a clause "states a
11 condition that is material to patentability, it cannot be ignored in order to change the substance of
12 the invention."⁴⁵⁶⁵ The claim term "to effect" acts as a positive limitation if the term represents
13 "unexpected and improved effects of administration of the claimed compound."⁴⁵⁶⁶ In addition,
14 the elements represent unexpected and improved effects of administration of purified EPA,
15 because a person of ordinary skill would not have expected no substantial increase in LDL-C or
16 reduction in Apo-B when administering EPA to treat severe hypertriglyceridemia. Therefore, the

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19 _____
20 ⁴⁵⁶¹ *In re Spormann*, 363 F.2d 444, 448 (CCPA 1966) ("That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown.").

21 ⁴⁵⁶² See discussions below for Grimsgaard, Park, Nozaki Kurabayashi and Hayashi.

22 ⁴⁵⁶³ Defendants' Joint Invalidity Contentions at 624.

23 ⁴⁵⁶⁴ See MPEP 2173.05(g) (citing *In re Swinehart*, 439 F.2d 210 (CCPA 1971)).

24 ⁴⁵⁶⁵ *Hoffer v. Microsoft Corp.*, 405 F.3d 1326, 1329 (Fed. Cir. 2005).

⁴⁵⁶⁶ *AstraZeneca AB v. Dr. Reddy's Labs., Ltd.*, No. CIV.A.05-5553 JAP, 2010 WL 1981790, at *11-12 (D.N.J. May 18, 2010).

1 requirements for no substantial increase in LDL-C and reduction in Apo-B must be accorded
2 patentable weight.

3 b) Identification of Claim Elements Absent from Each Item of Prior
4 Art

5 Plaintiffs identify each limitation of each asserted claim that Plaintiffs believe is absent.
6 Where a limitation is absent from any Independent Claim, that limitation is absent from all
7 asserted claims, and that analysis is incorporated by reference into each dependent claim. For
8 any reference, the fact that Plaintiffs do not list a particular limitation as absent from the asserted
9 claims is not a concession that such limitation is present in the reference. By discussing
10 Defendants' analysis of the "limitations" in the claims, Plaintiffs do not concede that Defendants
11 have appropriately divided the claim language for any purpose.

12 (1) WO '118

13 WO '118 discloses a composition containing EPA-E for preventing the occurrence of
14 cardiovascular events in multiple risk patients.

15 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of WO
16 '118 disclose or suggest elements of the '650 Claims. The cited portions of WO '118 do not
17 disclose or suggest these elements at least because they do not disclose or suggest administration
18 of EPA with the recited purity to a subject with the recited very high TG levels. The cited
19 portions of WO '118 further do not disclose or suggest the claimed pharmaceutical composition
20 with the recited fatty acid compositions or dosage. The cited portions of WO '118 further do not
21 disclose or suggest a method to effect the recited TG reduction in the subject with the claimed
22 TG level.

23 With respect to Claims 1 and 8 of the '650 Patent (and therefore all asserted claims), WO
24 '118 does not disclose or suggest a subject with the recited very high TG level. WO '118 also

1 does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid
2 compositions or dosage. WO '118 further does not disclose or suggest a method to effect the
3 recited TG reduction in the subject with the claimed TG level. With respect to Claim 8, WO
4 '118 does not disclose or suggest the recited effect based on a comparison to a placebo control.

5 Further, with respect to Claims 2 and 9, this reference fails to disclose or suggest the
6 subject having the recited baseline LDL-C levels. With respect to Claims 4, 7, 11 and 14, this
7 reference fails to disclose or suggest the recited TG and LDL-C effects in the subject with the
8 claimed TG level. With respect to Claims 5 and 12, this reference fails to disclose or suggest the
9 recited reduction in Apolipoprotein B in the subject with the claimed TG level. With respect to
10 Claims 6 and 13, this reference fails to disclose or suggest the recited reduction in VLDL-C in
11 the subject with the claimed TG level.

12 (2) WO '900

13 WO '900 describes methods for obtaining EPA-rich compositions.

14 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of WO
15 '900 disclose or suggest elements of the '650 Claims. The cited portions of WO '900 do not
16 disclose or suggest these elements at least because they do not disclose or suggest administration
17 of EPA with the recited purity to a subject with the recited very high TG levels. The cited
18 portions of WO '900 further do not disclose or suggest the claimed pharmaceutical composition
19 with the recited fatty acid dosage or administration period. The cited portions of WO '900
20 further do not disclose or suggest a method to effect the recited TG reduction in the subject with
21 the claimed TG level.

22 With respect to Claims 1 and 8 of the '650 Patent (and therefore all asserted claims), WO
23 '900 does not disclose or suggest a subject with the recited very high TG level. WO '900 also
24 does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid

1 dosage or administration period. WO '900 further does not disclose or suggest a method to
2 effect the recited TG reduction in the subject with the claimed TG level. With respect to Claim 8,
3 WO '900 does not disclose or suggest the recited effect based on a comparison to a placebo
4 control.

5 Further, with respect to Claims 2 and 9, this reference fails to disclose or suggest the
6 subject having the recited baseline LDL-C levels. With respect to Claims 3 and 10, this
7 reference does not disclose or suggest the subject having the recited baseline lipid levels. With
8 respect to Claims 4, 7, 11 and 14, this reference fails to disclose or suggest the recited TG and
9 LDL-C effects in the subject with the claimed TG level. With respect to Claims 5 and 12, this
10 reference fails to disclose or suggest the recited reduction in Apolipoprotein B in the subject with
11 the claimed TG level. With respect to Claims 6 and 13, this reference fails to disclose or suggest
12 the recited reduction in VLDL-C in the subject with the claimed TG level.

13 (3) Contacos

14 Contacos describes a study designed to determine the safety and efficacy of a statin
15 (pravastatin) combined with fish oil either alone or in combination, for the management of
16 patients with mixed hyperlipidemia. Contacos does not administer EPA of the purity recited in
17 the claims.

18 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of
19 Contacos disclose or suggest elements of the '650 Claims. The cited portions of Contacos do not
20 disclose or suggest these elements at least because they do not disclose or suggest administration
21 of EPA with the recited purity to a subject with the recited very high TG levels. The cited
22 portions of Contacos further do not disclose or suggest the claimed pharmaceutical composition
23 with the recited fatty acid compositions, dosage, or administration period. The cited portions of
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1 Contacos further do not disclose or suggest a method of administering the claimed
2 pharmaceutical composition to effect the recited TG reduction.

3 With respect to Claim 1 of the '650 Patent (and therefore all asserted claims), Contacos
4 does not disclose or suggest a subject with the recited very high TG level. Contacos also does
5 not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid
6 compositions, dosage, or administration period. Contacos further does not disclose or suggest a
7 method of administering the claimed pharmaceutical composition to effect the recited TG
8 reduction. With respect to Claim 8, Contacos does not disclose or suggest a method of
9 administering the claimed pharmaceutical composition to effect the recited TG reduction the
10 recited effect based on a comparison to a placebo control.

11 Further, with respect to Claims 4, 7, 11 and 14, this reference fails to disclose or suggest
12 the administration of the claimed pharmaceutical composition to effect the recited TG and LDL-
13 C effects. With respect to Claims 5 and 12, this reference fails to disclose or suggest the
14 administration of the claimed pharmaceutical composition to effect the recited reduction in
15 Apolipoprotein B. With respect to Claims 6 and 13, this reference fails to disclose or suggest the
16 administration of the claimed pharmaceutical composition to effect the recited reduction in
17 VLDL-C.

18 (4) Grimsgaard

19 Grimsgaard conducted a double-blind, randomized, placebo-controlled, parallel design
20 intervention study to evaluate the dietary supplementation with EPA or DHA on serum lipids,
21 apolipoproteins, and serum phospholipid fatty acid composition in subjects with normal TG
22 levels.

23 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of
24 Grimsgaard disclose or suggest elements of the '650 Claims. The cited portions of Grimsgaard

1 do not disclose or suggest these elements at least because they do not disclose or suggest
2 administration of EPA with the recited purity to a subject with the recited very high TG levels.
3 The cited portions of Grimsgaard further do not disclose or suggest the claimed pharmaceutical
4 composition with the recited administration period. The cited portions of Grimsgaard further do
5 not disclose or suggest a method to effect the recited TG reduction in the subject with the
6 claimed TG level.

7 With respect to Claims 1 and 8 of the '650 Patent (and therefore all asserted claims),
8 Grimsgaard does not disclose or suggest a subject with the recited very high TG level.
9 Grimsgaard also does not disclose or suggest the claimed pharmaceutical composition with the
10 recited administration period. Grimsgaard further does not disclose or suggest a method to effect
11 the recited TG reduction in the subject with the claimed TG level. With respect to Claim 8,
12 Grimsgaard does not disclose or suggest the recited effect based on a comparison of the subject
13 with the claimed TG levels to a placebo control.

14 Further, with respect to Claims 4, 7, 11 and 14, this reference fails to disclose or suggest
15 the recited TG and LDL-C effects in the subject with the claimed TG level. With respect to
16 Claims 5 and 12, this reference fails to disclose or suggest the recited reduction in
17 Apolipoprotein B in the subject with the claimed TG level. With respect to Claims 6 and 13, this
18 reference fails to disclose or suggest the recited reduction in VLDL-C in the subject with the
19 claimed TG level.

20 (5) Hayashi

21 Hayashi is directed to administration of ethyl icosapentate 1800mg (6 capsules) daily for
22 8 weeks. The purity of the composition is not reported. The study was not placebo controlled
23 and was conducted in 28 patients with familial combined hyperlipidemia and a serum trygliceride
24

1 concentration higher than 150 mg/dl or serum total cholesterol concentration higher than 220
2 mg/dl.

3 The portions of Hayashi cited by Defendants do not disclose or suggest elements of the
4 '650 patent claims. For example, the cited portions of Hayashi do not disclose or suggest
5 administration of EPA with the recited purity to a subject with the recited very high TG levels
6 who does not receive concurrent lipid altering therapy. Figure 2 demonstrates that no subject
7 had a TG level above 400 mg/dl. The cited portions of Hayashi further do not disclose or
8 suggest the claimed pharmaceutical composition with the recited fatty acid compositions or
9 dosage. The cited portions of Hayashi further do not disclose or suggest a method to effect the
10 recited TG reduction without substantially increasing LDL-C in a subject with the recited very
11 high TG levels.

12 With respect to Claims 1 and 8 of the '650 Patent (and therefore all asserted claims),
13 Hayashi does not disclose or suggest a subject with the recited very high TG level. Hayashi also
14 does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid
15 compositions or dosage. Hayashi further does not disclose or suggest a method to effect the
16 recited TG reduction in the subject with the claimed TG level. With respect to Claim 8, Hayashi
17 does not disclose or suggest the recited effect based on a comparison to a placebo control.

18 Further, with respect to Claims 2 and 9, this reference fails to disclose or suggest the
19 subject having the recited baseline LDL-C levels. With respect to Claims 4, 7, 11 and 14, this
20 reference fails to disclose or suggest the recited TG and LDL-C effects in the subject with the
21 claimed TG level. With respect to Claims 5 and 12, this reference fails to disclose or suggest the
22 recited reduction in Apolipoprotein B in the subject with the claimed TG level. With respect to
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1 Claims 6 and 13, this reference fails to disclose or suggest the recited reduction in VLDL-C in
2 the subject with the claimed TG level.

3 (6) Katayama

4 Katayama was directed to an investigation of the safety and efficacy of Epadel during
5 long term treatment in patients with hyperlipidemia that was not placebo controlled. Notably,
6 Katayama did not disclose or suggest any LDL-C related data or describe any LDL-C effects and
7 was not placebo controlled.

8 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of
9 Katayama disclose or suggest elements of the '650 Claims. The cited portions of Katayama do
10 not disclose or suggest these elements at least because they do not disclose or suggest
11 administration of EPA with the recited purity to a subject with the recited very high TG levels.
12 The cited portions of Katayama further do not disclose or suggest the claimed pharmaceutical
13 composition with the recited fatty acid compositions or dosage. The cited portions of Katayama
14 further do not disclose or suggest a method to effect the recited TG reduction in the subject with
15 the claimed TG level.

16 With respect to Claims 1 and 8 of the '650 Patent (and therefore all asserted claims),
17 Katayama does not disclose or suggest a subject with the recited very high TG level. Katayama
18 also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty
19 acid compositions or dosage. Katayama further does not disclose or suggest a method to effect
20 the recited TG reduction in the subject with the claimed TG level. With respect to Claim 8,
21 Katayama does not disclose or suggest the recited effect based on a comparison to a placebo
22 control.

23 Further, with respect to Claims 2 and 9, this reference fails to disclose or suggest the
24 subject having the recited baseline LDL-C levels. With respect to Claims 4, 7, 11 and 14, this

1 reference fails to disclose or suggest the recited TG and LDL-C effects in the subject with the
2 claimed TG level. With respect to Claims 5 and 12, this reference fails to disclose or suggest the
3 recited reduction in Apolipoprotein B in the subject with the claimed TG level. With respect to
4 Claims 6 and 13, this reference fails to disclose or suggest the recited reduction in VLDL-C in
5 the subject with the claimed TG level.

6 (7) Leigh-Firbank

7 Leigh-Firbank studied the impact of fish-oil intervention on LDL oxidation, particle
8 density and concentration in subjects with an atherogenic lipoprotein phenotype. Leigh-Firbank
9 does not administer EPA of the purity recited in the claims.

10 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of
11 Leigh-Firbank disclose or suggest elements of the '650 Claims. The cited portions of Leigh-
12 Firbank do not disclose or suggest these elements at least because they do not disclose or suggest
13 administration of EPA with the recited purity to a subject with the recited very high TG levels.
14 The cited portions of Leigh-Firbank further do not disclose or suggest the claimed
15 pharmaceutical composition with the recited fatty acid compositions, dosage, or administration
16 period. The cited portions of Leigh-Firbank further do not disclose or suggest a method of
17 administering the claimed pharmaceutical composition to effect the recited TG reduction.

18 With respect to Claim 1 of the '650 Patent (and therefore all asserted claims), Leigh-
19 Firbank does not disclose or suggest a subject with the recited very high TG level. Leigh-
20 Firbank also does not disclose or suggest the claimed pharmaceutical composition with the
21 recited fatty acid compositions, dosage, or administration period. Leigh-Firbank further does not
22 disclose or suggest a method of administering the claimed pharmaceutical composition to effect
23 the recited TG reduction. With respect to Claim 8, Leigh-Firbank does not disclose or suggest a
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1 method of administering the claimed pharmaceutical composition to effect the recited TG
2 reduction based on a comparison to a placebo control.

3 Further, with respect to Claims 4, 7, 11 and 14, this reference fails to disclose or suggest
4 the administration of the claimed pharmaceutical composition to effect the recited TG and LDL-
5 C effects. With respect to Claims 5 and 12, this reference fails to disclose or suggest the
6 administration of the claimed pharmaceutical composition to effect the recited reduction in
7 Apolipoprotein B. With respect to Claims 6 and 13, this reference fails to disclose or suggest the
8 administration of the claimed pharmaceutical composition to effect the recited reduction in
9 VLDL-C.

10 (8) Lovaza PDR

11 The Lovaza PDR is the Physicians' Desk Reference describing Lovaza.

12 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of the
13 Lovaza PDR disclose or suggest elements of the '650 Claims. The cited portions of the Lovaza
14 PDR do not disclose or suggest these elements at least because they do not disclose or suggest
15 administration of EPA with the recited purity to a subject with the recited very high TG levels.
16 The cited portions of the Lovaza PDR further do not disclose or suggest the claimed
17 pharmaceutical composition with the recited fatty acid compositions or administration period.
18 The cited portions of the Lovaza PDR further do not disclose or suggest a method of
19 administering the claimed pharmaceutical composition to effect the recited TG reduction.

20 With respect to Claim 1 of the '650 Patent (and therefore all asserted claims), the Lovaza
21 PDR does not disclose or suggest the claimed pharmaceutical composition with the recited fatty
22 acid compositions or administration period. The Lovaza PDR further does not disclose or
23 suggest a method of administering the claimed pharmaceutical composition to effect the recited
24 TG reduction. With respect to Claim 8, the Lovaza PDR does not disclose or suggest a method

1 of administering the claimed pharmaceutical composition to effect the recited TG reduction
2 based on a comparison to a placebo control.

3 Further, with respect to Claims 4, 7, 11 and 14, this reference fails to disclose or suggest
4 the administration of the claimed pharmaceutical composition to effect the recited TG and LDL-
5 C effects. With respect to Claims 5 and 12, this reference fails to disclose or suggest the
6 administration of the claimed pharmaceutical composition to effect the recited reduction in
7 Apolipoprotein B. With respect to Claims 6 and 13, this reference fails to disclose or suggest the
8 administration of the claimed pharmaceutical composition to effect the recited reduction in
9 VLDL-C.

10 (9) Maki

11 Maki administered 1.52g/day DHA supplements to patients with below-average levels of
12 HDL-C. Maki does not administer EPA of the purity recited in the claims.

13 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Maki
14 disclose or suggest elements of the '650 Claims. The cited portions of Maki do not disclose or
15 suggest these elements at least because they do not disclose or suggest administration of EPA
16 with the recited purity to a subject with the recited very high TG levels. The cited portions of
17 Maki further do not disclose or suggest the claimed pharmaceutical composition with the recited
18 fatty acid compositions, dosage, or administration period. The cited portions of Maki further do
19 not disclose or suggest a method of administering the claimed pharmaceutical composition to
20 effect the recited TG reduction.

21 With respect to Claim 1 of the '650 Patent (and therefore all asserted claims), Maki does
22 not disclose or suggest a subject with the recited very high TG level. Maki also does not disclose
23 or suggest the claimed pharmaceutical composition with the recited fatty acid compositions,
24 dosage, or administration period. Maki further does not disclose or suggest a method of

1 administering the claimed pharmaceutical composition to effect the recited TG reduction. With
2 respect to Claim 8, Maki does not disclose or suggest a method of administering the claimed
3 pharmaceutical composition to effect the recited TG reduction based on a comparison to a
4 placebo control.

5 Further, with respect to Claims 4, 7, 11 and 14, this reference fails to disclose or suggest
6 the administration of the claimed pharmaceutical composition to effect the recited TG and LDL-
7 C effects. With respect to Claims 5 and 12, this reference fails to disclose or suggest the
8 administration of the claimed pharmaceutical composition to effect the recited reduction in
9 Apolipoprotein B. With respect to Claims 6 and 13, this reference fails to disclose or suggest the
10 administration of the claimed pharmaceutical composition to effect the recited reduction in
11 VLDL-C.

12 (10) Matsuzawa

13 Matsuzawa administered Epadel to patients with hyperlipaemia in order to study its long-
14 term use in the treatment of the disease and was not placebo controlled.

15 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of
16 Matsuzawa disclose or suggest elements of the '650 Claims. The cited portions of Matsuzawa
17 do not disclose or suggest these elements at least because they do not disclose or suggest
18 administration of EPA with the recited purity to a subject with the recited very high TG levels.
19 The cited portions of Matsuzawa further do not disclose or suggest the claimed pharmaceutical
20 composition with the recited fatty acid compositions or dosage. The cited portions of
21 Matsuzawa further do not disclose or suggest a method of administering the claimed
22 pharmaceutical composition to effect the recited TG reduction in the subject with the claimed TG
23 level.

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CONFIDENTIAL

1 With respect to Claims 1 and 8 of the '650 Patent (and therefore all asserted claims),
2 Matsuzawa does not disclose or suggest a subject with the recited very high TG level.
3 Matsuzawa also does not disclose or suggest the claimed pharmaceutical composition with the
4 recited fatty acid compositions or dosage. Matsuzawa further does not disclose or suggest a
5 method of administering the claimed pharmaceutical composition to effect the recited TG
6 reduction in the subject with the claimed TG level. With respect to Claim 8, Matsuzawa does
7 not disclose or suggest the recited effect based on a comparison to a placebo control.

8 Further, with respect to Claims 2 and 9, this reference fails to disclose or suggest the
9 subject having the recited baseline LDL-C levels. With respect to Claims 4, 7, 11 and 14, this
10 reference fails to disclose or suggest the administration of the claimed pharmaceutical
11 composition to effect the recited TG and LDL-C effects in the subject with the claimed TG level.
12 With respect to Claims 5 and 12, this reference fails to disclose or suggest the administration of
13 the claimed pharmaceutical composition to effect the recited reduction in Apolipoprotein B in
14 the subject with the claimed TG level. With respect to Claims 6 and 13, this reference fails to
15 disclose or suggest the administration of the claimed pharmaceutical composition to effect the
16 recited reduction in VLDL-C in the subject with the claimed TG level.

17 (11) Mori 2000

18 Mori 2000 aimed to determine whether EPA and DHA have differential effects on serum
19 lipids and lipoproteins, glucose and insulin in humans.

20 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Mori
21 2000 disclose or suggest elements of the '650 Claims. The cited portions of Mori 2000 do not
22 disclose or suggest these elements at least because they do not disclose or suggest administration
23 of EPA with the recited purity to a subject with the recited very high TG levels. The cited
24 portions of Mori 2000 further do not disclose or suggest the claimed pharmaceutical composition

1 with the recited administration period. The cited portions of Mori 2000 further do not disclose or
2 suggest a method to effect the recited TG reduction in the subject with the claimed TG level.

3 With respect to Claims 1 and 8 of the '650 Patent (and therefore all asserted claims),
4 Mori 2000 does not disclose or suggest a subject with the recited very high TG level. Mori 2000
5 also does not disclose or suggest the claimed pharmaceutical composition with the recited
6 administration period. Mori 2000 further does not disclose or suggest a method to effect the
7 recited TG reduction in the subject with the claimed TG level. With respect to Claim 8, Mori
8 2000 does not disclose or suggest the recited effect based on a comparison of the subject with the
9 claimed TG levels to a placebo control.

10 Further, with respect to Claims 4, 7, 11 and 14, this reference fails to disclose or suggest
11 the recited TG and LDL-C effects in the subject with the claimed TG level. With respect to
12 Claims 5 and 12, this reference fails to disclose or suggest the recited reduction in
13 Apolipoprotein B in the subject with the claimed TG level. With respect to Claims 6 and 13, this
14 reference fails to disclose or suggest the recited reduction in VLDL-C in the subject with the
15 claimed TG level.

16 (12) Mori 2006

17 Mori 2006 is a review which reports data from clinical trials which compared the
18 independent effects of EPA and DHA in individuals at increased risk of cardiovascular disease.

19 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Mori
20 2006 disclose or suggest elements of the '650 Claims. The cited portions of Mori 2006 do not
21 disclose or suggest these elements at least because they do not disclose or suggest administration
22 of EPA with the recited purity to a subject with the recited very high TG levels. The cited
23 portions of Mori 2006 further do not disclose or suggest the claimed pharmaceutical composition
24 with the recited fatty acid dosage or administration period. The cited portions of Mori 2006

1 further do not disclose or suggest a method to effect the recited TG reduction in the subject with
2 the claimed TG level.

3 With respect to Claims 1 and 8 of the '650 Patent (and therefore all asserted claims),
4 Mori 2006 does not disclose or suggest a subject with the recited very high TG level. Mori 2006
5 also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty
6 acid dosage or administration period. Mori 2006 further does not disclose or suggest a method to
7 effect the recited TG reduction in the subject with the claimed TG level. With respect to Claim 8,
8 Mori 2006 does not disclose or suggest the recited effect based on a comparison to a placebo
9 control.

10 Further, with respect to Claims 2 and 9, this reference fails to disclose or suggest the
11 subject having the recited baseline LDL-C levels. With respect to Claims 3 and 10, this
12 reference does not disclose or suggest the subject having the recited baseline lipid levels. With
13 respect to Claims 4, 7, 11 and 14, this reference fails to disclose or suggest the recited TG and
14 LDL-C effects in the subject with the claimed TG level. With respect to Claims 5 and 12, this
15 reference fails to disclose or suggest the recited reduction in Apolipoprotein B in the subject with
16 the claimed TG level. With respect to Claims 6 and 13, this reference fails to disclose or suggest
17 the recited reduction in VLDL-C in the subject with the claimed TG level.

18 (13) Nozaki

19 Nozaki is directed to administration of 2.7 g ethyl icosapentate per day for 6 months. The
20 purity of the composition is reported as 90%. The study was not placebo controlled and was
21 conducted in 14 hypercholesterolemic subjects. The average baseline TG level was only 165
22 mg/dL, while the baseline LDL-C level was 185 mg/dL, which is unusually high for this TG
23 patient population.

1 The portions of Nozaki cited by Defendants do not disclose or suggest elements of the
2 '650 patent claims. For example, the cited portions of Nozaki do not disclose or suggest
3 administration of EPA with the recited purity to a subject with the recited very high TG levels
4 who does not receive concurrent lipid altering therapy. The cited portions of Nozaki further do
5 not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid
6 compositions or dosage. The cited portions of Nozaki further do not disclose or suggest a
7 method to effect the recited TG reduction without substantially increasing LDL-C in a subject
8 with the recited very high TG levels.

9 Defendants assert that certain cited sections of Nozaki disclose or suggest elements of the
10 '650 Claims. The cited portions of Nozaki do not disclose or suggest these elements at least
11 because they do not disclose or suggest administration of EPA with the recited purity to a subject
12 with the recited very high TG levels who does not receive concurrent lipid altering therapy. The
13 cited portions of Nozaki further do not disclose or suggest the claimed pharmaceutical
14 composition with the recited fatty acid compositions or dosage. The cited portions of Nozaki
15 further do not disclose or suggest a method to effect the recited TG reduction without
16 substantially increasing LDL-C.

17 With respect to Claims 1 and 8 of the '650 Patent (and therefore all asserted claims),
18 Nozaki does not disclose or suggest a subject with the recited very high TG level. Nozaki also
19 does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid
20 compositions or dosage. Nozaki further does not disclose or suggest a method to effect the
21 recited TG reduction in the subject with the claimed TG level. With respect to Claim 8, Nozaki
22 does not disclose or suggest the recited effect based on a comparison to a placebo control.

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1 Further, with respect to Claims 2 and 9, this reference fails to disclose or suggest the
2 subject having the recited baseline LDL-C levels. With respect to Claims 4, 7, 11 and 14, this
3 reference fails to disclose or suggest the recited TG and LDL-C effects in the subject with the
4 claimed TG level. With respect to Claims 5 and 12, this reference fails to disclose or suggest the
5 recited reduction in Apolipoprotein B in the subject with the claimed TG level. With respect to
6 Claims 6 and 13, this reference fails to disclose or suggest the recited reduction in VLDL-C in
7 the subject with the claimed TG level.

8 (14) Omacor PDR

9 The Omacor PDR is the Physicians' Desk Reference describing Omacor.

10 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of the
11 Omacor PDR disclose or suggest elements of the '650 Claims. The cited portions of the Omacor
12 PDR do not disclose or suggest these elements at least because they do not disclose or suggest
13 administration of EPA with the recited purity to a subject with the recited very high TG levels.
14 The cited portions of the Omacor PDR further do not disclose or suggest the claimed
15 pharmaceutical composition with the recited fatty acid compositions or administration period.
16 The cited portions of the Omacor PDR further do not disclose or suggest a method of
17 administering the claimed pharmaceutical composition to effect the recited TG reduction.

18 With respect to Claim 1 of the '650 Patent (and therefore all asserted claims), the Omacor
19 PDR does not disclose or suggest the claimed pharmaceutical composition with the recited fatty
20 acid compositions or administration period. The Omacor PDR further does not disclose or
21 suggest a method of administering the claimed pharmaceutical composition to effect the recited
22 TG reduction. With respect to Claim 8, the Omacor PDR does not disclose or suggest a method
23 of administering the claimed pharmaceutical composition to effect the recited TG reduction
24 based on a comparison to a placebo control.

1 Further, with respect to Claims 4, 7, 11 and 14, this reference fails to disclose or suggest
2 the administration of the claimed pharmaceutical composition to effect the recited TG and LDL-
3 C effects. With respect to Claims 5 and 12, this reference fails to disclose or suggest the
4 administration of the claimed pharmaceutical composition to effect the recited reduction in
5 Apolipoprotein B. With respect to Claims 6 and 13, this reference fails to disclose or suggest the
6 administration of the claimed pharmaceutical composition to effect the recited reduction in
7 VLDL-C.

8 (15) Satoh

9 Satoh administered 1.8g/day of >98% EPA to patients in order to measure the effects of
10 PEA on C-reactive protein and examine how alteration of lipoprotein profile by EPA affects
11 systemic inflammation.

12 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of
13 Satoh disclose or suggest elements of the '650 Claims. The cited portions of Satoh do not
14 disclose or suggest these elements at least because they do not disclose or suggest administration
15 of EPA with the recited purity to a subject with the recited very high TG levels. The cited
16 portions of Satoh further do not disclose or suggest the claimed pharmaceutical composition with
17 the recited fatty acid dosage. The cited portions of Satoh further do not disclose or suggest a
18 method to effect the recited TG reduction in the subject with the claimed TG level.

19 With respect to Claims 1 and 8 of the '650 Patent (and therefore all asserted claims),
20 Satoh does not disclose or suggest a subject with the recited very high TG level. Satoh also does
21 not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid
22 dosage. Satoh further does not disclose or suggest a method to effect the recited TG reduction in
23 the subject with the claimed TG level. With respect to Claim 8, Satoh does not disclose or
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1 suggest the recited effect based on a comparison of the subject with the claimed TG levels to a
2 placebo control.

3 Further, with respect to Claims 4, 7, 11 and 14, this reference fails to disclose or suggest
4 the recited TG and LDL-C effects in the subject with the claimed TG level. With respect to
5 Claims 5 and 12, this reference fails to disclose or suggest the recited reduction in
6 Apolipoprotein B in the subject with the claimed TG level. With respect to Claims 6 and 13, this
7 reference fails to disclose or suggest the recited reduction in VLDL-C in the subject with the
8 claimed TG level.

9 (16) Shinozaki

10 Shinozaki studied the long-term effect of EPA on serum levels of Lipoprotein (a) and
11 lipids such as triglycerides, total cholesterol, and low density lipoprotein particles.

12 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of
13 Shinozaki disclose or suggest elements of the '650 Claims. The cited portions of Shinozaki do
14 not disclose or suggest these elements at least because they do not disclose or suggest
15 administration of EPA with the recited purity to a subject with the recited very high TG levels.
16 The cited portions of Shinozaki further do not disclose or suggest the claimed pharmaceutical
17 composition with the recited fatty acid dosage. The cited portions of Shinozaki further do not
18 disclose or suggest a method to effect the recited TG reduction in the subject with the claimed
19 TG level.

20 With respect to Claims 1 and 8 of the '650 Patent (and therefore all asserted claims),
21 Shinozaki does not disclose or suggest a subject with the recited very high TG level. Shinozaki
22 also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty
23 acid dosage. Shinozaki further does not disclose or suggest a method to effect the recited TG
24 reduction in the subject with the claimed TG level. With respect to Claim 8, Shinozaki does not

1 disclose or suggest the recited effect based on a comparison of the subject with the claimed TG
2 levels to a placebo control.

3 Further, with respect to Claims 2 and 9, this reference fails to disclose or suggest the
4 subject having the recited baseline LDL-C levels. With respect to Claims 3 and 10, this
5 reference does not disclose or suggest the subject having the recited baseline lipid levels. With
6 respect to Claims 4, 7, 11 and 14, this reference fails to disclose or suggest the recited TG and
7 LDL-C effects in the subject with the claimed TG level. With respect to Claims 5 and 12, this
8 reference fails to disclose or suggest the recited reduction in Apolipoprotein B in the subject with
9 the claimed TG level. With respect to Claims 6 and 13, this reference fails to disclose or suggest
10 the recited reduction in VLDL-C in the subject with the claimed TG level.

11 (17) Takaku

12 Takaku administered Epadel to patients with hyperlipaemia in order to study its long-
13 term use and was not placebo controlled.

14 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of
15 Takaku disclose or suggest elements of the '650 Claims. The cited portions of Takaku do not
16 disclose or suggest these elements at least because they do not disclose or suggest administration
17 of EPA with the recited purity to a subject with the recited very high TG levels. The cited
18 portions of Takaku further do not disclose or suggest the claimed pharmaceutical composition
19 with the recited fatty acid compositions or dosage. The cited portions of Takaku further do not
20 disclose or suggest a method of administering the claimed pharmaceutical composition to effect
21 the recited TG reduction in the subject with the claimed TG level.

22 With respect to Claims 1 and 8 of the '650 Patent (and therefore all asserted claims),
23 Takaku does not disclose or suggest a subject with the recited very high TG level. Takaku also
24 does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid

1 compositions or dosage. Takaku further does not disclose or suggest a method of administering
2 the claimed pharmaceutical composition to effect the recited TG reduction in the subject with the
3 claimed TG level. With respect to Claim 8, Takaku does not disclose or suggest the recited
4 effect based on a comparison to a placebo control.

5 Further, with respect to Claims 2 and 9, this reference fails to disclose or suggest the
6 subject having the recited baseline LDL-C levels. With respect to Claims 3 and 10, this
7 reference does not disclose or suggest the subject having the recited baseline lipid levels. With
8 respect to Claims 4, 7, 11 and 14, this reference fails to disclose or suggest the recited TG and
9 LDL-C effects in the subject with the claimed TG level. With respect to Claims 5 and 12, this
10 reference fails to disclose or suggest the recited reduction in Apolipoprotein B in the subject with
11 the claimed TG level. With respect to Claims 6 and 13, this reference fails to disclose or suggest
12 the recited reduction in VLDL-C in the subject with the claimed TG level.

13 c) The Prior Art Does Not Render the Claims Obvious

14 Defendants have not identified by clear and convincing evidence that the asserted claims
15 of the '650 patent would have been *prima facie* obvious in light of the references cited, either
16 alone or in combination. As described above, none of the references discloses all of the elements
17 in any of the asserted claims. Defendants chart a laundry list of 66 separate references, without
18 explanation, and argue they somehow must be combined to render obvious the asserted claims.
19 Where Defendants have failed to make disclosures with the specificity required by Local Patent
20 Rule 1-8(d), it has failed to put Plaintiffs on notice of how these references allegedly disclose the
21 claim elements at issue.

22 Defendants' contentions fail to disclose each and every element of the claims of the '650
23 patent. Specifically, Defendants do not contend that the relied upon references disclose the
24 following elements of Claim 8 (and therefore its asserted dependent claims as well):

1 administering the claimed pharmaceutical composition to the recited subject to effect a reduction
2 in triglycerides based on a comparison to placebo control. Therefore, Defendants' prior art
3 combinations cannot render the claims *prima facie* obvious.

4 Facts supporting the non-obviousness of the claims of the '650 patent are discussed in
5 detail below. The objective indicia discussed in Section V.O further demonstrate that the '650
6 patent is not obvious. In short, Defendants have not met their burden of showing that the claims
7 would have been obvious.

8 (1) Defendants Do Not Demonstrate that the Independent
9 Claims of the '650 patent Would Have Been Obvious

10 (a) Defendants Do Not Demonstrate that a Person of
11 Ordinary Skill in the Art Would Have Had Any
Reason to Replace the Mixed Fish Oil Active
Ingredient in Lovaza with Pure EPA

12 (i) The '650 Patent is not Obvious Over the
13 Omacor PDR/Lovaza PDR, in Combination
with Katayama and/or Matsuzawa, Further
14 in View of Nozaki and/or Hayashi and
Further in View of Leigh-Firbank and/or
Mori 2000

15 With respect to the '650 patent, Defendants present a combination of seven references:

16 "the Omacor PDR/Lovaza PDR in combination with the known clinical benefits of administering
17 pure EPA as evidenced by Katayama and/or Matsuzawa, further in view of Nozaki and/or
18 Hayashi, and further in view of Leigh-Firbank and/or Mori 2000."⁴⁵⁶⁷ Defendants also present
19 charts purporting to assert that an additional 61 references may be combined in order to render
20 the Claims obvious. Not only do Defendants ignore the improbability that a person of ordinary
21 skill would combine 61 separate references, they additionally do not identify any motivation for
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24 ⁴⁵⁶⁷ Defendants' Joint Invalidity Contentions at 618.

1 combining these references.^{4568, 4569} Although Defendants need not point to an explicit statement
2 in the prior art motivating the combination of these references, any assertion of an “apparent
3 reason” to combine must find a basis in the factual record.⁴⁵⁷⁰ Defendants’ unsupported cobbling
4 of selective disclosures represents hindsight reconstruction.⁴⁵⁷¹ Defendants’ contentions are no
5 more than an assertion that certain claim elements were known in the prior art. Throughout their
6 contentions, Defendants’ selectively cite to data points in a reference without considering other
7 disclosures or even the reference as a whole. Each reference, however, must be evaluated for all
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10 ⁴⁵⁶⁸ Defendants’ bare assertion that the asserted claims are obvious “in view of one or more of Omacor or Lovaza (as
11 described in the references cited above in Section V.B.2 in view of, at least, the references cited in V.B.3 and 4,
12 including, the ‘954 publication, WO ‘900, WO ‘118, Ando, Grimsgaard, Hayashi, Katayama, Matsuzawa, Mataka,
13 Mori 2000, Nakamura, Nozaki, Okumura, Park, Saito 1998, Saito 2008 Satoh, Shinozaki, Takaku, Yokoyama 2003,
14 Yokoyama 2007, Calabresi, Chan 2002, Chan 2003, Contacos, Geppert, Kelley, Leigh-Firbank, Maki, Mori 2000,
15 Mori 2006, Rambjør, Sanders or Theobald,” similarly fails to meet the disclosure requirements of the Nevada Local
16 Patent Rules, and fails to provide any motivation to combine these references. *See* Defendants’ Joint Invalidity
17 Contentions at 617.

18 ⁴⁵⁶⁹ Defendants’ bare assertion that “the motivation or reason to combine or modify the prior art to create
19 invalidating combinations under 35 U.S.C. §103 can be found in the references identified above in Section III.C,”
20 and that “[c]ommon sense, design incentives. Market forces, and the background knowledge possessed by a person
21 having ordinary skill in the art provide the reasons or rationales for combining the teachings of multiple references
22 or modifying references to render obvious the claimed inventions of the asserted claims,” fails to meet the disclosure
23 requirements of the Nevada Local Patent Rules. *See* Defendants’ Joint Invalidity Contentions at 616-617.

24 ⁴⁵⁷⁰ *See, e.g., In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the
formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did
not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply
the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi
Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must
avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to
select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and
elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp.
2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie*
obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding
that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been
motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

⁴⁵⁷¹ *See, e.g., Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under
KSR, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention
without any explanation as to how or why the references would be combined to produce the claimed invention”).

1 that it teaches.⁴⁵⁷² Accordingly, Defendants fail to meet their burden to establish *prima facie*
2 obviousness.

3 The Lovaza PDR fails to disclose or even suggest the claimed method of reducing
4 triglycerides in a subject with the claimed pharmaceutical composition containing the claimed
5 fatty acid compositions or administration period. The Lovaza PDR further does not disclose a
6 method to effect the specified TG reduction without substantially increasing LDL-C. Indeed, the
7 Lovaza PDR discloses the exact opposite. The EPA/DHA composition of Lovaza causes a
8 significant increase in LDL-C levels in the very high TG patient population, for whom the
9 product is indicated. At most, the Lovaza PDR discloses administration of a prescription fish oil,
10 a combination of approximately 465 mg EPA and 375 mg DHA, as an adjunct to diet to reduce
11 TG levels in adult patients with very-high (≥ 500 mg/dL) TG levels.

12 The proposed combinations do not render the independent claims of the '650 patent
13 obvious and Defendants' burden to prove otherwise is especially difficult because the PTO
14 considered Matsuzawa, Katayama, Mori 2000, and Lovaza (both generally and the Lovaza
15 package insert specifically) during prosecution.⁴⁵⁷³

16 The analysis of the independent claims of the '650 patent is incorporated into all asserted
17 claims that depend from those Claims.

18 (a) A Person of Ordinary Skill Would
19 Not Have Been Motivated to
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22 ⁴⁵⁷² *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

23 ⁴⁵⁷³ *See, e.g., Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012)(taking into account that “the
24 examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention.
Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear
and convincing standard came into play”).

For an invention to be obvious, there must have been an “apparent reason” to make it.

The subject matter of the ‘650 patent claims would not have been obvious in light of these references because a person of ordinary skill would not have been motivated to purify EPA or been able to reasonably expect that the claimed pharmaceutical composition would reduce TG levels without an increase in LDL-C levels.

(i) Katayama and/or Matsuzawa
Do Not Disclose Purported
Known Clinical Benefits of
Administering Pure EPA

Both Katayama and Matsuzawa are long term studies directed to an investigation of the safety and efficacy of Epadel in patients with a wide range of baseline TG levels. These studies were not placebo controlled. A person of ordinary skill in the art understood that a placebo may itself cause an effect. Without accounting for the placebo effect, a person of ordinary skill in the art would not and could not attribute any observed effect (and the magnitude of that effect) to that of the drug. Any observed effect could be placebo dependent.⁴⁵⁷⁴ As discussed above in Section III, a person of ordinary skill would not expect the same LDL-C effect in patients with lower baseline TG levels—the subjects of Katayama and Matsuzawa—as in very-high TG patients because patients with higher TG levels had different lipid responses compared to patients with lower TG levels. Patients with very-high TG levels were considered fundamentally different from patients with borderline-high or high TGs from a lipid chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint. As previously discussed, a person of ordinary

⁴⁵⁷⁴See Grimsgaard at 652 (Although administration of EPA reduced Apo-B compared to baseline, it was not a statistically significant effect when compared to placebo. Grimsgaard’s disclosure highlights the importance of a placebo-controlled study and why results compared only to baseline may be misleading.)

1 skill in the art would expect to see an increase in LDL-C levels when omega-3 fatty acids were
2 administered to patients with normal, borderline-high or high TG levels. Therefore, the prior art
3 Defendants rely upon to show that EPA did not increase LDL-C levels in normal, borderline-
4 high or high TG patients, was expected. At the priority date of the '650 patent, a person of
5 ordinary skill in the art would have expected an *increase* in LDL-C for very-high TG patients
6 receiving a TG-lowering agent, as a natural consequence of lowering TGs. This pattern had been
7 demonstrated for both fibrates and fish oils and was understood as a direct consequence of TG
8 lowering through increased VLDL particle conversion.

9 Defendants argue that these studies disclose known “clinical benefits” of administering
10 pure EPA, lowering triglycerides without raising LDL-C.⁴⁵⁷⁵ This is an incorrect characterization
11 of these two studies. Katayama and Matsuzawa both were only designed to confirm the safety of
12 long term treatment of Epadel and its ability to lower both serum total cholesterol and TG levels.
13 They do just that. They do not discuss any purported “benefits” observed related to LDL-C.
14 Defendants’ selective citation of LDL-C data from these references represents the improper use
15 of hindsight bias. A person of ordinary skill would understand the focus of Katayama and
16 Matsuzawa to be TG and total cholesterol effects and not LDL-C levels, and would not draw
17 conclusions regarding LDL-C from these studies. Indeed, Katayama does not mention LDL-C
18 levels at all. Defendants’ characterization of Katayama and Matsuzawa as disclosing the
19 lowering of TG levels without increasing LDL-C to be a “clinical benefit” is incorrect.⁴⁵⁷⁶ The
20 references don’t disclose or suggest that the LDL-C results obtained were a clinical benefit, nor
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23 ⁴⁵⁷⁵ Defendants’ Joint Invalidation Contentions at 618, 619.

24 ⁴⁵⁷⁶ Defendants’ Joint Invalidation Contentions at 618, 619.

1 would a person of ordinary skill view these references as teaching such a benefit for very-high
2 TG patients.

3 Further, both Katayama and Matsuzawa administered only EPA and studied its lipid
4 effects. These studies fail to provide a head to head comparison of EPA versus DHA.
5 Therefore, a person of ordinary skill in the art would not rely on Katayama or Matsuzawa to
6 draw any conclusions related to possible differences between the lipid effects of EPA and DHA.

7 In addition, Katayama and Matsuzawa do not disclose the purity of the Epadel used. The
8 purity of Epadel has varied over time and across different formulations of the product, therefore
9 it is difficult to determine the purity of the version of Epadel used unless it is specified by the
10 disclosure. One cannot simply rely on the fact that Epadel was administered and assume that the
11 composition comprised at least about 90%, by weight of all fatty acids present, EPA, and
12 substantially no DHA, as required by the asserted claims. Defendants fail to provide a reference
13 disclosing the purity of the form of Epadel used in the Katayama and Matsuzawa studies.

14 Further, Katayama and Matsuzawa were small studies conducted in only Japanese
15 patients. These studies would not have been extrapolated to Western populations because the
16 Japanese diet contains much more fish and has a number of other different attributes. The
17 Japanese consume a higher amount of EPA and DHA in their diets than Western populations. In
18 fact, Yokoyama 2007 (cited in Defendants' contentions) states that the results from studies where
19 the patient population is exclusively Japanese cannot be generalized to other populations.⁴⁵⁷⁷
20 The Japanese diet comprises between 8 and 15 times more EPA and DHA than the typical
21 Western Diet. The Western diet typically consists of higher amounts of polyunsaturated omega-

23 ⁴⁵⁷⁷ Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to
24 other populations.").

1 6 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand
2 that the Japanese respond differently to lipid lowering agents than Westerners.

3 Defendants rely on Katayama to demonstrate the “known clinical benefits of
4 administering pure EPA - lowering triglycerides without raising LDL-C.”⁴⁵⁷⁸ However,
5 Katayama was directed to an investigation of the safety and efficacy of Epadel during long-term
6 treatment in patients with hyperlipidemia.⁴⁵⁷⁹ Katayama does not disclose *any* LDL-C related
7 data or describe *any* LDL-C effects, and a person of ordinary skill would not understand that
8 reference to provide any such disclosure. The only results disclosed by Katayama were a
9 significant reduction in TGs and total cholesterol when Epadel (EPA of undisclosed purity) was
10 administered to patients with borderline-high to high TG levels, and its safety for long term use
11 in this patient population.⁴⁵⁸⁰ In addition to Katayama’s lack of disclosure regarding LDL-C,
12 Defendants identify no other basis upon which a person of ordinary skill would have sought to
13 combine the composition disclosed in Katayama with the Lovaza PDR.

14 Defendants similarly rely on Matsuzawa to demonstrate the “known clinical benefits of
15 administering pure EPA - lowering triglycerides without raising LDL-C.”⁴⁵⁸¹ However,
16 Matsuzawa included 26 participants, of whom 23 were adopted for the evaluation of overall
17 safety, 22 were adopted for the evaluation of usefulness, 20 were adopted for evaluation of
18 general improvement, 15 were adopted for improvement in serum total cholesterol levels, and 13
19 were evaluated for improvement in serum triglycerides levels.⁴⁵⁸² It is unclear which of the 26
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21 ⁴⁵⁷⁸ Defendants’ Joint Invalidation Contentions at 619.

22 ⁴⁵⁷⁹ Katayama at 2.

23 ⁴⁵⁸⁰ *Id.* at 16.

24 ⁴⁵⁸¹ Defendants’ Joint Invalidation Contentions at 619.

⁴⁵⁸² Matsuzawa at 7 and 19.

1 patients were included in each separate evaluation; therefore one cannot determine the baseline
2 lipid characteristics for each subset of patients evaluated. Further, the small sample size and lack
3 of a placebo control makes it less likely that the results of this study can be generalized as an
4 effect on any population as a whole and provides no insight with respect to the very-high TG
5 patient population.

6 Matsuzawa discloses that 3 of the 26 participants had 400 mg/dL < TG < 1000 mg/dL,
7 and one participant with TG levels > 1,000 mg/dL.⁴⁵⁸³ However, when analyzing the lipid
8 impact of Epadel, Matsuzawa excluded the patient with a TG level greater than 1,000 mg/dL
9 because he was a “heavy drinker” and the “effect of alcohol made it impossible to assess
10 triglyceride levels.”⁴⁵⁸⁴ Fig. 4, which depicts the changes in serum triglycerides, shows that the
11 mean triglycerides of the 12 patients with TG greater than 150 mg/dL was well below 500
12 mg/dL. Furthermore, as shown in Table 4, patients with TG levels above 500 mg/dL (other than
13 the excluded patient who had TG above 1,000 mg/dL) were not treated in the study with EPA (of
14 undisclosed purity). The identification of three patients with TG levels between 400 and less
15 than 1,000 mg/dL does not disclose a patient with TG levels above 500 mg/dL, and a person of
16 ordinary skill would not understand that the reference makes any such disclosure. As discussed
17 above, one of ordinary skill in the art would not expect LDL-C to increase in a patient with TG
18 less than 500 mg/dL upon treatment with a TG-lowering agent. Matsuzawa provides no
19 evidence to the contrary.

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23 ⁴⁵⁸³ *Id.* at 23.

24 ⁴⁵⁸⁴ *Id.* at 10.

1 Matsuzawa demonstrated mixed results related to LDL-C over time, at first showing a
2 2% decrease, and then a 1% increase in LDL-C by the end of 52 weeks.⁴⁵⁸⁵ The disclosure
3 further reflects that the 4 patients with serum triglyceride levels of at least 400 mg/dL were
4 excluded from the LDL-C results because the Friedewald's Equation was used to calculate LDL-
5 C levels. The Friedewald's Equation cannot be used for patients with triglyceride levels of at
6 least 400 mg/dL. Therefore, the LDL-C results only reflect the LDL-C changes in patients with
7 triglyceride levels below 400 mg/dL. Matsuzawa fails to provide any information to a person of
8 ordinary skill regarding the LDL-C effect in the very-high TG population. A person of ordinary
9 skill in the art, however, would have expected the same treatment in patients with very high TG
10 levels to produce a substantial increase in LDL-C. In addition, Matsuzawa acknowledges that
11 there have been conflicting results related to the LDL-C impact of EPA preparations that lowered
12 triglyceride levels.⁴⁵⁸⁶ At best, Matsuzawa demonstrates the uncertainty and confusion related to
13 the LDL-C effect EPA had on patients with hyperlipidemia. Further, Defendants fail to identify
14 any other basis upon which a person of ordinary skill would have sought to combine the
15 composition disclosed in Matsuzawa with the Lovaza PDR.

16 Therefore, Katayama and Matsuzawa fail to substantiate Defendants' assertion that
17 compositions comprising EPA as recited in the asserted claims lowers triglycerides without
18 substantially increasing LDL-C. Further, other studies cited by Defendants suggest that EPA
19 increases LDL-C.⁴⁵⁸⁷ Defendants identify no other basis upon which a person of ordinary skill
20

21 _____
⁴⁵⁸⁵ *Id.* at 11.

22 ⁴⁵⁸⁶ *Id.* at 15. Matsuzawa suggests the conflicting results are due to differences in the EPA content of the EPA
23 preparation administered. However, Matsuzawa fails to identify the specific conflicting studies, disclose the specific
24 compositions used, or identify the patient populations were observed.

⁴⁵⁸⁷ *See, e.g.,* Rambjor.

1 would have sought to combine the Lovaza PDR with Katayama, Matsuzawa, Leigh-Firbank
2 and/or Mori 2000 or reasonably expected that such a combination would successfully yield the
3 asserted claims of the '650 patent.

4 (ii) Nozaki and/or Hayashi
5 Would Not Have Rendered
6 the Asserted Claims Obvious

7 Defendants contend that the asserted claims of the '650 patent would have been obvious
8 in view Nozaki and/or Hayashi in combination with other references, but they do not explain
9 why Nozaki and/or Hayashi render the asserted claims obvious or what element of the asserted
10 claims is found in Nozaki or Hayashi. Nozaki and Hayashi do not disclose or suggest a
11 reduction in triglycerides without increasing LDL-C when purified EPA is administered to the
12 very high TG patient population.

13 Nozaki administered 2.7 g/day of 90% EPA (DHA < 1%) to 14 primary
14 hypercholesterolemia subjects. A person of ordinary skill would not have found the results of
15 Nozaki reliable. Nozaki was not placebo-controlled, nor did the study compare lipid effect of
16 EPA to that of DHA. The average baseline TG level was only 165 mg/dL, while the baseline
17 LDL-C level was 185 mg/dL, which is unusually high for this TG patient population. A person
18 of skill in the art would not look to a study consisting of patients with baseline TG levels of 165
19 mg/dL in order to understand the impact of EPA therapy on the very high TG patient population.
20 Further, a person of ordinary skill would understand that the baseline LDL-C level in this small
21 patient population were abnormally high and would not have relied upon these results. Further,
22 the person of skill in the art would not have looked to this patient population to predict the Apo-
23 B or LDL-C effect of EPA therapy on very high TG patients. Nozaki acknowledges that as of
24 1991, "[t]here is still controversy concerning the effects of fish oil" on LDL and HDL cholesterol

1 levels.⁴⁵⁸⁸ Nozaki does not provide a motivation or reasonable expectation of success for
2 administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA and
3 substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL, to
4 effect a reduction in triglycerides without increasing LDL-C when purified EPA is administered
5 to the very high TG patient population.

6 In Hayashi, 1.8 g/day of EPA was administered to 28 patients for 8 weeks. The purity of
7 the EPA and the DHA content in the composition that was administered is unknown. A person
8 of ordinary skill would not have found the results of Hayashi reliable. The study involved 28
9 patients and it was conducted for only 8 weeks. Hayashi shows that changes in Apo-B and LDL-
10 C were not statistically significant.⁴⁵⁸⁹ Further, the person of skill in the art would not have
11 looked to this patient population to predict the Apo-B or LDL-C effect of EPA therapy on very
12 high TG patients. Hayashi does not provide a motivation or reasonable expectation of success
13 for administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA
14 and substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL,
15 to effect a reduction in triglycerides without increasing LDL-C when purified EPA is
16 administered to the very high TG patient population.

17 Further, Hayashi was a small study conducted in only Japanese patients and was not
18 placebo controlled. This study would not have been extrapolated to Western populations
19 because the Japanese diet contains much more fish and has a number of other different attributes.
20 The Japanese consume a higher amount of EPA and DHA in their diets than Western
21 populations. In fact, Defendants' own reference states that the results from studies where the

22 _____
23 ⁴⁵⁸⁸ Nozaki at 256.

24 ⁴⁵⁸⁹ Hayashi at 26, Table I.

1 patient population is exclusively Japanese cannot be generalized to other populations.⁴⁵⁹⁰ The
2 Japanese diet comprises between 8 and 15 times more EPA and DHA than typical the typical
3 Western diet. The Western diet typically consists of higher amounts of polyunsaturated omega-6
4 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand that
5 the Japanese respond differently to lipid lowering agents than Westerners.

6 Further, Defendants have failed to offer a purported combination of references as part of
7 their obviousness contentions that include Nozaki and Hayashi. Similarly, they fail to offer any
8 motivation to combine Nozaki and Hayashi with the other references of their purported
9 obviousness combinations. Therefore, Defendants should be precluded from relying on these
10 references.

11 (iii) Leigh-Firbank and/or Mori
12 2000 Do Not Disclose
13 Purported Knowledge that
14 DHA was Responsible for the
15 Increase in LDL-C

14 Defendants assert, incorrectly, that “it was known in the art as of February 2009 that
15 administration of DHA (alone or in a mixture) resulted in the negative effect of increasing LDL-
16 C levels.”⁴⁵⁹¹ Defendants’ caveat of DHA being “alone or in a mixture” is telling that it was *not*
17 known that DHA alone resulted in an increase in LDL-C levels. Further, the prior art Defendants
18 rely upon to support this statement does not categorize the increase in LDL-C as a “negative
19 effect” in light of the overall impact of the disclosed composition on all lipid parameters.
20 Further, the patients in Leigh Firbank and Mori 2000 had normal to high baseline TG levels. As
21 discussed above in Section III, a person of ordinary skill would not expect the same LDL-C

22 _____
23 ⁴⁵⁹⁰ Yokoyama 2007 at 1097 (“Because our population was exclusively Japanese, we cannot generalise our results to
24 other populations.”).

⁴⁵⁹¹ Defendants’ Joint Invalidity Contentions at 621.

1 effect in patients with lower baseline TG levels—the subjects of Leigh-Firbank and Mori 2000—
2 as in very-high TG patients because patients with higher TG levels had different lipid responses
3 compared to patients with lower TG levels. Patients with very-high TG levels were considered
4 fundamentally different from patients with borderline-high or high triglycerides from a lipid
5 chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint. Instead, a person
6 of ordinary skill in the art would have expected that fish oils (and other TG lowering agents)
7 would not increase LDL-C substantially in patients with normal to borderline high TG levels, but
8 would substantially increase LDL-C in patients with very high TG levels.

9 Defendants rely upon Leigh-Firbank to demonstrate that it was known that “DHA was
10 responsible for the increase in LDL-C levels.” Leigh-Firbank, however, administered fish oil,
11 comprising 1.67 g of EPA and 1.34 g of DHA per day, for six weeks, to patients with triglyceride
12 levels between 133 mg/dL and 354 mg/dL. Leigh-Firbank does not evaluate the effect of either
13 EPA or DHA alone because it did not disclose the administration of EPA or DHA alone. A
14 person of ordinary skill would similarly understand that Leigh-Firbank does not offer any
15 disclosure regarding the effect of EPA and DHA separately or gain any understanding of the
16 separate impact of DHA or EPA on any lipid parameter. Mori 2006 (also cited by defendants)
17 acknowledges that EPA- and DHA-enriched oils, which are contaminated with other saturated
18 and polyunsaturated fatty acids, are not suitable for evaluating the independent effects of EPA
19 and DHA.⁴⁵⁹² A person of ordinary skill would understand that studies directed to EPA and
20 DHA-enriched oils are not indicative or predictive of the impact of the EPA or DHA alone on
21 lipid parameters. Defendants’ own prior art refutes the validity of the results disclosed by Leigh-
22 Firbank, because purified EPA and DHA were not administered separately.

23
24 ⁴⁵⁹² Mori 2006 at 96.

1 Leigh-Firbank is a poor quality study. Leigh-Firbank makes conclusion on independent
2 effects of EPA and DHA individually, even though it administered a combination of EPA and
3 DHA, not EPA alone and DHA alone. The error in this approach is evident from the conclusions
4 of Leigh-Firbank itself. For example, Leigh-Firbank concludes that changes in platelet
5 phospholipid EPA were *independently* associated with the decrease in fasting TGs,⁴⁵⁹³ and DHA
6 is *not* associated with decreases in fasting TGs. This is incorrect and inconsistent with the state
7 of the art and numerous publications cited by Defendants.⁴⁵⁹⁴ It is widely accepted that DHA
8 also has a hypotriglyceridemic effect.

9 Mori 2000 compared the administration of 4g daily of EPA, DHA, or olive oil to patients
10 with borderline-high TG levels for 6 weeks. Although Mori 2000 discloses an increase in LDL-
11 C for patients administered DHA, it also teaches that DHA is preferable to EPA—thus teaching
12 away from the claimed invention. “A reference may be said to teach away when a person of
13 ordinary skill, upon [examining] the reference, would be discouraged from following the path set
14 out in the reference, or would be led in a direction divergent from the path that was taken by the
15 applicant.”⁴⁵⁹⁵ Although teaching away is fact-dependent, “in general, a reference will teach
16 away if it suggests that the line of development flowing from the reference’s disclosures is
17 unlikely to be productive of the result sought by the applicant.”⁴⁵⁹⁶

20 ⁴⁵⁹³ Leigh-Firbank at 440.

21 ⁴⁵⁹⁴ See, e.g. Grimsgaard at 654.

22 ⁴⁵⁹⁵ *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994).

23 ⁴⁵⁹⁶ *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994); see also *Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354
24 (Fed. Cir. 2012) (quoting *Gurley*); *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1552 (Fed. Cir. 1983)
 (“[P]roceed[ing] contrary to the accepted wisdom of the prior art ... is strong evidence of nonobviousness.”).

1 Mori 2000 concludes that the changes effected by DHA supplementation “may represent
2 a more favorable lipid profile than after EPA supplementation.”⁴⁵⁹⁷ For example, it states that
3 “DHA, but not EPA, improved serum lipid status, in particular a small increase in HDL
4 cholesterol and a significant increase in the HDL₂-cholesterol subfraction, without adverse
5 effects on fasting glucose concentrations.”⁴⁵⁹⁸ Mori 2000 also states that “[d]espite an increase
6 in LDL cholesterol after DHA supplementation, LDL particle size increased—a finding that may
7 be favorable.”⁴⁵⁹⁹ Therefore, based on the “favorable lipid profile” of DHA over EPA in Mori
8 2000, a person of ordinary skill would *not* have been motivated to use EPA to treat patients, the
9 exact opposite of what Defendants argue in their contentions. Therefore, the art taught away
10 from using purified EPA. At a minimum, the teachings of Mori 2000 provide reasons for
11 favoring or selecting DHA over EPA and highlight Defendants’ hindsight-driven focus on EPA,
12 despite disclosed advantages of DHA. A person of ordinary skill would take into consideration
13 the entire disclosure, including lipid effects other than LDL-C. Engaging in hindsight bias,
14 Defendants ignore, without explanation, the other effects of DHA that a person of ordinary skill
15 would consider. Defendants fail to identify any other basis upon which a person of ordinary skill
16 would have sought to combine Mori 2000 with the Lovaza PDR.

17 Therefore, Leigh-Firbank and Mori 2000 fail to substantiate Defendants’ assertion that it
18 was known that DHA alone was responsible for the increase in LDL-C levels. Further,
19 Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or
20 has little effect on LDL-C levels.⁴⁶⁰⁰ Defendants identify no other basis upon which a person of

21
22 ⁴⁵⁹⁷ Mori 2000 at 1092.

23 ⁴⁵⁹⁸ Mori 2000 at 1088.

24 ⁴⁵⁹⁹ Mori 2000 at 1092.

⁴⁶⁰⁰ See e.g., Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

1 ordinary skill would have sought to combine the Lovaza PDR with Katayama, Matsuzawa,
2 Leigh-Firbank and/or Mori 2000.

3 (ii) The '650 Patent is not Obvious Over the
4 Omacor PDR/Lovaza PDR, in Combination
5 with Katayama and/or Matsuzawa, and/or
6 Takaku, Further in View of Nozaki and/or
7 Hayashi, and Further in View of
8 Grimsgaard, Mori 2000 and/or Maki

9 With respect to the '650 patent, Defendants present a combination of nine references:

10 "the Omacor PDR/Lovaza PDR, in combination with the known clinical benefits of
11 administering pure EPA as evidenced by Katayama, Matsuzawa, and/or Takaku, further in view
12 of Nozaki and/or Hayashi, and further in view of Grimsgaard, Mori 2000 and/or Maki."⁴⁶⁰¹

13 Defendants also present charts purporting to assert that an additional 58 references may be

14 combined in order to render the Claims obvious. Not only do Defendants ignore the

15 improbability that a person of ordinary skill would combine 58 separate references, they

16 additionally do not identify any motivation for combining these references. Although

17 Defendants need not point to an explicit statement in the prior art motivating the combination of

18 these references, any assertion of an "apparent reason" to combine must find a basis in the

19 factual record.⁴⁶⁰² Defendants' unsupported cobbling of selective disclosures represents

20 ⁴⁶⁰¹ Defendants' Joint Invalidity Contentions at 618.

21 ⁴⁶⁰² See, e.g., *In re Vaidyanathan*, 381 F. App'x 985, 993–94 (Fed. Cir. 2010) ("[W]hile KSR relaxed some of the
22 formalism of earlier decisions requiring a 'teaching, suggestion, or motivation' to combine prior art references, it did
23 not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply
24 the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight."); *Daiichi
Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point "must
avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to
select and then modify a lead compound to arrive at the claimed invention." This turns on the known "properties and
elements of the prior art compounds.") (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp.
2d 479, 492-93 (D. Del. 2006) (rejecting defendants' contention that claims to (+)-citalopram were "*prima facie*
obvious in light of . . . claims [to] racemic citalopram" despite its use to "treat the same condition," and concluding

1 hindsight reconstruction.⁴⁶⁰³ Defendants’ contentions are no more than an assertion that certain
2 claim elements were known in the prior art. Throughout their contentions, Defendants’
3 selectively cite to data points in a reference without considering other disclosures or even the
4 reference as a whole. Each reference, however, must be evaluated for all that it teaches.⁴⁶⁰⁴
5 Accordingly, Defendants fail to meet their burden to establish *prima facie* obviousness.

6 The Omacor PDR and Lovaza PDR fail to disclose or even suggest the claimed method
7 of reducing triglycerides in a subject with the claimed pharmaceutical composition with the
8 recited fatty acid compositions or administration period. The Omacor PDR and Lovaza PDR
9 further do not disclose a method to effect the claimed TG reduction without substantially
10 increasing LDL-C. Indeed, the Omacor PDR and Lovaza PDR disclose the opposite: EPA/DHA
11 causes a significant increase in LDL-C levels in a very high TG patient population, for whom the
12 product (Lovaza/Omacor) is indicated. At most, the Omacor PDR and Lovaza PDR disclose
13 administration of a prescription fish oil, a combination of approximately 465 mg EPA and 375
14 mg DHA, as an adjunct to diet to reduce TG levels in adult patients with very-high (at least 500
15 mg/dL) TG levels. The proposed combinations do not render the independent claims of the ’650
16 patent obvious and Defendants’ burden to prove otherwise is especially difficult because the
17 PTO considered Matsuzawa, Katayama, and Mori 2000, Grimsgaard, Maki, and Lovaza (both
18 generally and the Lovaza package insert specifically) during prosecution.⁴⁶⁰⁵

19 _____
20 that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been
motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

21 ⁴⁶⁰³ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under
KSR, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention
22 without any explanation as to how or why the references would be combined to produce the claimed invention”).

⁴⁶⁰⁴ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

23 ⁴⁶⁰⁵ See, e.g., *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012)(taking into account that “the
24 examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention.

1 The analysis of the independent claims of the '650 patent is incorporated into all asserted
2 claims that depend from those Claims.

3 (a) A Person of Ordinary Skill Would
4 Not Have Been Motivated to
5 Replace the Mixed Fish Oil Active
6 Ingredient in Omacor/Lovaza with
7 EPA of the Claimed Purity

8 For an invention to be obvious, there must have been an “apparent reason” to make it.

9 The subject matter of the '650 patent claims would not have been obvious in light of these
10 references because a person of ordinary skill would not have been motivated to purify EPA or
11 been able to reasonably expect that the claimed pharmaceutical composition would reduce TG
12 levels without an increase in LDL-C levels.

13 (i) Grimsgaard, Katayama,
14 Matsuzawa and/or Takaku
15 Do Not Disclose Purported
16 Known Clinical Benefits of
17 Administering Pure EPA

18 Defendants rely on Grimsgaard, Katayama, Matsuzawa and/or Takaku to demonstrate the
19 “known clinical benefits of administering pure EPA - lowering triglycerides without raising
20 LDL-C.” As discussed in Section V.J.3.c.1.a.i.a.i, incorporated herein by reference, Katayama
21 and Matsuzawa merely confirm the safety of long term treatment of Epadel and its ability to
22 lower both serum total cholesterol and triglyceride levels. They do not discuss any purported
23 “benefits” observed related to LDL-C. Katayama and Matsuzawa do not disclose or suggest that
24 the LDL-C results obtained were a clinical benefit.

25 Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear
26 and convincing standard came into play”).

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1 Defendants also rely on Grimsgaard to support their assertion that “administration of
2 purified EPA-E reduced TG levels while minimally impacting the LDL-C levels.”⁴⁶⁰⁶ However,
3 the results of Grimsgaard demonstrate that both EPA and DHA had no measureable impact on
4 LDL-C levels, and in fact were indistinguishable from the control (placebo) group.

5 Grimsgaard examined the effect of 3.8g/day of EPA versus 3.6g/day of DHA
6 administered to people with normal triglyceride levels for 7 weeks.⁴⁶⁰⁷ The results from the
7 Grimsgaard study show that both DHA and EPA reduce triglycerides. The authors state that the
8 net decrease in triglycerides was consistently greater for DHA. Grimsgaard also concludes that
9 DHA may be responsible for the beneficial increase in HDL-C observed with some n-3 fatty acid
10 supplements, which is consistent with previous studies which “suggested that serum HDL-C is
11 better maintained with oil rich in DHA than oil rich in EPA.”⁴⁶⁰⁸ Although Grimsgaard states
12 that EPA may produce a small decrease in serum total cholesterol, it does not specifically
13 comment on EPA’s effect on LDL-C.

14 Defendants completely misconstrue the results of Grimsgaard. Defendants attempt to
15 characterize a non-significant increase in LDL-C by DHA and a non-significant decrease in
16 LDL-C by EPA, as confirmation “that administration of purified DHA results in increased LDL-
17 C levels while administration of purified EPA resulted in a decrease in LDL-C levels.”⁴⁶⁰⁹ The
18 results of Grimsgaard, reproduced below, show that EPA and DHA’s impact on LDL-C were the
19 same as placebo (corn oil); that is, there was no difference between EPA, DHA, or placebo’s
20

21 ⁴⁶⁰⁶ Defendants’ Joint Invalidation Contentions at 621-22.

22 ⁴⁶⁰⁷ Defendants state in their Joint Invalidation Contentions at 211 that Grimsgaard was conducted in patients with TG
23 levels in the borderline-high/high ranges. This is incorrect; Grimsgaard was conducted in patients with normal TG
24 levels. (See Grimsgaard at Abstract (describing participants as “healthy”) and Table 4).

⁴⁶⁰⁸ Grimsgaard at 654.

⁴⁶⁰⁹ Defendants’ Joint Invalidation Contentions at 621 n.113.

effect on LDL-C levels. Further, although administration of EPA reduced Apo-B compared to baseline, it was not a statistically significant effect when compared to placebo. Grimsgaard's disclosure highlights the importance of a placebo-controlled study and why results compared only to baseline may be misleading. This type of exaggeration and misinterpretation of the results published in the prior art is seen throughout the Defendants' Joint Invalidity Contentions.

TABLE 4
Serum lipids and apolipoproteins at baseline and change after 7 wk of supplementation with docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), or corn oil

	DHA (n = 72)		EPA (n = 75)		Corn oil (n = 77)		F test: P ¹	Contrasts between groups: P		
	Baseline	Change	Baseline	Change	Baseline	Change		DHA vs EPA	DHA vs corn oil	EPA vs corn oil
Triacylglycerols (mmol/L)	1.24 ± 0.58 ²	-0.22 ± 0.31 ²	1.23 ± 0.57	-0.15 ± 0.40 ⁴	1.22 ± 0.55	0.11 ± 0.34 ⁴	0.0001	0.14	0.0001	0.0001
Total cholesterol (mmol/L)	6.00 ± 0.95	0.03 ± 0.49	5.98 ± 0.94	-0.15 ± 0.55 ⁵	6.02 ± 1.08	0.10 ± 0.55	0.01	0.04	0.4	0.004
LDL cholesterol (mmol/L)	4.06 ± 0.86	0.07 ± 0.46	4.06 ± 0.83	-0.08 ± 0.48	4.04 ± 0.98	0.06 ± 0.48	0.10	—	—	—
HDL cholesterol (mmol/L)	1.36 ± 0.30	0.06 ± 0.13 ²	1.33 ± 0.31	0.01 ± 0.12	1.41 ± 0.28	-0.01 ± 0.11	0.001	0.009	0.0005	0.4
Apolipoprotein A-I (g/L)	1.38 ± 0.21	0.02 ± 0.13	1.38 ± 0.20	-0.04 ± 0.10 ⁴	1.46 ± 0.23	0.00 ± 0.12	0.003	0.0008	0.3	0.02
Apolipoprotein B (g/L)	1.00 ± 0.21	-0.01 ± 0.11	1.01 ± 0.23	-0.03 ± 0.11 ⁵	1.02 ± 0.28	0.02 ± 0.11	0.05	—	—	—
HDL:apolipoprotein A-I	0.97 ± 0.14	0.04 ± 0.07 ²	0.96 ± 0.13	0.04 ± 0.08 ²	0.97 ± 0.12	-0.01 ± 0.06	0.0001	0.8	0.0003	0.0001
Total:HDL cholesterol	4.62 ± 1.19	-0.19 ± 0.52 ⁴	4.70 ± 1.24	-0.13 ± 0.47 ⁵	4.43 ± 1.19	0.11 ± 0.62	0.002	0.4	0.0006	0.007

¹ ANOVA for between-group comparisons of change.

² $\bar{x} \pm$ SD.

³⁻⁵ One-sample t test of difference between baseline and 7 wk: ³ P < 0.001, ⁴ P < 0.01, ⁵ P < 0.05.

Grimsgaard concludes that both DHA and EPA lower TG levels but have “differential effects on lipoprotein and fatty acid metabolism.”⁴⁶¹⁰ However, Grimsgaard does not conclude that DHA and EPA have differential effects on LDL-C because Table 4 clearly demonstrates that neither DHA nor EPA had a measurable impact on LDL-C. Table 4 demonstrates that EPA and DHA had the same effect on LDL-C. In fact, one of ordinary skill in the art, when reading Grimsgaard, may have been motivated to use purified DHA instead of EPA for the treatment of patients with very-high triglycerides, because net decrease in triglycerides was consistently greater for DHA and DHA caused a statistically significant increase in HDL-C when compared to placebo. Grimsgaard states that “DHA may be responsible for the increase in HDL

⁴⁶¹⁰ Grimsgaard at 657.

1 cholesterol observed with some n-3 fatty acid supplements.”⁴⁶¹¹ Grimsgaard makes no such
2 statement regarding LDL-C.

3 Defendants cherry-pick results, regardless of whether the effect is found to be statistically
4 significant compared to placebo, in an attempt to force the studies to support their argument that
5 it was well known to one of ordinary skill in the art that DHA increases LDL-C while EPA did
6 not. This illustrates the hindsight reasoning driving Defendants’ analysis of the prior art and
7 proposed combinations of prior art. Defendants point to a non-significant increase in DHA and
8 non-significant decrease in EPA in Grimsgaard as confirmation “that administration of purified
9 DHA results in increased LDL-C levels while administration of purified EPA resulted in a
10 decrease in LDL-C levels.” The results from Grimsgaard clearly show that EPA and DHA did
11 not have statistically significant effects on LDL-C compared to placebo.⁴⁶¹² A person of
12 ordinary skill would not draw conclusions regarding differences between EPA and DHA based
13 on statistically insignificant results.

14 Defendants also rely on Takaku to support their assertion that “clinical benefits of
15 administering purified EPA—lowering triglycerides without raising LDL-C” was known in the
16
17
18
19

20 ⁴⁶¹¹ Grimsgaard at 654.

21 ⁴⁶¹²In Mori 2000, EPA resulted in a non-significant 0.18 mmol/L increase in LDL-C, while DHA caused a
22 statistically significant 0.37 mmol/L increase in LDL-C compared to placebo. Applying the same logic used to
23 interpret Grimsgaard, that non-significant effects are nonetheless confirmation of an effect, Defendants should have
24 argued that Mori 2000 was confirmation that both EPA and DHA increases LDL-C. However, they do not make
such arguments for the obvious reason that it does not support their argument that EPA was known to have little or
no impact on LDL-C levels.

1 art.⁴⁶¹³ Similar to Katayama and Matsuzawa, Takaku was conducted to test the efficacy and
2 safety of Epadel (of undisclosed purity)⁴⁶¹⁴ based on long-term administration.⁴⁶¹⁵

3 A person of ordinary skill would not have concluded based on Takaku that EPA lowers
4 triglycerides without raising LDL-C, because of its unreliable study method. Takaku candidly
5 acknowledges that “only a few subjects were examined” and cautions against drawing a
6 conclusion “only from the results of the present study.”⁴⁶¹⁶ Because the study did not include
7 any placebo control, a person of ordinary skill in the art would understand these reports do not
8 provide the ability to conclude that the observed lipid effects would have occurred independent
9 of the drug that is administered. In addition, the study was conducted exclusively in Japanese
10 patients, and a person of ordinary skill would not have expected the results to be applicable to the
11 general population.⁴⁶¹⁷

12 The mean baseline triglyceride level of the patients in Takaku was 245 mg/dL, and a
13 person of ordinary skill would not have expected the results to be applicable to patients with
14 triglycerides above 500 mg/dL. Takaku also excluded 6 subjects from the LDL-C study because
15 measurement was not feasible due to “insufficient sample.”⁴⁶¹⁸ It is possible that patients with
16 triglycerides above 500 mg/dL were among those excluded because of the challenges involved in
17

18 _____
⁴⁶¹³ Defendants’ Joint Invalidity Contentions at 619.

19 ⁴⁶¹⁴ It is possible that the version of Epadel used in the Katayama study fails to meet the purity limitation required by
20 the claims. See Nishikawa (91% E-EPA preparation), Ando at 2177 (Epadel with purity greater than 91%),
Nakamura at 23 (Epadel with purity > 90%).

21 ⁴⁶¹⁵ Takaku at ICOSAPENT_DFNDT00006834.

22 ⁴⁶¹⁶ Takaku at ICOSAPENT_DFNDT00006897.

23 ⁴⁶¹⁷ Yokoyama 2007 at 1097 (“[b]ecause our population was exclusively Japanese, we cannot generalise our results
to other populations.”)

24 ⁴⁶¹⁸ Takaku at ICOSAPENT_DFNDT00006884.

1 calculating LDL-C levels when triglyceride level is above 400 mg/dL.⁴⁶¹⁹ Moreover, the study
2 does not provide different LDL-C graphs based on the baseline triglyceride levels.⁴⁶²⁰ Therefore,
3 it is impossible to determine whether the patients with triglycerides above 500 mg/dL had
4 increased or decreased LDL-C after taking MND-21. In addition, the graph of the rate of LDL-C
5 change in patients with normal baseline LDL-C shows that the LDL-C change was volatile
6 throughout the study period, decreasing slightly at times but increasing by more than 8% at other
7 times.⁴⁶²¹ Because of this volatility, a person of ordinary skill would not be able to conclude
8 what effect EPA has on LDL-C. Indeed, Takaku did not conclude that there was no increase in
9 LDL-C, stating only that the fluctuation in LDL-C was not significant.⁴⁶²²

10 A person of ordinary skill would not have concluded, based on Takaku, that purified EPA
11 had any advantage over fish oil in its effect on LDL-C. Takaku states that a previous study has
12 “confirmed a decrease in serum VLDL-cholesterol and serum LDL-cholesterol through the
13 administration of *fish oil* to hypercholesterolemia patients.”⁴⁶²³ In contrast, Takaku states merely
14 that the fluctuation in LDL-C was not significant in its study. Therefore, a person of ordinary
15 skill would have concluded based on Takaku that any favorable LDL-C effect seen in the study
16 was attributable to fish oil in general, not EPA specifically.

17 Therefore, Grimsgaard, Katayama, Matsuzawa and/or Takaku fail to substantiate
18 Defendants’ assertion that pure EPA lowers triglycerides without raising LDL-C. Further, other
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21 ⁴⁶¹⁹ See Matsuzawa at ICOSPENT_DFNDTS00006450.

22 ⁴⁶²⁰ Takaku at Fig. 13, ICOSAPENT_DFNDT00006882.

23 ⁴⁶²¹ Takaku at Fig. 14, ICOSAPENT_DFNDT00006883.

24 ⁴⁶²² Takaku at ICOSAPENT_DFNDT00006897.

⁴⁶²³ Takaku at ICOSAPENT_DFNDT00006897.

1 studies cited by Defendants suggest that EPA increases LDL-C.⁴⁶²⁴ Defendants identify no other
2 basis upon which a person of ordinary skill would have sought to combine the Omacor
3 PDR/Lovaza PDR with Katayama, Matsuzawa, Takaku, Grimsgaard, Mori 2000 and/or Maki.

4 (ii) Nozaki and/or Hayashi
5 Would Not Have Rendered
6 the Asserted Claims Obvious

7 Defendants contend that the asserted claims of the '650 patent would have been obvious
8 in view Nozaki and/or Hayashi in combination with other references, but they do not explain
9 why Nozaki and/or Hayashi render the asserted claims obvious or what element of the asserted
10 claims is found in Nozaki or Hayashi. Nozaki and Hayashi do not disclose or suggest a
11 reduction in triglycerides without increasing LDL-C when purified EPA is administered to the
12 very high TG patient population.

13 Nozaki administered 2.7 g/day of 90% EPA (DHA < 1%) to 14 primary
14 hypercholesterolemia subjects. A person of ordinary skill would not have found the results of
15 Nozaki reliable. Nozaki was not placebo-controlled, nor did the study compare lipid effect of
16 EPA to that of DHA. The average baseline TG level was only 165 mg/dL, while the baseline
17 LDL-C level was 185 mg/dL, which is unusually high for this TG patient population. A person
18 of skill in the art would not look to a study consisting of patients with baseline TG levels of 165
19 mg/dL in order to understand the impact of EPA therapy on the very high TG patient population.
20 Further, a person of ordinary skill would understand that the baseline LDL-C level in this small
21 patient population were abnormally high and would not have relied upon these results. Further,
22 the person of skill in the art would not have looked to this patient population to predict the Apo-

23 ⁴⁶²⁴ See, e.g., Rambjor.
24

1 B or LDL-C effect of EPA therapy on very high TG patients. Nozaki acknowledges that as of
2 1991, “[t]here is still controversy concerning the effects of fish oil” on LDL and HDL cholesterol
3 levels.⁴⁶²⁵ Nozaki does not provide a motivation or reasonable expectation of success for
4 administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA and
5 substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL, to
6 effect a reduction in triglycerides without increasing LDL-C when purified EPA is administered
7 to the very high TG patient population.

8 In Hayashi, 1.8 g/day of EPA was administered to 28 patients for 8 weeks. The purity of
9 the EPA and the DHA content in the composition that was administered is unknown. A person
10 of ordinary skill would not have found the results of Hayashi reliable. The study involved 28
11 patients and it was conducted for only 8 weeks. Hayashi shows that changes in Apo-B and LDL-
12 C were not statistically significant.⁴⁶²⁶ Further, the person of skill in the art would not have
13 looked to this patient population to predict the Apo-B or LDL-C effect of EPA therapy on very
14 high TG patients. Hayashi does not provide a motivation or reasonable expectation of success
15 for administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA
16 and substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL,
17 to effect a reduction in triglycerides without increasing LDL-C when purified EPA is
18 administered to the very high TG patient population.

19 Further, Hayashi was a small study conducted in only Japanese patients and was not
20 placebo controlled. This study would not have been extrapolated to Western populations
21 because the Japanese diet contains much more fish and has a number of other different attributes.

23 ⁴⁶²⁵ Nozaki at 256.

24 ⁴⁶²⁶ Hayashi at 26, Table I.

1 The Japanese consume a higher amount of EPA and DHA in their diets than Western
2 populations. In fact, Defendants’ own reference states that the results from studies where the
3 patient population is exclusively Japanese cannot be generalized to other populations.⁴⁶²⁷ The
4 Japanese diet comprises between 8 and 15 times more EPA and DHA than typical the typical
5 Western diet. The Western diet typically consists of higher amounts of polyunsaturated omega-6
6 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand that
7 the Japanese respond differently to lipid lowering agents than Westerners.

8 Further, Defendants have failed to offer a purported combination of references as part of
9 their obviousness contentions that include Nozaki and Hayashi. Similarly, they fail to offer any
10 motivation to combine Nozaki and Hayashi with the other references of their purported
11 obviousness combinations. Therefore, Defendants should be precluded from relying on these
12 references.

13 (iii) Grimsgaard, Mori 2000
14 and/or Maki Do Not Disclose
15 Purported Knowledge that
16 DHA was Responsible for the
17 Increase in LDL-C

18 Defendants assert, incorrectly, that “it was known in the art as of February 2009 that
19 administration of DHA (alone or in a mixture) resulted in the negative effect of increasing LDL-
20 C levels.”⁴⁶²⁸ Defendants’ caveat of DHA being “alone or in a mixture” is telling that it was *not*
21 known that DHA alone resulted in an increase in LDL-C levels. Further, the prior art Defendants
22 rely on to support this statement does not categorize the increase in LDL-C as a “negative effect”
23 in light of the overall impact of the disclosed composition on all lipid parameters. Further, the

23 ⁴⁶²⁷ Yokoyama 2007 at 1097 (“Because our population was exclusively Japanese, we cannot generalise our results to
other populations.”).

24 ⁴⁶²⁸ Defendants’ Joint Invalidity Contentions at 621.

1 patients in Grimsgaard, Mori 2000 and Maki had normal to borderline-high baseline TG levels.
2 As discussed above in Section III, a person of ordinary skill would not expect the same LDL-C
3 effect in patients with lower baseline TG levels—the subjects of Grimsgaard, Mori 2000 and/or
4 Maki—as in very-high TG patients because patients with higher TG levels had different lipid
5 responses compared to patients with lower TG levels. Patients with very-high TG levels were
6 considered fundamentally different from patients with borderline-high or high triglycerides from
7 a lipid chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint. A person of
8 ordinary skill in the art would have expected that fish oils (and other TG lowering agents) would
9 not increase LDL-C substantially in patients with normal to borderline high TG levels, but would
10 substantially increase LDL-C in patients with very high TG levels.

11 Defendants rely on Grimsgaard, Mori 2000 and/or Maki to demonstrate that it was known
12 that “DHA was responsible for the increase in LDL-C levels.”⁴⁶²⁹ The discussion related to
13 Grimsgaard in Section V.J.3.c.1.a.ii.a.i and Mori 2000 in Section V.J.3.c.1.a.i.a.iii is
14 incorporated herein by reference.

15 Defendants argue that Maki discloses the administration of purified DHA resulted in the
16 desired reduction of TGs, but also significantly increased LDL-C levels.⁴⁶³⁰ Maki was designed
17 to assess the impact of 1.52g/day DHA supplements on the serum lipid profile of patients with
18 below-average levels of HDL-C levels.⁴⁶³¹ The DHA supplemented group was administered
19 capsules containing 1.52 g/day DHA **and** 0.84 g/day palmitic acid, in addition to other saturated,
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22 ⁴⁶²⁹ Defendants’ Joint Invalidity Contentions at 619.

23 ⁴⁶³⁰ Defendants’ Joint Invalidity Contentions at 621.

24 ⁴⁶³¹ Maki at 190.

1 monounsaturated and polyunsaturated fatty acids.⁴⁶³² Therefore, Maki demonstrated that when
2 1.52 g/day DHA and 0.84 g/day palmitic acid is administered to patients with below-average
3 levels of HDL-C levels and borderline-high TG levels, a significant increase in LDL-C is
4 observed.⁴⁶³³ However, one cannot attribute the rise in LDL-C solely to DHA, because the
5 authors admit that “changes in fatty acid intake other than DHA, particularly palmitate, may have
6 also contributed to the elevation in LDL cholesterol.”⁴⁶³⁴ Further, Maki admits that the
7 “mechanism(s) responsible for the changes in the lipid profile associated with DHA
8 supplementation are not fully understood.”⁴⁶³⁵ Therefore, the results of Maki are inconclusive as
9 to DHA’s effect alone on LDL-C levels.

10 Defendants mischaracterize the rise in LDL-C associated with the administration of
11 omega-3 fatty acids as being a “negative effect” because they incorrectly focus on only the LDL-
12 C effect and fail to look at the lipid effects as a whole. In fact, Maki does not find the increase in
13 LDL-C to be troublesome; Maki states that “the lack of increase in the total/HDL cholesterol
14 ratio, the decline in the triglyceride/HDL cholesterol ratio and the reduction in the proportion of
15 cholesterol carried by small, dense LDL particles render the changes in LDL cholesterol level
16 less worrisome.”⁴⁶³⁶ Therefore, when one of ordinary skill in the art reviewed all the lipid effects
17 of the DHA-rich algal triglycerides, they would have understood that the increase in LDL-C was
18 “less worrisome” because of the “potentially favorable effects on triglycerides, the
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20 ⁴⁶³² Maki at 191.

21 ⁴⁶³³ Maki at 195.

22 ⁴⁶³⁴ Maki at 197; Yu et al., *Plasma Cholesterol-Predictive Equations Demonstrate that Stearic Acid is Neutral and Monounsaturated Fatty Acids are Hypocholesterlemic*, 61 AM J CLIN NUTR 1129, 1136 (1995).

23 ⁴⁶³⁵ Maki at 197.

24 ⁴⁶³⁶ Maki at 197.

1 triglyceride/HDL cholesterol ratio and the fraction of LDL cholesterol carried by small, dense
2 particles.”⁴⁶³⁷

3 Therefore, Grimsgaard, Mori 2000 and/or Maki fail to substantiate Defendants’ assertion
4 that it was known that DHA was responsible for the increase in LDL-C levels. Further,
5 Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or
6 has little effect on LDL-C levels.⁴⁶³⁸ Defendants identify no other basis upon which a person of
7 ordinary skill would have sought to combine the Omacor PDR/Lovaza PDR with Katayama,
8 Matsuzawa, Takaku, Grimsgaard, Mori 2000 and/or Maki.

9 (iii) The ‘650 Patent is not Obvious Over the
10 Omacor PDR/Lovaza PDR, in Combination
11 with Katayama in View of Satoh and/or in
View of Satoh or Shinozaki in Further View
of Contacos

12 With respect to the ‘650 patent, Defendants present a combination of five references: “the
13 Omacor PDR/Lovaza PDR, in combination with the known clinical benefits of administering
14 pure EPA as evidenced by Katayama in view of Satoh and/or in view of Satoh or Shinozaki in
15 further view of Contacos.”⁴⁶³⁹ Defendants also present charts purporting to assert that an
16 additional 60 references may be combined in order to render the Claims obvious. Not only do
17 Defendants ignore the improbability that a person of ordinary skill would combine 60 separate
18 references, they additionally do not suggest any identify for combining these references.
19 Although Defendants need not point to an explicit statement in the prior art motivating the
20 combination of these references, any assertion of an “apparent reason” to combine must find a
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22 ⁴⁶³⁷ Maki at 197.

23 ⁴⁶³⁸ See e.g., Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

24 ⁴⁶³⁹ Defendants’ Joint Invalidity Contentions at 619.

1 basis in the factual record.⁴⁶⁴⁰ Defendants’ unsupported cobbling of selective disclosures
2 represents hindsight reconstruction.⁴⁶⁴¹ Defendants’ contentions are no more than an assertion
3 that certain claim elements were known in the prior art. Throughout their contentions,
4 Defendants’ selectively cite to data points in a reference without considering other disclosures or
5 even the reference as a whole. Each reference, however, must be evaluated for all that it
6 teaches.⁴⁶⁴² Accordingly, Defendants fail to meet their burden to establish *prima facie*
7 obviousness.

8 The Lovaza PDR fails to disclose or even suggest the claimed method of reducing
9 triglycerides in a subject with the claimed pharmaceutical composition with the specified fatty
10 acid compositions or administration period. The Lovaza PDR further does not disclose a method
11 to effect the specified TG reduction without substantially increasing LDL-C. Indeed, the Lovaza
12 PDR discloses the exact opposite, that the EPA/DHA composition contained within the reference
13 would cause a significant increase in LDL-C levels in the very high TG patient population, for
14 whom the product is indicated. At most, the Lovaza PDR discloses administration of a
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16 ⁴⁶⁴⁰ See, e.g., *In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the
17 formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did
18 not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply
19 the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi*
20 *Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must
21 avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to
22 select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and
23 elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp.
24 2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie*
obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding
that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been
motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

⁴⁶⁴¹ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under
KSR, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention
without any explanation as to how or why the references would be combined to produce the claimed invention”).

⁴⁶⁴² *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

1 prescription fish oil, a combination of approximately 465 mg EPA and 375 mg DHA, as an
2 adjunct to diet to reduce TG levels in adult patients with very-high (at least 500 mg/dL) TG
3 levels.

4 Defendants formulate an obviousness argument that relies on Contacos.⁴⁶⁴³ However,
5 Defendants fail to provide any factual or legal basis as to why Contacos discloses a claim
6 element or an “apparent reason” or motivation to combine the elements in the manner
7 claimed,⁴⁶⁴⁴.

8 Contacos disclosed administration of fish oil, pravastatin, and combination of fish oil and
9 pravastatin, but it does not disclose administration of EPA of the recited composition. Therefore,
10 Contacos fails to provide motivation to administer purified EPA to a very high TG patient
11 population. Contacos also fails to provide motivation to administer purified EPA to a very high
12 TG patient population.

13 The proposed combinations do not render the independent claims of the ’650 patent
14 obvious and Defendants’ burden to prove otherwise is especially difficult because the PTO
15 considered Katayama, Satoh, Shinozaki, Contacos, Geppert, Kelley and Lovaza (both generally
16 and the Lovaza package insert specifically) during prosecution.⁴⁶⁴⁵

17 The analysis of the independent claims of the ’650 patent is incorporated into all asserted
18 claims that depend from those Claims.

19 ⁴⁶⁴³ *Id.*

20 ⁴⁶⁴⁴ *KSR*, 550 U.S. at 417–19; *TriMed, Inc. v. Stryker Corp.*, 608 F.3d 1333, 1341 (Fed. Cir. 2010). Hindsight may
21 not be employed to identify relevant prior art and relevant teachings therein: *Heidelberger Druckmaschinen AG v.*
22 *Hantscho Comm. Prods., Inc.*, 21 F.3d 1068, 1071–72 (Fed. Cir. 1994); *Monarch Knitting Mach. Corp. v. Sulzer*
Morat GmbH, 139 F.3d 877, 881 (Fed. Cir. 1998).

23 ⁴⁶⁴⁵ See, e.g., *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012)(taking into account that “the
24 examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention.
Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear
and convincing standard came into play”).

1 (a) A Person of Ordinary Skill Would
2 Not Have Been Motivated to
3 Replace the Mixed Fish Oil Active
Ingredient in Lovaza with EPA of
4 the Recited Composition

5 For an invention to be obvious, there must have been an “apparent reason” to make it.
6 The subject matter of the ‘650 patent claims would not have been obvious in light of these
7 references because a person of ordinary skill would not have been motivated to purify EPA or
8 been able to reasonably expect that the claimed pharmaceutical composition would reduce TG
9 levels without an increase in LDL-C levels.

10 (i) Katayama, Satoh and/or
11 Shinozaki Do Not Disclose
12 Purported Known Clinical
13 Benefits of Administering
14 Pure EPA

15 Defendants rely on Katayama, Satoh and/or Shinozaki to demonstrate the “known clinical
16 benefits of administering pure EPA - lowering triglycerides without raising LDL-C.” As
17 discussed in Section V.J.3.c.1.a.i.a.i, incorporated herein by reference, Katayama merely
18 confirms the safety of long term treatment of Epadel and its ability to lower both serum total
19 cholesterol and triglyceride levels. Katayama does not mention LDL-C levels at all, let alone
20 discuss any purported “benefits” observed related to LDL-C. Katayama does not disclose or
21 suggest that the LDL-C results obtained were a clinical benefit, nor would a person of ordinary
22 skill view these references as teaching such a benefit for very-high TG patients.

23 Satoh administered 1.8g/day of >98% EPA to patients in order to measure the effects of
24 EPA on C-reactive protein and examine how alteration of lipoprotein profile by EPA affects
systemic inflammation. Satoh reported a statistically significant reduction in LDL-C only when

1 compared to baseline, there was no significant effect when compared to placebo.⁴⁶⁴⁶
2 Defendants' characterization of Satoh as disclosing the lowering of TG levels without increasing
3 LDL-C to be a "clinical benefit" is incorrect.⁴⁶⁴⁷ Satoh does not disclose or suggest that the
4 LDL-C results obtained were a clinical benefit, nor would a person of ordinary skill view these
5 references as teaching such a benefit for very-high TG patients. As discussed above, one of
6 ordinary skill in the art would not expect LDL-C to increase in a patient with TG below 500
7 mg/dL and Satoh provides no evidence to the contrary. A person of ordinary skill in the art,
8 however, would have expected that fish oils (and other TG lowering agents) would substantially
9 increase LDL-C in patients with very high TG levels. Satoh fails to provide motivation to
10 administer purified EPA to a very high TG patient population.

11 Further, Satoh was a small study conducted in only Japanese patients. This study would
12 not have been extrapolated to Western populations because the Japanese diet contains much
13 more fish and has a number of other different attributes. The Japanese consume a higher amount
14 of EPA and DHA in their diets than Western populations. In fact, Defendants' own reference
15 states that the results from studies where the patient population is exclusively Japanese cannot be
16 generalized to other populations.⁴⁶⁴⁸ The Japanese diet comprises between 8 and 15 times more
17 EPA and DHA than typical the typical Western diet. The Western diet typically consists of
18 higher amounts of polyunsaturated omega-6 fatty acids and saturated fatty acids. Therefore, a
19 person of ordinary skill would understand that the Japanese respond differently to lipid lowering
20 agents than Westerners.

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22 ⁴⁶⁴⁶ Satoh at 145.

23 ⁴⁶⁴⁷ Defendants' Joint Invalidation Contentions at 618, 619.

24 ⁴⁶⁴⁸ Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to other populations.").

1 Shinozaki studied the long-term effect of EPA on serum levels of Lipoprotein (a) (Lp(a))
2 and lipids such as triglycerides, total cholesterol, and low density lipoprotein particles.
3 Defendants' characterization of Shinozaki as disclosing the lowering of TG levels without
4 increasing LDL-C to be a "clinical benefit" is incorrect.⁴⁶⁴⁹ Shinozaki says nothing about an
5 LDL-C effect because it measured LDL particle number, not LDL-C. The finding disclosed by
6 Shinozaki was that "long term administration of EPA may lower Lp(a) and serum lipids."⁴⁶⁵⁰ In
7 addition to Shinozaki's lack of disclosure regarding LDL-C, Defendants identify no other basis
8 upon which a person of ordinary skill would have sought to combine the composition disclosed
9 in Shinozaki.

10 Therefore, Katayama, Satoh and/or Shinozaki fail to substantiate Defendants' assertion
11 that pure EPA lowers triglycerides without raising LDL-C. Further, other studies cited by
12 Defendants suggest that EPA increases LDL-C.⁴⁶⁵¹ Defendants identify no other basis upon
13 which a person of ordinary skill would have sought to combine the Lovaza PDR with Katayama,
14 Satoh, Shinozaki and/or Contacos.

(ii) Geppert and/or Kelley Do
Not Disclose Purported
Knowledge that DHA was
Responsible for the Increase
in LDL-C

18 Defendants assert, incorrectly, that "it was known in the art as of February 2009 that
19 administration of DHA (alone or in a mixture) resulted in the negative effect of increasing LDL-
20 C levels."⁴⁶⁵² Defendants' caveat of DHA being "alone or in a mixture" is telling that it was *not*

22 ⁴⁶⁴⁹ Defendants' Joint Invalidation Contentions at 618, 619.

23 ⁴⁶⁵⁰ Shinozaki at 107-109.

24 ⁴⁶⁵¹ See, e.g., Rambjor.

⁴⁶⁵² Defendants' Joint Invalidation Contentions at 621.

1 known that DHA alone resulted in an increase in LDL-C levels. Further, the prior art Defendants
2 rely on to support this statement do not categorize the increase in LDL-C as a “negative effect”
3 in light of the overall impact of the disclosed composition on all lipid parameters. Further, the
4 patients in Geppert and Kelley had normal and borderline-high/high baseline TG levels,
5 respectively. As discussed above in Section III, a person of ordinary skill would not expect the
6 same LDL-C effect in patients with lower baseline TG levels—the subjects of Geppert and/or
7 Kelley—as in very-high TG patients because patients with higher TG levels had different lipid
8 responses compared to patients with lower TG levels. Patients with very-high TG levels were
9 considered fundamentally different from patients with borderline-high or high triglycerides from
10 a lipid chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint. Although a
11 person of ordinary skill in the art would have expected that fish oils (and other TG lowering
12 agents) would not increase LDL-C substantially in patients with normal to borderline high TG
13 levels, a person of ordinary skill in the art would expect a substantial increase in LDL-C in
14 patients with very high TG levels.

15 Defendants rely on Geppert and/or Kelley to demonstrate that it was known that “DHA
16 was responsible for the increase in LDL-C levels.”⁴⁶⁵³ Both Geppert and Kelley administer
17 DHA-rich oil that is contaminated with other saturated and polyunsaturated fatty acids.
18 Therefore, a person of ordinary skill would have known it is unsuitable for evaluating the
19 independent effects of DHA because it is not clear how much of the supplement’s effects can be
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23 ⁴⁶⁵³ Defendants’ Joint Invalidation Contentions at 619.
24

1 attributed to DHA.⁴⁶⁵⁴ For example, Defendants’ own prior art teaches that changes in fatty acid
2 intake other than DHA, particularly palmitate, may contribute to elevations in LDL-C.⁴⁶⁵⁵

3 In Geppert, 0.94 g/day of DHA derived from microalgae oil was administered to
4 normolipidaemic vegetarians for 8 weeks. A person of ordinary skill would not have been
5 convinced that DHA increases LDL-C based on Geppert. As Geppert acknowledges, prior
6 studies have shown “[i]nconsistent effects of DHA on LDL cholesterol.”⁴⁶⁵⁶ Rather than reading
7 Geppert in isolation, a person of ordinary skill would have read Geppert together with the prior
8 studies cited in Geppert. As such, a person of ordinary skill would have concluded that there
9 was confusion in the art and it was unclear whether DHA increased LDL-C.

10 A person of ordinary skill would have expected that Geppert’s results would be
11 applicable to other components of fish oil such as EPA. Nothing in Geppert suggests that DHA
12 was the only component of fish oil to increase LDL-C. For example, there is no data comparing
13 DHA to fish oil or EPA. In fact, Geppert discusses DHA and fish oil together when trying
14 explain the mechanism of LDL-C increase.⁴⁶⁵⁷ A person of ordinary skill would have not
15 expected that EPA and DHA would have different effects on LDL-C based on Geppert.

16 Defendants contend that Kelley shows that DHA was responsible for the increase in
17 LDL-C.⁴⁶⁵⁸ In Kelley, patients fasting serum TG levels of 150 to 400 mg/dL received 7.5 g/day
18 of DHA oil containing 3 g of DHA for 90 days. Kelley does not show that DHA is responsible
19 for the increase in LDL-C. Kelley suggests that increase in LDL-C is a general phenomenon

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21 ⁴⁶⁵⁴ See Mori 2006 at 96.

22 ⁴⁶⁵⁵ Maki at 197.

23 ⁴⁶⁵⁶ Geppert at 784.

24 ⁴⁶⁵⁷ *Id.*

⁴⁶⁵⁸ Defendants’ Joint Invalidation Contentions at 619.

1 associated with triglyceride-lowering drugs, stating that a similar increase was induced by fibrate
2 therapy.⁴⁶⁵⁹ Further, Kelley teaches that the increase in LDL-C is not harmful when viewed in
3 context with the other lipid effects reported in the study. Kelley states that:

4 DHA supplementation may lower the risk of CVD by reducing
5 plasma triacylglycerols; triacylglycerol:HDL; the number of small,
6 dense LDL particles; and mean diameter of VLDL particles. An
7 increase was observed in fasting LDL cholesterol, but it is unlikely
8 this increase is detrimental because no increase was observed in the
9 overall number of LDL particles; actually, there was an 11%
reduction that was statistically not significant. The reason LDL
cholesterol increased despite no change in LDL particle number was
that the LDL particles were made larger and hence more cholesterol
rich by DHA treatment.⁴⁶⁶⁰

10 Kelley specifically teaches that the increase in LDL-C caused by DHA supplementation
11 is unlikely to be “detrimental” because there was not a parallel increase in overall LDL particle
12 number. Kelley’s ultimate conclusion is that “[o]verall, DHA supplementation reduced the
13 concentrations of atherogenic lipids and lipoproteins and increased concentrations of
14 cardioprotective lipoproteins” and that “DHA supplementation may improve cardiovascular
15 health.”⁴⁶⁶¹ Rather than concluding that DHA was uniquely responsible for a rise in LDL-C
16 levels, a person of ordinary skill would understand Kelley to disclose that DHA had uniquely
17 beneficial cardioprotective effects. Indeed, instead of identifying DHA as composition with
18 negative attributes, a person of ordinary skill would understand that the reference taught towards
19 the use of DHA. In addition, none of the study subjects in Kelley had a TG level above 400
20 mg/dL and, for the reasons previously discussed, a person of ordinary skill would understand the
21 very high TG patient population to be different in terms of their response to lipid therapy,

22 _____
⁴⁶⁵⁹ Kelley at 329.

23 ⁴⁶⁶⁰ Kelley at 329

24 ⁴⁶⁶¹ Kelley at 324, 332.

1 including administration of DHA. A person of ordinary skill in the art would have expected that
2 fish oils (and other TG lowering agents) would not increase LDL-C substantially in patients with
3 normal to borderline high TG levels, but a person of ordinary skill in the art would expect a
4 substantial increase in LDL-C in patients with very high TG levels.

5 Therefore, Geppert and/or Kelley fail to substantiate Defendants' assertion that it was
6 known that DHA was responsible for the increase in LDL-C levels.

7 Throughout their contentions, Defendants' selectively cite to data points in a reference
8 without considering other disclosures or even the reference as a whole. Each reference,
9 however, must be evaluated for all that it teaches.⁴⁶⁶² As is the case with Kelley, Defendants use
10 hindsight to characterize a reference based on LDL-C levels alone without considering the other
11 lipid effects studied, considered and reported.⁴⁶⁶³ The isolated manner in which Defendants
12 select such data points is not the approach that a person of ordinary skill would have taken at the
13 time of the invention. Defendants' approach represents the use of impermissible hindsight bias.
14 A person of ordinary skill would take into consideration the entire disclosure of a reference,
15 including lipid effects other than LDL-C. In pointing only to LDL-C, Defendants ignore,
16 without explanation, the other effects of DHA that a person of ordinary skill would consider.
17 With respect to Kelley, These effects would teach a person of ordinary skill that DHA has a
18 favorable effect in hypertriglyceridemic patients.

19 Therefore, Geppert and/or Kelley fail to substantiate Defendants' assertion that it was
20 known that DHA was responsible for the increase in LDL-C levels. Further, Defendants ignore,

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22 ⁴⁶⁶² *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

23 ⁴⁶⁶³ Kelley at 324 (providing that the objectives of the study were to determine "the effects of DHA supplementation
24 on the concentrations of apoproteins; large, medium, and small VLDL, LDL, and HDL particles; and the mean
diameters of these particles in fasting and postprandial plasma.").

1 without explanation, other studies that demonstrate that DHA decreases or has little effect on
2 LDL-C levels.⁴⁶⁶⁴ Defendants identify no other basis upon which a person of ordinary skill
3 would have sought to combine the Lovaza PDR with Katayama, Satoh, Shinozaki, Contacos,
4 Geppert and/or Kelley.

5 (iv) A Person of Ordinary Skill Would Not Have
6 been Motivated to Find an Omega-3 Fatty
7 Acid “Therapy that Would Reduce TG
8 Levels in Patients with TG Levels \geq 500
9 mg/dL Without Negatively Impacting LDL-
10 C Levels.”

11 Plaintiffs agree that although there was a *need* to find a therapy that would reduce TG
12 levels in patients with very-high TG levels, without negatively impacting LDL-C levels, there
13 was no motivation to find an *omega-3 fatty acid* therapy, or to modify Lovaza/Omacor, to effect
14 a reduction in TG levels without increasing LDL-C levels for very-high TG patients at the time
15 of the invention. A person of ordinary skill in the art understood that the rise in LDL-C caused
16 by omega-3 fatty acids (or fibrates) and Lovaza/Omacor was a consequence of the TG-lowering
17 mechanism. The therapies that were available at the time of the invention to treat very-high TGs
18 were niacin, fibrates and prescription omega-3 fatty acids (Lovaza/Omacor). However, niacin
19 was associated with a highly undesirable side effects—including “flushing” (or reddening of the
20 face and other areas with a burning sensation) and dyspepsia—that limited their usefulness.⁴⁶⁶⁵
21 Fibrates were effective at reducing TGs, but they also caused an increase in LDL-C levels in
22 patients with very-high TG levels. To combat the rise of LDL-C, doctors often prescribed

23 ⁴⁶⁶⁴ See e.g., Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

24 ⁴⁶⁶⁵ See *id.* at 991-92; McKenney 2007, at 718; ATP-III at 3315 (noting that patients often could not tolerate higher doses of niacin due to side effects).

1 fibrates in combination with an LDL-C lowering medication such as a statin.⁴⁶⁶⁶ However, the
 2 risk of rhabdomyolysis increased five-fold if fibrates were administered with a statin.⁴⁶⁶⁷
 3 Therefore, physicians were reluctant to recommend, and patients were hesitant embrace, a
 4 combination fibrate/statin course of treatment.⁴⁶⁶⁸ Finally, Lovaza/Omacor were also effective at
 5 reducing TG levels, but, similar to fibrates, could cause a substantial increase in LDL-C levels
 6 for very-high TG patients. However, Lovaza/Omacor could be safely administered with statins
 7 in order to mitigate increased LDL-C.

8 In any event, a person of ordinary skill in the art would have understood that omega 3-
 9 fatty acids, including DHA and EPA, and fibrates cause an increase in LDL-C among very high
 10 TG patients, as reflected in the prior art. Accordingly, a person of ordinary skill in the art would
 11 not have been motivated to look to omega 3-fatty acids in order to obtain a reduction in TGs
 12 without increasing LDL-C in very high TG patients:

	LDL-C Effect	
	Borderline-High or High TG Patients	Very-High TG Patients
Fibrate ⁴⁶⁶⁹	-20%	+45%
Lovaza/Omacor ⁴⁶⁷⁰	-6%	+45%

16 That Epadel has been approved for decades but not approved for use in the very high TG
 17 patient population prior to the invention of the asserted patents is a real-world reflection of the
 18 lack of motivation. Research into the pharmaceutical uses of EPA started as early as the 1970s.
 19

20 ⁴⁶⁶⁶ Bays May 16, 2011 Decl., ¶ 8; Topol, at 71 (noting that in high TG patients “the addition of a statin to a fibrate
 is often required to achieve LDL-C and non-HDL-C goals”);

21 ⁴⁶⁶⁷ See *Id.*; McKenney 2007, at 719 (“[F]ibrates may cause rhabdomyolysis, especially when combined with
 statins.”).

22 ⁴⁶⁶⁸ See *Id.*, ¶ 17

23 ⁴⁶⁶⁹ Tricor®, Physicians’ Desk Reference 502-505 (62d ed. 2008).

24 ⁴⁶⁷⁰ Chan 2002 I at 2381 (Table 3).

1 In 1990, Mochida Pharmaceutical, began to market Epadel, a high purity EPA drug. There have
2 been countless studies conducted which administer Epadel and report the effects observed.
3 Although a few studies administer Epadel to a patient population which included a few patients
4 with TG levels > 500 mg/dL, Defendants fail to identify a single reference directed to the
5 administration of Epadel to patients with very-high TG levels, reflecting the lack of motivation.

6 Defendants offer no “apparent reason” to administer EPA as claimed to patients with
7 fasting baseline TG levels of 500 mg/dl to about 1500 mg/dl. Defendants rely on
8 Lovaza/Omacor as the starting point to “find a therapy that would reduce TG levels in patients
9 with TG levels of at least 500 mg/dL without negatively impacting LDL-C levels.”⁴⁶⁷¹
10 Ironically, Lovaza/Omacor significantly reduces TGs in patients with TG levels of at least 500
11 mg/dL but significantly increases LDL-C--an effect understood to be a consequence of TG
12 reduction and the increased conversion of VLDL to LDL particles.⁴⁶⁷²

13 It was well known at the time of the invention that omega-3 fatty acids, including both
14 EPA and DHA, caused significant decrease in the production of VLDL particles and a significant
15 increase in the conversion of VLDL to IDL and LDL, supporting the understanding that omega-3
16 fatty acids worked in part by inhibiting VLDL production and improving the conversion of
17 VLDL particles to LDL.⁴⁶⁷³ A person of ordinary skill in the art understood that EPA and DHA
18 had the *same* TG-lowering mechanism and did not differentiate between EPA and DHA when
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20 ⁴⁶⁷¹ Defendants’ Joint Invalidity Contentions at 620.

21 ⁴⁶⁷² See Bays 2008 Rx Omega-3 p. 402; McKenny 2007 Role of Prescription Omega-3 at 720 (finding that “[t]hese
22 results illustrate that with prescription omega-3, fewer VLDL particles are secreted into the systemic circulation, and
secreted VLDL particles are rapidly converted to LDL particle, thus explaining why LDL levels may increase in
patients with very-high triglyceride levels when given prescription omega-3 therapy”); Chan 2003

23 ⁴⁶⁷³ Chan 202 at 2378-84; see also Westphal at 917 (stating “our data confirm the well-known and pronounced
24 decrease in VLDLs after n-3 fatty acid treatment”)

1 discussing the TG-lowering mechanism of omega-3 fatty acids.⁴⁶⁷⁴ The discussion related to the
2 TG-lowering mechanism of omega-3 fatty acids is discussed above in Section III and
3 incorporated herein by reference.

4 In fact, it was well understood that the degree of LDL-C elevation observed with
5 prescription omega-3 therapy, such as Lovaza/Omacor, generally related to pretreatment TG
6 levels; that is, prescription omega-3 therapy, such as Lovaza/Omacor, increased LDL-C levels
7 the most in patients with the highest pretreatment TG levels.⁴⁶⁷⁵ Therefore, a person of ordinary
8 skill in the art would have viewed increased LDL-C levels caused by Lovaza/Omacor as a direct
9 consequence of lowering triglycerides in patients with TG levels ≥ 500 mg/dL. The rise in LDL-
10 C was often offset by concurrent treatment with statins.⁴⁶⁷⁶ The safety and efficacy of using
11 prescription omega-3 in combination with a statin has been well-established.⁴⁶⁷⁷

12 Although an increase in LDL-C was generally observed when omega-3 fatty acids were
13 administered to patients with very-high TG levels, the increase in LDL-C was not necessarily a
14 cause for concern because LDL-C is often low in patients with severe hypertriglyceridemia.
15 Therefore, the final LDL-C concentration may still be in the normal range.⁴⁶⁷⁸ Furthermore, it
16 was understood that the overall lipid effect of Lovaza/Omacor was beneficial.⁴⁶⁷⁹

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18 ⁴⁶⁷⁴ Bays I, at 398; Harold E. Bays, *Fish Oils in the Treatment of Dyslipidemia and Cardiovascular Disease*, in *The Johns Hopkins Textbook of Dyslipidemia* 245, 247 (Peter O. Kwiterovich Jr. ed., 2009 (Bays III))

19 ⁴⁶⁷⁵ See Bays 2008 Rx Omega-3 p. 402.

20 ⁴⁶⁷⁶ See Harris 2008 at 14, McKenney at 722.

21 ⁴⁶⁷⁷ McKenney at 722-23.

22 ⁴⁶⁷⁸ See Westphal at 918, Harris 1997 at 389.

23 ⁴⁶⁷⁹ See Pownall at 295 (stating that “[t]reatment with ω -3 fatty acids appear to change the lipid profile of individuals
24 with elevated TG to one that may be less atherogenic by changing LDL structure; lowering serum [cholesterol] ester transfer activity), serum TG and VLDL-C; and increasing serum HDL-C”); Harris 1997 at 389 (stating that “[t]he increase in LDL, which was substantial on a percentage basis, has been a common finding in past studies in [very-high TG] patients. It may not be as problematic as it appears, however,” and “the use of omega-3 fatty acids for the

1 In two pivotal studies in very-high TG patients, both of which used prospective,
2 randomized, double-blind, placebo-controlled study designs, Lovaza/Omacor increased HDL
3 levels from baseline 13% (p=0.014) and 5.9% (p=0.057).⁴⁶⁸⁰ Correspondingly, prescription
4 omega-3 fatty acids were known to have favorable effects on non-HDL-C levels.⁴⁶⁸¹ Therefore,
5 “[i]n patients with very-high triglyceride levels, prescription omega-3 fatty acids 4 g/day can
6 substantially reduce triglycerides and VLDL levels and may increase LDL levels, but the net
7 effect is a reduction in non-HDL levels. Modest increases in HDL level are also common in
8 patients treated with prescription omega-3 fatty acids.” Prescription omega-3 therapy was also
9 known to alter lipoprotein particle size and composition in a favorable manner by decreasing the
10 number of small, dense LDL particles to larger LDL particles.⁴⁶⁸² Lovaza/Omacor “adversely
11 raise[d] LDL cholesterol concentration but the increase in LDL cholesterol concentration
12 reflect[ed] a less atherogenic light LDL subfraction profile that may be favorable.”⁴⁶⁸³
13 Therefore, one of ordinary skill in the art believed that the use of Lovaza/Omacor, and omega-3
14 fatty acids generally, “for the treatment of severe hypertriglyceridemia may be beneficial not

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19 treatment of severe hypertriglyceridemia may be beneficial not only for the short-term prevention of acute
20 pancreatitis, but also for the long-term prevention of CHD”); Bays III at 248 (“No clinical trial data exist that this
21 rise in LDL-C represents harm or potential “toxicity” to patients. In fact, most evidence supports that omega-3 fatty
22 acids reduce cardiovascular risk as do fibrates. Importantly, clinical trials mostly support that even with increases in
23 LDL-C, omega-3 fatty acids decrease the total cholesterol (TC) carried by atherogenic lipoproteins, as reflected by
24 decreased non-HDL-C levels (TC minus HDL-C”).

⁴⁶⁸⁰ McKenney 2007 at 721 (citing Harris 1997 and Pownall).

⁴⁶⁸¹ McKenney 2007 at 722 (see Fig. 1).

⁴⁶⁸² McKenney 2007 at 722 (citing Calabresi and Stalenhoef).

⁴⁶⁸³ Stalenhoef at 134.

1 only for the short-term prevention of acute pancreatitis, but also for the longer-term prevention
2 of [coronary heart disease].”⁴⁶⁸⁴

3 Therefore, contrary to Defendants’ assertion that “a person of ordinary skill in the art at
4 the time of the claimed inventions would have been motivated to find a therapy that would
5 reduce TG levels in patients with TG levels of at least 500 mg/dL without negatively impacting
6 LDL-C levels,”⁴⁶⁸⁵ one of ordinary skill in the art at the time of the invention understood that the
7 rise in LDL-C caused by omega-3 fatty acids was a by-product of reducing TGs in patients with
8 very-high TG levels. A person of ordinary skill in the art would have expected LDL-C to
9 increase in very-high TG patients, and in some instances the rise was not concerning because
10 LDL-C is often low in patients with severe hypertriglyceridemia and therefore final
11 concentration would still be in the normal range. When LDL-C levels increased beyond what
12 was recommended by the ATP-III, prescribers often relied on statins to safely and effectively
13 reduce LDL-C levels. Furthermore, it was well known that the overall lipid effect of
14 Lovaza/Omacor was beneficial because non-HDL-C levels often increased. Defendants fail to
15 identify any other basis upon which a person of ordinary skill would have been motivated to find
16 a therapy that would reduce TG levels in patients with very-high TG levels without negatively
17 impacting LDL-C levels. Further, a person of ordinary skill in the art would have understood
18 that EPA therapy would *not* reduce Apo-B⁴⁶⁸⁶ (which is a reflection of total atherogenic
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22 ⁴⁶⁸⁴ Harris 1997 at 389.

23 ⁴⁶⁸⁵ Defendants’ Joint Invalidation Contentions at 620.

24 ⁴⁶⁸⁶ *see* Section V.O.

1 lipoproteins)⁴⁶⁸⁷ in very high TG patients, and accordingly would not have been motivated to
2 administer the claimed EPA composition to the very high TG patient population.

3 Defendants make the conclusory allegation that “routine optimization” by a person of
4 ordinary skill would yield the claimed invention.⁴⁶⁸⁸ Defendants, however, have offered no
5 explanation to support that allegation and they further fail to establish any of the required criteria
6 of “routine optimization” or the prerequisites to this argument. They also fail to provide any
7 factual detail to support their allegation and they fail to link the allegation to any particular claim
8 or claim element. Defendants mere allegation constitute an improper placeholder to later
9 advance arguments not disclosed in their contentions as required by the Local Rules. In addition,
10 for the reasons discussed herein, a person of ordinary skill would not be motivated to make the
11 combinations alleged by Defendants and, for the same reasons, it would not be routine to
12 combine such references. Where, for example, Defendants argue that it would be “obvious” to
13 go from the high TG patient population, to the very high TG patient population,⁴⁶⁸⁹ they provide
14 no basis for that conclusory assertion and are incorrect. As discussed, a person of ordinary skill
15 would have understood these patient populations to be distinct with different impacts of lipid
16 therapy on blood-lipid chemistry for each group. Accordingly, a person of ordinary skill would
17 not have considered the dosage modification suggested by defendants to be routine; Defendants’
18 argument to the contrary represents hindsight bias.

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⁴⁶⁸⁷ *see* Section III.

23 ⁴⁶⁸⁸ *See, e.g.*, Defendants’ Joint Invalidation Contentions at 616, 629, 645.

24 ⁴⁶⁸⁹ Defendants’ Joint Invalidation Contentions at 623 & n.116.

1 In addition, a person of ordinary skill would have no motivation to combine these
2 references because EPA would have been expected to have same result as the mixture of EPA
3 and DHA used in Lovaza/Omacor.

4 (b) Defendants Have Not Shown It Would Have Been
5 Obvious to Administer Purified EPA in the Dosing
Regimen Recited in the Claims

6 (i) The '650 Patent is not Obvious Over WO
7 '118 or WO '900, in Combination with the
Lovaza PDR, and Further in View of Leigh-
8 Firbank and/or Mori 2000

9 With respect to the '650 patent, Defendants present a combination of five references:
10 "WO '118 or WO '900, in combination with treatment regimen of Lovaza as evidenced by the
11 Lovaza PDR, and further in view of Leigh-Firbank and/or Mori 2000."⁴⁶⁹⁰ Defendants also
12 present charts arguing that an additional 61 references may be combined in order to render the
13 Claims obvious. Not only do Defendants ignore the improbability that a person of ordinary skill
14 would combine 61 separate references, they additionally do not identify any motivation for
15 combining these references.^{4691, 4692} Although Defendants need not point to an explicit statement

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⁴⁶⁹⁰ Defendants' Joint Invalidity Contentions at 625.

17 ⁴⁶⁹¹ Defendants' bare assertion that the asserted claims are obvious "in view of one or more the references cited in
18 Sections III and V.A and B, including, the '954 publication, WO '900, WO '118, Ando, Grimsgaard, Hayashi,
19 Katayama, Matsuzawa, Matak, Mori 2000, Nakamura, Nozaki, Okumura, Park, Saito 1998, Saito 2008 Satoh,
20 Shinozaki, Takaku, Yokoyama 2003, Yokoyama 2007, Calabresi, Chan 2002, Chan 2003, Contacos, Geppert,
Kelley, Leigh-Firbank, Maki, Mori 2006, Rambjør, Sanders or Theobold in combination with the knowledge of a
person of ordinary skill in the art in light of the dosing regimen employed with Lovaza/Omacor" similarly fails to
meet the disclosure requirements of the Nevada Local Patent Rules, and fails to provide any motivation to combine
these references. *See* Defendants' Joint Invalidity Contentions at 625.

21 ⁴⁶⁹² Defendants' bare assertion that "the motivation or reason to combine or modify prior art to create invalidating
22 combinations under 35 U.S.C. §103 can be found in the references identified above in Section III.C," and that
23 "[c]ommon sense, design incentives, market forces, and the background knowledge possessed by a person having
ordinary skill in the art provide the reasons or rationales for combining the teachings of multiple references or
modifying references to render obvious the claimed inventions of the asserted claims," fails to meet the disclosure
requirements of the Nevada Local Patent Rules. *See* Defendants' Joint Invalidity Contentions at 616.

1 in the prior art motivating the combination of these references, any assertion of an “apparent
2 reason” to combine must find a basis in the factual record.⁴⁶⁹³ Defendants’ unsupported cobbling
3 of selective disclosures represents hindsight reconstruction.⁴⁶⁹⁴ Defendants’ contentions are no
4 more than an assertion that certain claim elements were known in the prior art. Throughout their
5 contentions, Defendants’ selectively cite to data points in a reference without considering other
6 disclosures or even the reference as a whole. Each reference, however, must be evaluated for all
7 that it teaches.⁴⁶⁹⁵ Accordingly, Defendants fail to meet their burden to establish *prima facie*
8 obviousness.

9 WO ‘118 is directed at the composition containing EPA for the purpose of preventing the
10 occurrence of cardiovascular events in multiple risk patients. Further, the invention of WO ‘118
11 is directed, “in particular, [to] preventing occurrence of cardiovascular events in
12 hypercholesterolemia patients who have been treated with HMG-CoA RI but still suffer from the
13 risk of the cardiovascular events.”⁴⁶⁹⁶ Contrary to Defendants’ assertion that WO ‘118 discloses
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15 ⁴⁶⁹³ See, e.g., *In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the
16 formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did
17 not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply
18 the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi*
19 *Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (stating that the assertion of a starting point
20 “must avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation
21 to select and then modify a lead compound to arrive at the claimed invention,” which turns on the known “properties
22 and limitations of the prior art compounds”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F.
23 Supp. 2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima*
24 *facie* obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and
concluding that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art
would have been motivated to resolve citalopram in June 1988”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

21 ⁴⁶⁹⁴ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under
22 *KSR*, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention
without any explanation as to how or why the references would be combined to produce the claimed invention”).

23 ⁴⁶⁹⁵ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

24 ⁴⁶⁹⁶ WO ‘118 at 9.

1 “the administration of 4 g of pure EPA with no DHA,”⁴⁶⁹⁷ WO ’118 fails to disclose the claimed
2 subject with the specified very high TG levels (500-1500 mg/dL) who does not receive
3 concurrent lipid altering therapy, the claimed pharmaceutical composition with the specified
4 fatty acid compositions or dosage, or the claimed method to effect the specified TG reduction
5 without substantially increasing LDL-C. WO ’118 discloses a composition with a wide range of
6 possible EPA content, dosages, and teaches that DHA is a “preferable fatty acid” to include in
7 the disclosed composition.⁴⁶⁹⁸

8 WO ’118 does not disclose administration of highly-purified ethyl-EPA to the target
9 population of the claimed invention. The asserted claims are directed to persons with severe
10 hypertriglyceridemia (i.e. TG level above 500 mg/dL). WO ’118 on the other hand only
11 discloses administration of EPA to persons with triglyceride of at least 150 mg/dL.⁴⁶⁹⁹ WO
12 ’118’s emphasis on reducing cardiovascular events suggests that its disclosure is directed to
13 patients with borderline-high to high TG levels, since the primary goal for patients with very-
14 high TG is to prevent acute pancreatitis by decreasing TG levels.⁴⁷⁰⁰

15 WO ’118 also does not distinguish EPA from DHA in its disclosures regarding the
16 effectiveness of the substances for treating hypertriglyceridemia.⁴⁷⁰¹ WO ’118 states that
17 “[a]nother preferable fatty acid . . . is DHA-E,” and that “the compositional ratio of EPA-
18 E/DHA-E, content of EPA-E and DHA-E . . . in the total fatty acid, and dosage of (EPA-E +
19

20 ⁴⁶⁹⁷ Defendants’ Joint Invalidity Contentions at 625.

21 ⁴⁶⁹⁸ WO ’118 at 22-23.

22 ⁴⁶⁹⁹ WO ’118 at 8.

23 ⁴⁷⁰⁰ See Section III.

24 ⁴⁷⁰¹ WO ’118 at 11, 13, 16-21 (“the composition containing at least EPA-E and/or DHA-E as its effective component”).

1 DHA-E) are not particularly limited as long as intended effects of the present invention are
2 attained.”⁴⁷⁰² It further states that “the composition is preferably the one having a high purity of
3 EPA-E and DHA-E.”⁴⁷⁰³ Further, WO ’118 does not disclose EPA’s effect on LDL-C, VLDL-C,
4 Apo-B, or Lp-PLA2.

5 WO ’900 is directed to a process for producing purified EPA from a culture of micro-
6 organisms. WO ’900 fails to disclose the claimed subject with the specified very high TG levels
7 (500-1500 mg/dL) who does not receive concurrent lipid altering therapy, the claimed
8 pharmaceutical composition with the specified dosage or administration period, or the claimed
9 method to effect the specified TG reduction without substantially increasing LDL-C. WO ’900
10 only discloses the method of producing purified EPA for therapeutic use, it does not teach
11 *administration* of pure EPA. WO ’900 has no discussion, for example, regarding claimed patient
12 population or method of treatment.

13 WO ’900 does not teach administration of pure EPA to treat hypertriglyceridemia. It lists
14 more than 30 diseases that can be treated with pure EPA, but hypertriglyceridemia is not one of
15 them.⁴⁷⁰⁴ Moreover, WO ’900 does not teach the desired effect of EPA other than commenting
16 generally that it “may promote health and ameliorate or even reverse the effects of a range of
17 common diseases.”⁴⁷⁰⁵ It has no discussion, for example, on any TG-lowering effect of EPA.
18 Although WO ’900 identifies DHA as an “undesired molecule”, it does not identify the *specific*
19 undesired effect of DHA or other impurities it is trying to prevent other than commenting
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21 ⁴⁷⁰² WO ’118 at 22-23.

22 ⁴⁷⁰³ WO ’118 at 23.

23 ⁴⁷⁰⁴ *See, e.g.*, ’900 Pub. at 16-17.

24 ⁴⁷⁰⁵ ’900 Pub. at 5.

1 generally that “the desired effects of EPA may be limited or reversed” by them.⁴⁷⁰⁶ It has no
2 discussion related to any LDL-C effects caused by DHA.

3 The proposed combination does not render the independent claims of the ’650 patent
4 obvious and Defendants’ burden to prove otherwise is especially difficult because the PTO
5 considered WO ’118, WO ’900, Mori 2000, and Lovaza (both generally and the Lovaza package
6 insert specifically) during prosecution.⁴⁷⁰⁷

7 The analysis of the independent claims of the ’650 patent is incorporated into all asserted
8 claims that depend from those Claims.

9 (a) Leigh-Firbank and Mori 2000 Do
10 Not Disclose Purported Knowledge
11 that DHA was Responsible for the
12 Increase in LDL-C

12 Defendants contend that a “person of ordinary skill in the art would have been motivated
13 to administer pure EPA to severely hypertriglyceridemic patients according to Lovaza’s known
14 regimen, particularly in light of the knowledge that DHA is responsible for the increase in LDL-
15 C levels as evidenced by Leigh-Firbank or Mori 2000.”⁴⁷⁰⁸

16 Defendants fail to identify a specific motivation to combine WO ’118 or WO ’900 with
17 the treatment regimen of Lovaza, as evidenced by the Lovaza PDR. Although Defendants need
18 not point to an explicit statement in the prior art motivating the combination of these references,
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21 ⁴⁷⁰⁶ ’900 Pub. at 39.

22 ⁴⁷⁰⁷ See, e.g., *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012)(taking into account that “the
23 examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention.
24 Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear
and convincing standard came into play”).

⁴⁷⁰⁸ Defendants’ Joint Invalidity Contentions at 626.

1 any assertion of an “apparent reason” to combine must find a basis in the factual record.⁴⁷⁰⁹
2 Defendants’ unsupported cobbling of selective disclosures represents hindsight
3 reconstruction.⁴⁷¹⁰ Defendants’ contentions are no more than an assertion that certain claim
4 elements were known in the prior art. Accordingly, Defendants fail to meet their burden to
5 establish *prima facie* obviousness.

6 Contrary to Defendants’ assertion, Leigh-Firbank and Mori 2000 do *not* disclose that
7 DHA is responsible for the increase in LDL-C level. The discussion regarding Leigh-Firbank
8 and Mori 2000 in Section V.J.3.c.1.a.i.a.iii is incorporated herein by reference. Leigh-Firbank
9 cannot comment on the effect of EPA and DHA alone because it did not administer EPA and
10 DHA separately. A person of ordinary skill would similarly understand that Leigh-Firbank does
11 not offer any disclosure regarding the effect of EPA and DHA separately or gain any
12 understanding of the separate impact of DHA or EPA on lipid parameters. Although Mori 2000
13 discloses an increase in LDL-C for patients administered DHA, it also teaches that DHA is
14 preferable to EPA—thus teaching away from the claimed invention and reflecting no motivation
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17 ⁴⁷⁰⁹ See, e.g., *In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the
18 formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did
19 not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply
20 the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi*
21 *Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must
22 avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to
23 select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and
24 elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp.
2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie*
obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding
that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been
motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

⁴⁷¹⁰ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under
KSR, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention
without any explanation as to how or why the references would be combined to produce the claimed invention”).

1 to combine with WO '118 or WO '900. Engaging in hindsight bias, Defendants ignore, without
2 explanation, the other effects of DHA that a person of ordinary skill would consider. Defendants
3 fail to identify any other basis upon which a person of ordinary skill would have sought to
4 combine Mori 2000 with the Lovaza PDR.

5 Therefore, Leigh-Firbank and Mori 2000 fail to substantiate Defendants' assertion that it
6 was known that DHA was responsible for the increase in LDL-C levels. Further, Defendants
7 ignore, without explanation, other studies that demonstrate that DHA decreases or has little
8 effect on LDL-C levels.⁴⁷¹¹ Defendants identify no other basis upon which a person of ordinary
9 skill would have sought to combine WO '118, WO '900, the Lovaza PDR, Leigh-Firbank and/or
10 Mori.

11 (ii) The '650 Patent is not Obvious Over WO
12 '118, WO '900, Grimsgaard, Mori 2000
13 and/or Maki in Combination with the
14 Omacor PDR/Lovaza PDR, and Further in
View of Katayama, Matsuzawa and/or
Takaku.

15 With respect to the '650 patent, Defendants present a combination of nine references:
16 "WO '118, WO '900, Grimsgaard, Mori 2000 and/or Maki in combination with treatment
17 regimen of Omacor/Lovaza as evidenced by the Omacor PDR/Lovaza PDR, and further in view
18 of Katayama, Matsuzawa and/or Takaku."⁴⁷¹² Defendants also present charts arguing that an
19 additional 56 references may be combined in order to render the Claims obvious. Not only do
20 Defendants ignore the improbability that a person of ordinary skill would combine 56 separate
21 references, they additionally do not identify any motivation for combining these references.

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23 ⁴⁷¹¹ See e.g., Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

24 ⁴⁷¹² Defendants' Joint Invalidity Contentions at 626.

1 Although Defendants need not point to an explicit statement in the prior art motivating the
2 combination of these references, any assertion of an “apparent reason” to combine must find a
3 basis in the factual record.⁴⁷¹³ Defendants’ unsupported cobbling of selective disclosures
4 represents hindsight reconstruction.⁴⁷¹⁴ Defendants’ contentions are no more than an assertion
5 that certain claim elements were known in the prior art. Throughout their contentions,
6 Defendants’ selectively cite to data points in a reference without considering other disclosures or
7 even the reference as a whole. Each reference, however, must be evaluated for all that it
8 teaches.⁴⁷¹⁵ Accordingly, Defendants fail to meet their burden to establish *prima facie*
9 obviousness.

10 The discussion related to WO ‘118 and WO ‘900 in Section V.J.3.c.1.b.i is incorporated
11 herein by reference. The discussion related to Grimsgaard, Mori 2000 and/or Maki in Section
12 V.J.3.c.1.a.ii.a.iii is incorporated herein by reference. Defendants contend that “Grimsgaard and
13 Mori 2000 also disclose the administration of 4 g per day of highly purified EPA with no DHA.”
14 However, neither Grimsgaard nor Mori 2000 discloses the administration of 4g/day EPA to the
15

16 ⁴⁷¹³ See, e.g., *In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the
17 formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did
18 not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply
19 the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi*
20 *Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must
21 avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to
22 select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and
23 elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp.
24 2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie*
obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding
that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been
motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

⁴⁷¹⁴ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under
KSR, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention
without any explanation as to how or why the references would be combined to produce the claimed invention”).

⁴⁷¹⁵ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

1 very high TG patient population. Neither Grimsgaard nor Mori 2000 provides motivation to
2 administer 4g/day EPA to the very high TG patient population. Defendants identify no other
3 basis upon which a person of ordinary skill would have sought to combine the composition
4 disclosed in Grimsgaard or Mori 2000.

5 Defendants argue that it “would have been obvious to a person of ordinary skill in the art
6 to use EPA as described in WO ’118, WO ’900, Grimsgaard or Mori 2000 in the treatment
7 regimen used for Omacor/Lovaza as described in the Omacor PDR/Lovaza PDR,” but their
8 assertions fail to provide a motivation for combining the references.⁴⁷¹⁶ Although Defendants
9 need not point to an explicit statement in the prior art motivating the combination of these
10 references, any assertion of an “apparent reason” to combine must find a basis in the factual
11 record.⁴⁷¹⁷ Defendants’ assertions related to motivation are insufficient,⁴⁷¹⁸ and accordingly
12 Defendants fail to meet their burden to establish *prima facie* obviousness.

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15 ⁴⁷¹⁶ Defendants’ Joint Invalidation Contentions at 626.

16 ⁴⁷¹⁷ See, e.g., *In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the
17 formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did
18 not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply
19 the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi*
20 *Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must
21 avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to
22 select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and
23 elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp.
24 2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie*
obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding
that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been
motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

⁴⁷¹⁸ For example, Defendants’ assertion that “WO ’118 may be combined with other prior art in the field of treating
hypertriglyceridemia” is nothing more than a statement that a reference can be combined but fails to provide any
basis for that statement. While the paragraph associated with that statement makes assertions regarding the
disclosure of certain other references, it does not provide a basis for the assertion of motivation to combine with WO
’118. See Defendants’ Joint Invalidation Contentions at 627.

1 Defendants formulate an obviousness argument that relies on Katayama, Matsuzawa, or
2 Takaku. However, they've failed to provide any factual or legal basis as to why each reference
3 discloses a claim element, an "apparent reason" or motivation to combine the elements in the
4 manner claimed.⁴⁷¹⁹ Therefore, Defendants should be precluded from relying on this these
5 references.

6 As discussed above in Section V.J.3.c.1.a.i.a.i, Katayama and Matsuzawa were both only
7 designed to confirm the safety of long term treatment of Epadel and its ability to lower both
8 serum total cholesterol and triglyceride levels. They fail to provide motivation to administer
9 purified EPA to the very high TG patient population. As discussed above in Section
10 V.J.3.c.1.a.ii.a.i, Takaku candidly acknowledges that "only a few subjects were examined" and
11 cautions against drawing a conclusion "only from the results of the present study."⁴⁷²⁰ Further,
12 the study did not include any placebo control, therefore, a person of ordinary skill in the art
13 would understand these reports do not provide the ability to conclude that the observed lipid
14 effects would have occurred independent of the drug that is administered. In addition, the study
15 was conducted exclusively in Japanese patients, and a person of ordinary skill would not have
16 expected the results to be applicable to the general population.⁴⁷²¹

17 The proposed combination does not render the independent claims of the '650 patent
18 obvious and Defendants' burden to prove otherwise is especially difficult because the PTO
19

20 ⁴⁷¹⁹ *KSR*, 550 U.S. at 417–19; *TriMed, Inc. v. Stryker Corp.*, 608 F.3d 1333, 1341 (Fed. Cir. 2010). Hindsight may
21 not be employed to identify relevant prior art and relevant teachings therein: *Heidelberger Druckmaschinen AG v.*
Hantscho Comm. Prods., Inc., 21 F.3d 1068, 1071–72 (Fed. Cir. 1994); *Monarch Knitting Mach. Corp. v. Sulzer*
Morat GmbH, 139 F.3d 877, 881 (Fed. Cir. 1998).

22 ⁴⁷²⁰ Takaku at ICOSAPENT_DFNDT00006897.

23 ⁴⁷²¹ Yokoyama 2007 at 1097 ("[b]ecause our population was exclusively Japanese, we cannot generalise our results
24 to other populations.")

1 considered WO '118, WO '900, Grimsgaard, Mori 2000, Maki, Katayama, Matsuzawa and
2 Lovaza (both generally and the Lovaza package insert specifically) during prosecution.⁴⁷²²

3 The analysis of the independent claims of the '650 patent is incorporated into all asserted
4 claims that depend from those Claims.

5 (a) Grimsgaard, Mori 2000 and/or Maki
6 Do Not Disclose Purported
7 Knowledge that DHA was
8 Responsible for the Increase in LDL-
9 C

8 Defendants contend that a “person of ordinary skill in the art would have been motivated
9 to administer pure EPA to hypertriglyceridemic patients according to Omacor/Lovaza’s known
10 regimen, Katayama, Matsuzawa or Takaku, particularly in light of the knowledge that DHA is
11 responsible for the increase in LDL-C levels as evidenced by Grimsgaard, Mori 2000 or
12 Maki.”⁴⁷²³

13 Contrary to Defendants’ assertion, Grimsgaard, Mori 2000 and/or Maki do *not* disclose
14 that DHA is responsible for the increase in LDL-C level. The discussion related to Grimsgaard,
15 Mori 2000 and/or Maki in Section V.J.3.c.1.a.ii.a.iii is incorporated herein by reference. A
16 person of ordinary skill would understand that the results of Grimsgaard demonstrated that EPA
17 and DHA’s impact on LDL-C were the same as the effect of the placebo corn oil group; that is,
18 there was no difference between EPA, DHA, or placebo’s effect on LDL-C levels. Although
19 Mori 2000 discloses an increase in LDL-C for patients administered DHA, the reference does not
20

21 ⁴⁷²² See, e.g., *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012) (taking into account that “the
22 examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention.
23 Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear
24 and convincing standard came into play”).

⁴⁷²³ Defendants’ Joint Invalidity Contentions at 626.

1 disclose administration of DHA to the requisite patient population and teaches that DHA is
2 preferable to EPA—thus teaching away from the claimed invention. Engaging in hindsight bias,
3 Defendants ignore, without explanation, the other effects of DHA that a person of ordinary skill
4 would consider. Most controlled studies in patients with normal to high baseline TG levels
5 indicated that DHA had little or no effect on LDL-C.⁴⁷²⁴ Therefore, a person of ordinary skill
6 would not have concluded that DHA increases LDL-C in patients with normal to high baseline
7 TG levels. Maki demonstrated that when 1.52 g/day DHA and 0.84 g/day palmitic acid is
8 administered to patients with below-average levels of HDL-C levels and borderline-high TG
9 levels, a significant increase in LDL-C is observed.⁴⁷²⁵ However, one of ordinary skill in the art
10 knew that saturated fatty acids, such as palmitate, may contributed to the elevation in LDL-C.⁴⁷²⁶
11 Therefore, the results of Maki are inconclusive as to DHA’s effect alone on LDL-C levels.

12 Therefore, Grimsgaard, Mori 2000 and/or Maki fail to substantiate Defendants’ assertion
13 that it was known that DHA was responsible for the increase in LDL-C levels. Further,
14 Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or
15 has little effect on LDL-C levels.⁴⁷²⁷ Defendants identify no other basis upon which a person of
16 ordinary skill would have sought to combine WO ‘118, WO ‘900, Grimsgaard, Mori 2000, Maki,
17 the Omacor PDR/the Lovaza PDR, Katayama, Matsuzawa and/or Takaku.

18
19 _____
20 ⁴⁷²⁴ Mori 2006 at 98. Moreover, Mori 2000, the only study which compared EPA versus DHA, and is placebo
controlled, found an increase in LDL-C after DHA administration.

21 ⁴⁷²⁵ Maki at 195.

22 ⁴⁷²⁶ Maki at 197; Yu et al., *Plasma Cholesterol-Predictive Equations Demonstrate that Stearic Acid is Neutral and*
Monounsaturated Fatty Acids are Hypocholesterlemic, 61 AM J CLIN NUTR 1129, 1136 (1995); Weber 2000 (“A
23 number of the earlier-formulated (older) omega-3 fatty acid supplements contained significant amounts of saturated
fat and cholesterol, both of which are known to elevate LDL-C.”).

24 ⁴⁷²⁷ See e.g., Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

1 (iii) A Person of Ordinary Skill Would Not Have
2 Been Motivated to Administer Purified EPA
3 in the Treatment Regimen Recited in the
4 Claims

5 For an invention to be obvious, there must have been an “apparent reason” to make it.

6 Defendants assert that a “person of ordinary skill in the art would have been motivated to
7 administer 4 grams of highly-purified EPA to patients with triglycerides greater than or equal to
8 500 mg/dL, with a reasonable expectation of success in lowering triglycerides.”⁴⁷²⁸ However, as
9 set forth below, Defendants fail to address why a person of ordinary skill in the art would have
10 been motivated to administer 4 grams of highly-purified EPA to patients with triglycerides
11 greater than or equal to 500 mg/dL.

12 A person of ordinary skill in the art would have understood that omega 3-fatty acids,
13 including DHA and EPA, and fibrates cause an increase in LDL-C among very high TG patients,
14 as reflected in the prior art. Accordingly, a person of ordinary skill in the art would not have been
15 motivated to look to omega 3-fatty acids in order to obtain a reduction in TGs without increasing
16 LDL-C in very high TG patients:

	LDL-C Effect	
	Borderline-High or High TG Patients	Very-High TG Patients
Fibrate ⁴⁷²⁹	-20%	+45%
Lovaza/Omacor ⁴⁷³⁰	-6%	+45%

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18
19 That Epadel has been approved for decades but not approved for use in the very high TG
20 patient population prior to the invention of the asserted patents is a real-world reflection of the
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22 ⁴⁷²⁸ Defendants’ Joint Invalidity Contentions at 627.

23 ⁴⁷²⁹ Tricor®, Physicians’ Desk Reference 502-505 (62d ed. 2008).

24 ⁴⁷³⁰ Chan 2002 I at 2381 (Table 3).

1 lack of motivation. Research into the pharmaceutical uses of EPA started as early as the 1970s.
2 In 1990, Mochida Pharmaceutical, began to market Epadel, a high purity EPA drug. There have
3 been countless studies conducted which administer Epadel and report the effects observed.
4 Although a few studies administer Epadel to a patient population which included a few patients
5 with TG levels > 500 mg/dL, Defendants fail to identify a single reference directed to the
6 administration of Epadel to patients with very-high TG levels, reflecting a lack of motivation.

7 Defendants further argue that the disclosure in WO '118 would combine with the prior art
8 concerning Lovaza for at least two reasons; first, "products containing DHA were reported to
9 increase LDL-C levels while products containing only EPA did not," and second, "WO '118
10 reports a reduction in cardiovascular events in hypertriglyceridemic patients administered highly-
11 purified ethyl-EPA."⁴⁷³¹ Both of the "reasons" identified by Defendants are false.

12 Regarding Defendants' first reason, that "products containing DHA were reported to
13 increase LDL-C levels while products containing only EPA did not," most controlled studies in
14 patients with normal to high baseline TG levels indicated that DHA had little or no effect on
15 LDL-C.⁴⁷³² Therefore, a person of ordinary skill would not have concluded that DHA increases
16 LDL-C in patients with normal to high baseline TG levels. Specifically, Leigh-Firbank, Kelley,
17 and Theobald does *not* disclose that "DHA raises LDL-C, an effect associated with heart disease,
18 while EPA does not."⁴⁷³³ First, Leigh-Firbank cannot comment on the effect of EPA and DHA
19 alone because it did not administer EPA and DHA separately.⁴⁷³⁴ A person of ordinary skill
20

21 ⁴⁷³¹ Defendants' Joint Invalidation Contentions at 627.

22 ⁴⁷³² Mori 2006 at 98. Moreover, Mori 2000, the only study which compared EPA versus DHA, and is placebo
controlled, found an increase in LDL-C after DHA administration.

23 ⁴⁷³³ Defendants' Joint Invalidation Contentions at 632.

24 ⁴⁷³⁴ The discussion related to Leigh-Firbank in Section V.J.3.c.1.a.i.a.iii is incorporated herein by reference.

1 would similarly understand that Leigh-Firbank does not offer any disclosure regarding the effect
2 of EPA and DHA separately or gain any understanding of the separate impact of DHA or EPA
3 on lipid parameters. Second, Kelley administered DHA-rich oil that was contaminated with
4 other saturated and polyunsaturated fatty acids.⁴⁷³⁵ Therefore, a person of ordinary skill would
5 have known it is unsuitable for evaluating the independent effects of DHA because it is not clear
6 how much of the supplement's effects can be attributed to DHA.⁴⁷³⁶ Kelley does not show that
7 DHA is responsible for the increase in LDL-C. Kelley suggests that increase in LDL-C is a
8 general phenomenon associated with triglyceride-lowering drugs, stating that a similar increase
9 was induced by fibrate therapy.⁴⁷³⁷ Kelley specifically teaches that the increase in LDL-C
10 caused by DHA supplementation is unlikely to be "detrimental" because there was not a parallel
11 increase in overall LDL particle number. Rather than concluding that DHA was uniquely
12 responsible for a rise in LDL-C levels, a person of ordinary skill would understand Kelley to
13 disclose that DHA had uniquely beneficial cardioprotective effects.⁴⁷³⁸ Finally, Theobald also
14 does not teach that DHA increases LDL-C. In Theobald, 0.7 g/day of DHA was administered for
15 3 months in patients with normal baseline TG levels. Theobald found that LDL-C increased by
16 7% when compared to placebo. However, the DHA composition that was administered in
17 Theobald contained significant amounts of other fatty acids, such as myristic acid, palmitic acid,
18 and oleic acid. Therefore, a person of ordinary skill would have known that the DHA

20 ⁴⁷³⁵ The discussion related to Kelley in Section V.J.3.c.1.a.iii.a.ii is incorporated herein by reference.

21 ⁴⁷³⁶ See Mori 2006 at 96.

22 ⁴⁷³⁷ Kelley at 329.

23 ⁴⁷³⁸ Kelley at 324, 332 (Kelley's ultimate conclusion is that "[o]verall, DHA supplementation reduced the
24 concentrations of atherogenic lipids and lipoproteins and increased concentrations of cardioprotective lipoproteins"
and that "DHA supplementation may improve cardiovascular health.")

1 administered by Theobald is unsuitable for evaluating the independent effects of DHA because it
2 impossible to determine whether or how much of the supplement's effects can be attributed to
3 DHA.⁴⁷³⁹ Contrary to Defendants' assertion that there was "a reported advantage to using EPA
4 vs. DHA in hypertriglyceridemic subjects,"⁴⁷⁴⁰ there was no known advantage to using EPA vs.
5 DHA. In fact, a number of the references Defendants cite in their contentions ultimately
6 conclude that DHA supplementation "may represent a more favorable lipid profile than after
7 EPA supplementation."⁴⁷⁴¹ In addition, a person of ordinary skill would have recognized any
8 impact of DHA reported by the study to be applicable to EPA because they would have
9 understood these substances to function by the same mechanism. Furthermore, as discussed
10 above in Section III, a person of ordinary skill would not expect the same LDL-C effect in
11 patients with lower baseline TG levels, including healthy patients, as in very-high TG patients
12 because patients with higher TG levels had different lipid responses compared to patients with
13 lower TG levels.

14 Regarding Defendants' second reason, that "WO '118 reports a reduction in
15 cardiovascular events in hypertriglyceridemic patients administered highly-purified ethyl-EPA,"
16 the cardioprotective effects of omega-3 fatty acids, including both EPA and DHA, have been
17 well documented.⁴⁷⁴² Lovaza/Omacor has been shown to reduce the risk for cardiovascular

20 ⁴⁷³⁹ See Mori 2006 at 96.

21 ⁴⁷⁴⁰ Defendants' Joint Invalidity Contentions at 627.

22 ⁴⁷⁴¹ Mori 2000 at 1092.

23 ⁴⁷⁴² Harris et al., *Tissue n-3 and n-6 Fatty Acids and Risk for Coronary Heart Disease Events*, 193
ATHEROSCLEROSIS, 1, 8 (2007) ("Overall, these findings confirm the well-known relationship between the n-3 FA
and CHD risk.") ("Harris 2007"); Bays 2008 II at 229-230.

1 death plus nonfatal myocardial infarction and nonfatal stroke.⁴⁷⁴³ Omega-3 fatty acids have been
2 shown to exert cardioprotective effects in both primary and secondary coronary heart disease
3 prevention trials.⁴⁷⁴⁴ Omega-3 fatty acids were known to reduce TG concentration, have
4 antiarrhythmic effects, decrease platelet aggregation, stabilize plaque, reduce blood pressure
5 and/or reduce heart rate.⁴⁷⁴⁵

6 Defendants argue that a “person of ordinary skill in the art would have appreciated the
7 fact that highly-purified ethyl-EPA, and not Lovaza, had been demonstrated to reduce
8 cardiovascular events in high-risk hypertriglyceridemic patients, and understood the benefits of
9 replacing the EPA+DHA of Lovaza with the highly purified ethyl-EPA of WO ’118.”⁴⁷⁴⁶ As
10 discussed above, the cardioprotective effects of omega-3 fatty acids, including both EPA, DHA
11 and Lovaza/Omacor have been well documented.⁴⁷⁴⁷

12 In fact, a meta-analysis of twenty-five studies which examined the risk of coronary heart
13 disease endpoints as a function of tissue FA composition found that the evidence suggested that
14 DHA is *more* cardioprotective than EPA.⁴⁷⁴⁸ This study found that “depressed levels of long-
15 chain *n*-3 FA (especially DHA) in tissues is a consistent marker of increased risk for coronary
16
17

18 ⁴⁷⁴³ See Bays, *Clinical Overview of Omacor: A Concentrated Formulation of Omega-3 Polyunsaturated Fatty Acids*,
98 AM. J. CARDIOL 71i (2006) (“Bays 2006”).

19 ⁴⁷⁴⁴ Harris et al., *Omega-3 Fatty Acids and Coronary Heart Disease Risk: Clinical and Mechanistic Perspectives*,
197 ATHEROSCLEROSIS 12, 13 (2008) (“Harris 2008”).

20 ⁴⁷⁴⁵ Harris 2008 at 13.

21 ⁴⁷⁴⁶ Defendants’ Joint Invalidation Contentions at 628.

22 ⁴⁷⁴⁷ Harris et al., *Tissue n-3 and n-6 Fatty Acids and Risk for Coronary Heart Disease Events*, 193
ATHEROSCLEROSIS, 1, 8 (2007) (“Overall, these findings confirm the well-known relationship between the *n*-3 FA
and CHD risk.”) (“Harris 2007”).

23 ⁴⁷⁴⁸ Harris 2007 at 8.

1 heart disease events.”⁴⁷⁴⁹ Further, the study found that DHA levels, with or without EPA, were
2 significantly lower in fatal endpoints.⁴⁷⁵⁰ This study suggests that DHA is preferable to EPA—
3 thus teaching away from the claimed invention.⁴⁷⁵¹ Defendants rely on hindsight bias to argue
4 that a person of ordinary skill would have been motivated to use purified EPA, when both EPA
5 and DHA were known to have cardioprotective effects, and there were studies suggesting DHA
6 was *more* cardioprotective than EPA.

7 Defendants argue that the following claim elements were known: the administration of
8 highly-purified EPA-E to reduce TG levels in patients with normal to high TG levels, the
9 administration of purified EPA to patients with TG levels > 500 mg/dL, to administer EPA-E to
10 patients with high and very high TG levels who were not receiving concurrent lipid altering
11 therapy, and the dose of 4g/day and 12-week regimen.⁴⁷⁵² Defendants then argue that the “only
12 question is whether one skilled in the art would have been motivated to use the DHA-free,
13 highly-purified EPA-E of the prior art for the treatment of patients with triglyceride levels of at
14 least 500 mg/dL as part of the claimed dosage regimen.”⁴⁷⁵³

15 Defendants’ contentions are no more than a recitation that certain claim elements were
16 known in the prior art. Defendants’ assertions to the contrary represent hindsight

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18 ⁴⁷⁴⁹ *Id.*

19 ⁴⁷⁵⁰ Harris 2007 at 7, Table 5; *see also* Harris 2007 at 8 (“Low DHA was the most common finding across all studies, suggesting that this FA was perhaps more cardioprotective than EPA as others have suggested.”).

20 ⁴⁷⁵¹ *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994) (A reference may be said to teach away when a person of ordinary skill, upon [examining] the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant.”); *see also Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012) (quoting Gurley); *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1552 (Fed. Cir. 1983) (“[P]roceed[ing] contrary to the accepted wisdom of the prior art ... is strong evidence of nonobviousness.”).

22 ⁴⁷⁵² Defendants’ Joint Invalidity Contentions at 629.

23 ⁴⁷⁵³ Defendants’ Joint Invalidity Contentions at 629.

1 reconstruction.⁴⁷⁵⁴ Notably, Defendants *do not* assert that a person of ordinary skill would have
2 known that purified EPA, when administered to patients with very-high TG levels (≥ 500 mg/dL),
3 *would not substantially increase LDL-C*. Further, Defendants point to three Japanese studies,⁴⁷⁵⁵
4 which included a small minority of patients with baseline TG levels > 500 mg/dL to argue that “a
5 number of prior art references disclosed the administration of purified EPA to patients with
6 triglyceride levels > 500 mg/dL.”^{4756, 4757} The disclosures of Nakamura (one patient), Matsuzawa
7 (disclosure of three patients with TG between 400 and 1000 mg/dL, with no evidence or support
8 for the assertion that the patients had very high TGs), and Takaku (three patients) reflect that a
9 person of ordinary skill in the art would *not* understand these references to relate to the use of
10 EPA in patients with very high TGs, nor would a person of ordinary skill in the art draw any
11 conclusions regarding these references in terms of the very high TG patient population. In
12 Nakamura, one patient had a baseline TG level > 500 mg/dL.⁴⁷⁵⁸ However, the mean baseline
13 TG for all patients was 2.07 mmol/l (183 mg/dL), indicating that the baseline TG values for the
14 other patients was well below 500 mg/dL.⁴⁷⁵⁹ In Matsuzawa, three patients had TG levels
15 between 400 and 1000 mg/dL and one patient had TG levels $> 1,000$ mg/dL.⁴⁷⁶⁰ Based on this
16

17 ⁴⁷⁵⁴ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that even under
18 KSR, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention
without any explanation as to how or why the references would be combined to produce the claimed invention.”).

19 ⁴⁷⁵⁵ Nakamura, Matsuzawa, and Takaku.

20 ⁴⁷⁵⁶ Defendants’ Joint Invalidity Contentions at 629.

21 ⁴⁷⁵⁷ Okumura and Hayashi also fail to disclose administration of purified EPA to patients with TG levels > 500
22 mg/dL. Hayashi states that the baseline TG level was 300 +/- 233 mg/dL. However, the standard error is unusually
23 high and there is no specific disclosure of a single subject with TG levels > 500 mg/dL. Okumura specifically
states that its hypertriglyceridemia patients had baseline TG levels between 150 and 500 mg/dL.

24 ⁴⁷⁵⁸ Nakamura at 23, Table 1.

⁴⁷⁵⁹ Nakamura at 23, Tables 1 and 2.

⁴⁷⁶⁰ *Id.* at 23.

1 disclosure, only one patient definitively had a baseline TG level ≥ 500 mg/dL. Further, this one
2 patient was excluded when analyzing the lipid impact because he was a “heavy drinker” and the
3 “effect of alcohol made it impossible to assess triglyceride levels.”⁴⁷⁶¹ In Takaku, three patients
4 had baseline TG levels above 500 mg/dL.⁴⁷⁶² However, the mean baseline TG level for all
5 patients was 245 mg/dL.⁴⁷⁶³ Indeed, the mean baseline TG level of the patients in all three
6 studies was well below 500 mg/dL; therefore, a person of ordinary skill would not have expected
7 the results to be applicable to patients with triglycerides above 500 mg/dL. Further, in each of
8 these studies, patients with >500 mg/dL were most likely excluded from the LDL-C calculations
9 because the Friedewald’s Equation cannot be used for patients with triglyceride levels ≥ 400
10 mg/dL.⁴⁷⁶⁴ Defendants have failed to identify all of the claimed elements and fail to provide
11 motivation to use the DHA-free, highly-purified EPA-E of the prior art for the treatment of
12 patients with triglyceride levels of at least 500 mg/dL as part of the claimed dosage regimen.

13 Defendants contend that a “person of ordinary skill in the art would have been motivated
14 to administer highly-purified EPA-E capsules, for at least 12 weeks . . . in order to achieve the
15 known TG-lowering effects of highly-purified EPA-E.”⁴⁷⁶⁵ This argument is flawed. The prior
16 art demonstrates a wide range of administration periods utilized in different clinical studies. For
17 example, EPA was administered for 4 weeks in Park, for 7 weeks in Grimsgaard, for 8 weeks in
18 Hayashi, for 1 year in Takaku, for 2 years in Katayama, and for 5 years in Yokoyama 2007.
19 Given the large number of choices of administration periods disclosed in prior art, Defendants
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21 ⁴⁷⁶¹ *Id.* at 10.

22 ⁴⁷⁶² Takaku at ICOSAPENT_DFNDTS00006895.

23 ⁴⁷⁶³ Takaku at ICOSAPENT_DFNDTS00006875.

24 ⁴⁷⁶⁴ *See* Matsuzawa at ICOSAPENT_DFNDTS00006450.

⁴⁷⁶⁵ Defendants’ Joint Invalidation Contentions at 630.

1 have not shown that a person of ordinary skill would not have been motivated to administer
2 highly-purified EPA-E capsules for 12 weeks and offer no basis for their assertions.

3 Moreover, a person of ordinary skill would not have been motivated to administer highly-
4 purified *EPA-E* capsules, as opposed to DHA or a combination of EPA and DHA (such as
5 Lovaza), for 12 weeks. It was well known that both EPA and DHA reduced blood
6 triglycerides.⁴⁷⁶⁶ In fact, Defendants acknowledge in their Joint Invalidation Contentions that
7 “DHA and EPA were both known to comparably reduce triglycerides, independently of one
8 another.”⁴⁷⁶⁷ Data from some studies even suggested that DHA or fish oil may reduce
9 triglyceride more effectively than EPA.⁴⁷⁶⁸ Therefore, a person of ordinary skill would not have
10 been motivated to administer highly-purified *EPA-E* capsules instead of DHA or a combination
11 of EPA and DHA (such as Lovaza) for 12 weeks.

12 Defendants argue that a “person of ordinary skill in the art also would have been
13 motivated to administer 4 g/day highly-pure ethyl EPA . . . because of the observed significant
14 reduction in TG . . . that was achieved in six weeks of treatment,” citing Mori 2000.⁴⁷⁶⁹ This
15 argument is incorrect. The administration of 4 g/day of highly-pure ethyl EPA to patients with
16 *mild* hypertriglyceridemia for *six* weeks does not provide a person of ordinary skill motivation to
17 administer the same dose to patients with *severe* hypertriglyceridemia for *twelve* weeks.

18 Defendants also, once again, fail to demonstrate that a person of ordinary skill would have
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21 ⁴⁷⁶⁶ Mori 2006 at 98.

22 ⁴⁷⁶⁷ Defendants’ Joint Invalidation Contentions at 634.

23 ⁴⁷⁶⁸ Mori 2000 (showing that EPA reduced triglyceride by 18% while DHA reduced triglyceride by 20%); Rambjor
(showing that fish oil reduced triglyceride more than EPA); Grimsgaard (showing that decrease in triglyceride was
greater with DHA supplementation than EPA supplementation).

24 ⁴⁷⁶⁹ Defendants’ Joint Invalidation Contentions at 630.

1 chosen to administer 4g/day EPA as opposed to DHA or a combination of EPA and DHA (such
2 as Lovaza).

3 Defendants further argue that “because Katayama and Saito 1998 teach that higher doses
4 of highly-purified EPA-E reduce TG level to a greater extent than lower doses . . . a person of
5 ordinary skill in the art would have been motivated to administer highly-purified EPA-E at a
6 dose of 4 g/day rather than a lower dose.”⁴⁷⁷⁰ A person of ordinary skill would not have relied
7 on either reference to determine the EPA dosage required to treat severe hypertriglyceridemia,
8 because these studies were not designed to determine the effect of dose on the degree of TG
9 reduction. Second, Katayama and Saito do not suggest that 4 g/day of EPA, rather than a lower
10 dose or a higher dose, would be the right dosage to treat severe hypertriglyceridemia.

11 Moreover, as discussed above, it was well known that both EPA and DHA reduced blood
12 triglycerides.⁴⁷⁷¹ Therefore, a person of ordinary skill would not have been motivated to
13 administer 4 g/day of highly-purified *EPA-E* capsules, as opposed to DHA or a combination of
14 EPA and DHA (such as Lovaza).

15 Defendants further argue that a “person of ordinary skill in the art would have also been
16 motivated to treat subjects having baseline TG levels of 500 mg/dl to about 1500 mg/dl with
17 highly-purified EPA-E, as suggested by Yokoyama’s teaching that TG was reduced to a much
18 greater extent in subjects having higher baseline TG levels . . . and because Katayama and Saito
19 treated subjects having baseline triglyceride levels greater than 500 mg/dl.”⁴⁷⁷² This argument is
20 incorrect. It was well known that any TG-reducing therapy will reduce TG to a greater extent in a
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⁴⁷⁷⁰ Defendants’ Joint Invalidity Contentions at 630.

23 ⁴⁷⁷¹ See Section III.

24 ⁴⁷⁷² Defendants’ Joint Invalidity Contentions at 630.

1 patient having higher baseline TG levels. Therefore, a person of ordinary skill would not have
2 been motivated to administer highly-purified *EPA-E* capsules as opposed to any other omega-3
3 fatty acid composition, fibrate, or other TG-lowering therapy, to treat subjects having baseline
4 TG levels above 500mg/dL. Further, a person of ordinary skill would have expected that a
5 greater decrease in TG levels, in the very high TG patient population, would lead to a greater
6 increase in LDL-C levels.

7 Defendants contend that a “person of ordinary skill in the art would have been motivated
8 to administer highly-purified EPA-E—either on its own or with statin therapy—to effect a
9 reduction in TG levels without affecting LDL-C if treatment was without statin therapy, or to
10 effect a reduction in TG and LDL-C, if treatment was with statin therapy.”⁴⁷⁷³ Defendants first
11 support this argument by asserting that a person of ordinary skill in the art would have known
12 that EPA could lower TG levels without increasing LDL-C in very high TG patients. That is
13 incorrect. As discussed above, a person of ordinary skill in the art would not have expected EPA
14 to raise LDL-C levels in very high TG patients. Defendants’ broadly cite to “Yokoyama 2003,
15 Yokoyama 2007, Mori 2000, Mori 2006, Saito 1998, and the other references discussed in
16 V.B.4. and 5” to support this proposition,⁴⁷⁷⁴ however these references do not disclose or suggest
17 to a person of ordinary skill that EPA could lower TG levels without increasing LDL-C in very
18 high TG patients.⁴⁷⁷⁵

19 Defendants next argue again that DHA was known to be responsible for the increase in
20 LDL-C levels in very high TG patients, but as discussed above, *see* Section III, a person of

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⁴⁷⁷³ Defendants’ Joint Invalidation Contentions at 631.

23 ⁴⁷⁷⁴ Defendants’ Joint Invalidation Contentions at 631-32.

24 ⁴⁷⁷⁵ *See* Section IV.

1 ordinary skill would understand that both EPA and DHA function similarly, and that both would
2 have little to no impact on borderline-high TG patients in terms of LDL-C levels and would
3 increase LDL-C levels in patients with very high TGs.

4 Defendants argue that a person of ordinary skill in the art “would have known that an
5 increase in LDL-C was an adverse health effect to be avoided.”⁴⁷⁷⁶ While an increase in LDL-C
6 was seen as a *possible* adverse health effect, a person of ordinary skill in the art understood that
7 the increase in LDL-C seen in the very-high TG patient population with Lovaza, and omega-3
8 fatty acids generally, was related to increased conversion of VLDL to LDL particles.⁴⁷⁷⁷

9 Defendants rely on Kelley and the Lovaza label to argue that “one of ordinary skill in the
10 art would have been motivated, with a reasonable expectation of success, to administer a highly-
11 purified EPA-E dosage form, with little to no DHA, in order to avoid the expected increase in
12 LDL-C with DHA.”⁴⁷⁷⁸ However, a person of ordinary skill in the art expected an increase in
13 LDL-C in the very high TG population, with both EPA and DHA. It was well known at the time
14 of the invention that omega-3 fatty acids, including both EPA and DHA, caused significant
15 decrease in the production of VLDL particles and a significant increase in the conversion of
16 VLDL to IDL and LDL, supporting the theory that omega-3 fatty acids worked in part by
17 inhibiting VLDL production and improving the conversion of VLDL particles to LDL.⁴⁷⁷⁹ A
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⁴⁷⁷⁶ Defendants’ Joint Invalidation Contentions at 633.

20 ⁴⁷⁷⁷ See Bays 2008 I at 402; McKenny 2007 at 720 (finding that “[t]hese results illustrate that with prescription
21 omega-3, fewer VLDL particles are secreted into the systemic circulation, and secreted VLDL particles are rapidly
22 converted to LDL particle, thus explaining why LDL levels may increase in patients with very-high triglyceride
23 levels when given prescription omega-3 therapy”); Chan 2003.

22 ⁴⁷⁷⁸ Defendants’ Joint Invalidation Contentions at 634.

23 ⁴⁷⁷⁹ Chan 202 at 2378-84; *see also* Westphal at 917 (stating “our data confirm the well-known and pronounced
24 decrease in VLDLs after n-3 fatty acid treatment”).

1 person of ordinary skill in the art understood that EPA and DHA had the *same* TG-lowering
2 mechanism and did not differentiate between EPA and DHA when discussing the TG-lowering
3 mechanism of omega-3 fatty acids.⁴⁷⁸⁰ The discussion related to the TG-lowering mechanism of
4 omega-3 fatty acids is discussed above in Section III and incorporated herein by reference.
5 Further, a person of ordinary skill in the art would have understood that EPA therapy would *not*
6 reduce Apo-B⁴⁷⁸¹ (which is a reflection of total atherogenic lipoproteins)⁴⁷⁸² in very high TG
7 patients, and accordingly would not have been motivated to administer the claimed EPA
8 composition to the very high TG patient population.

9 Defendants contend that “the use of approximately 4g of a pharmaceutical composition
10 comprising at least about 90%, by weight of all fatty acids present, ethyl eicosapentaenoate, and
11 not more than 3% docosahexaenoic acid or its esters for a period of 12 weeks to effect a
12 reduction in triglyceride levels, further comprising without increasing LDL-C, would have been
13 obvious over the prior art.” These contentions: 1) do not assert what the prior art discloses to a
14 person of ordinary skill in the art; 2) are irrelevant to an obvious analysis; 3) fail to address
15 whether the specific combination of claim elements were all present in the prior art references
16 that would have been combined by a person of ordinary skill in the art to produce the claimed
17 invention with a reasonable expectation of success; and 4) fail to establish *prima facie*
18 obviousness. Defendants do not offer an obvious analysis, but trivialize the claim element to the
19 point of reading the element out of the claim. Although convenient and expedient, Defendants’
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⁴⁷⁸⁰ Bays 2008 I, at 398; Bay *in* Kwiterovich at 247.

23 ⁴⁷⁸¹ *see* Section V.O.

24 ⁴⁷⁸² *see* Section III.

1 approach does not conform with the Local Patent Rules of this District, the law of claim
2 construction, or the law of obviousness.

3 Defendants do not identify any combination of references. Because Defendants do not
4 identify any combination of references, they necessarily fail to offer any evidence that a person
5 of skill in the art would be motivated to combine those references in order to achieve the
6 invention of the claim as a whole. Defendants' conclusory statement fails to provide a reason
7 that would have prompted a person of ordinary skill to reduce triglycerides by the recited
8 amount.⁴⁷⁸³ Defendants have not met the burden with the naked assertion that the claim is
9 obvious. Similarly, without the disclosure of a combination of references and a
10 motivation/reason to combine or modify the references, Defendants necessarily fail to offer any
11 evidence that a person of ordinary skill in the art would have had a reasonable expectation of
12 success in achieving the claimed invention.

13 Accordingly, a person of ordinary skill would not have been motivated to combine WO
14 '118, WO '900, Grimsgaard, Mori 2000 and/or Maki in with the Omacor PDR/Lovaza PDR, and
15 Katayama, Matsuzawa and/or Takaku. A person of ordinary skill in the art further would not
16 have been motivated to combine WO '118 or WO '900, with the Lovaza PDR, or with Leigh-
17 Firbank and/or Mori 2000.

20 ⁴⁷⁸³ *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) ("Rejections on obviousness grounds cannot be
21 sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational
22 underpinning to support the legal conclusion of obviousness.") (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir.
23 2006)) (internal quotation marks omitted); *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350,
24 1356-57 (Fed. Cir. 2007) ("While the *KSR* Court rejected a rigid application of the teaching, suggestion, or
motivation ('TSM') test in an obviousness inquiry, the Court acknowledged the importance of identifying 'a reason
that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the
claimed new invention does' in an obviousness determination.") (quoting *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S.
398, 418 (2007)).

1 (2) Dependent Claims

2 (a) Defendants Have Not Shown that Claims 2 and 9 of
3 the '650 Patent Would Have Been Obvious

4 Plaintiffs incorporate by reference the discussion related to the Independent Claims in
5 Section V.J.3. Because Defendants have not shown the obviousness of the Independent Claims
6 by clear and convincing evidence, they also have not adequately proven the obviousness of
7 Claims 2 and 9.

8 Defendants contend that it would be obvious that a person receiving the claimed EPA
9 compositions would have a fasting baseline LDL-C from 50 mg/dL to about 150 mg/dL or 50
10 mg/dL to about 300 mg/dL because hypertriglyceridemic patients in the Lovaza label had a mean
11 LDL-C level of 100 mg/dL. These contentions: 1) fail to address whether the specific
12 combination of claim elements were all present in the prior art references that would have been
13 combined by a person of ordinary skill in the art to produce the claimed invention with a
14 reasonable expectation of success; and 2) fail to establish *prima facie* obviousness. Defendants
15 do not offer an obvious analysis, but trivialize the claim element to the point of reading the
16 element out of the claim. Although convenient and expedient, Defendants' approach does not
17 conform with the Local Patent Rules of this District, the law of claim construction, or the law of
18 obviousness.

19 Defendants do not identify any combination of references. Because Defendants do not
20 identify any combination of references, they necessarily fail to offer any evidence that a person
21 of skill in the art would be motivated to combine those references in order to achieve the
22 invention of the claim as a whole. Further, Defendants do not discuss at all whether a person of
23 ordinary skill would have been motivated to combine the elements, other than stating that a
24 patient with LDL-C levels of 50 mg/dL to about 150 mg/dL or 50 mg/dL to about 300 mg/dL

1 would benefit from receiving the claimed fish oil treatment. Defendants also state erroneously
2 that a patient with LDL-C levels of 50 mg/dL to about 150 mg/dL or 50 mg/dL to about 300
3 mg/dL would be considered hypertriglyceridemic. Defendants do not establish that a person of
4 ordinary skill would have been motivated to combine the elements to achieve the claimed
5 invention.⁴⁷⁸⁴

6 Similarly, without the disclosure of a combination of references and a motivation/reason
7 to combine or modify the references, Defendants necessarily fail to offer any evidence that a
8 person of ordinary skill in the art would have had a reasonable expectation of success in
9 achieving the claimed invention. Defendants do not even discuss whether a person of ordinary
10 skill would have expected that the combination to work for its intended purpose for treating the
11 recited patient population.⁴⁷⁸⁵ As such, Defendants fail to demonstrate reasonable expectation of
12 success of the claimed invention.

13 (b) Defendants Have Not Shown that Claims 3 and 10
14 of the '650 Patent Would Have Been Obvious

15 Plaintiffs incorporate by reference the discussion related to the Independent Claims in
16 Section V.J.3. Because Defendants have not shown the obviousness of the Independent Claims
17 by clear and convincing evidence, they also have not adequately proven the obviousness of
18 Claims 3 and 10.

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20 ⁴⁷⁸⁴ *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the *KSR*
21 Court rejected a rigid application of the teaching, suggestion, or motivation (‘TSM’) test in an obviousness inquiry,
22 the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill
in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness
determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

23 ⁴⁷⁸⁵ *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable
24 result’ discussed in *KSR* refers not only to the expectation that prior art elements are capable of being physically
combined, but also that the combination would have worked for its intended purpose.”)

1 Defendants do not identify any combination of references and simply provide a laundry
2 list of references without explaining how each reference relates to the claimed invention.
3 Defendants further contend, without any support, that a person of ordinary skill would have been
4 able to determine the patient population in need of the claimed methods of treatment, would seek
5 to measure the HDL-C, VLDL-C and cholesterol baselines of a patient, and would seek to treat
6 those patients having very high triglycerides regardless of the baseline values of these lipids.⁴⁷⁸⁶
7 These contentions: 1) do not assert what the prior art discloses to a person of ordinary skill in
8 the art; 2) are irrelevant to an obvious analysis; 3) fail to address whether the specific
9 combination of claim elements were all present in the prior art references that would have been
10 combined by a person of ordinary skill in the art to produce the claimed invention with a
11 reasonable expectation of success; and 4) fail to establish *prima facie* obviousness. Defendants
12 do not offer an obvious analysis, but trivialize the claim element to the point of reading the
13 element out of the claim. Although convenient and expedient, Defendants' approach does not
14 conform with the Local Patent Rules of this District, the law of claim construction, or the law of
15 obviousness.

16 Defendants fail to show a specific combination of references that discloses each element
17 of the claimed invention. Defendants merely list references, without reference to a specific page
18 or section, that purportedly disclose disparate elements without explaining how they can be
19 combined.⁴⁷⁸⁷ As such, Defendants discuss the claim elements in isolation, and fail to address
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22 ⁴⁷⁸⁶ *Id.*

23 ⁴⁷⁸⁷ *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int'l Co. v.*
24 *Teleflex Inc.*, 550 U.S. 398, 418 (2007)) (“[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”).

1 the claimed invention as a whole.⁴⁷⁸⁸ Moreover, by simply identifying prior art references
2 without discussing the specific teachings of each reference, Defendants fail to consider each
3 prior art reference as a whole.⁴⁷⁸⁹ Each reference must be evaluated for all that it teaches.
4 Defendants’ unsupported cobbling of selective disclosures represents hindsight
5 reconstruction.⁴⁷⁹⁰

6 Because Defendants do not identify any combination of references, they necessarily fail
7 to offer any evidence that a person of skill in the art would be motivated to combine those
8 references in order to achieve the invention of the claim as a whole. Defendants make a
9 conclusory statement that a person of ordinary skill “would indeed seek” to perform the claimed
10 methods of treatment, without providing a reason that would have prompted a person of ordinary
11 skill to combine the elements.⁴⁷⁹¹ Such a naked assertion does not show why a person of
12 ordinary skill would have been motivated to treat the recited patient population using the claimed
13 methods of treatment.⁴⁷⁹²

15 ⁴⁷⁸⁸ *Sanofi Syntheolabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008) (“The determination of obviousness is made with respect to the subject matter as a whole, not separate pieces of the claim”).

16 ⁴⁷⁸⁹ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011) (“A prior patent must be considered in its entirety, i.e., as a whole, including portions that would lead away from the invention in suit.”) (internal citation and quotation marks omitted).

18 ⁴⁷⁹⁰ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under *KSR*, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention”).

20 ⁴⁷⁹¹ *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (“Rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.”) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)) (internal quotation marks omitted)

22 ⁴⁷⁹² *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the *KSR* Court rejected a rigid application of the teaching, suggestion, or motivation (“TSM”) test in an obviousness inquiry, the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

1 Similarly, without the disclosure of a combination of references and a motivation/reason
2 to combine or modify the references, Defendants necessarily fail to offer any evidence that a
3 person of ordinary skill in the art would have had a reasonable expectation of success in
4 achieving the claimed invention. In fact, other than simply identifying prior art references that
5 purportedly disclose disparate elements, Defendants do not even discuss whether a person of
6 ordinary skill would have expected that the combination to work for its intended purpose for
7 treating the recited patient population.⁴⁷⁹³ As such, Defendants fail to demonstrate reasonable
8 expectation of success of the claimed invention.

9 (c) Defendants Have Not Shown that Claims 4, 7, 11
10 and 14 of the '650 Patent Would Have Been
Obvious

11 Plaintiffs incorporate by reference the discussion related to the Independent Claims in
12 Section V.J.3. Because Defendants have not shown the obviousness of the Independent Claims
13 by clear and convincing evidence, they also have not adequately proven the obviousness of
14 Claims 4, 7, 11 and 14.

15 Defendants' contentions fail to disclose each and every element of the claims of the '560
16 patent. Specifically, Defendants do not contend that the relied upon references disclose the
17 following elements of Claims 4 and 11: *administering the claimed pharmaceutical composition*
18 *to the recited subject to effect the recited reduction in triglycerides without increasing LDL-C by*
19 *more than 5%*. Therefore, Defendants' prior art combinations cannot render the claims *prima*
20 *facie* obvious.

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23 ⁴⁷⁹³ *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable
24 result’ discussed in KSR refers not only to the expectation that prior art elements are capable of being physically
combined, but also that the combination would have worked for its intended purpose.”)

1 Defendants contend, without support, that the recited reduction in TG represents
2 therapeutic efficacy, and that a person of ordinary skill would naturally seek to reduce TG to
3 therapeutic efficacy. Defendants further contend that it would have been obvious to a person of
4 ordinary skill to seek to reduce TG by the recited amount because there is no significance
5 attached to the amount. Defendants conclude, without support, that there was a reasonable
6 expectation of success without identifying any combination of references and without explaining
7 how each reference relates to the claimed invention.⁴⁷⁹⁴ These contentions: 1) do not assert
8 what the prior art discloses to a person of ordinary skill in the art; 2) are irrelevant to an obvious
9 analysis; 3) fail to address whether the specific combination of claim elements were all present in
10 the prior art references that would have been combined by a person of ordinary skill in the art to
11 produce the claimed invention with a reasonable expectation of success; and 4) fail to establish
12 *prima facie* obviousness. Defendants do not offer an obvious analysis, but trivialize the claim
13 element to the point of reading the element out of the claim. Although convenient and expedient,
14 Defendants’ approach does not conform with the Local Patent Rules of this District, the law of
15 claim construction, or the law of obviousness.

16 Defendants further contend, without support, that a person of ordinary skill would
17 “reasonably expect to see the same hypotriglyceridemic effect from a pure EPA formulation
18 containing no DHA,” as a formulation containing both EPA and DHA. Defendants conclude,
19 without support, that it would have been obvious to administer a composition containing EPA,
20 but containing no DHA, with a reasonable expectation of success in reducing triglycerides while
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22 ⁴⁷⁹⁴ Ando, Calabresi, Contacos, Grimsgaard, Harris, Hayashi, Katayama, Kris_Etherton 2002, Kurabayashi, Leigh-
23 Firbank, Lovaza 2007 Label, Lovaza PDR, Omacor 2004 Label, Omacor PDR, Lovegrove, Matsuzawa, McKenney
24 2003, McKenney 2007, Mori 2000, Mori 2006, Nakamura, Nestel, Nozaki, Pownall, Sanders, Shinozaki, Takaku,
von Schacky, Wojenski, Yokoyama 2003, and/or Yokoyama 2007.

1 avoiding an increase in LDL. These contentions: 1) do not assert what the prior art discloses to
2 a person of ordinary skill in the art; 2) fail to address whether the specific combination of claim
3 elements were all present in the prior art references that would have been combined by a person
4 of ordinary skill in the art to produce the claimed invention with a reasonable expectation of
5 success; and 3) fail to establish *prima facie* obviousness. Defendants do not offer an obvious
6 analysis, but trivialize the claim element to the point of reading the element out of the claim.
7 Although convenient and expedient, Defendants’ approach does not conform with the Local
8 Patent Rules of this District, the law of claim construction, or the law of obviousness.

9 Defendants do not identify any combination of references and simply provide a laundry
10 list of references that purportedly disclose disparate elements without explaining how they can
11 be combined.⁴⁷⁹⁵ As such, Defendants discuss the claim elements in isolation, and fail to address
12 the claimed invention as a whole.⁴⁷⁹⁶ Defendants selectively cite to an unspecified isolated
13 disclosure within a reference without considering other disclosures or even the reference as a
14 whole. Each reference, however, must be evaluated for all that it teaches.⁴⁷⁹⁷ Defendants’
15 unsupported cobbling of selective disclosures represents hindsight reconstruction.⁴⁷⁹⁸

16 Because Defendants do not identify any combination of references, they necessarily fail
17 to offer any evidence that a person of skill in the art would be motivated to combine those
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19 ⁴⁷⁹⁵ *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int’l Co. v.*
20 *Teleflex Inc.*, 550 U.S. 398, 418 (2007)) (“[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”).

21 ⁴⁷⁹⁶ *Sanofi Syntheolabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008) (“The determination of obviousness is
made with respect to the subject matter as a whole, not separate pieces of the claim”).

22 ⁴⁷⁹⁷ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

23 ⁴⁷⁹⁸ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under
24 *KSR*, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention
without any explanation as to how or why the references would be combined to produce the claimed invention”).

1 references in order to achieve the invention of the claim as a whole. Defendants make a
2 conclusory statement that “it would have been obvious to the ordinarily skilled artisan to seek to
3 reduce triglycerides by 5% to 25%,” without providing a reason that would have prompted a
4 person of ordinary skill to reduce triglycerides by the recited amount.⁴⁷⁹⁹ Defendants’ burden to
5 establish *prima facie* obviousness is not discharged because there is allegedly “no significance”
6 attached to the recited TG reduction amount.⁴⁸⁰⁰ Defendants have not met the burden with the
7 naked assertion that it would have been obvious to seek the claim element.

8 Similarly, without the disclosure of a combination of references and a motivation/reason
9 to combine or modify the references, Defendants necessarily fail to offer any evidence that a
10 person of ordinary skill in the art would have had a reasonable expectation of success in
11 achieving the claimed invention. Defendants make a conclusory statement that there was a
12 reasonable expectation of success, without providing a support other than merely identifying
13 prior art references that purportedly disclose disparate elements.⁴⁸⁰¹ The mere fact that elements
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16 ⁴⁷⁹⁹ *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (“Rejections on obviousness grounds cannot be
17 sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational
18 underpinning to support the legal conclusion of obviousness.”) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir.
19 2006)) (internal quotation marks omitted); *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350,
20 1356-57 (Fed. Cir. 2007) (“While the *KSR* Court rejected a rigid application of the teaching, suggestion, or
21 motivation (‘TSM’) test in an obviousness inquiry, the Court acknowledged the importance of identifying ‘a reason
22 that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the
23 claimed new invention does’ in an obviousness determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S.
24 398, 418 (2007)).

⁴⁸⁰⁰ Plaintiffs do not have to show that a claimed range is critical unless a *prima facie* case of obviousness has been
established. See *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003) (“An applicant may overcome a *prima facie*
case of obviousness by establishing that the claimed range is critical”) (internal quotation marks omitted).

⁴⁸⁰¹ *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (“Rejections on obviousness grounds cannot be
sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational
underpinning to support the legal conclusion of obviousness.”) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir.
2006)) (internal quotation marks omitted).

1 are capable of being physically combined does not establish reasonable expectation of
2 success.⁴⁸⁰²

3 (i) A Person of Ordinary Skill Would Not Have
4 Had a Reasonable Expectation of Success in
5 Replacing the Mixed Fish Oil Active
6 Ingredient in Lovaza with Pure EPA

7 Defendants provide no evidence that a person or ordinary skill would have had a
8 reasonable expectation of successfully obtaining the claimed invention—a method of reducing
9 triglycerides in a subject having very-high triglyceride levels by administering EPA of the
10 recited purity to effect a reduction in triglycerides *with the claimed LDL-C effect*—by combining
11 the references cited by defendants. For a particular combination of references, there must be a
12 reasonable expectation that the combination will produce the claimed invention. In this case, the
13 art taught that DHA and EPA have similar effects on LDL-C levels in patients with very-high
14 TG levels.⁴⁸⁰³ A person of ordinary skill would have expected EPA, like Lovaza/Omacor, to
15 raise LDL-C levels when administered to patients in the very-high TG patient population. As
16 discussed in Section III and above, it was well known that TG-lowering agents, specifically
17 fibrates and Lovaza/Omacor, and little or no effect on LDL-C levels for normal to high TG
18 patients, but caused significant increases in LDL-C levels for patients with very-high
19 triglycerides. The art cited by Defendants provides no basis for a person of ordinary skill to

20 ⁴⁸⁰² *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable
21 result’ discussed in KSR refers not only to the expectation that prior art elements are capable of being physically
22 combined, but also that the combination would have worked for its intended purpose.”).

23 ⁴⁸⁰³ As discussed above, see *supra* section III, a person of ordinary skill would have understood EPA and DHA to
24 have the same TG lowering mechanism and would have further understood that the increase in LDL-C
accompanying the TG-lowering effects of Lovaza was a product of that same mechanism. Accordingly, a person of
ordinary skill would have expected EPA to increase LDL-C levels in patients with very-high TG levels in similar
fashion to Lovaza or DHA alone.

1 expect anything to the contrary. A person of ordinary skill would have understood that omega 3-
2 fatty acids, including DHA and EPA, and fibrates cause an increase in LDL-C among very high
3 TG patients, as reflected in the prior art:

	LDL-C Effect	
	Borderline-High or High TG Patients	Very-High TG Patients
Fibrate ⁴⁸⁰⁴	-20%	+45%
Lovaza/Omacor ⁴⁸⁰⁵	-6%	+45%

7 Accordingly, a person of ordinary skill would *not* have a reasonable expectation of
8 success in achieving a reduction in TG levels *with the claimed LDL-C effect* in patients with
9 very-high TG levels.⁴⁸⁰⁶

10 Defendants' position that a person of ordinary skill would have had a reasonable
11 expectation of success in administering purified EPA to patients with very high triglyceride
12 levels to achieve TG lowering *with the claimed LDL-C effect* is belied by the fact that
13 Defendants' provide no evidence that anyone thought to administer Epadel.⁴⁸⁰⁷ Epadel was
14 available for many years prior to the invention of the '650 patent, to patients with very-high TGs
15 as a treatment. A person of ordinary skill did not expect Epadel, which consisted of mostly EPA,
16 to have superior qualities over a drug such as Lovaza/Omacor, which comprised a mixture of
17 EPA and DHA, in patients with very-high triglycerides. Indeed, none of clinical studies cited by
18 Defendants are directed to the use of purified EPA in the very-high TG population.

21 ⁴⁸⁰⁴ Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

22 ⁴⁸⁰⁵ Chan 2002 I at 2381 (Table 3).

23 ⁴⁸⁰⁶ Indeed, as discussed above, a person of ordinary skill would have understood that DHA had a better overall
effect on lipid parameters, teaching away from this combination.

24 ⁴⁸⁰⁷ Although Epadel was available at different levels of purity, the fact that Epadel—at any level of purity—was not
examined in any study directed to the very-high TG patient population supports Amarin's position.

1 Research into the pharmaceutical uses of EPA started as early as the 1970s. In 1990,
2 Mochida Pharmaceutical, began to market Epadel, a high purity EPA drug. There have been
3 countless studies conducted which administer Epadel and report the effects observed. Although
4 a few studies administer Epadel to a patient population which included a few patients with TG
5 levels > 500 mg/dL, Defendants fail to identify a single reference directed to the administration
6 of Epadel to patients with very-high TG levels. The fact is, a person of ordinary skill did not
7 expect Epadel, which consisted of mostly EPA, to have superior qualities over a drug such as
8 Lovaza/Omacor, which comprised a mixture of EPA and DHA, in patients with very-high
9 triglycerides.

10 Defendants argue that because Grimsgaard administered purified ethyl EPA to patients
11 with borderline-high/high TG, it would have been obvious to try administering purified ethyl
12 EPA to patients with very-high TG levels with a reasonable expectation of success. Defendants
13 base this unsupported conclusion on Grimsgaard, Lovaza/Omacor, the known administration of
14 2.7 grams of purified EPA to patients with greater than 500 mg/dL TG by Matsuzawa.
15 Defendants' contentions are no more than a demonstration that certain claim elements was
16 known in the prior art and demonstrates impermissible hindsight reconstruction.⁴⁸⁰⁸ As is
17 reflected in Table 4 of Grimsgaard, the study authors found no difference between the DHA,
18 EPA, and control in terms of LDL-C levels. Defendants use hindsight to argue that, despite EPA
19 and DHA showing the same effect on LDL-C, one would have chosen EPA and expected that
20 administration to very-high TG would have resulted in little or no impact on LDL-C. Notably,
21 none of these references would provide a person of ordinary skill in the art with a reasonable

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23 ⁴⁸⁰⁸ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that even under
24 KSR, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention
without any explanation as to how or why the references would be combined to produce the claimed invention.”).

1 expectation of successfully obtaining the claimed invention even if there were reasons to
 2 combine disparate, independent elements found in the prior art, which there were not.

3 **TABLE 4**
 Serum lipids and apolipoproteins at baseline and change after 7 wk of supplementation with docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), or corn oil

	DHA (n = 72)		EPA (n = 75)		Corn oil (n = 77)		F test: P ¹	Contrasts between groups: P		
	Baseline	Change	Baseline	Change	Baseline	Change		DHA vs EPA	DHA vs corn oil	EPA vs corn oil
Triacylglycerols (mmol/L)	1.24 ± 0.58 ²	-0.22 ± 0.31 ²	1.23 ± 0.57	-0.15 ± 0.40 ⁴	1.22 ± 0.55	0.11 ± 0.34 ⁴	0.0001	0.14	0.0001	0.0001
Total cholesterol (mmol/L)	6.00 ± 0.95	0.03 ± 0.49	5.98 ± 0.94	-0.15 ± 0.55 ²	6.02 ± 1.08	0.10 ± 0.55	0.01	0.04	0.4	0.004
LDL cholesterol (mmol/L)	4.06 ± 0.86	0.07 ± 0.46	4.06 ± 0.83	-0.08 ± 0.48	4.04 ± 0.98	0.06 ± 0.48	0.10	—	—	—
HDL cholesterol (mmol/L)	1.36 ± 0.30	0.06 ± 0.13 ³	1.33 ± 0.31	0.01 ± 0.12	1.41 ± 0.28	-0.01 ± 0.11	0.001	0.009	0.0005	0.4
Apolipoprotein A-I (g/L)	1.38 ± 0.21	0.02 ± 0.13	1.38 ± 0.20	-0.04 ± 0.10 ³	1.46 ± 0.23	0.00 ± 0.12	0.003	0.0008	0.3	0.02
Apolipoprotein B (g/L)	1.00 ± 0.21	-0.01 ± 0.11	1.01 ± 0.23	-0.03 ± 0.11 ³	1.02 ± 0.28	0.02 ± 0.11	0.05	—	—	—
HDL:apolipoprotein A-I	0.97 ± 0.14	0.04 ± 0.07 ³	0.96 ± 0.13	0.04 ± 0.08 ³	0.97 ± 0.12	-0.01 ± 0.06	0.0001	0.8	0.0003	0.0001
Total:HDL cholesterol	4.62 ± 1.19	-0.19 ± 0.52 ⁴	4.70 ± 1.24	-0.13 ± 0.47 ³	4.43 ± 1.19	0.11 ± 0.62	0.002	0.4	0.0006	0.007

¹ ANOVA for between-group comparisons of change.

² $\bar{x} \pm$ SD.

³⁻⁵ One-sample *t* test of difference between baseline and 7 wk: ³ $P < 0.001$, ⁴ $P < 0.01$, ⁵ $P < 0.05$.

7 In addition, Grimsgaard was conducted in patients with normal TG levels, so a person of
 8 ordinary skill would have expected no difference between EPA and DHA in terms of LDL-C
 9 level change and would have expected no significant increase (or decrease) in LDL-C, as
 10 reported by that publication. A person of ordinary skill would further have understood that the
 11 data reported by Grimsgaard to be consistent with the understanding that while LDL-C levels are
 12 not significantly impacted in normal to high TG patient populations, LDL-C levels would
 13 increase significantly in very-high TG patients.

14 Matsuzawa similarly provides no basis for a reasonable expectation of success in
 15 achieving the claimed invention. The subjects of Matsuzawa had a wide range of baseline TG
 16 levels and the study was not directed to the very-high TG patient population. Accordingly, just
 17 as with Grimsgaard, Matsuzawa would not provide a reasonable expectation of success as a
 18 person of ordinary skill would understand patients with very-high TG levels to be different in
 19 terms of LDL-C effect than patients with lower TG levels.

20 To the extent that Defendants' arguments are based on results that are not statistically
 21 significant and not reported by Grimsgaard as significant, a person of ordinary skill would not
 22 draw conclusions from these statistically insignificant differences. Indeed, the standard
 23 deviation for the changes reported is greater than the value of the change itself.
 24

1 Defendants argue that it would have been obvious to try administering purified ethyl EPA
2 to patients with very-high TG levels with a reasonable expectation of success. However, the
3 Federal Circuit has often rejected the notion that showing something may have been “obvious-to-
4 try” proves that the claimed invention was obvious where the prior art did not suggest what to
5 try.⁴⁸⁰⁹ Rather than there being a limited number of options, the state of the art provided a
6 plethora of compositions and administration protocols associated with multiple kinds of TG-
7 lowering therapies.⁴⁸¹⁰ There were not a finite number of options for a person of ordinary skill
8 seeking to reduce TG levels without increasing LDL-C among the very-high TG patient
9 population.

10 Defendants argue that a person of ordinary skill at the time of the invention, based on
11 studies in normal, borderline-high and high TG patients, knew that administration of DHA alone
12 resulted in undesirable increased LDL-C levels while administration of EPA alone had little to
13 no impact on LDL-C levels. However, that statement does not conform with what was known
14 regarding the effect of Epadel and Lovaza/Omacor in normal, borderline-high and high TG
15 patients. Instead as Defendants’ own prior art demonstrates, Epadel and Lovaza/Omacor were
16 both known to have little or no effect on LDL-C in patients with borderline-high/high TG levels.

17 With the lack of any reasonable expectation of success, Defendants argue that their
18 proposed combination amounts to a simple substitution of one known element for another, and
19 that that these changes yield predictable results. Such an argument, however, represents pure
20 and impermissible hindsight bias and further does not consider that reasons for which a person of
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23 ⁴⁸⁰⁹ See *Sanofi*, 748 F.3d at 1360–61.

24 ⁴⁸¹⁰ See *supra* Section III.

1 ordinary skill would not be motivated to combine these references and affirmatives ways in
2 which the art taught away from these combinations.

3 (ii) A Person of Ordinary Skill Would Not Have
4 Had a Reasonable Expectation of Success in
5 Administering the Purified EPA in the
6 Dosing Regimen Recited in the Claims

7 Defendants contend that a “person of ordinary skill in the art would have been motivated
8 to administer 4 grams of highly-purified EPA to patients with triglycerides greater than or equal
9 to 500 mg/dL, with a reasonable expectation of success in lowering triglycerides.” Defendants
10 also argue that “[a]t least Katayama, Saito 1998, Yokoyama 2007, and Mori 2000 . . . would
11 have given a person of ordinary skill in the art a reasonable expectation of successfully
12 administering 4 g/day of highly-purified EPA-E for at least 12 weeks to lower triglycerides in
13 these subjects relative to baseline or placebo.” However, Defendants provide no evidence that a
14 person of ordinary skill would have had a reasonable expectation of success in a method of
15 reducing triglycerides in a subject having very-high triglyceride levels by administering purified
16 EPA to effect a reduction in triglycerides *with the claimed LDL-C effect*. Therefore, Defendants
17 fail to provide a reasonable expectation of success for the claimed invention.

18 Defendants further argue, that “because it was known that DHA and EPA were
19 comparably efficacious in reducing triglycerides . . . one of ordinary skill in the art would have
20 reasonably expected to see the same hypotriglyceridemic effect from a 4 g/day dose of purified
21 EPA-E as seen with 4 g/day of a combination of both EPA and DHA. Thus, it would have been
22 obvious to one of ordinary skill in the art to administer a highly-purified EPA-E composition
23 with a reasonable expectation of success that such administration would result in reducing
24 triglycerides while avoiding an increase in LDL.” Defendants argument is without any basis. To
the contrary, because a person of ordinary skill in the art would have understood DHA and EPA

1 to lower TGs via the same mechanism, the person of ordinary skill in the art would have
2 expected DHA and EPA to have the same impact on LDL-C levels. Defendants provide no
3 explanation and cite to no article to support their argument that the similar effects on TG levels is
4 a basis to differentiate the efficacy of DHA and EPA with respect to LDL-C impact. Based on
5 the hypotriglyceridemic effect alone, a person of ordinary skill would have reasonably expected
6 both EPA and DHA, whether administered alone or in combination, would cause an increase in
7 LDL-C when administered to the very high TG patient population.

8 The prior art taught that DHA and EPA have similar effects on LDL-C levels in patients
9 with very-high TG. A person of ordinary skill would have thus expected EPA, like
10 Lovaza/Omacor, to raise LDL-C levels when administered to the very-high TG patient
11 population. It was well known that TG-lowering agents, specifically fibrates and
12 Lovaza/Omacor, and little or no effect on LDL-C levels for normal to high TG patients, but
13 caused significant increases in LDL-C levels for patients with very-high triglycerides. The art
14 cited by Defendants provides no basis for a person of ordinary skill to expect anything to the
15 contrary. A person of ordinary skill would have understood that omega 3-fatty acids, including
16 DHA and EPA, and fibrates cause an increase in LDL-C among very high TG patients, as
17 reflected in the prior art:

	LDL-C Effect	
	Borderline-High or High TG Patients	Very-High TG Patients
Fibrate ⁴⁸¹¹	-20%	+45%
Lovaza/Omacor ⁴⁸¹²	-6%	+45%

23 ⁴⁸¹¹ Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

24 ⁴⁸¹² Chan 2002 I at 2381 (Table 3).

1 Accordingly, a person of ordinary skill would not have a reasonable expectation of
2 success in achieving a reduction in TG levels *with the claimed LDL-C effect* in patients with
3 very-high TG levels using EPA.

4 Defendants' position that a person of ordinary skill would have had a reasonable
5 expectation of success in administering purified EPA to the requisite patient population to
6 achieve a lowering in TG levels *with the claimed LDL-C effect* is belied by the fact that
7 Defendants' provide no evidence that anyone thought to administer Epadel, which was available
8 for many years prior to the invention of the '650 patent, to patients with very-high TGs as a
9 treatment. Indeed, none of clinical studies cited by Defendants are directed to the use of purified
10 EPA in the very-high TG population.

11 Research into the pharmaceutical uses of EPA started as early as the 1970s. In 1990,
12 Mochida Pharmaceutical, began to market Epadel, a high purity EPA drug. There have been
13 countless studies conducted which administer Epadel and report the effects observed. Although
14 a few studies administer Epadel to a patient population which included a few patients with TG
15 levels > 500 mg/dL, Defendants fail to identify a single reference directed to the administration
16 of Epadel to patients with very-high TG levels. The fact is, a person of ordinary skill did not
17 expect Epadel, which consisted of mostly EPA, to have superior qualities over a drug such as
18 Lovaza/Omacor, which comprised a mixture of EPA and DHA, in patients with very-high
19 triglycerides.

20 Accordingly, a person of ordinary skill would not have a reasonable expectation of
21 success in achieving the claimed invention.
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1 (d) Defendants Have Not Shown that Claims 5 and 12
2 of the '650 Patent Would Have Been Prima Facie
3 Obvious

4 Plaintiffs incorporate by reference the discussion related to the Independent Claims in
5 Section V.J.3. Because Defendants have not shown the obviousness of the Independent Claims
6 by clear and convincing evidence, they also have not adequately proven the obviousness of
7 Claims 5 and 12.

8 Defendants offer no reference in support of their contention that these claims are obvious.
9 Defendants contend, without providing any support, that it would be obvious to one of skill in
10 the art to administer a composition containing EPA, but containing no DHA, with a reasonable
11 expectation of success in reducing Apo-B levels and thus also reduce LDL-C levels. These
12 contentions: 1) do not assert what the prior art discloses to a person of ordinary skill in the art;
13 2) are irrelevant to an obvious analysis; 3) fail to address whether the specific combination of
14 claim elements were all present in the prior art references that would have been combined by a
15 person of ordinary skill in the art to produce the claimed invention with a reasonable expectation
16 of success; and 4) fail to establish *prima facie* obviousness. Defendants do not offer an obvious
17 analysis, but trivialize the claim element to the point of reading the element out of the claim.
18 Although convenient and expedient, Defendants' approach does not conform with the Local
19 Patent Rules of this District, the law of claim construction, or the law of obviousness.

20 Defendants fail to show a specific combination of references that discloses each element
21 of the claimed invention. None of the cited references discloses administration of the claimed
22 EPA to very high TG patients. Defendants further fail to explain how the cited references can be
23
24

1 combined to teach the administration of the claimed EPA to very high TG patients.⁴⁸¹³
2 Defendants selectively cite to an unspecified, isolated disclosure within a reference without
3 considering other disclosures or even the reference as a whole. Each reference, however, must
4 be evaluated for all that it teaches.⁴⁸¹⁴ Defendants' unsupported cobbling of selective disclosures
5 represents hindsight reconstruction.⁴⁸¹⁵

6 Defendants fail to show a motivation or reason to combine or modify the references
7 recited above. Defendants make a conclusory statement that the claimed methods of treatment
8 would have been obvious but such a naked assertion does not show why a person of ordinary
9 skill would have been motivated to combine the references to achieve the claimed invention.⁴⁸¹⁶

10 Defendants fail to show a reasonable expectation that a person of ordinary skill would
11 have successfully achieved the claimed invention. In fact, Defendants do not even discuss
12 whether a person of ordinary skill would have expected that the combination to work for its
13 intended purpose.⁴⁸¹⁷ As such, Defendants fail to demonstrate reasonable expectation of success
14 of the claimed invention.

16 ⁴⁸¹³ *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)) (“[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”).

18 ⁴⁸¹⁴ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

19 ⁴⁸¹⁵ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under *KSR*, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention”).

20 ⁴⁸¹⁶ *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the *KSR* Court rejected a rigid application of the teaching, suggestion, or motivation (‘TSM’) test in an obviousness inquiry, the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness determination.”) (quoting *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

21 ⁴⁸¹⁷ *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable result’ discussed in *KSR* refers not only to the expectation that prior art elements are capable of being physically combined, but also that the combination would have worked for its intended purpose.”)

1 Defendants rely on only one reference in their invalidity contentions with respect to this
2 claim, Theobald, and *not* for the proposition that the asserted claim is obvious. Instead,
3 Defendants cite Theobald for the proposition that “it was known that Apo-B is a component of
4 LDL-C.” Defendants cite to no passage or page of Theobald in connection with that argument
5 and no support for their argument that Theobald makes such a disclosure. Defendants appear to
6 suggest a correlation between Apo-B and LDL-C but ignore that Apo-B is present on all
7 atherogenic lipoproteins.⁴⁸¹⁸

8 Defendants then make the unsupported assertion that “one of ordinary skill in the art
9 would reasonably expect that a pure EPA composition would reduce Apo-B, as it is known to
10 reduce VLDL syntheses.” They are incorrect. Neither Defendants’ characterization of Theobald
11 nor the disclosures of that reference teach that EPA compositions would reduce Apo-B or render
12 this claim obvious. Defendants’ assertion that EPA was known to reduce VLDL synthesis
13 ignores that, as discussed above, *see* Section III, DHA was also understood to reduce VLDL
14 synthesis. Nor do defendants explain the relevance of VLDL synthesis to their arguments with
15 respect to these claims or Apo-B levels.

16 As discussed above, *see* Section IV, Theobald discloses the administration of a
17 triacylglycerol composition derived from *Cryptocodinium cohnii* to healthy subjects. While
18 Defendants make an unexplained citation to Theobald regarding the proposition that Apo-B is a
19 component of LDL-C, they fail to discuss the reference’s disclosures regarding the impact of
20 administration of the triacylglycerol composition on Apo-B levels. In doing so, they fail to
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22

23 ⁴⁸¹⁸ June 26, 2012 Bays Declaration; *see also* Section III.
24

consider the reference for all that it teaches. Theobald discloses an *increase* in Apo-B following administration of the triacylglycerol composition of that reference.⁴⁸¹⁹

TABLE 3
Serum lipoproteins before treatment and after 3 mo of docosahexaenoic acid (DHA) and placebo treatment in all subjects

	DHA		Placebo		Treatment effect ¹
	Before treatment	After treatment	Before treatment	After treatment	
Total cholesterol (mmol/L)	5.15 ± 0.145 ²	5.44 ± 0.174	5.08 ± 0.168	5.22 ± 0.155	0.22 (0.01, 0.42) ³
LDL cholesterol (mmol/L)	3.16 ± 0.129	3.48 ± 0.152	3.16 ± 0.146	3.25 ± 0.131	0.23 (0.08, 0.38) ⁴
HDL cholesterol (mmol/L) ⁵	1.47 ± 0.052	1.55 ± 0.064	1.46 ± 0.062	1.48 ± 0.056	0.07 (0.005, 0.14)
Triacylglycerol (mmol/L) ⁶	1.03 ± 0.094	1.01 ± 0.089	1.06 ± 0.106	1.19 ± 0.103	-0.18 (-0.37, 0.05)
Apolipoprotein B (g/L)	0.84 ± 0.027	0.87 ± 0.026	0.83 ± 0.028	0.84 ± 0.028	0.03 (0.002, 0.055)⁷
LDL cholesterol:apo B (mmol/g)	3.75 ± 0.376	3.96 ± 0.462	3.74 ± 0.521	3.84 ± 0.409	0.12 (0.004, 0.24) ³
Weight (kg) ⁸	70.1 ± 2.04	70.6 ± 2.06	70.5 ± 2.01	70.6 ± 2.01	0 (-0.85, 0.24)

¹ Mean difference between active treatment and placebo; 95% CI in parentheses.

² $\bar{x} \pm \text{SEM}$ (all such values); $n = 38$.

^{3,4,7} Paired t test: ³ $P = 0.04$, ⁴ $P = 0.004$, ⁷ $P = 0.03$.

⁵ HDL increased in subjects receiving DHA first. Significant treatment \times order effect, $P = 0.005$.

⁶ $n = 37$; data were log transformed before analysis by paired t test.

⁸ Weight increased over the entire study period. Significant order \times time effect, $P = 0.001$.

As discussed above, *see* Section III, a person of skill in the art would not have distinguished between the lipid effects of EPA and DHA therapy. To the extent, then that a person of ordinary skill would have considered Theobald, they would not conclude from the reference that EPA therapy decreases Apo-B levels in very high TG patients.

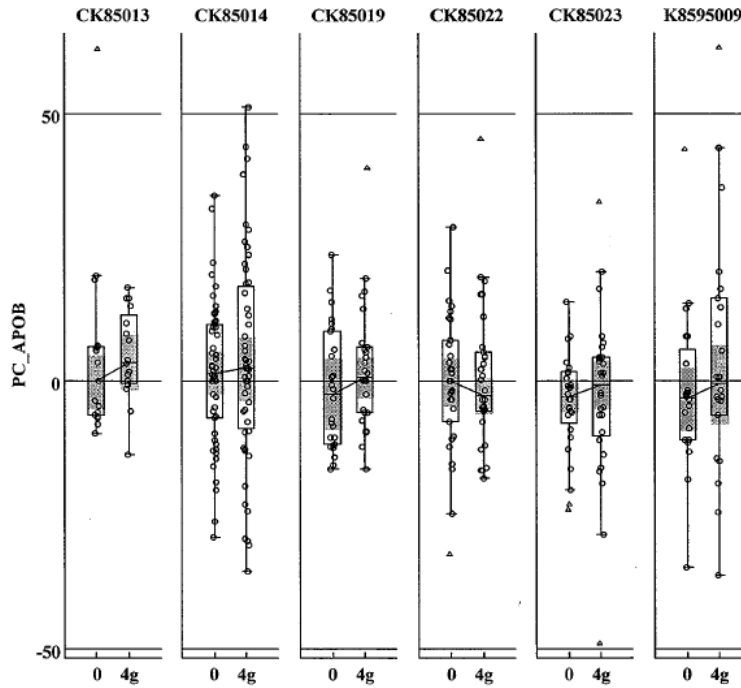
A person of skill in the art would *not* have understood that EPA therapy in very high TG patients would yield a reduction in Apo-B levels. A person of ordinary skill would have looked to the Lovaza clinical trials—the only clinical trial to study the effects of omega-3 fatty acids on Apo-B levels in patients with very high TG levels.⁴⁸²⁰ The Lovaza clinical trial, which was a large study conducted on patients with very high TG levels, shows no difference between a placebo-control group and the treatment group with respect to Apo-B levels.⁴⁸²¹

⁴⁸¹⁹ Theobald at 561, table 3.

⁴⁸²⁰ May 8, 2012 Bays Declaration.

⁴⁸²¹ Lovaza Approval Package at Table 14.

14. Box plot of individual Category I studies -% change of APOB

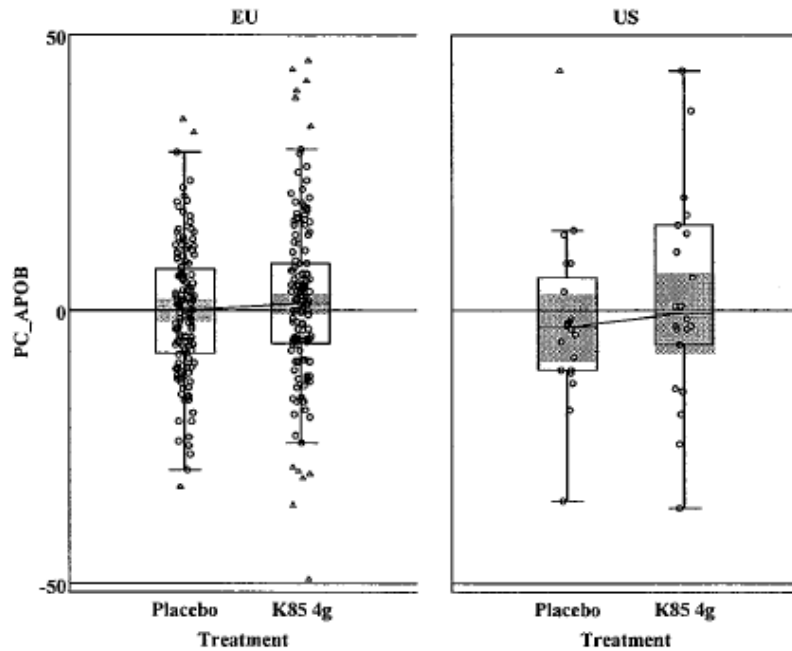


In each of these studies, including K8595009, where subjects had a median baseline TG level of 818 mg/dL,⁴⁸²² there was no change in Apo-B between the control and treatment groups. Likewise, pooling the data from the different studies of Lovaza in the EU and US also reflected that treatment with Lovaza did not impact Apo-B compared to placebo.⁴⁸²³

⁴⁸²² The parameters for each study reports can be located at page 4 of the Lovaza Approval Package.

⁴⁸²³ Lovaza Approval Package at Table 7.

7. Box plot of pooled Category I studies -% change of APOB



Indeed, none of the data reported in the Lovaza clinical trials reflects a decrease in Apo-B. In addition to the Lovaza studies, a person of ordinary skill would have understood that the literature reported, in a variety of clinical studies, that omega-3s do not impact Apo-B levels.⁴⁸²⁴ While Theobald does not even support Defendants' obviousness arguments, their selective citation of that reference represents impermissible hindsight bias. The examiner had before him a large number of prior art references reporting Apo-B effects and, even as defendants concede, agreed that the Apo-B effects reported by the claimed inventions were unexpected in light of

⁴⁸²⁴ See Grimsgaard, Okumura, Hayashi, Hayasaka 1995, and Aoki 1993.

1 those references, also reflecting a lack of motivation and no reasonable expectation of
2 success.⁴⁸²⁵

3 Further, a person of skill in the art would have understood Apo-B to be a surrogate for the
4 number of atherogenic lipoproteins (VLDL, IDL, LDL) present in the body.⁴⁸²⁶ The person of
5 skill in the art would also have recognized that, as TG levels in patients with very high TG levels
6 rose, an increasing amount of TGs in those patients were contained within chylomicrons. As
7 discussed above, *see* Section III, the processing of chylomicrons would not yield atherogenic
8 lipoproteins, but instead smaller, denser particles referred to as remnant.⁴⁸²⁷ Accordingly,
9 because very high TG patients had increasing levels of TGs stored in chylomicrons and because
10 chylomicron processing would not have been understood to yield changes in Apo-B, a person of
11 skill in the art would have believed that TG-lowering therapies directed to very high TG patients
12 would not significantly impact Apo-B.

13 Accordingly, a person of ordinary skill in the art would not have been motivated to
14 replace EPA with the composition of Lovaza, nor would the person of ordinary skill in the art
15 have been motivated to administer the EPA composition of the claimed invention to very high
16 TG patients. For the same reasons, a person of ordinary skill in the art would not have a
17 reasonable expectation of success in achieving the claimed invention.

18 (e) Defendants Have Not Shown that Claims 6 and 13
19 of the '650 Patent Would Have Been Obvious

20 Plaintiffs incorporate by reference the discussion related to the Independent Claims in
21 Section V.J.3. Because Defendants have not shown the obviousness of the Independent Claims

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⁴⁸²⁵ Defendants' Contentions at 236.

23 ⁴⁸²⁶ ATP-III at 3170; Bays 2008 I at 395.

24 ⁴⁸²⁷ Kwiterovich in Kwiterovich at 4.

1 by clear and convincing evidence, they also have not adequately proven the obviousness of
2 Claims 6 and 13.

3 Defendants contend that it would have been obvious to use the claimed composition to
4 reduce VLDL-C levels, and that the recited VLDL-C reduction represents therapeutic efficacy.
5 These contentions: 1) do not assert what the prior art discloses to a person of ordinary skill in
6 the art; 2) are irrelevant to an obvious analysis; 3) fail to address whether the specific
7 combination of claim elements were all present in the prior art references that would have been
8 combined by a person of ordinary skill in the art to produce the claimed invention with a
9 reasonable expectation of success; and 4) fail to establish *prima facie* obviousness. Defendants
10 do not offer an obvious analysis, but trivialize the claim element to the point of reading the
11 element out of the claim. Although convenient and expedient, Defendants' approach does not
12 conform with the Local Patent Rules of this District, the law of claim construction, or the law of
13 obviousness.

14 Defendants do not identify any combination of references. Because Defendants do not
15 identify any combination of references, they necessarily fail to offer any evidence that a person
16 of skill in the art would be motivated to combine those references in order to achieve the
17 invention of the claim as a whole. In fact, Defendants do not discuss at all whether a person of
18 ordinary skill would have been motivated to combine the elements.⁴⁸²⁸ As such, Defendants fail
19 to demonstrate that there was no motivation to combine the references to achieve the claimed
20 invention.

21
22 ⁴⁸²⁸ *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the *KSR*
23 Court rejected a rigid application of the teaching, suggestion, or motivation (‘TSM’) test in an obviousness inquiry,
24 the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill
in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness
determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

1 Similarly, without the disclosure of a combination of references and a motivation/reason
2 to combine or modify the references, Defendants necessarily fail to offer any evidence that a
3 person of ordinary skill in the art would have had a reasonable expectation of success in
4 achieving the claimed invention. Defendants make conclusory statements without providing any
5 support. What is more, Defendants do not even discuss the reasonable expectation of reducing
6 VLDDL-C levels. As such, Defendants fail to demonstrate reasonable expectation of success of
7 reducing VLDDL-C levels using the claimed methods.

8 **4. The '650 Patent is Not Invalid Under § 112**

9 a) Defendants Have Not Demonstrated that the Claims of the '650
10 patent Are Invalid for Indefiniteness

11 35 U.S.C. ¶ 112(b) requires that a patentee “particularly point[] out and distinctly claim[]
12 the subject matter which the applicant regards as his invention.”⁴⁸²⁹ Patent claims are valid in
13 light of an indefiniteness challenge if they “inform, with reasonable certainty, those skilled in the
14 art about the scope of the invention” in light of the specification and the prosecution history.⁴⁸³⁰
15 The Supreme Court has recognized that “absolute precision is unattainable” in claim language
16 and “the certainty which the law requires in patents is not greater than is reasonable.”⁴⁸³¹

17 Defendants allege that a number of terms containing the phrases “about” and
18 “substantially” are indefinite. Defendants do not provide any reason why these terms are
19 indefinite other than that they contain the phrases “about” and “substantially.” But, of course,

20 ⁴⁸²⁹ Defendants were required to disclose the basis for their assertion of indefiniteness with respect to each term, and
21 they have not met that requirement. They simply make conclusory assertions regarding indefiniteness despite
22 bearing the burden of proof. Moreover, Defendants’ failure prevents Plaintiffs from responding to their assertions
other than by making conclusory assertions in return. Therefore, Defendants should be precluded from
supplementing their naked assertions with new basis in the course of the litigation.

23 ⁴⁸³⁰ *Nautilus, Inc. v. Biosig Instruments, Inc.*, 134 S. Ct. 2120, 2124 (2014).

24 ⁴⁸³¹ *Id.* at 2129.

1 these terms are routinely used in patent claims, and are not *per se* indefinite.⁴⁸³² In particular,
2 courts have held repeatedly that claims that contain the words “about” and “substantially” are not
3 indefinite.⁴⁸³³ Here, a person of ordinary skill would understand with reasonable certainty what
4 is claimed when the claims are read in light of the specification and prosecution history.⁴⁸³⁴
5 Therefore, the terms that contain the words “about” and “substantially” are not invalid for being
6 indefinite.

7 Defendants further allege that the terms “4g per day of a pharmaceutical composition
8 comprising at least about 90%, by weight of all fatty acids present, ethyl eicosapentaenoate” and
9 “3% docosahexaenoic acid by weight of total fatty acids present ” are indefinite. They contend
10 that, because there is no indication of how much of the pharmaceutical composition is composed
11 of fatty acids, by extension it is indefinite how much of each fatty acid is present in the
12 composition. This is incorrect. A claim can use a ratio to define amounts of components in a
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14

15 ⁴⁸³² *Interval Licensing LLC v. AOL, Inc.*, 766 F.3d 1364, 1370 (Fed. Cir. 2014) (“Claim language employing terms
16 of degree has long been found definite where it provided enough certainty to one of skill in the art when read in the
17 context of the invention.”); *see also BJ Servs. Co. v. Halliburton Energy Servs., Inc.*, 338 F.3d 1368, 1372 (Fed. Cir.
18 2003) (“The question becomes whether one of ordinary skill in the art would understand what is claimed when the
19 claim is read in light of the specification.”) (discussing the term “about”); *Verve, LLC v. Crane Cams, Inc.*, 311 F.3d
20 1116, 1120 (Fed. Cir. 2002) (“It is well established that when the term ‘substantially’ serves reasonably to describe
21 the subject matter so that its scope would be understood by persons in the field of the invention, and to distinguish
22 the claimed subject matter from the prior art, it is not indefinite.”).

23 ⁴⁸³³ *See, e.g., Deere & Co. v. Bush Hog, LLC*, 703 F.3d 1349, 1359 (Fed. Cir. 2012) (rejecting contention that claim
24 term “substantially planar” is indefinite); *Enzo Biochem, Inc. v. Applera Corp.*, 599 F.3d 1325, 1335 (Fed. Cir.
2010) (holding that the claim phrase “not interfering substantially” was not indefinite even though the construction
“define[d] the term without reference to a precise numerical measurement”); *BJ Services Co. v. Halliburton Energy
Services, Inc.*, 338 F.3d 1368, 1372–73 (Fed. Cir. 2003) (affirming jury’s verdict that claims reciting a concentration
as “about 0.06” were not invalid for being indefinite); *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540,
1557 (Fed. Cir. 1983) (ruling that the claim term “stretching ... at a rate exceeding about 10% per second” is not
indefinite).

⁴⁸³⁴ *See generally* the ’650 patent and its prosecution history.

1 product, using terms such as “percent by weight.”⁴⁸³⁵ In light of the specification and
2 prosecution history, a person of ordinary skill would understand with reasonable certainty the
3 range of relative quantities of EPA, DHA and/or other fatty acids in the recited pharmaceutical
4 composition in relation to all fatty acids present.⁴⁸³⁶ Therefore, these terms are not indefinite and
5 do not render the claims indefinite.

6 Defendants also allege that it is impossible to ascertain the metes and bounds of “placebo
7 control.” A person of ordinary skill, however, would understand the metes and bounds of the
8 term in light of the specification and the prosecution history.⁴⁸³⁷ Moreover, the method of
9 comparing a subject to a second subject, such as a placebo controlled, randomized, double blind
10 study, would have been known to a person of ordinary skill at the time of the invention.
11 Therefore, the term does not render the claims indefinite.

12 Finally, Defendants contend that the asserted claims improperly mix methods and
13 formulations because Plaintiffs’ assertion of contributory infringement apparently suggests that
14 the scope of the claims includes formulations. This is a mistaken interpretation. Indefiniteness
15 analysis is based on what the claim language informs a person of ordinary skill in the art in light
16 of the specification and the prosecution history. Defendants do not identify any actual claim
17 language that mixes methods and formulations. Moreover, contributory infringement may be
18 asserted and proven when a party sells “a material or apparatus for use in *practicing a patented*
19

20 ⁴⁸³⁵ *T.F.H. Publications, Inc. v. Doskocil Mfg. Co.*, No. CIV.A. 08-4805 FLW, 2012 WL 715628, at *5–6 (D.N.J.
21 Mar. 5, 2012) (construing “by weight” to mean the weight of a first component was in a ratio to the weight of a
22 second component); *Allergan, Inc. v. Sandoz Inc.*, No. 2:09-CV-182, 2011 WL 1599049, at *10 (E.D. Tex. Apr. 27,
2011) (construing percent by weight to mean “ratio of the weight of the ingredient in question divided by the total
volume of the solution, with this ratio expressed as a percentage”).

23 ⁴⁸³⁶ See generally the ’650 patent and its prosecution history.

24 ⁴⁸³⁷ See generally the ’650 patent and its prosecution history.

1 *process . . . knowing the same to be especially made or especially adapted for use in an*
2 *infringement of such patent.”*⁴⁸³⁸ Plaintiffs assert that Defendants’ ANDA products will be used
3 in practicing the claimed methods. Plaintiffs do not assert that the pharmaceutical compound
4 itself directly infringes. Therefore, Defendants’ interpretations of Plaintiffs’ assertions are
5 mistaken and the ’650 patent claims are not indefinite for improperly mixing methods and
6 formulations.

7 b) Defendants Have Not Demonstrated that the Claims of the ‘650
8 patent Are Invalid for Insufficient Written Description

9 The first paragraph of 35 U.S.C. § 112 requires that a patent specification “contain a
10 written description of the invention.” This requires that the specification “reasonably convey”
11 that the applicant “invented” or “had possession” of the claimed subject matter when the
12 application was filed.⁴⁸³⁹ Support need not be literal⁴⁸⁴⁰—it may be implicit⁴⁸⁴¹ or inherent⁴⁸⁴² in
13 the disclosure. In addition, it is unnecessary to include information that is already known or
14 available to persons of ordinary skill.⁴⁸⁴³

15 Defendants make three arguments regarding the written description requirement. First,
16 Defendants contend that elements reciting the baseline TG levels of the asserted claims lack
17 written description. This is incorrect. The specification of asserted patents literally discloses the

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⁴⁸³⁸ 35 U.S.C. § 271(c) (emphasis added).

19 ⁴⁸³⁹ *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010).

20 ⁴⁸⁴⁰ *Id.* at 1352; *Cordis Corp. v. Medtronic AVE, Inc.*, 339 F.3d 1352, 1365 (Fed. Cir. 2003); *In re Wright*, 866 F.2d
422, 425 (Fed. Cir. 1989); *In re Smith*, 481 F.2d 910, 914 (C.C.P.A. 1973).

21 ⁴⁸⁴¹ *All Dental Prodx, LLC v. Advantage Dental Prods. Inc.*, 309 F.3d 774, 779 (Fed. Cir. 2002); *In re Wright*, 866
F.2d at 424–25.

22 ⁴⁸⁴² *In re Gay*, 309 F.2d 769, 771 (C.C.P.A. 1962).

23 ⁴⁸⁴³ *Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1367–68 (Fed. Cir. 2006); *Capon v. Eshhar*, 418 F.3d 1349,
1357 (Fed. Cir. 2005); *In re Gay*, 309 F.2d at 774.

1 | claimed invention.⁴⁸⁴⁴ Moreover, the recited baseline TG levels of the claimed invention appear
2 | in the original claims of the application to which the asserted patent claims priority. Thus, there
3 | is a strong presumption that the claimed invention is adequately described.⁴⁸⁴⁵ Defendants do
4 | not and cannot rebut this presumption. Specifically, the patient population is originally claimed
5 | as “a subject having a fasting baseline triglyceride level of about 500 mg/dl to about 1500
6 | mg/dl.”⁴⁸⁴⁶ The asserted claims recite the same patient population. Defendants do not contend
7 | that the patient population of the asserted claims is not literally described by the specification
8 | and in the original claims of the application to which the asserted patent claims priority. In fact,
9 | the specification and the provisional patent application claims at the time of filing described
10 | these limitations.⁴⁸⁴⁷ Therefore, Defendants have failed to explain whether and how an aspect of
11 | the claimed invention has not been described with sufficient particularity such that one skilled in
12 | the art would recognize that the applicant had possession of the claimed invention.

13 | Second, Defendants contend that “a person of skill in the art would not understand that
14 | the inventor was in possession of a method incorporating [] specific dosages and quantities.”
15 | Defendants’ assertion is incorrect. The specification of the asserted patents literally discloses the
16 | dosages and quantities of the claimed methods.⁴⁸⁴⁸ Moreover, the dosages and quantities of the
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18 | ⁴⁸⁴⁴ *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (“[T]he test requires an objective
19 | inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art.”);
Snitzer v. Etzel, 465 F.2d 899, 902 (C.C.P.A. 1972) (“[T]he literal description of a species provides the requisite
20 | legal foundation for claiming that species.”).

21 | ⁴⁸⁴⁵ *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976) (“we are of the opinion that the PTO has the
22 | initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure
23 | a description of the invention defined by the claims”).

24 | ⁴⁸⁴⁶ See U.S. Application No. 12/702,889.

⁴⁸⁴⁷ See e.g., ‘650 patent at 13:29-34; 14:49-51; U.S. Provisional Application No. 61/151,291.

⁴⁸⁴⁸ *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (“[T]he test requires an objective
inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art.”);

1 method appear in the claims, as originally filed. Thus, there is a strong presumption that the
2 claimed invention is adequately described.⁴⁸⁴⁹ Defendants do not and cannot rebut this
3 presumption. For example, the dosage of the composition was originally claimed as “about 1 g
4 to about 4g.”⁴⁸⁵⁰ The asserted claims recite “4 g.” Defendants do not contend that dosages and
5 quantities of the asserted claims are not literally described by the specification and in the original
6 claims. In fact, the specification and the provisional patent application claims, at the time of
7 filing, described these limitations. Therefore, Defendants have failed to explain whether and
8 how an aspect of the claimed invention has not been described with sufficient particularity such
9 that one skilled in the art would recognize that the applicant had possession of the claimed
10 invention.

11 Third, Defendants contend that “a person of skill in the art would not understand that the
12 inventor was in possession of a method comprising a comparison against placebo control.”
13 Although this allegation does not appear to implicate written description, the specification
14 describes such a comparison. Therefore, a person of ordinary skill would have understood that
15 the inventor was in possession of a method comprising administration of a composition with the
16 recited properties, based on a specific comparison of a subject or a population against placebo
17 control.

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21 *Snitzer v. Etzel*, 465 F.2d 899, 902 (C.C.P.A. 1972) (“[T]he literal description of a species provides the requisite
legal foundation for claiming that species.”).

22 ⁴⁸⁴⁹ *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976) (“we are of the opinion that the PTO has the
initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure
23 a description of the invention defined by the claims”).

24 ⁴⁸⁵⁰ See U.S. Provisional Application No. 61/151,291.

1 In its 2010 *en banc* decision in *Ariad Pharmaceuticals, Inc. v. Eli Lilly Co.*,⁴⁸⁵¹ the court
2 elaborated that “possession” means possession as evidenced by disclosure. In this case, the
3 specification of asserted patents literally disclose the claimed invention in the specification and
4 the claims as originally filed. Thus, an examination of the four corners of the specification from
5 the perspective of a person of ordinary skill in the art demonstrates that the inventors of the
6 asserted patents were in possession of the claimed invention.

7 Defendants conclude by alleging that the specification does not describe anything more
8 than what is obvious, and thus does not provide adequate support for any nonobvious claim.
9 That is incorrect and irrelevant. Nonobviousness does not have to be supported solely by the
10 specification; nonobviousness can be supported by post-filing date evidence for example.⁴⁸⁵²
11 Written description requires only that the specification reasonably conveys that the applicant had
12 possession of the claimed subject matter when the application was filed. Therefore, whether the
13 claims are obvious has no bearing on the adequacy of written description.

14 c) Defendants Have Not Demonstrated that the Claims of the ‘650
15 patent Are Invalid for Lack of Enablement

16 The first paragraph of 35 U.S.C. § 112 requires that the specification “enable any person
17 skilled in the art . . . to make and use [the claimed invention].” A claim is not enabled if it would
18 require undue experimentation for a person of ordinary skill to make or use the invention.

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⁴⁸⁵¹ *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1343-48 (Fed. Cir. 2010).

20 ⁴⁸⁵² See *Sanofi–Aventis Deutschland GmbH v. Glenmark Pharm., Inc.*, 748 F.3d 1354, 1360 (Fed. Cir. 2014)
21 (“Glenmark also argues that later-discovered benefits cannot be considered in an obviousness analysis.... That is
22 incorrect; patentability may consider all of the characteristics possessed by the claimed invention, whenever those
23 characteristics become manifest.”); *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291,
24 1307 (Fed. Cir. 2011) (“[E]vidence of unexpected results may be [considered] ... even if that evidence was obtained
after the patent's filing or issue date.”); *Knoll Pharm. Co. v. Teva Pharm. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir.
2004) (“Evidence developed after the patent grant is not excluded from consideration, for understanding of the full
range of an invention is not always achieved at the time of filing the patent application.”).

1 Factors that may be considered include the quantity of experimentation necessary, the amount of
2 direction or guidance presented, the presence or absence of working examples, the nature of the
3 invention, the state of the prior art, the relative skill of those in the art, the predictability or
4 unpredictability of the art, and the breadth of the claims.⁴⁸⁵³ The enablement requirement is
5 separate and distinct from the written description requirement,⁴⁸⁵⁴ and as such a claim does not
6 require descriptive support in the disclosure as originally filed for it to be enabled.⁴⁸⁵⁵

7 Defendants make two specific arguments regarding the enablement requirement. First,
8 Defendants contend that “[i]t would take undue experimentation to obtain the actual amounts of
9 the composition found in the ultimate claims.” This is incorrect. As Defendants admit, the
10 claims disclose amounts of the composition to be administered. Therefore, a person of ordinary
11 skill would be able to determine the amounts of the components in the pharmaceutical
12 composition without any experimentation, much less undue experimentation.

13 Second, Defendants contend that it would take undue experimentation to obtain the
14 claimed required results listed in the full scope of the patent claims, including the claimed lipid
15 effects. This is incorrect. The asserted claims require no experimentation to practice the claimed
16 method and certainly not undue experimentation. Administration of a recited amount of a recited
17 composition, for a recited duration, to a specific, recited patient population produces the recited
18 results. No additional experimentation is required, and Defendants do not explain their
19 allegation that undue experimentation would be required. Defendants also do not contend that
20 following the claimed method (each recited element) does not produce the recited results. The
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⁴⁸⁵³ See, e.g., *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

23 ⁴⁸⁵⁴ *Vas-. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991)

24 ⁴⁸⁵⁵ MPEP § 2164.

1 clinical studies included in the VASCEPA® label and submitted to the USPTO clearly
2 demonstrate that administration of EPA of the recited composition, when administered to
3 patients with very high TG levels for at least 12 weeks, as specified, produces the recited
4 results.⁴⁸⁵⁶ Therefore, the claims are not invalid for lack of enablement.

5 Defendants conclude by alleging that the specification does not enable anything more
6 than what is obvious over the prior art or was known to a person of skill in the art. First,
7 Defendants do not cite any case or present a legal theory to support this assertion. As such, they
8 do not allow Plaintiffs to adequately respond to the assertion. Therefore, Defendants should be
9 precluded in the future from raising any new legal theory to support this assertion. Moreover,
10 while the '650 patent's specification enables a person of ordinary skill to obtain the claimed
11 limitations without undue experiment, the claimed limitations would not have been obvious to a
12 person of ordinary skill, as discussed in Section V.J.3. Furthermore, Plaintiffs have initiated
13 human clinical trials and submitted the trial results to the USPTO to substantiate the utility of its
14 claimed methods.^{4857, 4858} Therefore, a person of ordinary skill would have concluded that the
15 claims possessed credible therapeutic utility, and the full scope of the claims was enabled.

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⁴⁸⁵⁶ See VASCEPA® Prescribing Information at Table 2.

21 ⁴⁸⁵⁷ *In re Brana*, 51 F.3d 1560, 1567 n.19 (Fed. Cir. 1995) (Post-filing evidence “can be used to substantiate any
22 doubts as to the asserted utility.”); MPEP § 2107.03 (“[A]s a general rule, if an applicant has initiated human clinical
23 trials for a therapeutic product or process, Office personnel should presume that the applicant has established that
the subject matter of that trial is reasonably predictive of having the asserted therapeutic utility.”).

24 ⁴⁸⁵⁸ See May 16, 2011 Bays Declaration at Appendix B.

1 **K. The ‘929 Patent**

2 **1. The ‘929 Patent Claims Eligible Subject Matter Under § 101**

3 Defendants’ allegation that the asserted claims of the ‘929 patent relate to ineligible
4 subject matter under Section 101 is without merit. Defendants do not establish a *prima facie*
5 case under Section 101 or provide a legal or factual basis to support their allegations.

6 As an initial matter, Defendants’ disclosure is also insufficient under the Nevada Local
7 Patent Rules as the grounds for any allegation of invalidity under Section 101 must be
8 provided.⁴⁸⁵⁹ The bare assertion of invalidity under Section 101 without providing the grounds
9 for such an allegation and examining the elements of the asserted claims of the ‘929 patent does
10 not meet this requirement and thwarts the purpose of the Rules.⁴⁸⁶⁰

11 The inquiry under Section 101 involves a two-step test: first, a court must determine
12 whether the claim at issue is directed to a patent-ineligible concept: a law of nature, physical
13 phenomenon, or abstract idea.⁴⁸⁶¹ Second, even if the claim is directed to one of these concepts,
14 it still may be patent eligible and the court must determine what else is part of the claim.⁴⁸⁶²

17 ⁴⁸⁵⁹ See Nevada Local Patent Rule 1.8(e) (“[E]ach party opposing a claim of patent infringement, shall serve on all
18 other parties Non-Infringement, Invalidity, and Unenforceability Contentions that must include . . . A detailed
statement of any grounds of invalidity based on 35 U.S.C. § 101.”).

19 ⁴⁸⁶⁰ Nor does the preceding paragraph, which provides only a purported summary of the claims of the ‘929 patent, or
20 subsequent paragraph, which makes what appears to be an argument entirely unrelated to Section 101, provide the
21 grounds for Defendants’ allegation of invalidity under 35 U.S.C. § 101. See, e.g., *Silver State Intellectual Techs.,
Inc. v. Garmin Int’l, Inc.*, 32 F. Supp. 3d 1155, 1161–62 (D. Nev. 2014) (“The District of Nevada’s Local Patent
Rules, like the local patent rules for the Northern District of California, are designed to require the parties to provide
early notice of their infringement and invalidity contentions, and to proceed with diligence in amending those
contentions when new information comes to light in the course of discovery”) (internal quotation marks omitted).

22 ⁴⁸⁶¹ *Alice Corp. Pty. v. CLS Bank Int’l*, 134 S. Ct. 2347, 2355 (2014) (“First, we determine whether the claims at
23 issue are directed to one of those patent-ineligible concepts.”).

24 ⁴⁸⁶² *Id.* (quoting *Mayo*, 132 S. Ct. at 1294) (“If so, we then ask, ‘[w]hat else is there in the claims before us?’”).

1 The sole Section 101 case identified by Defendants, *Mayo Collaborative Services v.*
2 *Prometheus Laboratories, Inc.*, 132 S. Ct. 1289 (2012), is inapplicable to the asserted claims of
3 the '929 patent. In *Mayo*, the claims were directed to “well-understood, routine, [and]
4 conventional” steps, and the only novel element related to administering the proper dosage based
5 on a natural law observation.⁴⁸⁶³ However, the claims merely recited this natural law without
6 reciting any novel application of it.⁴⁸⁶⁴ The Court found that providing protection to such
7 claims would result in pre-empting “a broad range of potential uses” and excluding others from
8 using “the basic tools of scientific and technical work.”⁴⁸⁶⁵ A method of treatment claim,
9 specifying the subjects, dosage levels, composition, and time course does not raise the concerns
10 of *Mayo* and instead is akin to the typical claims which *Mayo* acknowledges are entitled to patent
11 protection.⁴⁸⁶⁶

12 Defendants suggest that the recited EPA composition of each asserted claim is a naturally
13 occurring substance. It is not. Even references contained within Defendants’ own contentions
14 make clear that EPA of the requisite purity and characteristics is not found in nature.⁴⁸⁶⁷ As
15 expressed by the patents cited in Defendants’ contentions and well-established precedent, for
16 decades it has been accepted that compositions isolated from nature or purified beyond their

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18 ⁴⁸⁶³ *Mayo*, 132 S. Ct. at 1294.

19 ⁴⁸⁶⁴ *Id.* at 1301.

20 ⁴⁸⁶⁵ *Id.*

21 ⁴⁸⁶⁶ *Id.* at 1302 (contrasting the patent-ineligible claims of that case to “a typical patent on a new drug or a new way
22 of using an existing drug); *see also Diamond v. Diehr*, 450 U.S. 175, 177 , 191-193 (1981) (upholding patentability
23 for “a process for curing synthetic rubber which includes in several of its steps the use of a mathematical formula
24 and a programmed digital computer” under Section 101); *Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc.*, 827 F.3d
1042, 1048-49 (Fed. Cir. 2016) (finding claims patent eligible because by holding otherwise, a host of other patent
eligible claims, such as method of treatment claims, would also be necessarily ineligible).

⁴⁸⁶⁷ *See, e.g.*, U.S. Patent No. 5,215,630, “Method of Purifying Eicosapentaenoic Acid or the Ester Derivative
Thereof by Fractional Distillation” (cited in Defendants’ Joint Invalidity Contentions, *e.g.*, at 26–27).

1 natural state are patent-eligible.⁴⁸⁶⁸ Moreover, Defendants’ assertions are immaterial to a Section
2 101 defense because method of treatment claims like the ones asserted in this case are patent
3 eligible even if they are directed to administration of a naturally occurring substance.⁴⁸⁶⁹

4 To the extent Defendants are arguing that a law of nature both underlies the claims and
5 renders them ineligible, that argument is unsupported and incorrect. Defendants allege that “the
6 claimed effects are the natural result of ingesting a naturally-occurring substance.”⁴⁸⁷⁰ Since the
7 composition that is the subject of the claims is not naturally occurring, Defendants appear to
8 suggest that all method of treatment claims involve a law of nature. That is not what *Mayo* states
9 or even suggests, and indeed the Federal Circuit has refused to adopt Defendants’ overbroad
10 characterization of laws of nature.⁴⁸⁷¹ To say that the claims of the ’929 patent claim a law of
11 nature is to suggest that all patents claim such laws and engage in an infinitely regressive mode
12 of analysis that the Supreme Court did not adopt in which “all inventions can be reduced to
13 underlying principles of nature” that would “make all inventions unpatentable.”⁴⁸⁷² Indeed, even
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18 ⁴⁸⁶⁸ See, e.g., *In re Bergy*, 596 F.2d 952; *In re Kratz*, 592 F.2d 1169 (CCPA 1979); *In re Bergstrom*, 427 F.2d 1394
(CCPA 1970); *Parke-Davis & Co. v. H.K. Mulford Co.*, 189 F.95 (S.D.N.Y. 1911).

19 ⁴⁸⁶⁹ *Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc.*, 827 F.3d 1042, 1048-49 (Fed. Cir. 2016).

20 ⁴⁸⁷⁰ See Defendants’ Joint Invalidation Contentions at 655.

21 ⁴⁸⁷¹ See *CellzDirect*, 827 F.3d at 1048-49 (“The [asserted] claims are like thousands of others that recite processes
22 to achieve a desired outcome That one way of describing the process is to describe the natural ability of the
subject matter to *undergo* the process does not make the claim ‘directed to’ that natural ability. If that were so, we
would find patent-ineligible methods of . . . treating cancer with chemotherapy (as directed to cancer cells’ inability
to survive chemotherapy), or treating headaches with aspirin (as directed to the human body’s natural response to
aspirin).”).

23 ⁴⁸⁷² See *Mayo*, 132 S. Ct. at 1034 (quoting *Diamond v. Diehr*, 450 U.S. 175, 188 (1981)).
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1 those concerned about the implications of *Mayo* on future patents were focused on diagnostic
2 claims not treatment claims of the type that *Mayo* stated were typical and patentable.⁴⁸⁷³

3 Even if there is some underlying law of nature in the asserted claims, the subject matter
4 of the '929 patent remains eligible for protection under Section 101. As articulated by *Mayo* and
5 *Diehr*, patents claiming a law of nature, such as a mathematical equation, are entitled to
6 protection where claims “did not ‘seek to pre-empt the use of [the] equation,’ but sought ‘only to
7 foreclose from others the use of that equation in conjunction with all of the other steps in their
8 claimed process.’”⁴⁸⁷⁴ As discussed above, the asserted claims of the '929 patent contain a
9 novel, unconventional, and specific method of treatment comprising a particularized application
10 of a nonnaturally occurring substance and does not preempt the use of a law of nature.⁴⁸⁷⁵

11 Defendants also argue that any argument by Amarin in response to Defendants’ § 112
12 arguments are further evidence of invalidity under § 101. This argument is without merit. The
13 claims are enabled and written description is satisfied for the reasons discussed below. In
14 addition, as discussed above, the asserted claims are not merely a naturally-occurring
15 phenomena, and thus satisfy the requirements of § 101.

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20 ⁴⁸⁷³ See *Mayo*, 132 S. Ct. at 1034 (“Prometheus, supported by several *amici*, argues that a principle of law denying
21 patent coverage here will interfere significantly with the ability of medical researchers to make valuable discoveries,
particularly in the area of diagnostic research.”).

22 ⁴⁸⁷⁴ See *Mayo*, 132 S. Ct. at 1299 (quoting *Diehr*, 450 U.S. at 187).

23 ⁴⁸⁷⁵ See, e.g., *Tannas Electronics v. Luxell Technologies, Inc.*, 2012 WL 3800822, at *4 (C.D. Cal. July 24, 2012)
24 (rejecting a challenge to the patentability of a claim under Section 101 where the alleged natural phenomenon was
“just one step in the whole process” claimed by the invention).

1 **2. The Asserted Claims of the ‘929 Patent Are Not Anticipated by WO**
2 **‘118**

3 To anticipate, a single prior art reference must sufficiently describe a claimed invention
4 so that the public is in “possession” of that invention.⁴⁸⁷⁶ Therefore, to anticipate, a reference
5 must set forth every element of the claim, either expressly or inherently, in as complete detail as
6 is contained in the claim.⁴⁸⁷⁷ The claim elements must also be “arranged” in the prior art
7 reference, just as they are in the claim,⁴⁸⁷⁸ rather than as “multiple, distinct teachings that the
8 artisan might somehow combine to achieve the claimed invention.”⁴⁸⁷⁹ In addition, public
9 “possession” requires that the prior art enable a person of ordinary skill to make and use the
10 invention without undue experimentation.⁴⁸⁸⁰ Factors that may be included in this analysis
11 include the quantity of experimentation necessary, the amount of direction or guidance
12 presented, the presence or absence of working examples, the nature of the invention, the state of
13 the prior art, the relative skill of those in the art, the predictability or unpredictability of the art,
14 and the breadth of the claims.⁴⁸⁸¹ This inquiry is objective, and thus evidence of undue
15 experimentation need not be prior art.⁴⁸⁸²

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⁴⁸⁷⁶ *Akzo N.V. v. U.S. Int’l Trade Com’n*, 808 F.2d 1471, 1479 (Fed. Cir. 1986).

17 ⁴⁸⁷⁷ *Id.*; *In re Bond*, 910 F.2d 831, 832 (Fed. Cir. 1990); *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236
(Fed. Cir. 1989).

18 ⁴⁸⁷⁸ *Bond*, 910 F.2d at 833; *Akzo*, 808 F.2d at 1479.

19 ⁴⁸⁷⁹ *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369–71 (Fed. Cir. 2008); *In re Arkley*, 455 F.2d 586,
587 (C.C.P.A. 1972); *In re Ruschig*, 343 F.2d 965, 974 (C.C.P.A. 1965).

20 ⁴⁸⁸⁰ *Akzo*, 808 F.2d at 1479; *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1085 (Fed. Cir. 2008); *Forest*
Labs., Inc. v. Ivax Pharms., Inc., 501 F.3d 1263, 1268–69 (Fed. Cir. 2007).

21 ⁴⁸⁸¹ *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

22 ⁴⁸⁸² *Plant Genetic Sys., N.V. v. DeKalb Genetics Corp.*, 315 F.3d 1335, 1344 (Fed. Cir. 2003); *In re Wright*,
999 F.2d 1557, 1562 (Fed. Cir. 1993); *Liquid Dynamics Corp. v. Vaughan Co., Inc.*, 449 F.3d 1209, 1224–25 (Fed.
23 Cir. 2006); *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1336 (Fed. Cir. 2003); *Gould v. Quigg*, 822
24 F.2d 1074, 1078 (Fed. Cir. 1987).

1 Defendants assert that Claims 1-9 of the '929 Patent are anticipated by the WO '118
2 reference.⁴⁸⁸³ A element-by-element analysis, identifying each element of each asserted claim
3 that is absent from WO '118, is provided below. The contentions below are incorporated by
4 reference into Exhibit K, and vice-versa. WO '118 does not anticipate the claims of the '929
5 patent because it does not describe, properly arrange, or enable the '929 patent claims.

6 a) WO '118 Does Not Teach Every Element of the Claims of the
7 '929 Patent

8 (1) WO '118 Does Not Describe the Claimed Lipid Effects

9 It is well established that, for a prior art reference to anticipate, “every element of the
10 claimed invention must be identically shown in a single reference.”⁴⁸⁸⁴ Moreover, the elements
11 of the claimed invention must have “strict identity” with the elements of the reference; “minimal
12 and obvious” differences are sufficient to prevent anticipation.⁴⁸⁸⁵ Here, WO '118 entirely fails
13 to disclose the following elements of Claim 1 of the '929 Patent: *a method of reducing TG.*

14 Defendants appear to concede that WO '118 does not expressly teach these elements, as they fail
15 to set forth any basis for concluding that WO '118 teaches this element.⁴⁸⁸⁶ Indeed, Defendants
16 could not set forth any basis for concluding that WO '118 teaches this element because WO '118
17 does not.

18 Instead, Defendants argue that these elements express the intended result of a method that
19 is positively recited, and therefore is inherently anticipated. However, for the reasons set forth
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21 ⁴⁸⁸³ References to “WO '118” are to the English translation that was filed with the European application. Plaintiffs
reserve their right to obtain a certified translation of WO '118.

22 ⁴⁸⁸⁴ *Diversitech Corp. v. Century Steps, Inc.*, 850 F.2d 675, 677 (Fed. Cir. 1988); *see also Hybritech Inc. v.*
Monoclonal Antibodies, Inc., 802 F.2d 1367 (Fed. Cir. 1986).

23 ⁴⁸⁸⁵ *Trintech Industries, Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1296 (Fed. Cir. 2002).

24 ⁴⁸⁸⁶ Defendants' Invalidation Contentions at 202-204.

1 below, WO '118 fails to disclose each element of the independent claim of the '929 Patent, either
2 expressly or inherently. Therefore, WO '118 cannot anticipate the claimed method. Defendants
3 also argue that these elements represent inherent, natural properties of EPA, and are entitled to
4 no patentable weight. This conclusion is incorrect and inconsistent with the law of anticipation
5 and claim construction. Further, while Defendants argue that the inherent properties are
6 exemplified in the prior art, they fail to identify even a single prior art reference that makes such
7 a disclosure. Defendants cannot point to a single, specific prior art reference because the
8 claimed pharmaceutical composition has never been administered in the manner claimed to the
9 claimed patient population. Also, these elements are positively recited in the body of the claim
10 and therefore cannot be construed as a non-limiting preamble and must be given patentable
11 weight.

12 Further, Defendants entirely fail to prove that inherently discloses the claimed lipid
13 effects. A prior art reference that “only ‘probably’ or ‘possibly’ meets the claims cannot
14 inherently anticipate as a matter of law.”⁴⁸⁸⁷ “[A]nticipation by inherent disclosure is appropriate
15 only when the reference discloses prior art that must *necessarily* include the unstated
16 limitation.”⁴⁸⁸⁸ “It is not sufficient if a material element or limitation is ‘merely probably or
17 possibly present’ in the prior art.”⁴⁸⁸⁹ WO '118 fails to provide any data related to the lipid
18 effects of the disclosed invention on patients described in the publication. Therefore, Defendants
19 fail to prove by clear and convincing evidence that the composition disclosed by WO '118 meets
20 the elements of the independent claim every time it is administered.

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22 ⁴⁸⁸⁷ *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

23 ⁴⁸⁸⁸ *Transclean Corp. v. Bridgewood Servs., Inc.*, 290 F.3d 1364, 1373 (Fed. Cir. 2002) (emphasis in original).

24 ⁴⁸⁸⁹ *In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1378 (Fed. Cir. 2007).

1 Defendants fail to demonstrate that administration of the claimed EPA compositions
2 “necessarily” yields the claimed lipid effects. For example, one study cited by Defendants
3 suggests that EPA administration may increase LDL-C.⁴⁸⁹⁰ Rambjor is a clinical study which
4 administered EPA, DHA, fish oil or placebo to human subjects. Rambjor showed that both EPA
5 and fish oil caused a significant increase in LDL-C. On the other hand, DHA effected only a
6 non-significant increase in LDL-C. As reflected by the disclosure of Rambjor, EPA does *not*
7 decrease TG without increasing LDL-C *every time it is administered*.

8 Therefore, WO ‘118 cannot anticipate the independent claim of the ‘929 patent. Because
9 the dependent claims include all of the claim elements of the independent claim, WO’ 118
10 cannot anticipate any of the dependent claims as well.

11 (2) WO ‘118 Does Not Disclose Methods of Treating The
12 Claimed Patient Population

13 In addition, WO ‘118 fails to disclose or suggest the claimed pharmaceutical composition
14 be administered in the manner claimed to the claimed patient population. Defendants attempt to
15 eliminate these important elements by arguing that the preamble is non-limiting. A preamble is
16 the introductory clause of a patent claim and includes everything from the beginning of the claim
17 until a transitional phrase, such as “comprising.” Defendants improperly attempt to truncate the
18 preamble.

19 A claim preamble has patentable weight if, “when read in the context of the entire claim,
20 [it] recites limitations of the claim, or, if the claim preamble is ‘necessary to give life, meaning,
21 and vitality’ to the claim.”⁴⁸⁹¹ Additionally, the preamble constitutes a claim element when the

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23 ⁴⁸⁹⁰ See, e.g., Rambjor.

24 ⁴⁸⁹¹ *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305 (Fed. Cir. 1999) (citation omitted).

1 claim depends on it for antecedent basis because “it indicates reliance on both the preamble and
2 claim body to define the claimed limitation.”⁴⁸⁹²

3 The preamble of the asserted claims is limiting for several reasons. The term “subject” in
4 the preamble of the independent claim defines and provides antecedent basis for the “subject”
5 recited in the body of the claims. When reading the claim, one must rely on both the preamble
6 and the claim body to define the claimed invention.

7 If the preamble states “a fundamental characteristic of the claimed invention,” then it “is
8 properly construed as a limitation of the claim itself.”⁴⁸⁹³ It is clear that “the claim drafter chose
9 to use both the preamble and the body of the claim to define the subject matter of the claimed
10 invention.”⁴⁸⁹⁴ Thus, the entire preamble in the independent claim of the ‘929 must contain
11 patentable weight.

12 WO ‘118 fails to disclose the patentable elements of the preamble of the asserted claims.
13 WO ‘118 does not describe or suggest that the claimed pharmaceutical composition be
14 administered in the manner claimed to the claimed patient population.

15 First, WO ‘118 fails to expressly disclose “a method of reducing triglycerides.” In fact,
16 the invention disclosed by WO ‘118 relates to a composition for **preventing occurrence of**
17 **cardiovascular events**, as evidenced by the title which reads “Composition for Preventing the
18 Occurrence of Cardiovascular Event in Multiple Risk Patient.” The prevention of the occurrence
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20 ⁴⁸⁹² *Catalina Marketing Int’l v. Coolsavings.com, Inc.*, 289 F.3d 801, 808 (Fed. Cir. 2002) (citation omitted).

21 ⁴⁸⁹³ *Poly-Am. L.P. v. GSE Lining Tech., Inc.*, 383 F.3d 1303, 1309 (Fed. Cir. 2004); *see also e.g., Computer*
22 *Docking Station Corp. v. Dell, Inc.*, 519 F.3d 1366, 1375 (Fed. Cir. 2008) (concluding the preamble phrases
23 “portable computer” and “portable computer microprocessing system” limit the claims because they “clearly recite a
24 necessary and defining aspect of the invention, specifically its portability,” and because the specification and
prosecution history “emphasize this feature of the invention”).

⁴⁸⁹⁴ *Bicon, Inc. v. Straumann Co.*, 441 F.3d 945, 953 (Fed. Cir. 2006).

1 of cardiovascular events is defined in WO '118 as “all cases of primary prevention, and
2 exemplary cases include prevention of cardiovascular death, fatal myocardial infarction, sudden
3 cardiac death, nonfatal myocardial infarction, cardiovascular angioplasty, new occurrence of rest
4 angina and exercise-induced angina, and destabilization of the angina.”⁴⁸⁹⁵ The invention of WO
5 '118 is intended to be administered to any person in need of prevention of the occurrence of
6 cardiovascular events, who are typically hypercholesterolemia patients.⁴⁸⁹⁶ WO '118 does not
7 expressly describe its invention as a “method of reducing triglycerides,” therefore it cannot
8 anticipate the independent claim.

9 Second, WO '118 fails to disclose the subject as described in the claims. Defendants fail
10 to prove that these elements of the claimed invention have “strict identity” with the elements of
11 the reference.⁴⁸⁹⁷ WO '118 fails to anticipate this claim element because the broad disclosure
12 fails to anticipate the narrow claimed range, and the specific patient population defined in the
13 claims is an essential part of the claimed invention.

14 There is no evidence in that subject as described in the claims were ever treated. In fact,
15 WO '118 fails to disclose baseline lipid levels of a single subject. Defendants rely on the
16 definition of “hypertriglyceridemia” in WO '118 to argue that WO '118 discloses treatment of
17 the subject as described in the claims. It does not. Defendants’ argument rests on the definition
18 in WO '118 of “hypertriglyceridemia” as “fasting serum triglyceride levels of at least 150
19 mg/dL.” WO '118’s definition is not tied to a specific subject and there are no working
20 examples, data or other reference in WO '118 indicating that any subject with fasting TG levels
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⁴⁸⁹⁵ WO '118 at 12.

23 ⁴⁸⁹⁶ *Id.*

24 ⁴⁸⁹⁷ *Trintech Industries, Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1296 (Fed. Cir. 2002).

1 of at least 500 mg/dL received an EPA composition as claimed in the asserted patents, or any
2 EPA at all. In addition, Defendants rely on a reference to “Omacor” in WO ‘118 (at 32) as
3 evidence that a “person of ordinary skill in the art would have understood that the term
4 ‘hypertriglyceridemia’ when used in the WO ‘118 includes patients with triglyceride levels of
5 500 mg/dL to about 1500 mg/dL.” The cited section states that “soft capsules” are preferable
6 and then merely provides examples of commercially available “soft capsules,” such as Omacor.
7 The passage does not define “hypertriglyceridemia” as used in WO ‘118 as referring to patients
8 with triglyceride levels over 500 mg/dL. Nor does it suggest that the claimed EPA should be
9 used in the over 500 mg/dL TG patient population. A prior art reference that “only ‘probably’ or
10 ‘possibly’ meets the claims cannot inherently anticipate as a matter of law.”⁴⁸⁹⁸ Therefore,
11 Defendants fail to prove by clear and convincing evidence that the composition disclosed by WO
12 ‘118 meets the claim elements of the independent claim every time it is administered.

13 Further, the broad range disclosed by WO ‘118 is insufficient to anticipate the ranges
14 claimed by the ‘929 patent. In *Atofina*, the prior art disclosed a temperature range of 100 to 500
15 degrees and a preferred range of 150 to 350 degrees; the patent at issue claimed a range between
16 330 and 450 degrees. The court found that the broader prior art range could not anticipate the
17 claimed temperature range, “[g]iven the considerable difference between the claimed range and
18 the range in the prior art, no reasonable fact finder could conclude that the prior art describes the
19 claimed range with sufficient specificity to anticipate this element of the claim.”⁴⁸⁹⁹ A prior art’s
20 teaching of a broad genus does not necessarily disclose every species within that genus. The
21 court explained the slightly overlapping range between the preferred range and claimed range “is

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23 ⁴⁸⁹⁸ *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

24 ⁴⁸⁹⁹ *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006).

1 not disclosed as . . . a species of the claimed generic range of 330 to 450 °C,”⁴⁹⁰⁰ and therefore
2 failed to anticipate the claimed range. Likewise, WO ‘118’s broad disclosure of
3 hypertriglyceridemia as a “fasting serum triglyceride levels of at least 150 mg/dL” does not
4 anticipate the subject as described in the claims because it fails to described the claimed TG
5 range with sufficient specificity.

6 The court in *Atofina* ruled on an additional question of anticipation that also involved a
7 range of numbers. A prior art reference had disclosed a range of 0.001 to 1.0 percent, as
8 compared to the patent’s claimed range of 0.1 to 5.0 percent.⁴⁹⁰¹ The court explained that
9 “although there is a slight overlap, no reasonable fact finder could determine that this overlap
10 describes the entire claimed range with sufficient specificity to anticipate this limitation of the
11 claim. The ranges are different, not the same. . . . Thus, there is no anticipation.”⁴⁹⁰² Similarly,
12 although there may be overlap between the definition of hypertriglyceridemia taught by WO
13 ‘118 and the TG range recited by the claims of the asserted patents, WO ‘118 does not
14 specifically discuss, highlight or otherwise suggest treating patients with TG values above 500
15 mg/dL. In fact, WO ‘118 is directed to compositions and methods for preventing occurrence of
16 cardiovascular events, suggesting that the treatment was envisioned for patients with TG levels
17 below 500 mg/dL (the patient population the ATP III identifies the prevention of atherogenic
18 events as the primary clinical objective),⁴⁹⁰³ WO ‘118, therefore, does not expressly disclose the
19 specific patient population that is an essential element of the claims of the asserted patents.
20 Therefore, WO ‘118 cannot anticipate the claims of the asserted patents.

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22 ⁴⁹⁰⁰ *Atofina*, 441 F.3d at 1000.

23 ⁴⁹⁰¹ *Id.*

24 ⁴⁹⁰² *Id.*

⁴⁹⁰³ *See* Section III.

1 The treatment of a patient with elevated TG levels varies depending on their serum
2 triglyceride levels. Identification of the patient population with very high TG levels (at least 500
3 mg/dL) is central to the claimed invention. In the 2000s, physicians treating lipid disorders,
4 including hypertriglyceridemia, relied on the ATP-III for authoritative guidance on the treatment
5 of lipid disorders.⁴⁹⁰⁴ The ATP-III divided hypertriglyceridemia patients into three classes based
6 on the levels of TG in their blood—borderline-high (150-199 mg/dL), high (200-499 mg/dL),
7 and very-high TGs (≥ 500 mg/dL)—and recommended substantially different treatment
8 strategies for patients depending on classification.⁴⁹⁰⁵ For the borderline-high and high TG
9 groups (150-499 mg/dL), the primary goal was to reduce risk of coronary heart disease.⁴⁹⁰⁶
10 Accordingly, in these populations, physicians focused on lowering LDL-C.⁴⁹⁰⁷ In this patient
11 population, lowering of TG and non-HDL-C levels were considered secondary treatment goals.
12 In contrast, the primary goal for very-high TG patients (≥ 500 mg/dL) was to reduce the risk of
13 pancreatitis—a potentially life threatening condition expected to be precipitated by elevated
14 TGs— by lowering TG levels. In very high TG patients, lowering LDL-C is a secondary
15 treatment goal.⁴⁹⁰⁸ Therefore, as evidenced by the ATP-III, patients with very-high TG levels
16 were considered fundamentally different from patients with borderline-high or high TGs from a
17 lipid chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint.

18 Therefore, WO ‘118’s definition of “hypertriglyceridemia” as “fasting serum triglyceride
19 levels of at least 150 mg/dL” fails to anticipate the claimed subject with very high TG levels. In
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21 ⁴⁹⁰⁴ *Id.*

22 ⁴⁹⁰⁵ ATP III at 3335; *See also* Section III.

23 ⁴⁹⁰⁶ *Id.*

24 ⁴⁹⁰⁷ *Id.*

⁴⁹⁰⁸ *Id.*

1 fact, as described above, WO '118 is not directed toward patients with the claimed TG levels at
2 all. WO 118's disclosure is clearly directed towards preventing the occurrence of cardiovascular
3 risk, which is the primary aim for treatment of patients with high triglycerides (200-499 mg/dL).
4 Thus, WO '118's disclosure is *not* directed towards patients with very high triglyceride levels
5 (where the primary goal is to prevent acute pancreatitis and damage to the pancreas by
6 decreasing triglycerides), as required by the independent claims of the asserted patents, and
7 therefore cannot anticipate the independent claim of the '929 Patent.

8 (3) WO '118 Does Not Describe the Claimed Pharmaceutical
9 Composition or its Specific Administration

10 WO '118 further does not anticipate the claims of the '929 patent because it does not
11 disclose "administering orally to the subject." As WO '118 fails to disclose the subject as
12 claimed, it cannot anticipate oral administration to the claimed "subject."

13 WO '118 additionally cannot anticipate the claims of the '929 patent because it does not
14 disclose administering the pharmaceutical composition at a dose of about 4g per day.

15 Defendants argue that this element is disclosed by WO '118's teaching that the daily dose is
16 "typically 0.3 to 6 g/day." Defendants fail to provide the entire disclosure of WO '118, which
17 states that the daily dose is "typically 0.3 to 6 g/day, preferably 0.9 to 3.6 g/day, and still more
18 preferably 1.8 to 2.7 g/day. Another preferable daily dose is 0.3 to 2.7 g/day, and 0.3 to 1.8
19 g.day. Another preferable fatty acid included is DHA-E." WO '118 teaches that the dosage is
20 not particularly limited as long as the intended effect, preventing the occurrence of
21 cardiovascular events, is attained. However, Defendants fail to provide any evidence that a dose
22 that is effective to prevent the occurrence of cardiovascular event, is also a dose that would be
23 effective to reduce triglycerides in the claimed patient population. Furthermore, there are no
24 working examples, data or other reference in WO '118 indicating that any subject (much less

1 one with fasting TG levels of at least 500 mg/dL) received an EPA composition as claimed in the
2 asserted patents or any EPA at all, much less at the claimed dose of 4 grams/day.

3 As discussed above, in *Atofina*, the prior art disclosed a preferred temperature range of
4 150 to 350 degrees, and the patent at issue claimed a range between 330 and 450 degrees. The
5 court explained that this slight overlap “is not disclosed as . . . a species of the claimed generic
6 range of 330 to 450 °C,”⁴⁹⁰⁹ and therefore failed to anticipate the claimed range. The court in
7 *Atofina* also found that a prior art disclosure of a range of 0.001 to 1.0 percent failed to anticipate
8 the patent’s claimed range of 0.1 to 5.0 percent.⁴⁹¹⁰ The court explained that “although there is a
9 slight overlap, no reasonable fact finder could determine that this overlap describes the entire
10 claimed range with sufficient specificity to anticipate this limitation of the claim. The ranges are
11 different, not the same. . . . Thus, there is no anticipation.”⁴⁹¹¹ Similarly, although there may be
12 some overlap between the daily dose disclosed by WO ‘118 and the dose claimed by the ‘929
13 patent, WO ‘118 does not specifically highlight the overlapping area and, moreover, the range
14 claimed by the ‘929 patent does not fall within WO ‘118’s preferred range. Defendants
15 conveniently omit the preferred range and mischaracterize the teaching of WO ‘118. Notably,
16 the example indicates that up to 900 mg of the EPA composition could be used three times per
17 day (2.7 g). Thus, WO ‘118 does not expressly disclose the 4 g per day dose claimed by the ‘929
18 patent and cannot anticipate the independent claim of the ‘929 Patent.

19 WO ‘118 further does not anticipate the claims of the ‘929 patent because it does not
20 disclose the claimed EPA pharmaceutical composition. Defendants once again cite only a
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⁴⁹⁰⁹ *Atofina*, 441 F.3d at 1000.

23 ⁴⁹¹⁰ *Id.*

24 ⁴⁹¹¹ *Id.*

1 portion of the disclosure and exclude sections that show the breadth of WO ‘118’s teachings.
2 WO ‘118’s full disclosure recites that “the EPA-E used is preferably the one having a high
3 purity, for example, the one having the proportion of the EPA-E in the total fatty acid and
4 derivatives thereof of preferably 40% by weight or higher, more preferably 90% by weight or
5 higher, and still more preferably 96.5% by weight or higher.”⁴⁹¹² Therefore, WO ‘118 discloses
6 EPA-E with “high purity” is a composition which contains EPA-E of 40% by weight, of total
7 fatty acid and derivatives, or higher. This non-specific disclosure is not a species of the claimed
8 generic range for the EPA composition in the claimed pharmaceutical composition.

9 The Federal Circuit has explained that “a preferred . . . range . . . that slightly overlaps the
10 . . . range claimed in the” patent is insufficient for anticipation.⁴⁹¹³ In *Atofina*, the prior art
11 disclosed a preferred temperature range of 150 to 350 degrees, and the patent at issue claimed a
12 range between 330 and 450 degrees. The court explained that this slight overlap “is not
13 disclosed as . . . a species of the claimed generic range of 330 to 450 °C,”⁴⁹¹⁴ and therefore failed
14 to anticipate the claimed range.⁴⁹¹⁵ The court in *Atofina* also found that a prior art disclosure of a
15 range of 0.001 to 1.0 percent failed to anticipate the patent’s claimed range of 0.1 to 5.0
16 percent.⁴⁹¹⁶ The court explained that “although there is a slight overlap, no reasonable fact finder
17 could determine that this overlap describes the entire claimed range with sufficient specificity to
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21 ⁴⁹¹² WO ‘118 at 22.

22 ⁴⁹¹³ *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 1000 (Fed. Cir. 2006).

23 ⁴⁹¹⁴ *Atofina*, 441 F.3d at 1000.

24 ⁴⁹¹⁵ *Atofina*, 441 F.3d at 1000.

⁴⁹¹⁶ *Id.*

1 anticipate this element of the claim. The ranges are different, not the same. . . . Thus, there is no
2 anticipation.”⁴⁹¹⁷

3 Similarly, although there may be some overlap between the E-EPA content disclosed by
4 WO ‘118 and the ranges claimed by the ‘929 patent, WO ‘118 does not specifically highlight the
5 overlapping area. The high content of E-EPA in the claimed pharmaceutical composition is a
6 critical factor of the invention disclosed in the ‘929 patent. Therefore, WO ‘118’s broad
7 disclosure of the E-EPA content in its invention does not describe the claimed range with
8 sufficient specificity and cannot anticipate the independent claim of the ‘929 patent.

9 WO ‘118 is additionally insufficient for anticipation because it does not expressly
10 disclose the recited DHA content of the claimed pharmaceutical composition. In fact, WO ‘118
11 makes no distinction between EPA and DHA, stating that “[a]nother preferable fatty acid is
12 DHA-E.”⁴⁹¹⁸ The disclosure goes on to state that the composition of the invention is preferably
13 one having high purity of EPA-E and DHA-E. The recited DHA content of the claimed
14 pharmaceutical composition is a critical factor of the invention disclosed in the ‘929 patent.

15 The disclosure of WO ‘118 treats DHA and EPA interchangeably. The disclosed
16 concentrations of EPA and DHA may range from 0 to 100% and every concentration in between.
17 There is no express teaching or guidance directing the person of ordinary skill in the art to the
18 claimed EPA compositions, Therefore, WO ‘118’s broad disclosure, which indicates no
19 difference between the use of EPA or DHA in its invention, cannot anticipate the independent
20 claim of the ‘929 patent.

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⁴⁹¹⁷ *Id.*

24 ⁴⁹¹⁸ WO ‘118 at 22.

1 Defendants contend that Plaintiffs are estopped from arguing there is any material
2 difference between “not more than about 4% DHA” and “substantially no DHA.” Defendants
3 provide no legal basis for their argument of estoppel. Defendants appear to suggest that testing
4 data obtained by Plaintiffs constitutes the basis for their assertion of estoppel. That argument is
5 without merit. Plaintiffs’ clinical data cannot form the basis for an estoppel argument and
6 Defendants have cited no authority to support their position suggesting the contrary. The
7 language of “not more than about 4% DHA” and “substantially no DHA” are different phrases
8 and are not co-extensive. Accordingly, plaintiffs are not estopped.

9 In the same paragraph containing their allegation of estoppel, Defendants also quote from
10 Amarin’s 2011 10-K. It is unclear whether these quotations are associated with their
11 unexplained estoppel arguments. To the extent that they are, Plaintiffs disagree that these
12 statements form the basis for any theory of estoppel. To the extent that Defendants quote
13 Amarin’s post-invention 10-K to make any invalidity argument, that is also unavailing. The
14 quoted statements do not identify any recited claim element, including the specific
15 pharmaceutical composition, the recited patient population, administration in the manner
16 claimed, and recited lipid effects. Nor can these elements of the asserted claims be inferred from
17 the quoted statements.

18 (4) WO ‘118 Does Not Describe the Dependent Claims

19 Defendants fail to address any of the claim elements of the dependent claims.
20 Defendants appear to concede that WO ‘118 does not expressly teach these elements, as they fail
21 to set forth any meaningful basis for concluding that WO ‘118 teaches these elements.
22 Defendants further argue that “aspects of the claims relating to effects that are to be achieved by
23 practicing the claimed method represent inherent, natural properties of EPA, and are entitled to
24 no patentable weight.” To the extent the recited claim elements relate to the administration step,

1 the dosage form or characteristics of the treated subject and the specific effect produced by the
2 claimed method, Defendants’ contentions that the claim limitations are inherent properties of
3 EPA are unavailing. While Defendants assert that the inherent properties are exemplified in WO
4 ‘118, they fail to identify any basis, explanation, or even supporting argument for that assertion.
5 Defendants have not met the burden to establish anticipation with the naked assertion that the
6 effects are inherent, natural properties of EPA.

7 Further, Defendants entirely fail to prove that inherently discloses the recited claim
8 limitations. A prior art reference that “only ‘probably’ or ‘possibly’ meets the claims cannot
9 inherently anticipate as a matter of law.”⁴⁹¹⁹ “[A]nticipation by inherent disclosure is appropriate
10 only when the reference discloses prior art that must *necessarily* include the unstated
11 limitation.”⁴⁹²⁰ “It is not sufficient if a material element or limitation is ‘merely probably or
12 possibly present’ in the prior art.”⁴⁹²¹ Defendants fail to show that WO ‘118 “*necessarily*” meets
13 the recited claim elements relating to the administration step, the dosage form or characteristics
14 of the treated subject and the specific effect produced by the claimed method *every time*. WO
15 ‘118 fails to provide any data related to the TG, LDL-C, VLDL-C, non-HDL-C, Lp-PLA2, total
16 cholesterol, Apo-B, or any other lipid effect of the disclosed invention on patients described in
17 the publication. Further, WO ‘118 is a translated Japanese disclosure that makes no reference to,
18 let alone a disclosure of, a Western diet. Therefore, Defendants fail to prove by clear and
19 convincing evidence that the composition disclosed by WO ‘118 meets any dependent claim
20 elements.

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22 ⁴⁹¹⁹ *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

23 ⁴⁹²⁰ *Transclean Corp. v. Bridgewood Servs., Inc.*, 290 F.3d 1364, 1373 (Fed. Cir. 2002) (emphasis in original).

24 ⁴⁹²¹ *In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1378 (Fed. Cir. 2007).

1 **3. The Claims of the '929 Patent Would Not Have Been Obvious In**
2 **Light of the Asserted References**

3 Defendants identify 77 separate references that it asserts somehow render the claims of
4 the '929 patent obvious.⁴⁹²² Defendants fail to demonstrate by clear and convincing evidence
5 that any of these references, alone or in combination, would render obvious any claims of the
6 '929 patent. Defendants' arguments rely on hindsight by impermissibly using the blueprint of
7 the '929 patent itself to guide its combination of references.⁴⁹²³ Defendants chart a laundry list
8 of 77 separate references, without explanation. Defendants' disclosures do not comply with
9 Local Patent Rule 1-8(d) and fail to put Plaintiffs on notice of how these references allegedly
10 establish that the asserted claims are allegedly *prima facie* obviousness. Consequently, Plaintiffs
11 cannot respond to undisclosed combinations and arguments.⁴⁹²⁴

12 Despite the general, non-limiting nature of Defendants' Joint Invalidity Contentions,
13 Plaintiffs have discerned and will specifically respond to the following alleged prior art
14 combinations:

- 15 • 1) “. . .the asserted claims of the '929 patent would have been obvious over the
16 Omacor PDR/Lovaza PDR in combination with the known clinical benefits of
17 administering pure EPA as evidenced by Katayama and/or Matsuzawa, further in
18 view of Nozaki and/or Hayashi, and further in view of Leigh-Firbank and/or Mori
19 2000.”
- 20 • 2) “. . .the asserted claims of the '929 patent would have been obvious over the
21 Omacor PDR/Lovaza PDR in combination with the known clinical benefits of

19 ⁴⁹²² Defendants' Joint Invalidity Contentions at 13-25.

20 ⁴⁹²³ *In re Suong-Hyu Hyon*, 679 F.3d 1363, 1371 (Fed. Cir. 2012) (“It is impermissible to use the claimed invention
21 as an instruction manual or ‘template’ to piece together the teachings of the prior art so that the claimed invention is
22 obvious.” (citing *In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992))).

22 ⁴⁹²⁴ This includes Defendants' improper attempt to incorporate by reference any alleged prior art or argument,
23 including Defendants' attempt to incorporate by reference “the reasons set forth in the opposition proceedings for
24 EP 2 395 991 B1” in the European Patent Office. Such wholesale incorporation by reference does not satisfy the
25 Defendants' obligations or burden of proof and is contrary to the Nevada Local Patent Rules, which require that
26 each prior art be identified specifically. *See* Local Pat. R. 1-8. Plaintiffs reserve the right to strike any attempt to
27 rely on undisclosed or insufficiently disclosed references or argument.

1 administering purified EPA as evidenced by Katayama, Matsuzawa and/or Takaku,
2 further in view of Nozaki and/or Hayashi, and further in view of Grimsgaard, Mori
2000 and/or Maki.”

- 3 • 3) “. . .the asserted claims of the ’929 patent would have been obvious over the
4 Omacor PDR/Lovaza PDR in combination with the known clinical benefits of
5 administering pure EPA as evidenced by Katayama in view of Satoh and/or in view
6 of Satoh or Shinozaki in further view of Contacos.”
- 7 • 4) “. . . the asserted claims of the ’929 patent would have been obvious over WO ’118
8 or WO ’900 in combination with treatment regimen of Lovaza as evidenced by the
9 Lovaza PDR, and further in view of Leigh-Firbank and/or Mori 2000.”
- 10 • 5) “. . . the asserted claims of the ’929 patent are obvious over WO ’118, the ’900
11 publication, Grimsgaard, Mori 2000 and/or Maki in combination with treatment
12 regimen of Omacor/Lovaza as evidenced by the Omacor PDR/Lovaza PDR, and
13 further in view of Katayama, Matsuzawa and/or Takaku.”

14 A patent claim is invalid “if the differences between the subject matter sought to be
15 patented and the prior art are such that the subject matter as a whole would have been obvious at
16 the time the invention was made to a person having ordinary skill in the art.”⁴⁹²⁵ Obviousness is
17 a legal determination, but it turns on factual inquiries into (1) the level of ordinary skill in the art,
18 (2) the scope and content of the prior art, and (3) the differences between the prior art and the
19 claims at issue.⁴⁹²⁶

20 In evaluating obviousness, each prior art reference must be evaluated for all that it
21 teaches, including the portions that would lead away from the claimed invention.⁴⁹²⁷ Indeed, any
22 teaching in the art that points away from the claimed invention must be considered.⁴⁹²⁸ A
23 reference teaches away if a person of ordinary skill, upon reading the reference, would be
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21 ⁴⁹²⁵ 35 U.S.C. § 103(a).

22 ⁴⁹²⁶ *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966); *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007).

23 ⁴⁹²⁷ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011).

24 ⁴⁹²⁸ *Tec Air, Inc. v. Denso Mfg. Mich. Inc.*, 192 F.3d 1353, 1359-60 (Fed. Cir. 1999).

1 discouraged from following the path set out in the reference, or would be led in a direction
2 divergent from the path that was taken by the applicant.⁴⁹²⁹ For instance, a reference teaches
3 away if it suggests that the line of development flowing from the reference's disclosure is
4 unlikely to be productive of the result sought by the applicant.⁴⁹³⁰

5 In order to find obviousness based on a combination of references, there must be some
6 rationale for combining the references in the way claimed that is separate and apart from the
7 hindsight provided by the patented invention itself.⁴⁹³¹ The law prohibits an obviousness
8 challenge based on a hindsight reconstruction of the claimed invention from isolated prior art
9 references. It is improper for "the claims [to be] used as a frame, and individual, naked parts of
10 separate prior art references [to be] employed as a mosaic to recreate a facsimile of the claimed
11 invention."⁴⁹³² "The invention must be viewed not after the blueprint has been drawn by the
12 inventor, but as it would have been perceived in the state of the art that existed at the time the
13 invention was made."⁴⁹³³

14 "The determination of obviousness is made with respect to the subject matter as a whole,
15 not separate pieces of the claim."⁴⁹³⁴ "[A] patent composed of several elements is not proved
16 obvious merely by demonstrating that each of its elements was, independently, known in the
17 prior art."⁴⁹³⁵ "This is so because inventions in most, if not all, instances rely upon building

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19 ⁴⁹²⁹ *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994).

20 ⁴⁹³⁰ *Id.*

21 ⁴⁹³¹ *Immogenetics, N.V. v. Abbott Labs*, 512 F.3d 1363, 1373–74 (Fed. Cir. 2008).

22 ⁴⁹³² *See W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1552 (Fed. Cir. 1983)

23 ⁴⁹³³ *Sensonics, Inc. v. Aerosonic Corp.*, 81 F.3d 1566, 1570 (Fed. Cir. 1996)

24 ⁴⁹³⁴ *Sanofi Syntheolabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008)

⁴⁹³⁵ *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007))

1 blocks long since uncovered, and claimed discoveries almost of necessity will be combinations
2 of what, in some sense, is already known.”⁴⁹³⁶

3 Accordingly, it is improper to pick and choose isolated elements from the prior art and
4 combine them so as to yield the invention⁴⁹³⁷ or to modify a prior art reference in a way that
5 “would destroy the fundamental characteristics of that reference.”⁴⁹³⁸ Moreover, a combination
6 is not obvious where “it would be impossible to apply these teachings [of the secondary
7 reference] to the [primary reference] without entirely changing the basic mechanism and
8 procedure thereof,”⁴⁹³⁹ or where the proposed combination requires “material and radical
9 modification in order to conform to [the patentee’s] claims” or a “total reconstruction” of the
10 prior art device.⁴⁹⁴⁰ Furthermore, it is improper “to modify the secondary reference before it is
11 employed to modify the primary reference” in assessing obviousness.⁴⁹⁴¹

12 Further, a party asserting obviousness in view of a combination of prior art disclosures
13 must show that a person of ordinary skill in the relevant field had an “apparent reason” to
14 combine the elements in the manner claimed⁴⁹⁴² and “a reasonable expectation of success.”⁴⁹⁴³

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16 ⁴⁹³⁶ *KSR*, 550 U.S. at 418-419.

17 ⁴⁹³⁷ *Abbott Labs v. Sandoz, Inc.*, 544 F.3d 1341, 1348 (Fed. Cir. 2008)

18 ⁴⁹³⁸ *Apple, Inc. v. Samsung Elec. Co., Ltd.*, 678 F.3d 1314, 1331 (Fed. Cir. 2012)

19 ⁴⁹³⁹ *In re Irmischer*, 262 F.2d 85, 87 (CCPA 1958)

20 ⁴⁹⁴⁰ *Id.* at 88.

21 ⁴⁹⁴¹ *In re Hummer*, 241 F.2d 742, 745 (CCPA 1957)

22 ⁴⁹⁴² *KSR*, 550 U.S. at 417–19; *TriMed, Inc. v. Stryker Corp.*, 608 F.3d 1333, 1341 (Fed. Cir. 2010). Hindsight may
23 not be employed to identify relevant prior art and relevant teachings therein: *Heidelberger Druckmaschinen AG v.*
24 *Hantscho Comm. Prods., Inc.*, 21 F.3d 1068, 1071–72 (Fed. Cir. 1994); *Monarch Knitting Mach. Corp. v. Sulzer*
Morat GmbH, 139 F.3d 877, 881 (Fed. Cir. 1998).

⁴⁹⁴³ *Proctor & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (henceforth, “P&G”);
Takeda Chem. Indus. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1361 (Fed. Cir. 2007); *KSR*, 550 U.S. at 416 (a
combination of elements “must do more than yield a predictable result;” combining elements that work together “in
an unexpected and fruitful manner” would not have been obvious).

1 For chemical compounds, there must have been a reason both to select the prior art
2 compound “most promising to modify” and to make the necessary changes to arrive at the
3 claimed compound.⁴⁹⁴⁴ This protects against the use of hindsight to pick through the prior art
4 based solely on structural similarity to the claimed compound.⁴⁹⁴⁵ Any assertion of an “apparent
5 reason” must find a basis in the factual record.⁴⁹⁴⁶

6 The “reasonable expectation of success” for a chemical compound must be of all of a
7 claimed compound’s relevant properties,⁴⁹⁴⁷ including those discovered after the patent was filed
8 or even issued.⁴⁹⁴⁸ “The basic principle behind this rule is straight-forward—that which would
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10 ⁴⁹⁴⁴ *Daiichi Sankyo Co. v. Matrix Labs. Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010); *Takeda*, 492 F.3d at 1355, 1359–
11 60; P&G, 566 F.3d at 994–95; *Eisai Co. Ltd. v. Dr. Reddy’s Labs., Ltd.*, 533 F.3d 1533, 1358 (Fed. Cir. 2008); *Eli
Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 471 F.3d 1369, 1378–80 (Fed. Cir. 2006).

12 ⁴⁹⁴⁵ *Daiichi Sankyo*, 619 F.3d at 1354; *Pfizer*, 2010 WL 339042, at *14. *Accord In re Vaidyanathan*, 381. 985, 994
13 (Fed. Cir. 2010) (nonprecedential); *Processing Corp. v. Am. Maize-Products Co.*, 840 F.2d 902, 907 (Fed. Cir.
1988); *Power-One*, 599 F.3d at 1351–52; *Crown Ops. Int’l, Ltd. v. Solutia, Inc.*, 289 F.3d 1367, 1376 (Fed. Cir.
2002).

14 ⁴⁹⁴⁶ *See, e.g., Vaidyanathan*, 381. at 993–94 (“[W]hile KSR relaxed some of the formalism of earlier decisions
15 requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did not remove the need to
16 anchor the analysis in explanation of how a person of ordinary skill would select and apply the teachings of the
17 references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi Sankyo*, 619 F.3d at
18 1354 (The assertion of a starting point “must avoid hindsight bias; it must look at the state of the art *at the time the
invention was made* to find a motivation to select and then modify a lead compound to arrive at the claimed
19 invention.” This turns on the known “properties and elements of the prior art compounds.”); *Forest Labs.*, 438
F.Supp.2d at 492–93 (rejecting defendants’ contention that claims to (+)-citalopram were “prima facie obvious in
light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding that
20 defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been
21 motivated to resolve citalopram in June 1988”).

22 ⁴⁹⁴⁷ *Yamanouchi Pharm. Co., Ltd. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1345 (Fed. Cir. 2000) (“The success
of discovering famotidine . . . was finding a compound that had high activity, few side effects, and lacked toxicity. . .
23 . [T]he ordinary medicinal chemist would not have expected famotidine to have the ‘most desirable combination of
24 pharmacological properties’ that it possesses.”); *Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 364 F.Supp.2d
820, 908 (S.D. Ind. 2005) (“[S]uccess was not simply finding a compound as active as clozapine . . . Here, the
ordinary medicinal chemist . . . would not have expected olanzapine to have the highly desirable combination of
pharmacological properties that it possesses.”).

⁴⁹⁴⁸ *Knoll Pharm. Inc. v. Teva Pharms. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004); *Eli Lilly*, 364 F.Supp.2d at
908.

1 have been surprising to a person of ordinary skill in a particular art would not have been
2 obvious.”⁴⁹⁴⁹ Any assertion of a “reasonable expectation of success” must find a basis in the
3 factual record.⁴⁹⁵⁰

4 In an obviousness determination, any objective indicia of nonobviousness must be taken
5 into account.⁴⁹⁵¹ An objective indicium is any “event[] proved to have actually happened in the
6 real world” that evidences the nonobvious nature of the invention.⁴⁹⁵² The existence of an
7 enduring, unmet need, difficulties encountered by those skilled in the field, unexpected or
8 surprising results, expressions of skepticism, industry praise, commercial success, and copying
9 are classical indicia of nonobviousness.⁴⁹⁵³ These factual inquiries “guard against slipping into
10 use of hindsight,”⁴⁹⁵⁴ and “may often be the most probative and cogent evidence of
11 nonobviousness.”⁴⁹⁵⁵

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14 ⁴⁹⁴⁹ *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995) (“The principle applies most often to the less predictable fields, such as chemistry, where minor changes in a product or process may yield substantially different results.”).

15 ⁴⁹⁵⁰ See, e.g., *Sanofi-Synthelabo*, 550 F.3d at 1089 (“Apotex argues that the district court applied an incorrect inquiry, and that the correct inquiry is not whether the results obtained with the separated enantiomer were unexpected, but whether it would have been obvious to separate and test the enantiomers, based on the general knowledge that enantiomers can exhibit different properties. Apotex refers to *In re Adamson*, 275 F.2d [952,] 955 [(C.C.P.A. 1960)], where the CCPA held that an enantiomer would have been obvious in view of its racemate. However, the scientific facts differed from these herein, for in *Adamson* the court found that it was ‘particularly expected’ that the specific enantiomer would have the observed properties. In contrast, as Sanofi points out, in *In re May*, 574 F.2d at 1095, the CCPA held, as to the enantiomer claimed therein, that the appellant ‘established a substantial record of unpredictability vis-à-vis a highly significant combination of properties.’”).

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19 ⁴⁹⁵¹ *Graham*, 383 U.S. at 17–18; KSR, 550 U.S. at 406; *Jones v. Hardy*, 727 F.2d 1524, 1530–31 (Fed. Cir. 1984).

20 ⁴⁹⁵² *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1569 (Fed. Cir. 1987).

21 ⁴⁹⁵³ *Graham*, 383 U.S. at 17–18; KSR, 550 U.S. at 406; *U.S. v. Adams*, 383 U.S. 39, 52 (1966); *Merck & Co. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1376 (Fed. Cir. 2005); *Panduit*, 810 F.2d at 1569; *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995); *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988); *Janissen*, 456 F.Supp.2d at 669–72.

22 ⁴⁹⁵⁴ *Graham*, 383 U.S. at 36.

23 ⁴⁹⁵⁵ *Ortho-McNeil Pharm. Inc. v. Mylan Labs. Inc.*, 520 F.3d 1358, 1365 (Fed. Cir. 2008) (quoting *Catalina Lighting Inc. v. Lampros Plus, Inc.*, 295 F.3d 1277, 1288 (Fed. Cir. 2002)).

1 Also, as with assertions of anticipation, in order for an invention to be obvious, it must
2 have been fully “in possession” of the public—which requires that the claimed invention have
3 been enabled.⁴⁹⁵⁶

4 A element-by-element analysis, identifying each limitation of each asserted claim that is
5 absent from the prior art, is provided below, and also provided at Exhibit K. The contentions
6 below are incorporated by reference into Exhibit K, and vice-versa.

7 a) General Overview

8 Defendants fail to provide a single prior art reference that discloses administration of the
9 recited composition of EPA ethyl (in the recited purity) to the very-high TG patient population
10 (≥ 500 mg/dL) and the resulting lipid effects. Instead, they rely on a large number of studies,
11 many of which are not placebo controlled, which administer EPA, DHA, or both, in varying
12 degrees of purity, in a wide range of doses and administration periods, to subjects who have
13 baseline TG levels lower than 500 mg/dL and in many cases significantly lower. The importance
14 of a placebo-controlled study cannot be overstated. Randomized, double-blind placebo
15 controlled studies are considered the “gold standard” of clinical studies. Studies involving the
16 administration of fish oils or omega-3 fatty acids which are not placebo controlled cannot
17 distinguish between the effect of the placebo from that of the active agent. Studies which
18 administer mixtures enriched for either EPA or DHA are not suitable for evaluating the
19 independent effects of EPA and DHA.⁴⁹⁵⁷ Inconsistency in dosages and administration periods

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21 ⁴⁹⁵⁶ *In re Kumar*, 418 F.3d 1361, 1368 (Fed. Cir. 2005) (“[I]n order to render an invention unpatentable for
22 obviousness, the prior art must enable a person of ordinary skill to make and use the invention.”); *In re Hoeksema*,
399 F.2d 269, 274 (C.C.P.A. 1968) (“[I]f the prior art of record fails to disclose or render obvious a method for
23 making a claimed compound, at the time the invention was made, it may not be legally concluded that the compound
24 itself is in the possession of the public.”).

⁴⁹⁵⁷ *Mori* 2006 at 96.

1 and variations in the administered fatty acid compositions also complicate the interpretation of
2 the results and limit the application of these studies.

3 Defendants also rely on the ANCHOR study to argue that Amarin’s use of “patients with
4 very high TGs together with patients with high and borderline high TGs indicates that there is no
5 medical difference in responsiveness to treatment among the groups of people.”⁴⁹⁵⁸ Defendants
6 mischaracterize the ANCHOR study. The ANCHOR study was a multi-center, placebo-
7 controlled, randomized, double-blind, 12-week pivotal Phase 3 study on the effects of Vascepa in
8 patients with high triglycerides (≥ 200 mg/dL and < 500 mg/dL) who were also on statin therapy.
9 Defendants point to the reported “Min-max” TG levels, 157-782 mg/dL, for the AMR101 4g
10 daily group to argue that Amarin used very-high TG patients with high and borderline-high TG
11 patients. However, the mean TG level for this same group, 281.1 mg/dL, makes it clear that
12 almost all of the 233 patients in this group had baseline TG values well below 500 mg/dL.⁴⁹⁵⁹ In
13 addition, the mean baseline TG values for the Placebo and AMR101 2g daily groups were
14 reported as 270.6 mg/dL and 270.2 mg/dL, respectively. Further, Amarin did *not* attempt to use
15 the results of ANCHOR to predict lipid effects in the very high TG patient population. Neither a
16 person of ordinary skill, nor the FDA, would attempt to draw conclusions or gain insight into the
17 very high TG patient population from the ANCHOR trial. In fact, Amarin simultaneously (to
18 ANCHOR) conducted an independent study with Vascepa in patients with very high TG levels.
19 Contrary to Defendants’ assertion, the ANCHOR study does *not* indicate that there is no medical
20 difference in responsiveness to treatment between the very-high TG patient population and lower

21 _____
22 ⁴⁹⁵⁸ Defendants’ Joint Invalidity Contentions at 666 (*see* FN 126).

23 ⁴⁹⁵⁹ FDA Briefing Document, Oct. 16, 2013 at pg. 26 (The mean baseline TG value for the placebo group was 270.6
24 mg/dL, AMR101 2g group was 270.2 mg/dL, and AMR101 4g group was 281.1 mg/dL. While there may have been
a few patients with TG > 500mg/dL in the AMR101 4g group, it is clear that the overwhelming majority had baseline
TG values < 500 mg/dL).

1 TG patient populations merely because there was possibly one patient with baseline TG levels of
2 at least 500 mg/dL.

3 As discussed above in Section III, patients with very-high TG levels were considered
4 fundamentally different from patients with borderline-high or high TGs from a clinical,
5 regulatory, and therapeutic perspective.⁴⁹⁶⁰ Clinically, the authoritative guidance to physicians
6 on the treatment of lipid disorders throughout the last decade, the Adult Treatment Panel III
7 (ATP-III) divided hypertriglyceridemic patients into three groups: normal/borderline high TG;
8 high TG; and very high TG. The primary risk faced by borderline-high and high TG patients
9 was atherosclerosis, while the primary risk faced by very-high TG patients was acute
10 pancreatitis. Therefore, the primary focus of treatment, as described by the ATP III, for
11 borderline-high and high TG patients was to lower LDL-C levels. In contrast, the priority for
12 very-high TG patients was TG reduction. This distinction between patients with borderline-
13 high/high TG levels and patients with very high TG levels is also observed on the regulatory
14 level. The FDA recognized the different clinical status of the very-high TG population by
15 approving some drugs specifically for the very-high TG group without granting treatment
16 indications for the borderline-high or high TG populations (i.e. Lovaza/Omacor).⁴⁹⁶¹

17 Finally, from a therapeutic standpoint, a person of ordinary skill understood that the
18 effects of lipid-lowering therapies on lipid parameters, such as LDL-C, varied depending on the
19 patient's baseline TG level. Fibrates and prescription omega-3 therapies (two well-known
20 classes of drugs used to treat patient with very-high TGs to lower TG levels at the time of the
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⁴⁹⁶⁰ See Bays Jan. 8, 2012 Decl., ¶ 20.

24 ⁴⁹⁶¹ See Bays Jan. 8, 2012 Decl., ¶ 22.

1 invention), for example, exhibit different effects on LDL-C levels, depending on the baseline TG
2 level of the patient receiving treatment.

3 Fibrates lower both TGs and LDL-C in normal and borderline-high TG patients, but
4 increase LDL-C in very-high TG patients.⁴⁹⁶² The fibrate, Tricor (fenofibrate), for example,
5 decreased LDL-C significantly in both patients with normal baseline TG values (about 31%)⁴⁹⁶³
6 and high baseline TG values (mean baseline TG value of 231.9 mg/dL) (about 20%).⁴⁹⁶⁴ In
7 patients approaching very-high TGs levels (mean baseline TG value of 432 mg/dL), a non-
8 significant increase in LDL-C was observed.⁴⁹⁶⁵ In patients with very-high TGs (mean baseline
9 TG = 726 mg/dL), a significant increase in LDL-C was observed (about 45%).⁴⁹⁶⁶ Similar
10 results were seen with the administration of Lopid (gemfibrozil).⁴⁹⁶⁷ The differing effects of
11 fibrates, such as Tricor, on TG, LDL-C, HDL-C and Total-C based on baseline TG values
12 demonstrates how a person of ordinary skill at the time of the invention would have understood
13 that one could not simply assume that an observed effect of a TG-lowering agent on lipid
14 parameters in patients with normal, borderline-high or high TG levels would be the same in
15 patients with very-high TG levels (at least 500 mg/dL) compared to a patient with high or
16 borderline-high TG levels (150-499 mg/dL). As illustrated in the table, below, patients with
17 normal or high baseline TG levels experience reduced LDL-C levels upon treatment with a TG-

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19 ⁴⁹⁶² See Bays 2008 II, at 214-15 (noting that a fibrate caused LDL-C to go down in borderline-high group, remain roughly the same in high TG group, and increase by around 50% in the very-high TG group).

20 ⁴⁹⁶³ Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

21 ⁴⁹⁶⁴ *Id.*

22 ⁴⁹⁶⁵ *Id.* See also, Trilipix Label at 27.

23 ⁴⁹⁶⁶ *Id.* See also, Trilipix Label at 27.

24 ⁴⁹⁶⁷ See Otvos at 1558 (showing administration of Gemfibrozil to patients with borderline-high baseline TG levels had no impact on LDL-C levels); Manttari at 14 and 16 (stating that the effect of gemfibrozil on LDL-C was dependent on initial TG levels, no change was observed for LDL-C in subjects with high baseline TG levels while subjects with normal or borderline-high baseline TG levels showed significant decreases in LDL-C).

1 reducing agent such as the fibrate, Tricor. Patients approaching very high TG levels (mean
 2 baseline TG level of 432 mg/dL) and patients with very high TG levels (mean baseline TG level
 3 of 726 mg/dL) experience significantly increased LDL-C levels.

Fibrate	Mean Baseline TG Value	TG	LDL-C	HDL-C	Total-C
Tricor (fenofibrate) ⁴⁹⁶⁸	101.7 mg/dL	-23.5%*	-31.4%*	+9.8%*	-22.4%*
	231.9 mg/dL	-35.9%*	-20.1%*	+14.6%*	-16.8%*
	432 mg/dL	-46.2*	+14.5	+19.6*	-9.1*
	726 mg/dL	-54.5*	+45.0*	+22.9*	-13.8*

* = p < 0.05 vs. Placebo

11 Lovaza/Omacor was (and is) a prescription omega-3 therapy known to have differing
 12 lipid effects depending on the patient's baseline TG level. When administered to patients with
 13 borderline-high baseline TG levels, Lovaza/Omacor significantly reduced TGs and raised HDL-
 14 C.⁴⁹⁶⁹ It had no significant effect on other lipid-related variable, including LDL-C and Apo-
 15 B.⁴⁹⁷⁰ However, when administered to patients with very-high baseline TG levels, TGs were
 16 reduced significantly by nearly 50% while LDL-C increased sharply by nearly 50%.⁴⁹⁷¹

21 ⁴⁹⁶⁸ Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

22 ⁴⁹⁶⁹ Chan 2002 I at 2379-81.

23 ⁴⁹⁷⁰ *Id.*; *See also*, Westphal at 918.

24 ⁴⁹⁷¹ *See* Weintraub Sept. 7, 2011 Decl., ¶ 23 (citing Lovaza package insert); Bays May 16, 2011 Decl., ¶ 10; *see also*, Lovaza PDR and Omacor PDR.

1 Although the increase in LDL-C was concerning, it was understood that the overall lipid effect of
2 Lovaza/Omacor was beneficial.⁴⁹⁷²

3 Fibrates and prescription Omega-3 therapies demonstrate that one could not simply
4 assume that a lipid lowering agent would have the same effect in a patient with very-high TG
5 levels (≥ 500 mg/dL) as a patient with borderline-high or high TG levels (150-499 mg/dL). They
6 also demonstrate that one of ordinary skill would not expect to see an increase in LDL-C when
7 the normal, borderline-high or high TG patient populations were administered omega-3 fatty
8 acids. As discussed in Section III, the increase in LDL-C for very-high TG patients was
9 expected as a natural consequence of lowering TGs. A person of ordinary skill would have
10 considered the rise in LDL-C to be a direct consequence of TG lowering through increased
11 VLDL particle conversion.⁴⁹⁷³ Because normal to high TG patients did not have the large
12 backlog of VLDL particles that very high TG patients have, a person of ordinary skill did not
13

14 ⁴⁹⁷² See Pownall *et al.*, *Correlation of serum triglyceride and its reduction by ω -3 fatty acids with lipid transfer*
15 *activity and the neutral lipid compositions of high-density and low-density lipoproteins*, 143 *Atherosclerosis* 285,
16 295 (1999) (“Treatment with ω -3 fatty acids appear to change the lipid profile of individuals with elevated TG to
17 one that may be less atherogenic by changing LDL structure; lowering serum [cholesterol ester transfer activity],
18 serum TG and VLDL-C; and increasing serum HDL-C.”); Stalenhoef at 134 (stating that “Omacor . . . adversely
19 raise LDL cholesterol concentration but the increase in LDL cholesterol concentration reflects a less atherogenic
20 light LDL subfraction profile that may be favorable”); Harris 1997 at 389 (“The increase in LDL, which was
21 substantial on a percentage basis, has been a common finding in past studies in [very-high TG] patients. It may not
22 be as problematic as it appears, however.” And “the use of omega-3 fatty acids for the treatment of severe
23 hypertriglyceridemia may be beneficial not only for the short-term prevention of acute pancreatitis, but also for the
24 long-term prevention of CHD”); Bays III at 248 (“No clinical trial data exist that this rise in LDL-C represents harm
or potential “toxicity” to patients. In fact, most evidence supports that omega-3 fatty acids reduce cardiovascular
risk as do fibrates. Importantly, clinical trials mostly support that even with increases in LDL-C, omega-3 fatty
acids decrease the total cholesterol (TC) carried by atherogenic lipoproteins, as reflected by decreased non-HDL-C
levels (TC minus HDL-C.)”

21 ⁴⁹⁷³ Bays May 16, 2011 Decl., ¶ 11 (noting the “general knowledge in the art that omega-3 fatty acids as a class
22 increase LDL-C” in very-high TG patients); McKenney 2007, at 724 (“Because of the increase in LDL levels
23 observed in some patients treated with prescription omega-3, LDL levels also should be periodically assessed during
24 treatment.”); Bays in Kwiterovich at 247 (noting that increased LPL activity caused by fish oil “helps explain some
of the seemingly paradoxical lipid effects found with their clinical use, for example, the rise in LDL-C with the
decrease in VLDL.”).

1 expect LDL-C to increase in normal to high TG patients. It was also well known that the degree
2 of LDL-C elevation observed with prescription omega-3 fatty acids, such as Lovaza/Omacor,
3 was linked to baseline TG levels; that LDL-C levels increased the most in patients with the
4 highest baseline TG levels⁴⁹⁷⁴ and did not increase for patients with lower TG levels. Therefore,
5 the prior art defendants rely upon to show that EPA did *not* increase LDL-C levels in normal,
6 borderline-high or high TG patients was *expected*.

7 Defendants contend that “a composition and its properties are inseparable, and therefore
8 do not impart any additional patentability,” and that “all of the limitations regarding the
9 properties of the ethyl EPA compound identified in the claims of the ‘929 patent are inherent to
10 the compound when administered to a human subject.”⁴⁹⁷⁵ Inherency may not supply a missing
11 claim limitation in an obviousness analysis unless the inherency would have been obvious to one
12 of ordinary skill in the art.⁴⁹⁷⁶ Obviousness is based on what is *known* in the art at the time of the
13 invention.⁴⁹⁷⁷ It was not known or reasonably expected at the time of the claimed invention that
14 purified EPA, when administered to patients with very-high TG levels (≥ 500 mg/dL), would not
15 substantially increase LDL-C or would reduce Apo-B. Nor was EPA’s effect on LDL-C and
16 Apo-B necessarily present, or the natural result of the combination of elements explicitly

18 ⁴⁹⁷⁴ Bays 2008 I at 400-402.

19 ⁴⁹⁷⁵ Defendants’ Joint Invalidity Contentions at 667.

20 ⁴⁹⁷⁶ See, e.g., *PAR Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1195–96 (Fed. Cir. 2014) (“A party must . . .
21 meet a high standard in order to rely on inherency to establish the existence of a claim limitation in the prior art in an
22 obviousness analysis—the limitation at issue necessarily must be present, or the natural result of the combination of
elements explicitly disclosed by the prior art.”); *In re Rijckaert*, 9 F.3d 1531, 1533–34 (Fed. Cir. 1993) (“The mere
fact that a certain thing may result from a given set of circumstances is not sufficient [to establish inherency].”) (internal quotation omitted).

23 ⁴⁹⁷⁷ *In re Spormann*, 363 F.2d 444, 448 (CCPA 1966) (“That which may be inherent is not necessarily known.
24 Obviousness cannot be predicated on what is unknown.”).

1 disclosed by the prior art.⁴⁹⁷⁸ Therefore, inherency does not supply the missing claim elements
2 in the prior art cited by Defendants.

3 Defendants argue that the claims of the '929 patent which contain "a limiting clause, such
4 as 'to effect' or 'is effective to,'" simply express the intended result of a process step positively
5 recited and therefore are not elements.⁴⁹⁷⁹ This is incorrect. "There is nothing inherently wrong
6 with defining some part of an invention in functional terms."⁴⁹⁸⁰ When a clause "states a
7 condition that is material to patentability, it cannot be ignored in order to change the substance of
8 the invention."⁴⁹⁸¹ The claim term "to effect" acts as a positive limitation if the term represents
9 "unexpected and improved effects of administration of the claimed compound."⁴⁹⁸² In addition,
10 the elements represent unexpected and improved effects of administration of purified EPA,
11 because a person of ordinary skill would not have expected no substantial increase in LDL-C or
12 reduction in Apo-B when administering EPA to treat severe hypertriglyceridemia. Therefore, the
13 requirements for no substantial increase in LDL-C and reduction in Apo-B must be accorded
14 patentable weight.

15 b) Identification of Claim Elements Absent from Each Item of Prior
16 Art

17 Plaintiffs identify each limitation of each asserted claim that Plaintiffs believe is absent.
18 Where a limitation is absent from any Independent Claim, that limitation is absent from all
19 asserted claims, and that analysis is incorporated by reference into each dependent claim. For
20

21 ⁴⁹⁷⁸ See discussions below for Grimsgaard, Park, Nozaki Kurabayashi and Hayashi.

22 ⁴⁹⁷⁹ Defendants' Joint Invalidity Contentions at 668.

23 ⁴⁹⁸⁰ See MPEP 2173.05(g) (citing *In re Swinehart*, 439 F.2d 210 (CCPA 1971)).

24 ⁴⁹⁸¹ *Hoffer v. Microsoft Corp.*, 405 F.3d 1326, 1329 (Fed. Cir. 2005).

⁴⁹⁸² *AstraZeneca AB v. Dr. Reddy's Labs., Ltd.*, No. CIV.A.05-5553 JAP, 2010 WL 1981790, at *11-12 (D.N.J. May 18, 2010).

1 any reference, the fact that Plaintiffs do not list a particular limitation as absent from the asserted
2 claims is not a concession that such limitation is present in the reference. By discussing
3 Defendants' analysis of the "limitations" in the claims, Plaintiffs do not concede that Defendants
4 have appropriately divided the claim language for any purpose.

5 (1) WO '118

6 WO '118 discloses a composition containing EPA-E for preventing the occurrence of
7 cardiovascular events in multiple risk patients.

8 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of WO
9 '118 disclose or suggest elements of the '929 Claims. The cited portions of WO '118 do not
10 disclose or suggest these elements at least because they do not disclose or suggest administration
11 of EPA with the recited purity to a subject with the recited very high TG levels (at least 500
12 mg/dL). The cited portions of WO '118 also do not disclose or suggest the claimed
13 pharmaceutical composition with the recited fatty acid compositions or dosage.

14 With respect to Claim 1 of the '929 Patent (and therefore all asserted claims), WO '118
15 does not disclose or suggest a subject with the recited very high TG levels (at least 500 mg/dL).
16 WO '118 also does not disclose or suggest the claimed pharmaceutical composition with the
17 recited fatty acid composition or dosage.

18 Further, with respect to Claim 2, this reference fails to disclose or suggest or suggest the
19 subject having the recited baseline LDL-C levels. With respect to Claim 3, this reference fails to
20 disclose or suggest the subject having the recited baseline lipid levels reference. With respect to
21 Claim 4, this reference fails to disclose or suggest the recited reduction in TG without increasing
22 LDL-C in the subject with the claimed TG levels (at least 500 mg/dL). With respect to Claim 5,
23 this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in the subject
24 with the claimed TG levels (at least 500 mg/dL). With respect to Claim 6, this reference fails to

1 disclose or suggest the recited reduction in VLDL-C in the subject with the claimed TG levels (at
2 least 500 mg/dL). With respect to Claim 7, this reference fails to disclose or suggest the subject
3 with the recited very high TG levels (500-1500 mg/dL).

4 (2) WO '900

5 WO '900 describes methods for obtaining EPA-rich compositions.

6 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of WO
7 '900 disclose or suggest elements of the '929 Claims. The cited portions of WO '900 do not
8 disclose or suggest these elements at least because they do not disclose or suggest administration
9 of EPA with the recited purity to a subject with the recited very high TG levels (at least 500
10 mg/dL). The cited portions of WO '900 further do not disclose or suggest the claimed
11 pharmaceutical composition with the recited fatty acid composition, dosage or administration
12 period.

13 With respect to Claim 1 of the '929 Patent (and therefore all asserted claims), WO '900
14 does not disclose or suggest a subject with the recited very high TG levels (at least 500 mg/dL)
15 WO '900 also does not disclose or suggest the claimed pharmaceutical composition with the
16 recited fatty acid compositions, dosage or administration period.

17 Further, with respect to Claim 2, this reference does not disclose or suggest the subject
18 having the recited baseline LDL-C levels. With respect to Claim 3, this reference fails to
19 disclose or suggest the subject having the recited baseline lipid levels. With respect to Claim 4,
20 this reference fails to disclose or suggest the recited reduction in TG without increasing LDL-C
21 in the subject with the claimed very high TG levels (at least 500 mg/dL). With respect to Claim
22 5, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in the
23 subject with the claimed very high TG levels (at least 500 mg/dL). With respect to Claim 6, this
24 reference fails to disclose or suggest the recited reduction in VLDL-C in the subject with the

1 | claimed very high TG levels (at least 500 mg/dL). With respect to Claim 7, this reference fails to
2 | disclose or suggest the subject with the recited very high TG levels (500-1500 mg/dL).

3 | (3) Contacos

4 | Contacos describes a study designed to determine the safety and efficacy of a statin
5 | (pravastatin) combined with fish oil either alone or in combination, for the management of
6 | patients with mixed hyperlipidemia.

7 | In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of
8 | Contacos disclose or suggest elements of the '929 Claims. The cited portions of Contacos do not
9 | disclose or suggest these elements at least because they do not disclose or suggest administration
10 | of EPA with the recited purity to a subject with the recited very high TG levels (at least 500
11 | mg/dL). The cited portions of Contacos further do not disclose or suggest the claimed
12 | pharmaceutical composition with the recited fatty acid compositions, dosage, or administration
13 | period.

14 | With respect to Claim 1 of the '929 Patent (and therefore all asserted claims), Contacos
15 | does not disclose or suggest a subject with the recited very high TG levels (at least 500 mg/dL)
16 | Contacos also does not disclose or suggest the claimed pharmaceutical composition with the
17 | recited fatty acid compositions, dosage, or administration period.

18 | Further, with respect to Claim 4, this reference fails to disclose or suggest the
19 | administration of the claimed pharmaceutical composition to effect the recited reduction in TG
20 | without increasing LDL-C. With respect to Claim 5, this reference fails to disclose or suggest
21 | the administration of the claimed pharmaceutical composition to effect the recited reduction in
22 | Apolipoprotein B. With respect to Claim 6, this reference fails to disclose or suggest the
23 | administration of the claimed pharmaceutical composition to effect the recited reduction in
24 |

1 VLDL-C. With respect to Claim 7, this reference fails to disclose or suggest the subject with the
2 recited very high TG levels (500-1500 mg/dL).

3 (4) Grimsgaard

4 Grimsgaard conducted a double-blind, randomized, placebo-controlled, parallel design
5 intervention study to evaluate the dietary supplementation with EPA or DHA on serum lipids,
6 apolipoproteins, and serum phospholipid fatty acid composition in subjects with normal TG
7 levels.

8 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of
9 Grimsgaard disclose or suggest elements of '929 Claims. The cited portions of Grimsgaard do
10 not disclose or suggest these elements at least because they do not disclose or suggest
11 administration of EPA with the recited purity to a subject with the recited very high TG levels (at
12 least 500 mg/dL). The cited portions of Grimsgaard further do not disclose or suggest the
13 claimed pharmaceutical composition with the recited administration period.

14 With respect to Claim 1 of the '929 Patent (and therefore all asserted claims), Grimsgaard
15 does not disclose or suggest a subject with the recited very high TG levels (at least 500 mg/dL).
16 Grimsgaard also does not disclose or suggest the claimed pharmaceutical composition with the
17 recited administration period.

18 Further, with respect to Claim 4, this reference fails to disclose or suggest the recited
19 reduction in TG without increasing LDL-C in the subject with the claimed very high TG levels
20 (at least 500 mg/dL). With respect to Claim 5, this reference fails to disclose or suggest the
21 recited reduction in Apolipoprotein B in the subject with the claimed very high TG levels (at
22 least 500 mg/dL). With respect to Claim 6, this reference fails to disclose or suggest the recited
23 reduction in VLDL-C in the subject with the claimed very high TG levels (at least 500 mg/dL).
24

1 With respect to Claim 7, this reference fails to disclose or suggest the subject with the recited
2 very high TG levels (500-1500 mg/dL).

3 (5) Hayashi

4 Hayashi is directed to administration of ethyl icosapentate 1800mg (6 capsules) daily for
5 8 weeks. The purity of the composition is not reported. The study was not placebo controlled
6 and was conducted in 28 patients with familial combined hyperlipidemia and a serum tryglceride
7 concentration higher than 150 mg/dl or serum total cholestrol concentration higher than 220
8 mg/dl.

9 The portions of Hayashi cited by Defendants do not disclose or suggest elements of the
10 '929 patent claims. For example, the cited portions of Hayashi do not disclose or suggest
11 administration of EPA with the recited purity to a subject with the recited very high TG levels
12 who does not receive concurrent lipid altering therapy. Figure 2 demonstrates that no subject
13 had a TG level above 400 mg/dl. The cited portions of Hayahsi further do not disclose or
14 suggest the claimed pharmaceutical composition with the recited fatty acid compositions or
15 dosage. The cited portions of Hayashi further do not disclose or suggest a method to effect the
16 recited TG reduction without substantially increasing LDL-C in a subject with the recited very
17 high TG levels.

18 With respect to Claim 1 of the '929 Patent (and therefore all asserted claims), Hayashi
19 does not disclose or suggest a subject with the recited very high TG levels (at least 500 mg/dL)
20 Hayashi also does not disclose or suggest the claimed pharmaceutical composition with the
21 recited fatty acid compositions or dosage.

22 Further, with respect to Claim 2, this reference does not disclose or suggest the subject
23 having the recited baseline LDL-C levels. With respect to Claim 4, this reference fails to
24 disclose or suggest the administration of the claimed pharmaceutical composition to effect the

1 recited reduction in TG without increasing LDL-C in the subject with the claimed very high TG
2 levels (at least 500 mg/dL). With respect to Claim 5, this reference fails to disclose or suggest
3 the administration of the claimed pharmaceutical composition to effect the recited reduction in
4 Apolipoprotein B in the subject with the claimed very high TG levels (at least 500 mg/dL). With
5 respect to Claim 6, this reference fails to disclose or suggest the administration of the claimed
6 pharmaceutical composition to effect the recited reduction in VLDL-C in the subject with the
7 claimed very high TG levels (at least 500 mg/dL). With respect to Claim 7, this reference fails to
8 disclose or suggest the subject with the recited very high TG levels (500-1500 mg/dL).

9 (6) Katayama

10 Katayama was directed to an investigation of the safety and efficacy of Epadel during
11 long term treatment in patients with hyperlipidemia that was not placebo controlled. Notably,
12 Katayama did not disclose or suggest any LDL-C related data or describe any LDL-C effects and
13 was not placebo controlled.

14 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of
15 Katayama disclose or suggest elements of the '929 Claims. The cited portions of Katayama do
16 not disclose or suggest these elements at least because they do not disclose or suggest
17 administration of EPA with the recited purity to a subject with the recited very high TG levels (at
18 least 500 mg/dL). The cited portions of Katayama further do not disclose or suggest the claimed
19 pharmaceutical composition with the recited fatty acid compositions or dosage.

20 With respect to Claim 1 of the '929 Patent (and therefore all asserted claims), Katayama
21 does not disclose or suggest a subject with the recited very high TG levels (at least 500 mg/dL)
22 Katayama also does not disclose or suggest the claimed pharmaceutical composition with the
23 recited fatty acid compositions or dosage.

24

1 Further, with respect to Claim 2, this reference does not disclose or suggest the subject
2 having the recited baseline LDL-C levels. With respect to Claim 4, this reference fails to
3 disclose or suggest the administration of the claimed pharmaceutical composition to effect the
4 recited reduction in TG without increasing LDL-C in the subject with the claimed very high TG
5 levels (at least 500 mg/dL). With respect to Claim 5, this reference fails to disclose or suggest
6 the administration of the claimed pharmaceutical composition to effect the recited reduction in
7 Apolipoprotein B in the subject with the claimed very high TG levels (at least 500 mg/dL). With
8 respect to Claim 6, this reference fails to disclose or suggest the administration of the claimed
9 pharmaceutical composition to effect the recited reduction in VLDL-C in the subject with the
10 claimed very high TG levels (at least 500 mg/dL). With respect to Claim 7, this reference fails to
11 disclose or suggest the subject with the recited very high TG levels (500-1500 mg/dL).

12 (7) Leigh-Firbank

13 Leigh-Firbank studied the impact of fish-oil intervention on LDL oxidation, particle
14 density and concentration in subjects with an atherogenic lipoprotein phenotype.

15 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of
16 Leigh-Firbank disclose or suggest elements of the '929 Claims. The cited portions of Leigh-
17 Firbank do not disclose or suggest these elements at least because they do not disclose or suggest
18 administration of EPA with the recited purity to a subject with the recited very high TG levels (at
19 least 500 mg/dL). The cited portions of Leigh-Firbank further do not disclose or suggest the
20 claimed pharmaceutical composition with the recited fatty acid compositions, dosage, or
21 administration period.

22 With respect to Claim 1 of the '929 Patent (and therefore all asserted claims), Leigh-
23 Firbank does not disclose or suggest a subject with the recited very high TG levels (at least 500
24

1 mg/dL) Leigh-Firbank also does not disclose or suggest the claimed pharmaceutical composition
2 with the recited fatty acid compositions, dosage, or administration period.

3 Further, with respect to Claim 4, this reference fails to disclose or suggest the
4 administration of the claimed pharmaceutical composition to effect the recited reduction in TG
5 without increasing LDL-C. With respect to Claim 5, this reference fails to disclose or suggest
6 the administration of the claimed pharmaceutical composition to effect the recited reduction in
7 Apolipoprotein B. With respect to Claim 6, this reference fails to disclose or suggest the
8 administration of the claimed pharmaceutical composition to effect the recited reduction in
9 VLDL-C. With respect to Claim 7, this reference fails to disclose or suggest the subject with the
10 recited very high TG levels (500-1500 mg/dL).

11 (8) Lovaza PDR

12 The Lovaza PDR is the Physicians' Desk Reference describing Lovaza.

13 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of the
14 Lovaza PDR disclose or suggest elements of the '929 Claims. The cited portions of the Lovaza
15 PDR do not disclose or suggest these elements at least because they do not disclose or suggest
16 administration of EPA with the recited purity to a subject with the recited very high TG levels
17 (at least 500 mg/dL). The cited portions of the Lovaza PDR further do not disclose or suggest
18 the claimed pharmaceutical composition with the recited fatty acid compositions or
19 administration period.

20 With respect to Claim 1 of the '929 Patent (and therefore all asserted claims), the Lovaza
21 PDR does not disclose or suggest the claimed pharmaceutical composition with the recited fatty
22 acid compositions or administration period.

23 Further, with respect to Claim 4, this reference fails to disclose or suggest the
24 administration of the claimed pharmaceutical composition to effect the recited reduction in TG

1 without increasing LDL-C. With respect to Claim 5, this reference fails to disclose or suggest
2 the administration of the claimed pharmaceutical composition to effect the recited reduction in
3 Apolipoprotein B. With respect to Claim 6, this reference fails to disclose or suggest the
4 administration of the claimed pharmaceutical composition to effect the recited reduction in
5 VLDL-C. With respect to Claim 7, this reference fails to disclose or suggest the subject with the
6 recited very high TG levels (500-1500 mg/dL).

7 (9) Maki

8 Maki administered 1.52g/day DHA supplements to patients with below-average levels of
9 HDL-C. Maki does not administer EPA of the purity recited in the claims.

10 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Maki
11 disclose or suggest elements of the '929 Claims. The cited portions of Maki do not disclose or
12 suggest these elements at least because they do not disclose or suggest administration of EPA
13 with the recited purity to a subject with the recited very high TG levels (at least 500 mg/dL) The
14 cited portions of Maki further do not disclose or suggest the claimed pharmaceutical composition
15 with the recited fatty acid compositions, dosage, or administration period.

16 With respect to Claim 1 of the '929 Patent (and therefore all asserted claims), Maki does
17 not disclose or suggest a subject with the recited very high TG levels (at least 500 mg/dL) Maki
18 also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty
19 acid compositions, dosage, or administration period.

20 Further, with respect to Claim 4, this reference fails to disclose or suggest the
21 administration of the claimed pharmaceutical composition to effect the recited reduction in TG
22 without increasing LDL-C. With respect to Claim 5, this reference fails to disclose or suggest
23 the administration of the claimed pharmaceutical composition to effect the recited reduction in
24 Apolipoprotein B. With respect to Claim 6, this reference fails to disclose or suggest the

1 administration of the claimed pharmaceutical composition to effect the recited reduction in
2 VLDL-C. With respect to Claim 7, this reference fails to disclose or suggest the subject with the
3 recited very high TG levels (500-1500 mg/dL).

4 (10) Matsuzawa

5 Matsuzawa administered Epadel to patients with hyperlipaemia in order to study its long-
6 term use in the treatment of the disease and was not placebo controlled.

7 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of
8 Matsuzawa disclose or suggest elements of the '929 Claims. The cited portions of Matsuzawa
9 do not disclose or suggest these elements at least because they do not disclose or suggest
10 administration of EPA with the recited purity to a subject with the recited very high TG levels (at
11 least 500 mg/dL). The cited portions of Matsuzawa further do not disclose or suggest the
12 claimed pharmaceutical composition with the recited fatty acid compositions or dosage.

13 With respect to Claims 1 of the '929 Patent (and therefore all asserted claims),
14 Matsuzawa does not disclose or suggest the claimed pharmaceutical composition with the recited
15 fatty acid compositions or dosage.

16 Further, with respect to Claim 4, this reference fails to disclose or suggest the
17 administration of the claimed pharmaceutical composition to effect the recited reduction in TG
18 without increasing LDL-C in the subject with the claimed very high TG levels (at least 500
19 mg/dL). With respect to Claim 5, this reference fails to disclose or suggest the administration of
20 the claimed pharmaceutical composition to effect the recited reduction in Apolipoprotein B in
21 the subject with the claimed very high TG levels (at least 500 mg/dL). With respect to Claim 6,
22 this reference fails to disclose or suggest the administration of the claimed pharmaceutical
23 composition to effect the recited reduction in VLDL-C in the subject with the claimed very high
24

1 TG levels (at least 500 mg/dL). With respect to Claim 7, this reference fails to disclose or
2 suggest the subject with the recited very high TG levels (500-1500 mg/dL).

3 (11) Mori 2000

4 Mori 2000 aimed to determine whether EPA and DHA have differential effects on serum
5 lipids and lipoproteins, glucose and insulin in humans.

6 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Mori
7 2000 disclose or suggest elements of the '929 Claims. The cited portions of Mori 2000 do not
8 disclose or suggest these elements at least because they do not disclose or suggest administration
9 of EPA with the recited purity to a subject with the recited very high TG levels (at least 500
10 mg/dL). The cited portions of Mori 2000 further do not disclose or suggest the claimed
11 pharmaceutical composition administration period.

12 With respect to Claim 1 of the '929 Patent (and therefore all asserted claims), Mori 2000
13 does not disclose or suggest a subject with the recited very high TG levels (at least 500 mg/dL)
14 The cited portions of Mori 2000 further do not disclose or suggest the claimed pharmaceutical
15 composition with the recited fatty acid administration period.

16 Further, with respect to Claim 4, this reference fails to disclose or suggest the recited
17 reduction in TG without increasing LDL-C in the subject with the claimed very high TG levels
18 (at least 500 mg/dL). With respect to Claim 5, this reference fails to disclose or suggest the
19 recited reduction in Apolipoprotein B in the subject with the claimed very high TG levels (at
20 least 500 mg/dL). With respect to Claim 6, this reference fails to disclose or suggest the recited
21 reduction in VLDL-C in the subject with the claimed very high TG levels (at least 500 mg/dL).
22 With respect to Claim 7, this reference fails to disclose or suggest the subject with the recited
23 very high TG levels (500-1500 mg/dL).

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1 (12) Mori 2006

2 Mori 2006 is a review which reports data from clinical trials which compared the
3 independent effects of EPA and DHA in individuals at increased risk of cardiovascular disease.

4 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Mori
5 2006 disclose or suggest elements of the '929 Claims. The cited portions of Mori 2006 do not
6 disclose or suggest these elements at least because they do not disclose or suggest administration
7 of EPA with the recited purity to a subject with the recited very high TG levels (at least 500
8 mg/dL) The cited portions of Mori 2006 further do not disclose or suggest administration of the
9 claimed pharmaceutical composition with the recited fatty acid compositions, dosage, or
10 administration period to the subject with the claimed very high TG levels (at least 500 mg/dL).

11 With respect to Claim 1 of the '929 Patent (and therefore all asserted claims), Mori 2006
12 does not disclose or suggest a subject with the recited very high TG levels (at least 500
13 mg/dL) who does not receive concurrent lipid altering therapy. Mori 2006 also does not disclose
14 or suggest administration of the claimed pharmaceutical composition with the recited fatty acid
15 compositions, dosage, or administration period to the subject with the claimed very high TG
16 levels (at least 500 mg/dL).

17 Further, with respect to Claim 2, this reference does not disclose or suggest the subject
18 having the recited baseline LDL-C levels. With respect to Claim 3, this reference does not
19 disclose or suggest the subject with the recited baseline lipid values. With respect to Claim 4,
20 this reference fails to disclose or suggest the recited reduction in TG without increasing LDL-C
21 in the subject with the claimed very high TG levels (at least 500 mg/dL). With respect to Claim
22 5, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in the
23 subject with the claimed very high TG levels (at least 500 mg/dL). With respect to Claim 6, this
24 reference fails to disclose or suggest the recited reduction in VLDL-C in the subject with the

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1 | claimed very high TG levels (at least 500 mg/dL). With respect to Claim 7, this reference fails to
2 | disclose or suggest the subject with the recited very high TG levels (500-1500 mg/dL).

3 | (13) Nozaki

4 | Nozaki is directed to administration of 2.7 g ethyl icosapentate per day for 6 months. The
5 | purity of the composition is reported as 90%. The study was not placebo controlled and was
6 | conducted in 14 hypercholesterolemic subjects. The average baseline TG level was only 165
7 | mg/dL, while the baseline LDL-C level was 185 mg/dL, which is unusually high for this TG
8 | patient population.

9 | The portions of Nozaki cited by Defendants do not disclose or suggest elements of the
10 | '929 patent claims. For example, the cited portions of Nozaki do not disclose or suggest
11 | administration of EPA with the recited purity to a subject with the recited very high TG levels
12 | who does not receive concurrent lipid altering therapy. The cited portions of Nozaki further do
13 | not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid
14 | compositions or dosage. The cited portions of Nozaki further do not disclose or suggest a
15 | method to effect the recited TG reduction without substantially increasing LDL-C in a subject
16 | with the recited very high TG levels.

17 | Defendants assert that certain cited sections of Nozaki disclose or suggest elements of the
18 | '929 Claims. The cited portions of Nozaki do not disclose or suggest these elements at least
19 | because they do not disclose or suggest administration of EPA with the recited purity to a subject
20 | with the recited very high TG levels who does not receive concurrent lipid altering therapy. The
21 | cited portions of Nozaki further do not disclose or suggest the claimed pharmaceutical
22 | composition with the recited fatty acid compositions or dosage. The cited portions of Nozaki
23 | further do not disclose or suggest a method to effect the recited TG reduction without
24 | substantially increasing LDL-C.

1 With respect to Claim 1 of the '929 Patent (and therefore all asserted claims), Nozaki
2 does not disclose or suggest a subject with the recited very high TG levels (at least 500 mg/dL)
3 Nozaki also does not disclose or suggest the claimed pharmaceutical composition with the
4 recited fatty acid compositions or dosage.

5 Further, with respect to Claim 2, this reference does not disclose or suggest the subject
6 having the recited baseline LDL-C levels. With respect to Claim 4, this reference fails to
7 disclose or suggest the administration of the claimed pharmaceutical composition to effect the
8 recited reduction in TG without increasing LDL-C in the subject with the claimed very high TG
9 levels (at least 500 mg/dL). With respect to Claim 5, this reference fails to disclose or suggest
10 the administration of the claimed pharmaceutical composition to effect the recited reduction in
11 Apolipoprotein B in the subject with the claimed very high TG levels (at least 500 mg/dL). With
12 respect to Claim 6, this reference fails to disclose or suggest the administration of the claimed
13 pharmaceutical composition to effect the recited reduction in VLDL-C in the subject with the
14 claimed very high TG levels (at least 500 mg/dL). With respect to Claim 7, this reference fails to
15 disclose or suggest the subject with the recited very high TG levels (500-1500 mg/dL).

16 (14) Omacor PDR

17 The Omacor PDR is the Physicians' Desk Reference describing Omacor.

18 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of the
19 Omacor PDR disclose or suggest elements of the '929 Claims. The cited portions of the Omacor
20 PDR do not disclose or suggest these elements at least because they do not disclose or suggest
21 administration of EPA with the recited purity to a subject with the recited very high TG levels (at
22 least 500 mg/dL). The cited portions of the Omacor PDR further do not disclose or suggest the
23 claimed pharmaceutical composition with the recited fatty acid compositions or administration
24 period.

1 With respect to Claim 1 of the '929 Patent (and therefore all asserted claims), the Omacor
2 PDR does not disclose or suggest the claimed pharmaceutical composition with the recited fatty
3 acid compositions or administration period.

4 Further, with respect to Claim 4, this reference fails to disclose or suggest the
5 administration of the claimed pharmaceutical composition to effect the recited reduction in TG
6 without increasing LDL-C. With respect to Claim 5, this reference fails to disclose or suggest
7 the administration of the claimed pharmaceutical composition to effect the recited reduction in
8 Apolipoprotein B. With respect to Claim 6, this reference fails to disclose or suggest the
9 administration of the claimed pharmaceutical composition to effect the recited reduction in
10 VLDL-C. With respect to Claim 7, this reference fails to disclose or suggest the subject with the
11 recited very high TG levels (500-1500 mg/dL).

12 (15) Satoh

13 Satoh administered 1.8g/day of >98% EPA to patients in order to measure the effects of
14 PEA on C-reactive protein and examine how alteration of lipoprotein profile by EPA affects
15 systemic inflammation.

16 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of
17 Satoh disclose or suggest elements of the '929 Claims. The cited portions of Satoh do not
18 disclose or suggest these elements at least because they do not disclose or suggest administration
19 of EPA with the recited purity to a subject with the recited very high TG levels (at least 500
20 mg/dL). The cited portions of Satoh further do not disclose or suggest the claimed
21 pharmaceutical composition with the recited fatty acid compositions or dosage.

22 With respect to Claim 1 of the '929 Patent (and therefore all asserted claims), Satoh does
23 not disclose or suggest a subject with the recited very high TG levels (at least 500 mg/dL) Satoh
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1 also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty
2 acid compositions or dosage.

3 Further, with respect to Claim 4, this reference fails to disclose or suggest the recited
4 reduction in TG without increasing LDL-C in the subject with the claimed very high TG levels
5 (at least 500 mg/dL). With respect to Claim 5, this reference fails to disclose or suggest the
6 recited reduction in Apolipoprotein B in the subject with the claimed very high TG levels (at
7 least 500 mg/dL). With respect to Claim 6, this reference fails to disclose or suggest the recited
8 reduction in VLDL-C in the subject with the claimed very high TG levels (at least 500 mg/dL).
9 With respect to Claim 7, this reference fails to disclose or suggest the subject with the recited
10 very high TG levels (500-1500 mg/dL).

11 (16) Shinozaki

12 Shinozaki studied the long-term effect of EPA on serum levels of Lipoprotein (a) and
13 lipids such as triglycerides, total cholesterol, and low density lipoprotein particles.

14 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of
15 Shinozaki disclose or suggest elements of the '929 Claims. The cited portions of Shinozaki do
16 not disclose or suggest these elements at least because they do not disclose or suggest
17 administration of EPA with the recited purity to a subject with the recited very high TG levels (at
18 least 500 mg/dL). The cited portions of Shinozaki further do not disclose or suggest the claimed
19 pharmaceutical composition with the recited fatty acid dosage.

20 With respect to Claim 1 of the '929 Patent (and therefore all asserted claims), Shinozaki
21 does not disclose or suggest a subject with the recited very high TG levels (at least 500 mg/dL)
22 Shinozaki also does not disclose or suggest the claimed pharmaceutical composition with the
23 recited fatty acid dosage.

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1 Further, with respect to Claim 2, this reference does not disclose or suggest the subject
2 having the recited baseline LDL-C levels. With respect to Claim 3, this reference fails to
3 disclose or suggest the subject having the recited baseline lipid levels. With respect to Claim 4,
4 this reference fails to disclose or suggest the recited reduction in TG without increasing LDL-C
5 in the subject with the claimed very high TG levels (at least 500 mg/dL). With respect to Claim
6 5, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in the
7 subject with the claimed very high TG levels (at least 500 mg/dL). With respect to Claim 6, this
8 reference fails to disclose or suggest the recited reduction in VLDL-C in the subject with the
9 claimed very high TG levels (at least 500 mg/dL). With respect to Claim 7, this reference fails to
10 disclose or suggest the subject with the recited very high TG levels (500-1500 mg/dL).

11 (17) Takaku

12 Takaku administered Epadel to patients with hyperlipaemia in order to study its long-
13 term use and was not placebo controlled.

14 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of
15 Takaku disclose or suggest elements of the '929 Claims. The cited portions of Takaku do not
16 disclose or suggest these elements at least because they do not disclose or suggest administration
17 of EPA with the recited purity to a subject with the recited very high TG levels (at least 500
18 mg/dL). The cited portions of Takaku further do not disclose or suggest the claimed
19 pharmaceutical composition with the recited fatty acid compositions or dosage.

20 With respect to Claims 1 of the '929 Patent (and therefore all asserted claims), Takaku
21 does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid
22 compositions or dosage.

23 Further, with respect to Claim 2, this reference does not disclose or suggest the subject
24 having the recited baseline LDL-C levels. With respect to Claim 3, this reference fails to

1 disclose or suggest the subject having the recited baseline lipid levels. With respect to Claim 4,
2 this reference fails to disclose or suggest the administration of the claimed pharmaceutical
3 composition to effect the recited reduction in TG without increasing LDL-C in the subject with
4 the claimed very high TG levels (at least 500 mg/dL). With respect to Claim 5, this reference
5 fails to disclose or suggest the administration of the claimed pharmaceutical composition to
6 effect the recited reduction in Apolipoprotein B in the subject with the claimed very high TG
7 levels (at least 500 mg/dL). With respect to Claim 6, this reference fails to disclose or suggest
8 the administration of the claimed pharmaceutical composition to effect the recited reduction in
9 VLDL-C in the subject with the claimed very high TG levels (500-1500 mg/dL).

10 c) The Prior Art Does Not Render the Claims Obvious

11 Defendants have not identified by clear and convincing evidence that the asserted claims
12 of the '929 patent would have been *prima facie* obvious in light of the references cited, either
13 alone or in combination. As described above, none of the references discloses all of the elements
14 in any of the asserted claims. Defendants chart a laundry list of 66 separate references, without
15 explanation, and argue they somehow must be combined to render obvious the asserted claims.
16 Where Defendants have failed to make disclosures with the specificity required by Local Patent
17 Rule 1-8(d), it has failed to put Plaintiffs on notice of how these references allegedly disclose the
18 claim elements at issue.

19 Facts supporting the non-obviousness of the claims of the '929 patent are discussed in
20 detail below. The objective indicia discussed in Section V.O further demonstrate that the '929
21 patent is not obvious. In short, Defendants have not met their burden of showing that the claims
22 would have been obvious.

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1 (1) Defendants Do Not Demonstrate that the Independent
2 Claims of the '929 patent Would Have Been Obvious

3 (a) Defendants Do Not Demonstrate that a Person of
4 Ordinary Skill in the Art Would Have Had Any
5 Reason to Replace the Mixed Fish Oil Active
6 Ingredient in Lovaza with Pure EPA

7 (i) The '929 Patent is not Obvious Over the
8 Omacor PDR/Lovaza PDR, in Combination
9 with Katayama and/or Matsuzawa, Further
10 in View of Nozaki and/or Hayashi and
11 Further in View of Leigh-Firbank and/or
12 Mori 2000

13 With respect to the '929 patent, Defendants present a combination of seven references:
14 "the Omacor PDR/Lovaza PDR in combination with the known clinical benefits of administering
15 pure EPA as evidenced by Katayama and/or Matsuzawa, further in view of Nozaki and/or
16 Hayashi and further in view of Leigh-Firbank and/or Mori 2000."⁴⁹⁸³ Defendants also present
17 charts purporting to assert that an additional 61 references may be combined in order to render
18 the Claims obvious. Not only do Defendants ignore the improbability that a person of ordinary
19 skill would combine 61 separate references, they additionally do not identify any motivation for
20 combining these references.^{4984, 4985} Although Defendants need not point to an explicit statement

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22 ⁴⁹⁸³ Defendants' Joint Invalidity Contentions at 669.

23 ⁴⁹⁸⁴ Defendants' bare assertion that the asserted claims are obvious "in view of one or more of Omacor or Lovaza (as
24 described in the references cited above in Section V.B.2 in view of, at least, the references cited in V.B.3 and 4,
including, the '954 publication, WO '900, WO '118, Ando, Grimsgaard, Hayashi, Katayama, Matsuzawa, Matak, Mori 2000, Nakamura, Nozaki, Okumura, Park, Saito 1998, Saito 2008 Satoh, Shinozaki, Takaku, Yokoyama 2003, Yokoyama 2007, Calabresi, Chan 2002, Chan 2003, Contacos, Geppert, Kelley, Kris-Etherton, Leigh-Firbank, Maki, Mori 2000, Mori 2006, Rambjør, Sanders or Theobald," similarly fails to meet the disclosure requirements of the Nevada Local Patent Rules, and fails to provide any motivation to combine these references. *See* Defendants' Joint Invalidity Contentions at 668.

⁴⁹⁸⁵ Defendants' bare assertion that "the motivation or reason to combine or modify the prior art to create invalidating combinations under 35 U.S.C. §103 can be found in the references identified above in Section III.C," and that "[c]ommon sense, design incentives. Market forces, and the background knowledge possessed by a person having ordinary skill in the art provide the reasons or rationales for combining the teachings of multiple references

1 in the prior art motivating the combination of these references, any assertion of an “apparent
2 reason” to combine must find a basis in the factual record.⁴⁹⁸⁶ Defendants’ unsupported cobbling
3 of selective disclosures represents hindsight reconstruction.⁴⁹⁸⁷ Defendants’ contentions are no
4 more than an assertion that certain claim elements were known in the prior art. Throughout their
5 contentions, Defendants’ selectively cite to data points in a reference without considering other
6 disclosures or even the reference as a whole. Each reference, however, must be evaluated for all
7 that it teaches.⁴⁹⁸⁸ Accordingly, Defendants fail to meet their burden to establish *prima facie*
8 obviousness.

9 The Lovaza PDR fails to disclose or even suggest the claimed method of reducing
10 triglycerides in a subject with the claimed pharmaceutical composition containing the claimed
11 fatty acid compositions or administration period. The Lovaza PDR further does not disclose a
12 method to effect the specified TG reduction without substantially increasing LDL-C. Indeed, the
13 Lovaza PDR discloses the exact opposite. The EPA/DHA composition of Lovaza causes a

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15 or modifying references to render obvious the claimed inventions of the asserted claims,” fails to meet the disclosure
16 requirements of the Nevada Local Patent Rules. See Defendants’ Joint Invalidation Contentions at 659-60.

17 ⁴⁹⁸⁶ See, e.g., *In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the
18 formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did
19 not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply
20 the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi*
21 *Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must
22 avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to
23 select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and
24 elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp.
2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie*
obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding
that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been
motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

⁴⁹⁸⁷ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under
KSR, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention
without any explanation as to how or why the references would be combined to produce the claimed invention”).

⁴⁹⁸⁸ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

1 significant increase in LDL-C levels in the very high TG patient population, for whom the
2 product is indicated. At most, the Lovaza PDR discloses administration of a prescription fish oil,
3 a combination of approximately 465 mg EPA and 375 mg DHA, as an adjunct to diet to reduce
4 TG levels in adult patients with very-high (≥ 500 mg/dL) TG levels.

5 The proposed combinations do not render the independent claims of the '929 patent
6 obvious and Defendants' burden to prove otherwise is especially difficult because the PTO
7 considered Matsuzawa, Katayama, Mori 2000, and Lovaza (both generally and the Lovaza
8 package insert specifically) during prosecution.⁴⁹⁸⁹

9 The analysis of the independent claims of the '929 patent is incorporated into all asserted
10 claims that depend from those Claims.

11 (a) A Person of Ordinary Skill Would
12 Not Have Been Motivated to
13 Replace the Mixed Fish Oil Active
Ingredient in Lovaza with Pure EPA

14 For an invention to be obvious, there must have been an "apparent reason" to make it.
15 The subject matter of the '929 patent claims would not have been obvious in light of these
16 references because a person of ordinary skill would not have been motivated to purify EPA or
17 been able to reasonably expect that the claimed pharmaceutical composition would reduce TG
18 levels without an increase in LDL-C levels.

19 (i) Katayama and/or Matsuzawa
20 Do Not Disclose Purported

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23 ⁴⁹⁸⁹ See, e.g., *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012)(taking into account that "the
24 examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention.
Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear
and convincing standard came into play").

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2
3 Both Katayama and Matsuzawa are long term studies directed to an investigation of the
4 safety and efficacy of Epadel in patients with a wide range of baseline TG levels. These studies
5 were not placebo controlled. A person of ordinary skill in the art understood that a placebo may
6 itself cause an effect. Without accounting for the placebo effect, a person of ordinary skill in the
7 art would not and could not attribute any observed effect (and the magnitude of that effect) to
8 that of the drug. Any observed effect could be placebo dependent.⁴⁹⁹⁰ As discussed above in
9 Section III, a person of ordinary skill would not expect the same LDL-C effect in patients with
10 lower baseline TG levels—the subjects of Katayama and Matsuzawa—as in very-high TG
11 patients because patients with higher TG levels had different lipid responses compared to
12 patients with lower TG levels. Patients with very-high TG levels were considered fundamentally
13 different from patients with borderline-high or high TGs from a lipid chemistry, medical, clinical
14 guideline, regulatory, and therapeutic standpoint. As previously discussed, a person of ordinary
15 skill in the art would expect to see an increase in LDL-C levels when omega-3 fatty acids were
16 administered to patients with normal, borderline-high or high TG levels. Therefore, the prior art
17 Defendants rely upon to show that EPA did not increase LDL-C levels in normal, borderline-
18 high or high TG patients, was expected. At the priority date of the ‘929 patent, a person of
19 ordinary skill in the art would have expected an *increase* in LDL-C for very-high TG patients
20 receiving a TG-lowering agent, as a natural consequence of lowering TGs. This pattern had been

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23 ⁴⁹⁹⁰See Grimsgaard at 652 (Although administration of EPA reduced Apo-B compared to baseline, it was not a
24 statistically significant effect when compared to placebo. Grimsgaard’s disclosure highlights the importance of a
placebo-controlled study and why results compared only to baseline may be misleading.)

1 demonstrated for both fibrates and fish oils and was understood as a direct consequence of TG
2 lowering through increased VLDL particle conversion.

3 Defendants argue that these studies disclose known “clinical benefits” of administering
4 pure EPA, lowering triglycerides without raising LDL-C. This is an incorrect characterization of
5 these two studies. Katayama and Matsuzawa both were only designed to confirm the safety of
6 long term treatment of Epadel and its ability to lower both serum total cholesterol and TG levels.
7 They do just that. They do not discuss any purported “benefits” observed related to LDL-C.
8 Defendants’ selective citation of LDL-C data from these references represents the improper use
9 of hindsight bias. A person of ordinary skill would understand the focus of Katayama and
10 Matsuzawa to be TG and total cholesterol effects and not LDL-C levels, and would not draw
11 conclusions regarding LDL-C from these studies. Indeed, Katayama does not mention LDL-C
12 levels at all. Defendants’ characterization of Katayama and Matsuzawa as disclosing the
13 lowering of TG levels without increasing LDL-C to be a “clinical benefit” is incorrect. The
14 references don’t disclose or suggest that the LDL-C results obtained were a clinical benefit, nor
15 would a person of ordinary skill view these references as teaching such a benefit for very-high
16 TG patients.

17 Further, both Katayama and Matsuzawa administered only EPA and studied its lipid
18 effects. These studies fail to provide a head to head comparison of EPA versus DHA.
19 Therefore, a person of ordinary skill in the art would not rely on Katayama or Matsuzawa to
20 draw any conclusions related to possible differences between the lipid effects of EPA and DHA.

21 In addition, Katayama and Matsuzawa do not disclose the purity of the Epadel used. The
22 purity of Epadel has varied over time and across different formulations of the product, therefore
23 it is difficult to determine the purity of the version of Epadel used unless it is specified by the
24

1 disclosure. One cannot simply rely on the fact that Epadel was administered and assume that the
2 composition comprised at least about 96%, by weight of all fatty acids present, EPA, and
3 substantially no DHA, as required by the asserted claims. Defendants fail to provide a reference
4 disclosing the purity of the form of Epadel used in the Katayama and Matsuzawa studies.
5 Nishikawa,⁴⁹⁹¹ published in 1997, discloses a form of Epadel that was a 91% E-EPA preparation.
6 Nishikawa reflects that versions of Epadel used in some clinical studies do not have the requisite
7 purity.⁴⁹⁹²

8 Further, Katayama and Matsuzawa were small studies conducted in only Japanese
9 patients. These studies would not have been extrapolated to Western populations because the
10 Japanese diet contains much more fish and has a number of other different attributes. The
11 Japanese consume a higher amount of EPA and DHA in their diets than Western populations. In
12 fact, Yokoyama 2007 (cited in Defendants' contentions) states that the results from studies where
13 the patient population is exclusively Japanese cannot be generalized to other populations.⁴⁹⁹³
14 The Japanese diet comprises between 8 and 15 times more EPA and DHA than the typical
15 Western Diet. The Western diet typically consists of higher amounts of polyunsaturated omega-
16 6 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand
17 that the Japanese respond differently to lipid lowering agents than Westerners.

21 ⁴⁹⁹¹ Nishikawa et al., *Effects of Eicosapentaenoic Acid (EPA) on Prostacyclin Production in Diabetics: GC/MS*
22 *Analysis of PGI₂ and PGI₃ Levels*, 19 METHODS FIND EXP CLIN PHARMACOL. 429 (1997).

23 ⁴⁹⁹² See also, Ando at 2177 (Epadel with purity greater than 91%), Nakamura at 23 (Epadel with purity > 90%).

24 ⁴⁹⁹³ Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to other populations.").

1 Defendants rely on Katayama to demonstrate the “known clinical benefits of
2 administering pure EPA - lowering triglycerides without raising LDL-C.”⁴⁹⁹⁴ However,
3 Katayama was directed to an investigation of the safety and efficacy of Epadel during long-term
4 treatment in patients with hyperlipidemia.⁴⁹⁹⁵ Katayama does not disclose *any* LDL-C related
5 data or describe *any* LDL-C effects, and a person of ordinary skill would not understand that
6 reference to provide any such disclosure. The only results disclosed by Katayama were a
7 significant reduction in TGs and total cholesterol when Epadel (EPA of undisclosed purity) was
8 administered to patients with borderline-high to high TG levels, and its safety for long term use
9 in this patient population.⁴⁹⁹⁶ In addition to Katayama’s lack of disclosure regarding LDL-C,
10 Defendants identify no other basis upon which a person of ordinary skill would have sought to
11 combine the composition disclosed in Katayama with the Lovaza PDR.

12 Defendants similarly rely on Matsuzawa to demonstrate the “known clinical benefits of
13 administering pure EPA - lowering triglycerides without raising LDL-C.”⁴⁹⁹⁷ However,
14 Matsuzawa included 26 participants, of whom 23 were adopted for the evaluation of overall
15 safety, 22 were adopted for the evaluation of usefulness, 20 were adopted for evaluation of
16 general improvement, 15 were adopted for improvement in serum total cholesterol levels, and 13
17 were evaluated for improvement in serum triglycerides levels.⁴⁹⁹⁸ It is unclear which of the 26
18 patients were included in each separate evaluation; therefore one cannot determine the baseline
19 lipid characteristics for each subset of patients evaluated. Further, the small sample size and lack
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21 ⁴⁹⁹⁴ Defendants’ Joint Invalidity Contentions at 661 and 662.

22 ⁴⁹⁹⁵ Katayama at 2.

23 ⁴⁹⁹⁶ *Id.* at 16.

24 ⁴⁹⁹⁷ Defendants’ Joint Invalidity Contentions at 6761 and 662.

⁴⁹⁹⁸ Matsuzawa at 7 and 19.

1 of a placebo control makes it less likely that the results of this study can be generalized as an
2 effect on any population as a whole and provides no insight with respect to the very-high TG
3 patient population.

4 Matsuzawa discloses that 3 of the 26 participants had 400 mg/dL < TG < 1000 mg/dL,
5 and one participant with TG levels > 1,000 mg/dL.⁴⁹⁹⁹ However, when analyzing the lipid
6 impact of Epadel, Matsuzawa excluded the patient with a TG level greater than 1,000 mg/dL
7 because he was a “heavy drinker” and the “effect of alcohol made it impossible to assess
8 triglyceride levels.”⁵⁰⁰⁰ Fig. 4, which depicts the changes in serum triglycerides, shows that the
9 mean triglycerides of the 12 patients with TG greater than 150 mg/dL was well below 500
10 mg/dL. Furthermore, as shown in Table 4, patients with TG levels above 500 mg/dL (other than
11 the excluded patient who had TG above 1,000 mg/dL) were not treated in the study with EPA (of
12 undisclosed purity). The identification of three patients with TG levels between 400 and less
13 than 1,000 mg/dL does not disclose a patient with TG levels above 500 mg/dl, and a person of
14 ordinary skill would not understand that the reference makes any such disclosure. As discussed
15 above, one of ordinary skill in the art would not expect LDL-C to increase in a patient with TG
16 less than 500 mg/dL upon treatment with a TG-lowering agent. Matsuzawa provides no
17 evidence to the contrary.

18 Matsuzawa demonstrated mixed results related to LDL-C over time, at first showing a
19 2% decrease, and then a 1% increase in LDL-C by the end of 52 weeks.⁵⁰⁰¹ The disclosure
20 further reflects that the 4 patients with serum triglyceride levels of at least 400 mg/dL were
21

22 _____
⁴⁹⁹⁹ *Id.* at 23.

23 ⁵⁰⁰⁰ *Id.* at 10.

24 ⁵⁰⁰¹ *Id.* at 11.

1 excluded from the LDL-C results because the Friedewald's Equation was used to calculate LDL-
2 C levels. The Friedewald's Equation cannot be used for patients with triglyceride levels of at
3 least 400 mg/dL. Therefore, the LDL-C results only reflect the LDL-C changes in patients with
4 triglyceride levels below 400 mg/dL. Matsuzawa fails to provide any information to a person of
5 ordinary skill regarding the LDL-C effect in the very-high TG population. A person of ordinary
6 skill in the art, however, would have expected the same treatment in patients with very high TG
7 levels to produce a substantial increase in LDL-C. In addition, Matsuzawa acknowledges that
8 there have been conflicting results related to the LDL-C impact of EPA preparations that lowered
9 triglyceride levels.⁵⁰⁰² At best, Matsuzawa demonstrates the uncertainty and confusion related to
10 the LDL-C effect EPA had on patients with hyperlipidemia. Further, Defendants fail to identify
11 any other basis upon which a person of ordinary skill would have sought to combine the
12 composition disclosed in Matsuzawa with the Lovaza PDR.

13 Therefore, Katayama and Matsuzawa fail to substantiate Defendants' assertion that
14 compositions comprising EPA as recited in the asserted claims lowers triglycerides without
15 substantially increasing LDL-C. Further, other studies cited by Defendants suggest that EPA
16 increases LDL-C.⁵⁰⁰³ Defendants identify no other basis upon which a person of ordinary skill
17 would have sought to combine the Lovaza PDR with Katayama, Matsuzawa, Leigh-Firbank
18 and/or Mori 2000 or reasonably expected that such a combination would successfully yield the
19 asserted claims of the '929 patent.

22 ⁵⁰⁰² *Id.* at 15. Matsuzawa suggests the conflicting results are due to differences in the EPA content of the EPA
23 preparation administered. However, Matsuzawa fails to identify the specific conflicting studies, disclose the specific
24 compositions used, or identify the patient populations were observed.

⁵⁰⁰³ *See, e.g.,* Rambjor.

(ii) Nozaki and/or Hayashi
Would Not Have Rendered
the Asserted Claims Obvious

Defendants contend that the asserted claims of the '929 patent would have been obvious in view Nozaki and/or Hayashi in combination with other references, but they do not explain why Nozaki and/or Hayashi render the asserted claims obvious or what element of the asserted claims is found in Nozaki or Hayashi. Nozaki and Hayashi do not disclose or suggest a reduction in triglycerides without increasing LDL-C when purified EPA is administered to the very high TG patient population.

Nozaki administered 2.7 g/day of 90% EPA (DHA < 1%) to 14 primary hypercholesterolemia subjects. A person of ordinary skill would not have found the results of Nozaki reliable. Nozaki was not placebo-controlled, nor did the study compare lipid effect of EPA to that of DHA. The average baseline TG level was only 165 mg/dL, while the baseline LDL-C level was 185 mg/dL, which is unusually high for this TG patient population. A person of skill in the art would not look to a study consisting of patients with baseline TG levels of 165 mg/dL in order to understand the impact of EPA therapy on the very high TG patient population. Further, a person of ordinary skill would understand that the baseline LDL-C level in this small patient population were abnormally high and would not have relied upon these results. Further, the person of skill in the art would not have looked to this patient population to predict the Apo-B or LDL-C effect of EPA therapy on very high TG patients. Nozaki acknowledges that as of 1991, “[t]here is still controversy concerning the effects of fish oil” on LDL and HDL cholesterol levels.⁵⁰⁰⁴ Nozaki does not provide a motivation or reasonable expectation of success for administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA and

⁵⁰⁰⁴ Nozaki at 256.

1 substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL, to
2 effect a reduction in triglycerides without increasing LDL-C when purified EPA is administered
3 to the very high TG patient population.

4 In Hayashi, 1.8 g/day of EPA was administered to 28 patients for 8 weeks. The purity of
5 the EPA and the DHA content in the composition that was administered is unknown. A person
6 of ordinary skill would not have found the results of Hayashi reliable. The study involved 28
7 patients and it was conducted for only 8 weeks. Hayashi shows that changes in Apo-B and LDL-
8 C were not statistically significant.⁵⁰⁰⁵ Further, the person of skill in the art would not have
9 looked to this patient population to predict the Apo-B or LDL-C effect of EPA therapy on very
10 high TG patients. Hayashi does not provide a motivation or reasonable expectation of success
11 for administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA
12 and substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL,
13 to effect a reduction in triglycerides without increasing LDL-C when purified EPA is
14 administered to the very high TG patient population.

15 Further, Hayashi was a small study conducted in only Japanese patients and was not
16 placebo controlled. This study would not have been extrapolated to Western populations
17 because the Japanese diet contains much more fish and has a number of other different attributes.
18 The Japanese consume a higher amount of EPA and DHA in their diets than Western
19 populations. In fact, Defendants' own reference states that the results from studies where the
20 patient population is exclusively Japanese cannot be generalized to other populations.⁵⁰⁰⁶ The
21 Japanese diet comprises between 8 and 15 times more EPA and DHA than typical the typical

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23 ⁵⁰⁰⁵ Hayashi at 26, Table I.

24 ⁵⁰⁰⁶ Yokoyama 2007 at 1097 (“Because our population was exclusively Japanese, we cannot generalise our results to other populations.”).

1 Western diet. The Western diet typically consists of higher amounts of polyunsaturated omega-6
2 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand that
3 the Japanese respond differently to lipid lowering agents than Westerners.

4 Further, Defendants have failed to offer a purported combination of references as part of
5 their obviousness contentions that include Nozaki and Hayashi. Similarly, they fail to offer any
6 motivation to combine Nozaki and Hayashi with the other references of their purported
7 obviousness combinations. Therefore, Defendants should be precluded from relying on these
8 references.

9 (iii) Leigh-Firbank and/or Mori
10 2000 Do Not Disclose
11 Purported Knowledge that
12 DHA was Responsible for the
13 Increase in LDL-C

12 Defendants assert, incorrectly, that “it was known in the art as of February 2009 that
13 administration of DHA (alone or in a mixture) resulted in the negative effect of increasing LDL-
14 C levels.”⁵⁰⁰⁷ Defendants’ caveat of DHA being “alone or in a mixture” is telling that it was *not*
15 known that DHA alone resulted in an increase in LDL-C levels. Further, the prior art Defendants
16 rely upon to support this statement does not categorize the increase in LDL-C as a “negative
17 effect” in light of the overall impact of the disclosed composition on all lipid parameters.

18 Further, the patients in Leigh Firbank and Mori 2000 had normal to high baseline TG levels. As
19 discussed above in Section III, a person of ordinary skill would not expect the same LDL-C
20 effect in patients with lower baseline TG levels—the subjects of Leigh-Firbank and Mori 2000—
21 as in very-high TG patients because patients with higher TG levels had different lipid responses
22 compared to patients with lower TG levels. Patients with very-high TG levels were considered

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24 ⁵⁰⁰⁷ Defendants’ Joint Invalidity Contentions at 664.

1 fundamentally different from patients with borderline-high or high triglycerides from a lipid
2 chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint. Instead, a person
3 of ordinary skill in the art would have expected that fish oils (and other TG lowering agents)
4 would not increase LDL-C substantially in patients with normal to borderline high TG levels, but
5 would substantially increase LDL-C in patients with very high TG levels.

6 Defendants rely upon Leigh-Firbank to demonstrate that it was known that “DHA was
7 responsible for the increase in LDL-C levels.” Leigh-Firbank, however, administered fish oil,
8 comprising 1.67 g of EPA and 1.34 g of DHA per day, for six weeks, to patients with triglyceride
9 levels between 133 mg/dL and 354 mg/dL. Leigh-Firbank does not evaluate the effect of either
10 EPA or DHA alone because it did not disclose the administration of EPA or DHA alone. A
11 person of ordinary skill would similarly understand that Leigh-Firbank does not offer any
12 disclosure regarding the effect of EPA and DHA separately or gain any understanding of the
13 separate impact of DHA or EPA on any lipid parameter. Mori 2006 (also cited by defendants)
14 acknowledges that EPA- and DHA-enriched oils, which are contaminated with other saturated
15 and polyunsaturated fatty acids, are not suitable for evaluating the independent effects of EPA
16 and DHA.⁵⁰⁰⁸ A person of ordinary skill would understand that studies directed to EPA and
17 DHA-enriched oils are not indicative or predictive of the impact of the EPA or DHA alone on
18 lipid parameters. Defendants’ own prior art refutes the validity of the results disclosed by Leigh-
19 Firbank, because purified EPA and DHA were not administered separately.

20 Leigh-Firbank is a poor quality study. Leigh-Firbank makes conclusion on independent
21 effects of EPA and DHA individually, even though it administered a combination of EPA and
22 DHA, not EPA alone and DHA alone. The error in this approach is evident from the conclusions
23

24 ⁵⁰⁰⁸ Mori 2006 at 96.

1 of Leigh-Firbank itself. For example, Leigh-Firbank concludes that changes in platelet
2 phospholipid EPA were *independently* associated with the decrease in fasting TGs,⁵⁰⁰⁹ and DHA
3 is *not* associated with decreases in fasting TGs. This is incorrect and inconsistent with the state
4 of the art and numerous publications cited by Defendants.⁵⁰¹⁰ It is widely accepted that DHA
5 also has a hypotriglyceridemic effect.

6 Mori 2000 compared the administration of 4g daily of EPA, DHA, or olive oil to patients
7 with borderline-high TG levels for 6 weeks. Although Mori 2000 discloses an increase in LDL-
8 C for patients administered DHA, it also teaches that DHA is preferable to EPA—thus teaching
9 away from the claimed invention. “A reference may be said to teach away when a person of
10 ordinary skill, upon [examining] the reference, would be discouraged from following the path set
11 out in the reference, or would be led in a direction divergent from the path that was taken by the
12 applicant.”⁵⁰¹¹ Although teaching away is fact-dependent, “in general, a reference will teach
13 away if it suggests that the line of development flowing from the reference’s disclosures is
14 unlikely to be productive of the result sought by the applicant.”⁵⁰¹²

15 Mori 2000 concludes that the changes effected by DHA supplementation “may represent
16 a more favorable lipid profile than after EPA supplementation.”⁵⁰¹³ For example, it states that
17 “DHA, but not EPA, improved serum lipid status, in particular a small increase in HDL
18 cholesterol and a significant increase in the HDL₂-cholesterol subfraction, without adverse

19 ⁵⁰⁰⁹ Leigh-Firbank at 440.

20 ⁵⁰¹⁰ See, e.g. Grimsgaard at 654.

21 ⁵⁰¹¹ *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994).

22 ⁵⁰¹² *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994); see also *Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354
23 (Fed. Cir. 2012) (quoting *Gurley*); *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1552 (Fed. Cir. 1983)
24 (“[P]roceed[ing] contrary to the accepted wisdom of the prior art ... is strong evidence of nonobviousness.”).

⁵⁰¹³ Mori 2000 at 1092.

1 effects on fasting glucose concentrations.”⁵⁰¹⁴ Mori 2000 also states that “[d]espite an increase
2 in LDL cholesterol after DHA supplementation, LDL particle size increased—a finding that may
3 be favorable.”⁵⁰¹⁵ Therefore, based on the “favorable lipid profile” of DHA over EPA in Mori
4 2000, a person of ordinary skill would *not* have been motivated to use EPA to treat patients, the
5 exact opposite of what Defendants argue in their contentions. Therefore, the art taught away
6 from using purified EPA. At a minimum, the teachings of Mori 2000 provide reasons for
7 favoring or selecting DHA over EPA and highlight Defendants’ hindsight-driven focus on EPA,
8 despite disclosed advantages of DHA. A person of ordinary skill would take into consideration
9 the entire disclosure, including lipid effects other than LDL-C. Engaging in hindsight bias,
10 Defendants ignore, without explanation, the other effects of DHA that a person of ordinary skill
11 would consider. Defendants fail to identify any other basis upon which a person of ordinary skill
12 would have sought to combine Mori 2000 with the Lovaza PDR.

13 Therefore, Leigh-Firbank and Mori 2000 fail to substantiate Defendants’ assertion that it
14 was known that DHA alone was responsible for the increase in LDL-C levels. Further,
15 Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or
16 has little effect on LDL-C levels.⁵⁰¹⁶ Defendants identify no other basis upon which a person of
17 ordinary skill would have sought to combine the Lovaza PDR with Katayama, Matsuzawa,
18 Leigh-Firbank and/or Mori 2000.

- 19 (ii) The ‘929 Patent is not Obvious Over the
20 Omacor PDR/Lovaza PDR, in Combination
21 with Katayama and/or Matsuzawa, and/or
Takaku, Further in View of Nozaki and/or

22 _____
⁵⁰¹⁴ Mori 2000 at 1088.

23 ⁵⁰¹⁵ Mori 2000 at 1092.

24 ⁵⁰¹⁶ See e.g., Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

With respect to the '929 patent, Defendants present a combination of nine references:

“the Omacor PDR/Lovaza PDR, in combination with the known clinical benefits of administering pure EPA as evidenced by Katayama, Matsuzawa, and/or Takaku, further in view of Nozaki and/or Hayashi, and further in view of Grimsgaard, Mori 2000 and/or Maki.”⁵⁰¹⁷

Defendants also present charts purporting to assert that an additional 58 references may be combined in order to render the Claims obvious. Not only do Defendants ignore the improbability that a person of ordinary skill would combine 58 separate references, they additionally do not identify any motivation for combining these references. Although Defendants need not point to an explicit statement in the prior art motivating the combination of these references, any assertion of an “apparent reason” to combine must find a basis in the factual record.⁵⁰¹⁸ Defendants’ unsupported cobbling of selective disclosures represents hindsight reconstruction.⁵⁰¹⁹ Defendants’ contentions are no more than an assertion that certain

⁵⁰¹⁷ Defendants’ Joint Invalidity Contentions at 662.

⁵⁰¹⁸ See, e.g., *In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp. 2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie* obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

⁵⁰¹⁹ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under KSR, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention”).

1 claim elements were known in the prior art. Throughout their contentions, Defendants’
2 selectively cite to data points in a reference without considering other disclosures or even the
3 reference as a whole. Each reference, however, must be evaluated for all that it teaches.⁵⁰²⁰
4 Accordingly, Defendants fail to meet their burden to establish *prima facie* obviousness.

5 The Omacor PDR and Lovaza PDR fail to disclose or even suggest the claimed method
6 of reducing triglycerides in a subject with the claimed pharmaceutical composition with the
7 recited fatty acid compositions or administration period. The Omacor PDR and Lovaza PDR
8 further do not disclose a method to effect the claimed TG reduction without substantially
9 increasing LDL-C. Indeed, the Omacor PDR and Lovaza PDR disclose the opposite: EPA/DHA
10 causes a significant increase in LDL-C levels in a very high TG patient population, for whom the
11 product (Lovaza/Omacor) is indicated. At most, the Omacor PDR and Lovaza PDR disclose
12 administration of a prescription fish oil, a combination of approximately 465 mg EPA and 375
13 mg DHA, as an adjunct to diet to reduce TG levels in adult patients with very-high (at least 500
14 mg/dL) TG levels. The proposed combinations do not render the independent claims of the ’929
15 patent obvious and Defendants’ burden to prove otherwise is especially difficult because the
16 PTO considered Matsuzawa, Katayama, and Mori 2000, Grimsgaard, Maki, and Lovaza (both
17 generally and the Lovaza package insert specifically) during prosecution.⁵⁰²¹

18 The analysis of the independent claims of the ’929 patent is incorporated into all asserted
19 claims that depend from those Claims.

20 (a) A Person of Ordinary Skill Would
21 Not Have Been Motivated to

22 ⁵⁰²⁰ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

23 ⁵⁰²¹ *See, e.g., Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012)(taking into account that “the
24 examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention.
Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear
and convincing standard came into play”).

3 For an invention to be obvious, there must have been an “apparent reason” to make it.
4 The subject matter of the ‘929 patent claims would not have been obvious in light of these
5 references because a person of ordinary skill would not have been motivated to purify EPA or
6 been able to reasonably expect that the claimed pharmaceutical composition would reduce TG
7 levels without an increase in LDL-C levels.

8 (i) Grimsgaard, Katayama,
9 Matsuzawa and/or Takaku
10 Do Not Disclose Purported
Known Clinical Benefits of
Administering Pure EPA

11 Defendants rely on Grimsgaard, Katayama, Matsuzawa and/or Takaku to demonstrate the
12 “known clinical benefits of administering pure EPA - lowering triglycerides without raising
13 LDL-C.” As discussed in Section V.K.3.c.1.a.i.a.i, incorporated herein by reference, Katayama
14 and Matsuzawa merely confirm the safety of long term treatment of Epadel and its ability to
15 lower both serum total cholesterol and triglyceride levels. They do not discuss any purported
16 “benefits” observed related to LDL-C. Katayama and Matsuzawa do not disclose or suggest that
17 the LDL-C results obtained were a clinical benefit.

18 Defendants also rely on Grimsgaard to support their assertion that “administration of
19 purified EPA-E reduced TG levels while minimally impacting the LDL-C levels.”⁵⁰²² However,
20 the results of Grimsgaard demonstrate that both EPA and DHA had no measureable impact on
21 LDL-C levels, and in fact were indistinguishable from the control (placebo) group.

22
23 _____
⁵⁰²² Defendants’ Joint Invalidity Contentions at 665.

1 Grimsgaard examined the effect of 3.8g/day of EPA versus 3.6g/day of DHA
2 administered to people with normal triglyceride levels for 7 weeks.⁵⁰²³ The results from the
3 Grimsgaard study show that both DHA and EPA reduce triglycerides. The authors state that the
4 net decrease in triglycerides was consistently greater for DHA. Grimsgaard also concludes that
5 DHA may be responsible for the beneficial increase in HDL-C observed with some n-3 fatty acid
6 supplements, which is consistent with previous studies which “suggested that serum HDL-C is
7 better maintained with oil rich in DHA than oil rich in EPA.”⁵⁰²⁴ Although Grimsgaard states
8 that EPA may produce a small decrease in serum total cholesterol, it does not specifically
9 comment on EPA’s effect on LDL-C.

10 Defendants completely misconstrue the results of Grimsgaard. Defendants attempt to
11 characterize a non-significant increase in LDL-C by DHA and a non-significant decrease in
12 LDL-C by EPA, as confirmation “that administration of purified DHA results in increased LDL-
13 C levels while administration of purified EPA resulted in a decrease in LDL-C levels.”⁵⁰²⁵ The
14 results of Grimsgaard, reproduced below, show that EPA and DHA’s impact on LDL-C were the
15 same as placebo (corn oil); that is, there was no difference between EPA, DHA, or placebo’s
16 effect on LDL-C levels. Further, although administration of EPA reduced Apo-B compared to
17 baseline, it was not a statistically significant effect when compared to placebo. Grimsgaard’s
18 disclosure highlights the importance of a placebo-controlled study and why results compared
19
20

21
22 ⁵⁰²³ Defendants state in their Joint Invalidation Contentions at 211 that Grimsgaard was conducted in patients with TG
23 levels in the borderline-high/high ranges. This is incorrect; Grimsgaard was conducted in patients with normal TG
24 levels. (See Grimsgaard at Abstract (describing participants as “healthy”) and Table 4).

⁵⁰²⁴ Grimsgaard at 654.

⁵⁰²⁵ Defendants’ Joint Invalidation Contentions at 665 n.123.

only to baseline may be misleading. This type of exaggeration and misinterpretation of the results published in the prior art is seen throughout the Defendants' Joint Invalidity Contentions.

TABLE 4
Serum lipids and apolipoproteins at baseline and change after 7 wk of supplementation with docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), or corn oil

	DHA (n = 72)		EPA (n = 75)		Corn oil (n = 77)		F test: P ¹	Contrasts between groups: P		
	Baseline	Change	Baseline	Change	Baseline	Change		DHA vs EPA	DHA vs corn oil	EPA vs corn oil
Triacylglycerols (mmol/L)	1.24 ± 0.58 ²	-0.22 ± 0.31 ²	1.23 ± 0.57	-0.15 ± 0.40 ⁴	1.22 ± 0.55	0.11 ± 0.34 ⁴	0.0001	0.14	0.0001	0.0001
Total cholesterol (mmol/L)	6.00 ± 0.95	0.03 ± 0.49	5.98 ± 0.94	-0.15 ± 0.55 ⁵	6.02 ± 1.08	0.10 ± 0.55	0.01	0.04	0.4	0.004
LDL cholesterol (mmol/L)	4.06 ± 0.86	0.07 ± 0.46	4.06 ± 0.83	-0.08 ± 0.48	4.04 ± 0.98	0.06 ± 0.48	0.10	—	—	—
HDL cholesterol (mmol/L)	1.36 ± 0.30	0.06 ± 0.13 ²	1.33 ± 0.31	0.01 ± 0.12	1.41 ± 0.28	-0.01 ± 0.11	0.001	0.009	0.0005	0.4
Apolipoprotein A-I (g/L)	1.38 ± 0.21	0.02 ± 0.13	1.38 ± 0.20	-0.04 ± 0.10 ²	1.46 ± 0.23	0.00 ± 0.12	0.003	0.0008	0.3	0.02
Apolipoprotein B (g/L)	1.00 ± 0.21	-0.01 ± 0.11	1.01 ± 0.23	-0.03 ± 0.11 ²	1.02 ± 0.28	0.02 ± 0.11	0.05	—	—	—
HDL:apolipoprotein A-I	0.97 ± 0.14	0.04 ± 0.07 ²	0.96 ± 0.13	0.04 ± 0.08 ²	0.97 ± 0.12	-0.01 ± 0.06	0.0001	0.8	0.0003	0.0001
Total:HDL cholesterol	4.62 ± 1.19	-0.19 ± 0.52 ²	4.70 ± 1.24	-0.13 ± 0.47 ²	4.43 ± 1.19	0.11 ± 0.62	0.002	0.4	0.0006	0.007

¹ ANOVA for between-group comparisons of change.

² $\bar{x} \pm$ SD.

²⁻⁵ One-sample t test of difference between baseline and 7 wk: ³ P < 0.001, ⁴ P < 0.01, ⁵ P < 0.05.

Grimsgaard concludes that both DHA and EPA lower TG levels but have “differential effects on lipoprotein and fatty acid metabolism.”⁵⁰²⁶ However, Grimsgaard does not conclude that DHA and EPA have differential effects on LDL-C because Table 4 clearly demonstrates that neither DHA nor EPA had a measurable impact on LDL-C. Table 4 demonstrates that EPA and DHA had the same effect on LDL-C. In fact, one of ordinary skill in the art, when reading Grimsgaard, may have been motivated to use purified DHA instead of EPA for the treatment of patients with very-high triglycerides, because net decrease in triglycerides was consistently greater for DHA and DHA caused a statistically significant increase in HDL-C when compared to placebo. Grimsgaard states that “DHA may be responsible for the increase in HDL cholesterol observed with some n-3 fatty acid supplements.”⁵⁰²⁷ Grimsgaard makes no such statement regarding LDL-C.

Defendants cherry-pick results, regardless of whether the effect is found to be statistically significant compared to placebo, in an attempt to force the studies to support their argument that

⁵⁰²⁶ Grimsgaard at 657.

⁵⁰²⁷ Grimsgaard at 654.

1 | it was well known to one of ordinary skill in the art that DHA increases LDL-C while EPA did
2 | not. This illustrates the hindsight reasoning driving Defendants’ analysis of the prior art and
3 | proposed combinations of prior art. Defendants point to a non-significant increase in DHA and
4 | non-significant decrease in EPA in Grimsgaard as confirmation “that administration of purified
5 | DHA results in increased LDL-C levels while administration of purified EPA resulted in a
6 | decrease in LDL-C levels.” The results from Grimsgaard clearly show that EPA and DHA did
7 | not have statistically significantly effects on LDL-C compared to placebo.⁵⁰²⁸ A person of
8 | ordinary skill would not draw conclusions regarding differences between EPA and DHA based
9 | on statistically insignificant results.

10 | Defendants also rely on Takaku to support their assertion that “clinical benefits of
11 | administering purified EPA—lowering triglycerides without raising LDL-C” was known in the
12 | art.⁵⁰²⁹ Similar to Katayama and Matsuzawa, Takaku was conducted to test the efficacy and
13 | safety of Epadel (of undisclosed purity)⁵⁰³⁰ based on long-term administration.⁵⁰³¹

14 | A person of ordinary skill would not have concluded based on Takaku that EPA lowers
15 | triglycerides without raising LDL-C, because of its unreliable study method. Takaku candidly
16 | acknowledges that “only a few subjects were examined” and cautions against drawing a
17 |

18 | ⁵⁰²⁸In Mori 2000, EPA resulted in a non-significant 0.18 mmol/L increase in LDL-C, while DHA caused a
19 | statistically significant 0.37 mmol/L increase in LDL-C compared to placebo. Applying the same logic used to
20 | interpret Grimsgaard, that non-significant effects are nonetheless confirmation of an effect, Defendants should have
21 | argued that Mori 2000 was confirmation that both EPA and DHA increases LDL-C. However, they do not make
22 | such arguments for the obvious reason that it does not support their argument that EPA was known to have little or
23 | no impact on LDL-C levels.

21 | ⁵⁰²⁹ Defendants’ Joint Invalidity Contentions at 662.

22 | ⁵⁰³⁰ It is possible that the version of Epadel used in the Katayama study fails to meet the purity limitation required by
23 | the claims. See Nishikawa (91% E-EPA preparation), Ando at 2177 (Epadel with purity greater than 91%),
24 | Nakamura at 23 (Epadel with purity > 90%).

24 | ⁵⁰³¹ Takaku at ICOSAPENT_DFNDT00006834.

1 conclusion “only from the results of the present study.”⁵⁰³² Because the study did not include
2 any placebo control, a person of ordinary skill in the art would understand these reports do not
3 provide the ability to conclude that the observed lipid effects would have occurred independent
4 of the drug that is administered. In addition, the study was conducted exclusively in Japanese
5 patients, and a person of ordinary skill would not have expected the results to be applicable to the
6 general population.⁵⁰³³

7 The mean baseline triglyceride level of the patients in Takaku was 245 mg/dL, and a
8 person of ordinary skill would not have expected the results to be applicable to patients with
9 triglycerides above 500 mg/dL. Takaku also excluded 6 subjects from the LDL-C study because
10 measurement was not feasible due to “insufficient sample.”⁵⁰³⁴ It is possible that patients with
11 triglycerides above 500 mg/dL were among those excluded because of the challenges involved in
12 calculating LDL-C levels when triglyceride level is above 400 mg/dL.⁵⁰³⁵ Moreover, the study
13 does not provide different LDL-C graphs based on the baseline triglyceride levels.⁵⁰³⁶ Therefore,
14 it is impossible to determine whether the patients with triglycerides above 500 mg/dL had
15 increased or decreased LDL-C after taking MND-21. In addition, the graph of the rate of LDL-C
16 change in patients with normal baseline LDL-C shows that the LDL-C change was volatile
17 throughout the study period, decreasing slightly at times but increasing by more than 8% at other
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20 ⁵⁰³² Takaku at ICOSAPENT_DFNDT00006897.

21 ⁵⁰³³ Yokoyama 2007 at 1097 (“[b]ecause our population was exclusively Japanese, we cannot generalise our results
to other populations.”)

22 ⁵⁰³⁴ Takaku at ICOSAPENT_DFNDT00006884.

23 ⁵⁰³⁵ See Matsuzawa at ICOSPENT_DFNDTS00006450.

24 ⁵⁰³⁶ Takaku at Fig. 13, ICOSAPENT_DFNDT00006882.

1 times.⁵⁰³⁷ Because of this volatility, a person of ordinary skill would not be able to conclude
2 what effect EPA has on LDL-C. Indeed, Takaku did not conclude that there was no increase in
3 LDL-C, stating only that the fluctuation in LDL-C was not significant.⁵⁰³⁸

4 A person of ordinary skill would not have concluded, based on Takaku, that purified EPA
5 had any advantage over fish oil in its effect on LDL-C. Takaku states that a previous study has
6 “confirmed a decrease in serum VLDL-cholesterol and serum LDL-cholesterol through the
7 administration of *fish oil* to hypercholesterolemia patients.”⁵⁰³⁹ In contrast, Takaku states merely
8 that the fluctuation in LDL-C was not significant in its study. Therefore, a person of ordinary
9 skill would have concluded based on Takaku that any favorable LDL-C effect seen in the study
10 was attributable to fish oil in general, not EPA specifically.

11 Therefore, Grimsgaard, Katayama, Matsuzawa and/or Takaku fail to substantiate
12 Defendants’ assertion that pure EPA lowers triglycerides without raising LDL-C. Further, other
13 studies cited by Defendants suggest that EPA increases LDL-C.⁵⁰⁴⁰ Defendants identify no other
14 basis upon which a person of ordinary skill would have sought to combine the Omacor
15 PDR/Lovaza PDR with Katayama, Matsuzawa, Takaku, Grimsgaard, Mori 2000 and/or Maki.

16 (ii) Nozaki and/or Hayashi
17 Would Not Have Rendered
18 the Asserted Claims Obvious

18 Defendants contend that the asserted claims of the ’929 patent would have been obvious
19 in view Nozaki and/or Hayashi in combination with other references, but they do not explain
20 why Nozaki and/or Hayashi render the asserted claims obvious or what element of the asserted

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22 ⁵⁰³⁷ Takaku at Fig. 14, ICOSAPENT_DFNDT00006883.

23 ⁵⁰³⁸ Takaku at ICOSAPENT_DFNDT00006897.

24 ⁵⁰³⁹ Takaku at ICOSAPENT_DFNDT00006897.

⁵⁰⁴⁰ See, e.g., Rambjor.

1 claims is found in Nozaki or Hayashi. Nozaki and Hayashi do not disclose or suggest a
2 reduction in triglycerides without increasing LDL-C when purified EPA is administered to the
3 very high TG patient population.

4 Nozaki administered 2.7 g/day of 90% EPA (DHA < 1%) to 14 primary
5 hypercholesterolemia subjects. A person of ordinary skill would not have found the results of
6 Nozaki reliable. Nozaki was not placebo-controlled, nor did the study compare lipid effect of
7 EPA to that of DHA. The average baseline TG level was only 165 mg/dL, while the baseline
8 LDL-C level was 185 mg/dL, which is unusually high for this TG patient population. A person
9 of skill in the art would not look to a study consisting of patients with baseline TG levels of 165
10 mg/dL in order to understand the impact of EPA therapy on the very high TG patient population.
11 Further, a person of ordinary skill would understand that the baseline LDL-C level in this small
12 patient population were abnormally high and would not have relied upon these results. Further,
13 the person of skill in the art would not have looked to this patient population to predict the Apo-
14 B or LDL-C effect of EPA therapy on very high TG patients. Nozaki acknowledges that as of
15 1991, “[t]here is still controversy concerning the effects of fish oil” on LDL and HDL cholesterol
16 levels.⁵⁰⁴¹ Nozaki does not provide a motivation or reasonable expectation of success for
17 administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA and
18 substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL, to
19 effect a reduction in triglycerides without increasing LDL-C when purified EPA is administered
20 to the very high TG patient population.

21 In Hayashi, 1.8 g/day of EPA was administered to 28 patients for 8 weeks. The purity of
22 the EPA and the DHA content in the composition that was administered is unknown. A person
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24 ⁵⁰⁴¹ Nozaki at 256.

1 of ordinary skill would not have found the results of Hayashi reliable. The study involved 28
2 patients and it was conducted for only 8 weeks. Hayashi shows that changes in Apo-B and LDL-
3 C were not statistically significant.⁵⁰⁴² Further, the person of skill in the art would not have
4 looked to this patient population to predict the Apo-B or LDL-C effect of EPA therapy on very
5 high TG patients. Hayashi does not provide a motivation or reasonable expectation of success
6 for administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA
7 and substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL,
8 to effect a reduction in triglycerides without increasing LDL-C when purified EPA is
9 administered to the very high TG patient population.

10 Further, Hayashi was a small study conducted in only Japanese patients and was not
11 placebo controlled. This study would not have been extrapolated to Western populations
12 because the Japanese diet contains much more fish and has a number of other different attributes.
13 The Japanese consume a higher amount of EPA and DHA in their diets than Western
14 populations. In fact, Defendants' own reference states that the results from studies where the
15 patient population is exclusively Japanese cannot be generalized to other populations.⁵⁰⁴³ The
16 Japanese diet comprises between 8 and 15 times more EPA and DHA than typical the typical
17 Western diet. The Western diet typically consists of higher amounts of polyunsaturated omega-6
18 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand that
19 the Japanese respond differently to lipid lowering agents than Westerners.

20 Further, Defendants have failed to offer a purported combination of references as part of
21 their obviousness contentions that include Nozaki and Hayashi. Similarly, they fail to offer any

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23 ⁵⁰⁴² Hayashi at 26, Table I.

24 ⁵⁰⁴³ Yokoyama 2007 at 1097 (“Because our population was exclusively Japanese, we cannot generalise our results to other populations.”).

1 motivation to combine Nozaki and Hayashi with the other references of their purported
2 obviousness combinations. Therefore, Defendants should be precluded from relying on these
3 references.

4 (iii) Grimsgaard, Mori 2000
5 and/or Maki Do Not Disclose
6 Purported Knowledge that
7 DHA was Responsible for the
8 Increase in LDL-C

9 Defendants assert, incorrectly, that “it was known in the art as of February 2009 that
10 administration of DHA (alone or in a mixture) resulted in the negative effect of increasing LDL-
11 C levels.”⁵⁰⁴⁴ Defendants’ caveat of DHA being “alone or in a mixture” is telling that it was *not*
12 known that DHA alone resulted in an increase in LDL-C levels. Further, the prior art Defendants
13 rely on to support this statement does not categorize the increase in LDL-C as a “negative effect”
14 in light of the overall impact of the disclosed composition on all lipid parameters. Further, the
15 patients in Grimsgaard, Mori 2000 and Maki had normal to borderline-high baseline TG levels.
16 As discussed above in Section III, a person of ordinary skill would not expect the same LDL-C
17 effect in patients with lower baseline TG levels—the subjects of Grimsgaard, Mori 2000 and/or
18 Maki—as in very-high TG patients because patients with higher TG levels had different lipid
19 responses compared to patients with lower TG levels. Patients with very-high TG levels were
20 considered fundamentally different from patients with borderline-high or high triglycerides from
21 a lipid chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint. A person of
22 ordinary skill in the art would have expected that fish oils (and other TG lowering agents) would

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24 ⁵⁰⁴⁴ Defendants’ Joint Invalidity Contentions at 664.

1 not increase LDL-C substantially in patients with normal to borderline high TG levels, but would
2 substantially increase LDL-C in patients with very high TG levels.

3 Defendants rely on Grimsgaard, Mori 2000 and/or Maki to demonstrate that it was known
4 that “DHA was responsible for the increase in LDL-C levels.”⁵⁰⁴⁵ The discussion related to
5 Grimsgaard in Section V.K.3.c.1.a.ii.a.i and Mori 2000 in Section V.K.3.c.1.a.i.a.iii is
6 incorporated herein by reference.

7 Defendants argue that Maki discloses the administration of purified DHA resulted in the
8 desired reduction of TGs, but also significantly increased LDL-C levels. Maki was designed to
9 assess the impact of 1.52g/day DHA supplements on the serum lipid profile of patients with
10 below-average levels of HDL-C levels.⁵⁰⁴⁶ The DHA supplemented group was administered
11 capsules containing 1.52 g/day DHA **and** 0.84 g/day palmitic acid, in addition to other saturated,
12 monounsaturated and polyunsaturated fatty acids.⁵⁰⁴⁷ Therefore, Maki demonstrated that when
13 1.52 g/day DHA **and** 0.84 g/day palmitic acid is administered to patients with below-average
14 levels of HDL-C levels and borderline-high TG levels, a significant increase in LDL-C is
15 observed.⁵⁰⁴⁸ However, one cannot attribute the rise in LDL-C solely to DHA, because the
16 authors admit that “changes in fatty acid intake other than DHA, particularly palmitate, may have
17 also contributed to the elevation in LDL cholesterol.”⁵⁰⁴⁹ Further, Maki admits that the
18 “mechanism(s) responsible for the changes in the lipid profile associated with DHA
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20 ⁵⁰⁴⁵ Defendants’ Joint Invalidity Contentions at 662.

21 ⁵⁰⁴⁶ Maki at 190.

22 ⁵⁰⁴⁷ Maki at 191.

23 ⁵⁰⁴⁸ Maki at 195.

24 ⁵⁰⁴⁹ Maki at 197; Yu et al., *Plasma Cholesterol-Predictive Equations Demonstrate that Stearic Acid is Neutral and Monounsaturated Fatty Acids are Hypocholesterlemic*, 61 AM J CLIN NUTR 1129, 1136 (1995).

1 supplementation are not fully understood.”⁵⁰⁵⁰ Therefore, the results of Maki are inconclusive as
2 to DHA’s effect alone on LDL-C levels.

3 Defendants mischaracterize the rise in LDL-C associated with the administration of
4 omega-3 fatty acids as being a “negative effect” because they incorrectly focus on only the LDL-
5 C effect and fail to look at the lipid effects as a whole. In fact, Maki does not find the increase in
6 LDL-C to be troublesome; Maki states that “the lack of increase in the total/HDL cholesterol
7 ratio, the decline in the triglyceride/HDL cholesterol ratio and the reduction in the proportion of
8 cholesterol carried by small, dense LDL particles render the changes in LDL cholesterol level
9 less worrisome.”⁵⁰⁵¹ Therefore, when one of ordinary skill in the art reviewed all the lipid effects
10 of the DHA-rich algal triglycerides, they would have understood that the increase in LDL-C was
11 “less worrisome” because of the “potentially favorable effects on triglycerides, the
12 triglyceride/HDL cholesterol ratio and the fraction of LDL cholesterol carried by small, dense
13 particles.”⁵⁰⁵²

14 Therefore, Grimsgaard, Mori 2000 and/or Maki fail to substantiate Defendants’ assertion
15 that it was known that DHA was responsible for the increase in LDL-C levels. Further,
16 Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or
17 has little effect on LDL-C levels.⁵⁰⁵³ Defendants identify no other basis upon which a person of
18 ordinary skill would have sought to combine the Omacor PDR/Lovaza PDR with Katayama,
19 Matsuzawa, Takaku, Grimsgaard, Mori 2000 and/or Maki.

20 (iii) The ‘929 Patent is not Obvious Over the
21 Omacor PDR/Lovaza PDR, in Combination

22 ⁵⁰⁵⁰ Maki at 197.

23 ⁵⁰⁵¹ Maki at 197.

24 ⁵⁰⁵² Maki at 197.

⁵⁰⁵³ See e.g., Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

1 with Katayama in View of Satoh and/or in
2 View of Satoh or Shinozaki in Further View
of Contacos

3 With respect to the '929 patent, Defendants present a combination of five references: "the
4 Omacor PDR/Lovaza PDR, in combination with the known clinical benefits of administering
5 pure EPA as evidenced by Katayama in view of Satoh and/or in view of Satoh or Shinozaki in
6 further view of Contacos."⁵⁰⁵⁴ Defendants also present charts purporting to assert that an
7 additional 60 references may be combined in order to render the Claims obvious. Not only do
8 Defendants ignore the improbability that a person of ordinary skill would combine 60 separate
9 references, they additionally do not suggest any identify for combining these references.
10 Although Defendants need not point to an explicit statement in the prior art motivating the
11 combination of these references, any assertion of an "apparent reason" to combine must find a
12 basis in the factual record.⁵⁰⁵⁵ Defendants' unsupported cobbling of selective disclosures
13 represents hindsight reconstruction.⁵⁰⁵⁶ Defendants' contentions are no more than an assertion
14 that certain claim elements were known in the prior art. Throughout their contentions,
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16 ⁵⁰⁵⁴ Defendants' Joint Invalidity Contentions at 662.

17 ⁵⁰⁵⁵ See, e.g., *In re Vaidyanathan*, 381 F. App'x 985, 993–94 (Fed. Cir. 2010) ("[W]hile KSR relaxed some of the
18 formalism of earlier decisions requiring a 'teaching, suggestion, or motivation' to combine prior art references, it did
19 not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply
20 the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight."); *Daiichi
Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point "must
21 avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to
22 select and then modify a lead compound to arrive at the claimed invention." This turns on the known "properties and
elements of the prior art compounds.") (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp.
2d 479, 492-93 (D. Del. 2006) (rejecting defendants' contention that claims to (+)-citalopram were "*prima facie*
obvious in light of . . . claims [to] racemic citalopram" despite its use to "treat the same condition," and concluding
that defendants "have not demonstrated by clear and convincing evidence that one skilled in the art would have been
motivated to resolve citalopram in June 1988."), *aff'd*, 501 F.3d 1263 (Fed. Cir. 2007).

23 ⁵⁰⁵⁶ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under
24 *KSR*, "[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention
without any explanation as to how or why the references would be combined to produce the claimed invention").

1 Defendants’ selectively cite to data points in a reference without considering other disclosures or
2 even the reference as a whole. Each reference, however, must be evaluated for all that it
3 teaches.⁵⁰⁵⁷ Accordingly, Defendants fail to meet their burden to establish *prima facie*
4 obviousness.

5 The Lovaza PDR fails to disclose or even suggest the claimed method of reducing
6 triglycerides in a subject with the claimed pharmaceutical composition with the specified fatty
7 acid compositions or administration period. The Lovaza PDR further does not disclose a method
8 to effect the specified TG reduction without substantially increasing LDL-C. Indeed, the Lovaza
9 PDR discloses the exact opposite, that the EPA/DHA composition contained within the reference
10 would cause a significant increase in LDL-C levels in the very high TG patient population, for
11 whom the product is indicated. At most, the Lovaza PDR discloses administration of a
12 prescription fish oil, a combination of approximately 465 mg EPA and 375 mg DHA, as an
13 adjunct to diet to reduce TG levels in adult patients with very-high (at least 500 mg/dL) TG
14 levels.

15 Defendants formulate an obviousness argument that relies on Contacos.⁵⁰⁵⁸ However,
16 Defendants fail to provide any factual or legal basis as to why Contacos discloses a claim
17 element or an “apparent reason” or motivation to combine the elements in the manner
18 claimed,⁵⁰⁵⁹.

21 ⁵⁰⁵⁷ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

22 ⁵⁰⁵⁸ *Id.*

23 ⁵⁰⁵⁹ *KSR*, 550 U.S. at 417–19; *TriMed, Inc. v. Stryker Corp.*, 608 F.3d 1333, 1341 (Fed. Cir. 2010). Hindsight may
24 not be employed to identify relevant prior art and relevant teachings therein: *Heidelberger Druckmaschinen AG v. Hantscho Comm. Prods., Inc.*, 21 F.3d 1068, 1071–72 (Fed. Cir. 1994); *Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 881 (Fed. Cir. 1998).

1 Contacos disclosed administration of fish oil, pravastatin, and combination of fish oil and
2 pravastatin, but it does not disclose administration of EPA of the recited composition. Therefore,
3 Contacos fails to provide motivation to administer purified EPA to a very high TG patient
4 population. Contacos also fails to provide motivation to administer purified EPA to a very high
5 TG patient population.

6 The proposed combinations do not render the independent claims of the '929 patent
7 obvious and Defendants' burden to prove otherwise is especially difficult because the PTO
8 considered Katayama, Satoh, Shinozaki, Contacos, Geppert, Kelley and Lovaza (both generally
9 and the Lovaza package insert specifically) during prosecution.⁵⁰⁶⁰

10 The analysis of the independent claims of the '929 patent is incorporated into all asserted
11 claims that depend from those Claims.

12 (a) A Person of Ordinary Skill Would
13 Not Have Been Motivated to
14 Replace the Mixed Fish Oil Active
Ingredient in Lovaza with EPA of
the Recited Composition

15 For an invention to be obvious, there must have been an "apparent reason" to make it.
16 The subject matter of the '929 patent claims would not have been obvious in light of these
17 references because a person of ordinary skill would not have been motivated to purify EPA or
18 been able to reasonably expect that the claimed pharmaceutical composition would reduce TG
19 levels without an increase in LDL-C levels.

20 (i) Katayama, Satoh and/or
21 Shinozaki Do Not Disclose
Purported Known Clinical

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23 ⁵⁰⁶⁰ See, e.g., *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012)(taking into account that "the
24 examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention.
Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear
and convincing standard came into play").

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3 Defendants rely on Katayama, Satoh and/or Shinozaki to demonstrate the “known clinical
4 benefits of administering pure EPA - lowering triglycerides without raising LDL-C.” As
5 discussed in Section V.K.3.c.1.a.i.a.i, incorporated herein by reference, Katayama merely
6 confirms the safety of long term treatment of Epadel and its ability to lower both serum total
7 cholesterol and triglyceride levels. Katayama does not mention LDL-C levels at all, let alone
8 discuss any purported “benefits” observed related to LDL-C. Katayama does not disclose or
9 suggest that the LDL-C results obtained were a clinical benefit, nor would a person of ordinary
10 skill view these references as teaching such a benefit for very-high TG patients.

11 Satoh administered 1.8g/day of >98% EPA to patients in order to measure the effects of
12 EPA on C-reactive protein and examine how alteration of lipoprotein profile by EPA affects
13 systemic inflammation. Satoh reported a statistically significant reduction in LDL-C only when
14 compared to baseline, there was no significant effect when compared to placebo.⁵⁰⁶¹

15 Defendants’ characterization of Satoh as disclosing the lowering of TG levels without increasing
16 LDL-C to be a “clinical benefit” is incorrect. Satoh does not disclose or suggest that the LDL-C
17 results obtained were a clinical benefit, nor would a person of ordinary skill view these
18 references as teaching such a benefit for very-high TG patients. As discussed above, one of
19 ordinary skill in the art would not expect LDL-C to increase in a patient with TG below 500
20 mg/dL and Satoh provides no evidence to the contrary. A person of ordinary skill in the art,
21 however, would have expected that fish oils (and other TG lowering agents) would substantially

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⁵⁰⁶¹ Satoh at 145.

1 increase LDL-C in patients with very high TG levels. Satoh fails to provide motivation to
2 administer purified EPA to a very high TG patient population.

3 Further, Satoh was a small study conducted in only Japanese patients. This study would
4 not have been extrapolated to Western populations because the Japanese diet contains much
5 more fish and has a number of other different attributes. The Japanese consume a higher amount
6 of EPA and DHA in their diets than Western populations. In fact, Defendants' own reference
7 states that the results from studies where the patient population is exclusively Japanese cannot be
8 generalized to other populations.⁵⁰⁶² The Japanese diet comprises between 8 and 15 times more
9 EPA and DHA than typical the typical Western diet. The Western diet typically consists of
10 higher amounts of polyunsaturated omega-6 fatty acids and saturated fatty acids. Therefore, a
11 person of ordinary skill would understand that the Japanese respond differently to lipid lowering
12 agents than Westerners.

13 Shinozaki studied the long-term effect of EPA on serum levels of Lipoprotein (a) (Lp(a))
14 and lipids such as triglycerides, total cholesterol, and low density lipoprotein particles.
15 Defendants' characterization of Shinozaki as disclosing the lowering of TG levels without
16 increasing LDL-C to be a "clinical benefit" is incorrect.⁵⁰⁶³ Shinozaki says nothing about an
17 LDL-C effect because it measured LDL particle number, not LDL-C. The finding disclosed by
18 Shinozaki was that "long term administration of EPA may lower Lp(a) and serum lipids."⁵⁰⁶⁴ In
19 addition to Shinozaki's lack of disclosure regarding LDL-C, Defendants identify no other basis
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22 ⁵⁰⁶² Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to
other populations.").

23 ⁵⁰⁶³ Defendants' Joint Invalidity Contentions at 662.

24 ⁵⁰⁶⁴ Shinozaki at 107-109.

1 upon which a person of ordinary skill would have sought to combine the composition disclosed
2 in Shinozaki.

3 Therefore, Katayama, Satoh and/or Shinozaki fail to substantiate Defendants' assertion
4 that pure EPA lowers triglycerides without raising LDL-C. Further, other studies cited by
5 Defendants suggest that EPA increases LDL-C.⁵⁰⁶⁵ Defendants identify no other basis upon
6 which a person of ordinary skill would have sought to combine the Lovaza PDR with Katayama,
7 Satoh, Shinozaki and/or Contacos.

8 (ii) Geppert and/or Kelley Do
9 Not Disclose Purported
10 Knowledge that DHA was
11 Responsible for the Increase
12 in LDL-C

11 Defendants assert, incorrectly, that “it was known in the art as of February 2009 that
12 administration of DHA (alone or in a mixture) resulted in the negative effect of increasing LDL-
13 C levels.”⁵⁰⁶⁶ Defendants' caveat of DHA being “alone or in a mixture” is telling that it was *not*
14 known that DHA alone resulted in an increase in LDL-C levels. Further, the prior art Defendants
15 rely on to support this statement do not categorize the increase in LDL-C as a “negative effect”
16 in light of the overall impact of the disclosed composition on all lipid parameters. Further, the
17 patients in Geppert and Kelley had normal and borderline-high/high baseline TG levels,
18 respectively. As discussed above in Section III, a person of ordinary skill would not expect the
19 same LDL-C effect in patients with lower baseline TG levels—the subjects of Geppert and/or
20 Kelley—as in very-high TG patients because patients with higher TG levels had different lipid
21 responses compared to patients with lower TG levels. Patients with very-high TG levels were
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23 ⁵⁰⁶⁵ See, e.g., Rambjor.

24 ⁵⁰⁶⁶ Defendants' Joint Invalidity Contentions at 664.

1 considered fundamentally different from patients with borderline-high or high triglycerides from
2 a lipid chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint. Although a
3 person of ordinary skill in the art would have expected that fish oils (and other TG lowering
4 agents) would not increase LDL-C substantially in patients with normal to borderline high TG
5 levels, a person of ordinary skill in the art would expect a substantial increase in LDL-C in
6 patients with very high TG levels.

7 Defendants rely on Geppert and/or Kelley to demonstrate that it was known that “DHA
8 was responsible for the increase in LDL-C levels.”⁵⁰⁶⁷ Both Geppert and Kelley administer
9 DHA-rich oil that is contaminated with other saturated and polyunsaturated fatty acids.
10 Therefore, a person of ordinary skill would have known it is unsuitable for evaluating the
11 independent effects of DHA because it is not clear how much of the supplement’s effects can be
12 attributed to DHA.⁵⁰⁶⁸ For example, Defendants’ own prior art teaches that changes in fatty acid
13 intake other than DHA, particularly palmitate, may contribute to elevations in LDL-C.⁵⁰⁶⁹

14 In Geppert, 0.94 g/day of DHA derived from microalgae oil was administered to
15 normolipidaemic vegetarians for 8 weeks. A person of ordinary skill would not have been
16 convinced that DHA increases LDL-C based on Geppert. As Geppert acknowledges, prior
17 studies have shown “[i]nconsistent effects of DHA on LDL cholesterol.”⁵⁰⁷⁰ Rather than reading
18 Geppert in isolation, a person of ordinary skill would have read Geppert together with the prior
19 studies cited in Geppert. As such, a person of ordinary skill would have concluded that there
20 was confusion in the art and it was unclear whether DHA increased LDL-C.

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22 ⁵⁰⁶⁷ Defendants’ Joint Invalidation Contentions at 662.

23 ⁵⁰⁶⁸ See Mori 2006 at 96.

24 ⁵⁰⁶⁹ Maki at 197.

⁵⁰⁷⁰ Geppert at 784.

1 A person of ordinary skill would have expected that Geppert's results would be
2 applicable to other components of fish oil such as EPA. Nothing in Geppert suggests that DHA
3 was the only component of fish oil to increase LDL-C. For example, there is no data comparing
4 DHA to fish oil or EPA. In fact, Geppert discusses DHA and fish oil together when trying
5 explain the mechanism of LDL-C increase.⁵⁰⁷¹ A person of ordinary skill would have not
6 expected that EPA and DHA would have different effects on LDL-C based on Geppert.

7 Defendants contend that Kelley shows that DHA was responsible for the increase in
8 LDL-C. In Kelley, patients fasting serum TG levels of 150 to 400 mg/dL received 7.5 g/day of
9 DHA oil containing 3 g of DHA for 90 days. Kelley does not show that DHA is responsible for
10 the increase in LDL-C. Kelley suggests that increase in LDL-C is a general phenomenon
11 associated with triglyceride-lowering drugs, stating that a similar increase was induced by fibrate
12 therapy.⁵⁰⁷² Further, Kelley teaches that the increase in LDL-C is not harmful when viewed in
13 context with the other lipid effects reported in the study. Kelley states that:

14 DHA supplementation may lower the risk of CVD by reducing
15 plasma triacylglycerols; triacylglycerol:HDL; the number of small,
16 dense LDL particles; and mean diameter of VLDL particles. An
17 increase was observed in fasting LDL cholesterol, but it is unlikely
18 this increase is detrimental because no increase was observed in the
19 overall number of LDL particles; actually, there was an 11%
20 reduction that was statistically not significant. The reason LDL
21 cholesterol increased despite no change in LDL particle number was
22 that the LDL particles were made larger and hence more cholesterol
23 rich by DHA treatment.⁵⁰⁷³

20 Kelley specifically teaches that the increase in LDL-C caused by DHA supplementation
21 is unlikely to be "detrimental" because there was not a parallel increase in overall LDL particle

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⁵⁰⁷¹ *Id.*

23 ⁵⁰⁷² Kelley at 329.

24 ⁵⁰⁷³ Kelley at 329

1 number. Kelley’s ultimate conclusion is that “[o]verall, DHA supplementation reduced the
2 concentrations of atherogenic lipids and lipoproteins and increased concentrations of
3 cardioprotective lipoproteins” and that “DHA supplementation may improve cardiovascular
4 health.”⁵⁰⁷⁴ Rather than concluding that DHA was uniquely responsible for a rise in LDL-C
5 levels, a person of ordinary skill would understand Kelley to disclose that DHA had uniquely
6 beneficial cardioprotective effects. Indeed, instead of identifying DHA as composition with
7 negative attributes, a person of ordinary skill would understand that the reference taught towards
8 the use of DHA. In addition, none of the study subjects in Kelley had a TG level above 400
9 mg/dL and, for the reasons previously discussed, a person of ordinary skill would understand the
10 very high TG patient population to be different in terms of their response to lipid therapy,
11 including administration of DHA. A person of ordinary skill in the art would have expected that
12 fish oils (and other TG lowering agents) would not increase LDL-C substantially in patients with
13 normal to borderline high TG levels, but a person of ordinary skill in the art would expect a
14 substantial increase in LDL-C in patients with very high TG levels.

15 Therefore, Geppert and/or Kelley fail to substantiate Defendants’ assertion that it was
16 known that DHA was responsible for the increase in LDL-C levels.

17 Throughout their contentions, Defendants’ selectively cite to data points in a reference
18 without considering other disclosures or even the reference as a whole. Each reference,
19 however, must be evaluated for all that it teaches.⁵⁰⁷⁵ As is the case with Kelley, Defendants use
20 hindsight to characterize a reference based on LDL-C levels alone without considering the other
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23 ⁵⁰⁷⁴ Kelley at 324, 332.

24 ⁵⁰⁷⁵ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

1 lipid effects studied, considered and reported.⁵⁰⁷⁶ The isolated manner in which Defendants
2 select such data points is not the approach that a person of ordinary skill would have taken at the
3 time of the invention. Defendants' approach represents the use of impermissible hindsight bias.
4 A person of ordinary skill would take into consideration the entire disclosure of a reference,
5 including lipid effects other than LDL-C. In pointing only to LDL-C, Defendants ignore,
6 without explanation, the other effects of DHA that a person of ordinary skill would consider.
7 With respect to Kelley, These effects would teach a person of ordinary skill that DHA has a
8 favorable effect in hypertriglyceridemic patients.

9 Therefore, Geppert and/or Kelley fail to substantiate Defendants' assertion that it was
10 known that DHA was responsible for the increase in LDL-C levels. Further, Defendants ignore,
11 without explanation, other studies that demonstrate that DHA decreases or has little effect on
12 LDL-C levels.⁵⁰⁷⁷ Defendants identify no other basis upon which a person of ordinary skill
13 would have sought to combine the Lovaza PDR with Katayama, Satoh, Shinozaki, Contacos,
14 Geppert and/or Kelley.

(iv) A Person of Ordinary Skill Would Not Have
been Motivated to Find an Omega-3 Fatty
Acid "Therapy that Would Reduce TG
Levels in Patients with TG Levels \geq 500
mg/dL Without Negatively Impacting LDL-
C Levels."

18 Plaintiffs agree that although there was a *need* to find a therapy that would reduce TG
19 levels in patients with very-high TG levels, without negatively impacting LDL-C levels, there
20 was no motivation to find an *omega-3 fatty acid* therapy, or to modify Lovaza/Omacor, to effect
21

22 ⁵⁰⁷⁶ Kelley at 324 (providing that the objectives of the study were to determine "the effects of DHA supplementation
23 on the concentrations of apoproteins; large, medium, and small VLDL, LDL, and HDL particles; and the mean
diameters of these particles in fasting and postprandial plasma.").

24 ⁵⁰⁷⁷ See e.g., Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

1 a reduction in TG levels without increasing LDL-C levels for very-high TG patients at the time
2 of the invention. A person of ordinary skill in the art understood that the rise in LDL-C caused
3 by omega-3 fatty acids (or fibrates) and Lovaza/Omacor was a consequence of the TG-lowering
4 mechanism. The therapies that were available at the time of the invention to treat very-high TGs
5 were niacin, fibrates and prescription omega-3 fatty acids (Lovaza/Omacor). However, niacin
6 was associated with a highly undesirable side effects—including “flushing” (or reddening of the
7 face and other areas with a burning sensation) and dyspepsia—that limited their usefulness.⁵⁰⁷⁸
8 Fibrates were effective at reducing TGs, but they also caused an increase in LDL-C levels in
9 patients with very-high TG levels. To combat the rise of LDL-C, doctors often prescribed
10 fibrates in combination with an LDL-C lowering medication such as a statin.⁵⁰⁷⁹ However, the
11 risk of rhabdomyolysis increased five-fold if fibrates were administered with a statin.⁵⁰⁸⁰
12 Therefore, physicians were reluctant to recommend, and patients were hesitant embrace, a
13 combination fibrate/statin course of treatment.⁵⁰⁸¹ Finally, Lovaza/Omacor were also effective at
14 reducing TG levels, but, similar to fibrates, could cause a substantial increase in LDL-C levels
15 for very-high TG patients. However, Lovaza/Omacor could be safely administered with statins
16 in order to mitigate increased LDL-C.

17 In any event, a person of ordinary skill in the art would have understood that omega 3-
18 fatty acids, including DHA and EPA, and fibrates cause an increase in LDL-C among very high
19

20 ⁵⁰⁷⁸ See *id.* at 991-92; McKenney 2007, at 718; ATP-III at 3315 (noting that patients often could not tolerate higher doses of niacin due to side effects).

21 ⁵⁰⁷⁹ Bays May 16, 2011 Decl., ¶ 8; Topol, at 71 (noting that in high TG patients “the addition of a statin to a fibrate is often required to achieve LDL-C and non-HDL-C goals”);

22 ⁵⁰⁸⁰ See *Id.*; McKenney 2007, at 719 (“[F]ibrates may cause rhabdomyolysis, especially when combined with statins.”).

23 ⁵⁰⁸¹ See *Id.*, ¶ 17

1 TG patients, as reflected in the prior art. Accordingly, a person of ordinary skill in the art would
2 not have been motivated to look to omega 3-fatty acids in order to obtain a reduction in TGs
3 without increasing LDL-C in very high TG patients:

	LDL-C Effect	
	Borderline-High or High TG Patients	Very-High TG Patients
Fibrate ⁵⁰⁸²	-20%	+45%
Lovaza/Omacor ⁵⁰⁸³	-6%	+45%

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5
6
7
8 That Epadel has been approved for decades but not approved for use in the very high TG
9 patient population prior to the invention of the asserted patents is a real-world reflection of the
10 lack of motivation. Research into the pharmaceutical uses of EPA started as early as the 1970s.
11 In 1990, Mochida Pharmaceutical, began to market Epadel, a high purity EPA drug. There have
12 been countless studies conducted which administer Epadel and report the effects observed.
13 Although a few studies administer Epadel to a patient population which included a few patients
14 with TG levels > 500 mg/dL, Defendants fail to identify a single reference directed to the
15 administration of Epadel to patients with very-high TG levels, reflecting the lack of motivation.

16 Defendants offer no “apparent reason” to administer EPA as claimed to patients with
17 fasting baseline TG levels of 500 mg/dl to about 1500 mg/dl. Defendants rely on
18 Lovaza/Omacor as the starting point to “find a therapy that would reduce TG levels in patients
19 with TG levels of at least 500 mg/dL without negatively impacting LDL-C levels.”⁵⁰⁸⁴
20 Ironically, Lovaza/Omacor significantly reduces TGs in patients with TG levels of at least 500

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22 ⁵⁰⁸² Tricor®, Physicians’ Desk Reference 502-505 (62d ed. 2008).

23 ⁵⁰⁸³ Chan 2002 I at 2381 (Table 3).

24 ⁵⁰⁸⁴ Defendants’ Joint Invalidity Contentions at 664.

1 mg/dL but significantly increases LDL-C--an effect understood to be a consequence of TG
2 reduction and the increased conversion of VLDL to LDL particles.⁵⁰⁸⁵

3 It was well known at the time of the invention that omega-3 fatty acids, including both
4 EPA and DHA, caused significant decrease in the production of VLDL particles and a significant
5 increase in the conversion of VLDL to IDL and LDL, supporting the understanding that omega-3
6 fatty acids worked in part by inhibiting VLDL production and improving the conversion of
7 VLDL particles to LDL.⁵⁰⁸⁶ A person of ordinary skill in the art understood that EPA and DHA
8 had the *same* TG-lowering mechanism and did not differentiate between EPA and DHA when
9 discussing the TG-lowering mechanism of omega-3 fatty acids.⁵⁰⁸⁷ The discussion related to the
10 TG-lowering mechanism of omega-3 fatty acids is discussed above in Section III and
11 incorporated herein by reference.

12 In fact, it was well understood that the degree of LDL-C elevation observed with
13 prescription omega-3 therapy, such as Lovaza/Omacor, generally related to pretreatment TG
14 levels; that is, prescription omega-3 therapy, such as Lovaza/Omacor, increased LDL-C levels
15 the most in patients with the highest pretreatment TG levels.⁵⁰⁸⁸ Therefore, a person of ordinary
16 skill in the art would have viewed increased LDL-C levels caused by Lovaza/Omacor as a direct
17 consequence of lowering triglycerides in patients with TG levels ≥ 500 mg/dL. The rise in LDL-

19 ⁵⁰⁸⁵ See Bays 2008 Rx Omega-3 p. 402; McKenny 2007 Role of Prescription Omega-3 at 720 (finding that “[t]hese
20 results illustrate that with prescription omega-3, fewer VLDL particles are secreted into the systemic circulation, and
secreted VLDL particles are rapidly converted to LDL particle, thus explaining why LDL levels may increase in
patients with very-high triglyceride levels when given prescription omega-3 therapy”); Chan 2003

21 ⁵⁰⁸⁶ Chan 202 at 2378-84; *see also* Westphal at 917 (stating “our data confirm the well-known and pronounced
22 decrease in VLDLs after n-3 fatty acid treatment”)

23 ⁵⁰⁸⁷ Bays I, at 398; Harold E. Bays, *Fish Oils in the Treatment of Dyslipidemia and Cardiovascular Disease*, in *The*
Johns Hopkins Textbook of Dyslipidemia 245, 247 (Peter O. Kwiterovich Jr. ed., 2009 (Bays III))

24 ⁵⁰⁸⁸ See Bays 2008 Rx Omega-3 p. 402.

1 C was often offset by concurrent treatment with statins.⁵⁰⁸⁹ The safety and efficacy of using
2 prescription omega-3 in combination with a statin has been well-established.⁵⁰⁹⁰

3 Although an increase in LDL-C was generally observed when omega-3 fatty acids were
4 administered to patients with very-high TG levels, the increase in LDL-C was not necessarily a
5 cause for concern because LDL-C is often low in patients with severe hypertriglyceridemia.

6 Therefore, the final LDL-C concentration may still be in the normal range.⁵⁰⁹¹ Furthermore, it
7 was understood that the overall lipid effect of Lovaza/Omacor was beneficial.⁵⁰⁹²

8 In two pivotal studies in very-high TG patients, both of which used prospective,
9 randomized, double-blind, placebo-controlled study designs, Lovaza/Omacor increased HDL
10 levels from baseline 13% (p=0.014) and 5.9% (p=0.057).⁵⁰⁹³ Correspondingly, prescription
11 omega-3 fatty acids were known to have favorable effects on non-HDL-C levels.⁵⁰⁹⁴ Therefore,
12 “[i]n patients with very-high triglyceride levels, prescription omega-3 fatty acids 4 g/day can
13 substantially reduce triglycerides and VLDL levels and may increase LDL levels, but the net
14

15 ⁵⁰⁸⁹ See Harris 2008 at 14, McKenney at 722.

16 ⁵⁰⁹⁰ McKenney at 722-23.

17 ⁵⁰⁹¹ See Westphal at 918, Harris 1997 at 389.

18 ⁵⁰⁹² See Pownall at 295 (stating that “[t]reatment with ω-3 fatty acids appear to change the lipid profile of individuals
with elevated TG to one that may be less atherogenic by changing LDL structure; lowering serum [cholesterol] ester
transfer activity], serum TG and VLDL-C; and increasing serum HDL-C”); Harris 1997 at 389 (stating that “[t]he
19 increase in LDL, which was substantial on a percentage basis, has been a common finding in past studies in [very-
high TG] patients. It may not be as problematic as it appears, however,” and “the use of omega-3 fatty acids for the
20 treatment of severe hypertriglyceridemia may be beneficial not only for the short-term prevention of acute
pancreatitis, but also for the long-term prevention of CHD”); Bays III at 248 (“No clinical trial data exist that this
21 rise in LDL-C represents harm or potential “toxicity” to patients. In fact, most evidence supports that omega-3 fatty
acids reduce cardiovascular risk as do fibrates. Importantly, clinical trials mostly support that even with increases in
LDL-C, omega-3 fatty acids decrease the total cholesterol (TC) carried by atherogenic lipoproteins, as reflected by
22 decreased non-HDL-C levels (TC minus HDL-C”).

23 ⁵⁰⁹³ McKenney 2007 at 721 (citing Harris 1997 and Pownall).

24 ⁵⁰⁹⁴ McKenney 2007 at 722 (see Fig. 1).

1 effect is a reduction in non-HDL levels. Modest increases in HDL level are also common in
2 patients treated with prescription omega-3 fatty acids.” Prescription omega-3 therapy was also
3 known to alter lipoprotein particle size and composition in a favorable manner by decreasing the
4 number of small, dense LDL particles to larger LDL particles.⁵⁰⁹⁵ Lovaza/Omacor “adversely
5 raise[d] LDL cholesterol concentration but the increase in LDL cholesterol concentration
6 reflect[ed] a less atherogenic light LDL subfraction profile that may be favorable.”⁵⁰⁹⁶
7 Therefore, one of ordinary skill in the art believed that the use of Lovaza/Omacor, and omega-3
8 fatty acids generally, “for the treatment of severe hypertriglyceridemia may be beneficial not
9 only for the short-term prevention of acute pancreatitis, but also for the longer-term prevention
10 of [coronary heart disease].”⁵⁰⁹⁷

11 Therefore, contrary to Defendants’ assertion that “a person of ordinary skill in the art at
12 the time of the claimed inventions would have been motivated to find a therapy that would
13 reduce TG levels in patients with TG levels of at least 500 mg/dL without negatively impacting
14 LDL-C levels,”⁵⁰⁹⁸ one of ordinary skill in the art at the time of the invention understood that the
15 rise in LDL-C caused by omega-3 fatty acids was a by-product of reducing TGs in patients with
16 very-high TG levels. A person of ordinary skill in the art would have expected LDL-C to
17 increase in very-high TG patients, and in some instances the rise was not concerning because
18 LDL-C is often low in patients with severe hypertriglyceridemia and therefore final
19 concentration would still be in the normal range. When LDL-C levels increased beyond what
20 was recommended by the ATP-III, prescribers often relied on statins to safely and effectively

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22 ⁵⁰⁹⁵ McKenney 2007 at 722 (*citing* Calabresi and Stalenhoef).

23 ⁵⁰⁹⁶ Stalenhoef at 134.

24 ⁵⁰⁹⁷ Harris 1997 at 389.

⁵⁰⁹⁸ Defendants’ Joint Invalidation Contentions at 664.

1 reduce LDL-C levels. Furthermore, it was well known that the overall lipid effect of
2 Lovaza/Omacor was beneficial because non-HDL-C levels often increased. Defendants fail to
3 identify any other basis upon which a person of ordinary skill would have been motivated to find
4 a therapy that would reduce TG levels in patients with very-high TG levels without negatively
5 impacting LDL-C levels. Further, a person of ordinary skill in the art would have understood
6 that EPA therapy would *not* reduce Apo-B⁵⁰⁹⁹ (which is a reflection of total atherogenic
7 lipoproteins)⁵¹⁰⁰ in very high TG patients, and accordingly would not have been motivated to
8 administer the claimed EPA composition to the very high TG patient population.

9 Defendants make the conclusory allegation that “routine optimization” by a person of
10 ordinary skill would yield the claimed invention.⁵¹⁰¹ Defendants, however, have offered no
11 explanation to support that allegation and they further fail to establish any of the required criteria
12 of “routine optimization” or the prerequisites to this argument. They also fail to provide any
13 factual detail to support their allegation and they fail to link the allegation to any particular claim
14 or claim element. Defendants mere allegation constitute an improper placeholder to later
15 advance arguments not disclosed in their contentions as required by the Local Rules. In addition,
16 for the reasons discussed herein, a person of ordinary skill would not be motivated to make the
17 combinations alleged by Defendants and, for the same reasons, it would not be routine to
18 combine such references. Where, for example, defendants argue that it would be routine to go
19 from the high TG patient population to the very high TG patient population,⁵¹⁰² they provide no
20 basis for that conclusory assertion and are incorrect. As discussed, a person of ordinary skill

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22 ⁵⁰⁹⁹ *see* Section V.O.

23 ⁵¹⁰⁰ *see* Section III.

24 ⁵¹⁰¹ *See, e.g.*, Defendants’ Joint Invalidation Contentions at 673, 689.

⁵¹⁰² Defendants’ Joint Invalidation Contentions at 238.

1 would have understood these patient populations to be distinct with different impacts of lipid
2 therapy on blood-lipid chemistry for each group. Accordingly, a person of ordinary skill would
3 not have considered the dosage modification suggested by defendants to be routine; Defendants'
4 argument to the contrary represents hindsight bias.

5 In addition, a person of ordinary skill would have no motivation to combine these
6 references because EPA would have been expected to have same result as the mixture of EPA
7 and DHA used in Lovaza/Omacor.

8 (b) Defendants Have Not Shown It Would Have Been
9 Obvious to Administer Purified EPA in the Dosing
10 Regimen Recited in the Claims

11 (i) The '929 Patent is not Obvious Over WO
12 '118 or WO '900, in Combination with the
13 Lovaza PDR, and Further in View of Leigh-
14 Firbank and/or Mori 2000

15 With respect to the '929 patent, Defendants present a combination of five references:
16 "WO '118 or WO '900, in combination with treatment regimen of Lovaza as evidenced by the
17 Lovaza PDR, and further in view of Leigh-Firbank and/or Mori 2000."⁵¹⁰³ Defendants also
18 present charts arguing that an additional 61 references may be combined in order to render the
19 Claims obvious. Not only do Defendants ignore the improbability that a person of ordinary skill
20 would combine 61 separate references, they additionally do not identify any motivation for
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24 ⁵¹⁰³ Defendants' Joint Invalidity Contentions at 669.

1 combining these references.^{5104, 5105} Although Defendants need not point to an explicit statement
2 in the prior art motivating the combination of these references, any assertion of an “apparent
3 reason” to combine must find a basis in the factual record.⁵¹⁰⁶ Defendants’ unsupported cobbling
4 of selective disclosures represents hindsight reconstruction.⁵¹⁰⁷ Defendants’ contentions are no
5 more than an assertion that certain claim elements were known in the prior art. Throughout their
6 contentions, Defendants’ selectively cite to data points in a reference without considering other
7 disclosures or even the reference as a whole. Each reference, however, must be evaluated for all
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9
10 ⁵¹⁰⁴ Defendants’ bare assertion that the asserted claims are obvious “in view of one or more the references cited in
11 Sections III and V.A and B, including, the ’954 publication, WO ’900, WO ’118, Ando, Grimsgaard, Hayashi,
12 Katayama, Kris-Etherton, Matsuzawa, Mataka, Mori 2000, Nakamura, Nozaki, Okumura, Park, Saito 1998, Saito
13 2008 Satoh, Shinozaki, Takaku, Yokoyama 2003, Yokoyama 2007, Calabresi, Chan 2002, Chan 2003, Contacos,
14 Geppert, Kelley, Leigh-Firbank, Maki, Mori 2006, Rambjør, Sanders or Theobold in combination with the
15 knowledge of a person of ordinary skill in the art in light of the dosing regimen employed with Lovaza/Omacor”
16 similarly fails to meet the disclosure requirements of the Nevada Local Patent Rules, and fails to provide any
17 motivation to combine these references. *See* Defendants’ Joint Invalidity Contentions at 668.

18 ⁵¹⁰⁵ Defendants’ bare assertion that “the motivation or reason to combine or modify the prior art to create
19 invalidating combinations under 35 U.S.C. §103 can be found in the references identified above in Section III.C,”
20 and that “[c]ommon sense, design incentives. Market forces, and the background knowledge possessed by a person
21 having ordinary skill in the art provide the reasons or rationales for combining the teachings of multiple references
22 or modifying references to render obvious the claimed inventions of the asserted claims,” fails to meet the disclosure
23 requirements of the Nevada Local Patent Rules. *See* Defendants’ Joint Invalidity Contentions at 67659-60.

24 ⁵¹⁰⁶ *See, e.g., In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the
formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did
not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply
the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi
Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (stating that the assertion of a starting point
“must avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation
to select and then modify a lead compound to arrive at the claimed invention,” which turns on the known “properties
and limitations of the prior art compounds”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F.
Supp. 2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima
facie* obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and
concluding that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art
would have been motivated to resolve citalopram in June 1988”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

⁵¹⁰⁷ *See, e.g., Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under
KSR, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention
without any explanation as to how or why the references would be combined to produce the claimed invention”).

1 that it teaches.⁵¹⁰⁸ Accordingly, Defendants fail to meet their burden to establish *prima facie*
2 obviousness.

3 WO '118 is directed at the composition containing EPA for the purpose of preventing the
4 occurrence of cardiovascular events in multiple risk patients. Further, the invention of WO '118
5 is directed, "in particular, [to] preventing occurrence of cardiovascular events in
6 hypercholesterolemia patients who have been treated with HMG-CoA RI but still suffer from the
7 risk of the cardiovascular events."⁵¹⁰⁹ Contrary to Defendants' assertion that WO '118 discloses
8 "the administration of 4 g of pure EPA with no DHA,"⁵¹¹⁰ WO '118 fails to disclose the claimed
9 subject with the specified very high TG levels (500-1500 mg/dL) who does not receive
10 concurrent lipid altering therapy, the claimed pharmaceutical composition with the specified
11 fatty acid compositions or dosage, or the claimed method to effect the specified TG reduction
12 without substantially increasing LDL-C. WO '118 discloses a composition with a wide range of
13 possible EPA content, dosages, and teaches that DHA is a "preferable fatty acid" to include in
14 the disclosed composition.⁵¹¹¹

15 WO '118 does not disclose administration of highly-purified ethyl-EPA to the target
16 population of the claimed invention. The asserted claims are directed to persons with severe
17 hypertriglyceridemia (i.e. TG level above 500 mg/dL). WO '118 on the other hand only
18 discloses administration of EPA to persons with triglyceride of at least 150 mg/dL.⁵¹¹² WO
19 '118's emphasis on reducing cardiovascular events suggests that its disclosure is directed to

20 ⁵¹⁰⁸ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

21 ⁵¹⁰⁹ WO '118 at 9.

22 ⁵¹¹⁰ Defendants' Joint Invalidation Contentions at 669.

23 ⁵¹¹¹ WO '118 at 22-23.

24 ⁵¹¹² WO '118 at 8.

1 patients with borderline-high to high TG levels, since the primary goal for patients with very-
2 high TG is to prevent acute pancreatitis by decreasing TG levels.⁵¹¹³

3 WO '118 also does not distinguish EPA from DHA in its disclosures regarding the
4 effectiveness of the substances for treating hypertriglyceridemia.⁵¹¹⁴ WO '118 states that
5 “[a]nother preferable fatty acid . . . is DHA-E,” and that “the compositional ratio of EPA-
6 E/DHA-E, content of EPA-E and DHA-E . . . in the total fatty acid, and dosage of (EPA-E +
7 DHA-E) are not particularly limited as long as intended effects of the present invention are
8 attained.”⁵¹¹⁵ It further states that “the composition is preferably the one having a high purity of
9 EPA-E and DHA-E.”⁵¹¹⁶ Further, WO '118 does not disclose EPA's effect on LDL-C, VLDL-C,
10 Apo-B, or Lp-PLA2.

11 WO '900 is directed to a process for producing purified EPA from a culture of micro-
12 organisms. WO '900 fails to disclose the claimed subject with the specified very high TG levels
13 (500-1500 mg/dL) who does not receive concurrent lipid altering therapy, the claimed
14 pharmaceutical composition with the specified dosage or administration period, or the claimed
15 method to effect the specified TG reduction without substantially increasing LDL-C. WO '900
16 only discloses the method of producing purified EPA for therapeutic use, it does not teach
17 *administration* of pure EPA. WO '900 has no discussion, for example, regarding claimed patient
18 population or method of treatment.

21 ⁵¹¹³ See Section III.

22 ⁵¹¹⁴ WO '118 at 11, 13, 16-21 (“the composition containing at least EPA-E and/or DHA-E as its effective
component”).

23 ⁵¹¹⁵ WO '118 at 22-23.

24 ⁵¹¹⁶ WO '118 at 23.

1 WO '900 does not teach administration of pure EPA to treat hypertriglyceridemia. It lists
2 more than 30 diseases that can be treated with pure EPA, but hypertriglyceridemia is not one of
3 them.⁵¹¹⁷ Moreover, WO '900 does not teach the desired effect of EPA other than commenting
4 generally that it “may promote health and ameliorate or even reverse the effects of a range of
5 common diseases.”⁵¹¹⁸ It has no discussion, for example, on any TG-lowering effect of EPA.
6 Although WO '900 identifies DHA as an “undesired molecule”, it does not identify the *specific*
7 undesired effect of DHA or other impurities it is trying to prevent other than commenting
8 generally that “the desired effects of EPA may be limited or reversed” by them.⁵¹¹⁹ It has no
9 discussion related to any LDL-C effects caused by DHA.⁵¹²⁰

10 The proposed combination does not render the independent claims of the '929 patent
11 obvious and Defendants' burden to prove otherwise is especially difficult because the PTO
12 considered WO '118, WO '900, Mori 2000, and Lovaza (both generally and the Lovaza package
13 insert specifically) during prosecution.⁵¹²¹

16 ⁵¹¹⁷ See, e.g., '900 Pub. at 16-17.

17 ⁵¹¹⁸ '900 Pub. at 5.

18 ⁵¹¹⁹ '900 Pub. at 39.

19 ⁵¹²⁰ Defendants also argue that “[t]he administration of about 4 grams of ethyl eicosapentaenoate would have been
20 obvious to one of skill in the art based on the teaching of Kris-Etherton.” Defendants’ Joint Invalidity Contentions at
21 670. They are incorrect. Kris-Etherton teaches that patients in need of TG lowering should consume “two to four
grams of EPA+DHA per day.” Kris-Etherton at 9. Kris-Etherton does not distinguish between EPA and DHA and in
fact recommends the administration of EPA and DHA together. Kris-Etherton does not provide any teaching related
to the administration of EPA alone. In addition, Defendants have offered no specific combination of references that
includes Kris-Etherton and accordingly have not met the requirements of the Local Patent Rules and the law of
obviousness.

22 ⁵¹²¹ See, e.g., *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012)(taking into account that “the
23 examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention.
Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear
and convincing standard came into play”).

1 The analysis of the independent claims of the ‘929 patent is incorporated into all asserted
2 claims that depend from those Claims.

3 (a) Leigh-Firbank and Mori 2000 Do
4 Not Disclose Purported Knowledge
5 that DHA was Responsible for the
6 Increase in LDL-C

7 Defendants contend that a “person of ordinary skill in the art would have been motivated
8 to administer pure EPA to severely hypertriglyceridemic patients according to Lovaza’s known
9 regimen, particularly in light of the knowledge that DHA is responsible for the increase in LDL-
10 C levels as evidenced by Leigh-Firbank or Mori 2000.”⁵¹²²

11 Defendants fail to identify a specific motivation to combine WO ‘118 or WO ‘900 with
12 the treatment regimen of Lovaza, as evidenced by the Lovaza PDR. Although Defendants need
13 not point to an explicit statement in the prior art motivating the combination of these references,
14 any assertion of an “apparent reason” to combine must find a basis in the factual record.⁵¹²³
15 Defendants’ unsupported cobbling of selective disclosures represents hindsight
16 reconstruction.⁵¹²⁴ Defendants’ contentions are no more than an assertion that certain claim

16 ⁵¹²² Defendants’ Joint Invalidation Contentions at 669.

17 ⁵¹²³ See, e.g., *In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the
18 formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did
19 not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply
20 the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi
21 Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must
22 avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to
23 select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and
24 elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp.
2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie*
obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding
that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been
motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

⁵¹²⁴ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under
KSR, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention
without any explanation as to how or why the references would be combined to produce the claimed invention”).

1 elements were known in the prior art. Accordingly, Defendants fail to meet their burden to
2 establish *prima facie* obviousness.

3 Contrary to Defendants' assertion, Leigh-Firbank and Mori 2000 do *not* disclose that
4 DHA is responsible for the increase in LDL-C level. The discussion regarding Leigh-Firbank
5 and Mori 2000 in Section V.K.3.c.1.a.i.a.iii is incorporated herein by reference. Leigh-Firbank
6 cannot comment on the effect of EPA and DHA alone because it did not administer EPA and
7 DHA separately. A person of ordinary skill would similarly understand that Leigh-Firbank does
8 not offer any disclosure regarding the effect of EPA and DHA separately or gain any
9 understanding of the separate impact of DHA or EPA on lipid parameters. Although Mori 2000
10 discloses an increase in LDL-C for patients administered DHA, it also teaches that DHA is
11 preferable to EPA—thus teaching away from the claimed invention and reflecting no motivation
12 to combine with WO '118 or WO '900. Engaging in hindsight bias, Defendants ignore, without
13 explanation, the other effects of DHA that a person of ordinary skill would consider. Defendants
14 fail to identify any other basis upon which a person of ordinary skill would have sought to
15 combine Mori 2000 with the Lovaza PDR.

16 Therefore, Leigh-Firbank and Mori 2000 fail to substantiate Defendants' assertion that it
17 was known that DHA was responsible for the increase in LDL-C levels. Further, Defendants
18 ignore, without explanation, other studies that demonstrate that DHA decreases or has little
19 effect on LDL-C levels.⁵¹²⁵ Defendants identify no other basis upon which a person of ordinary
20 skill would have sought to combine WO '118, WO '900, the Lovaza PDR, Leigh-Firbank and/or
21 Mori.

22 (ii) The '929 Patent is Not Obvious Over WO
23 '118, WO '900, Grimsgaard, Mori 2000

24 ⁵¹²⁵ See *e.g.*, Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

1 and/or Maki in Combination with the
2 Omacor PDR/Lovaza PDR, and Further in
3 View of Katayama, Matsuzawa and/or
4 Takaku.

5 With respect to the '929 patent, Defendants present a combination of nine references:

6 “WO '118, WO '900, Grimsgaard, Mori 2000 and/or Maki in combination with treatment
7 regimen of Omacor/Lovaza as evidenced by the Omacor PDR/Lovaza PDR, and further in view
8 of Katayama, Matsuzawa and/or Takaku.”⁵¹²⁶ Defendants also present charts arguing that an
9 additional 56 references may be combined in order to render the Claims obvious. Not only do
10 Defendants ignore the improbability that a person of ordinary skill would combine 56 separate
11 references, they additionally do not identify any motivation for combining these references.
12 Although Defendants need not point to an explicit statement in the prior art motivating the
13 combination of these references, any assertion of an “apparent reason” to combine must find a
14 basis in the factual record.⁵¹²⁷ Defendants’ unsupported cobbling of selective disclosures
15 represents hindsight reconstruction.⁵¹²⁸ Defendants’ contentions are no more than an assertion

16 ⁵¹²⁶ Defendants’ Joint Invalidity Contentions at 669.

17 ⁵¹²⁷ See, e.g., *In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the
18 formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did
19 not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply
20 the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi
21 Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must
22 avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to
23 select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and
24 elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp.
2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie*
obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding
that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been
motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

⁵¹²⁸ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under
KSR, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention
without any explanation as to how or why the references would be combined to produce the claimed invention”).

1 that certain claim elements were known in the prior art. Throughout their contentions,
2 Defendants’ selectively cite to data points in a reference without considering other disclosures or
3 even the reference as a whole. Each reference, however, must be evaluated for all that it
4 teaches.⁵¹²⁹ Accordingly, Defendants fail to meet their burden to establish *prima facie*
5 obviousness.

6 The discussion related to WO ‘118 and WO ‘900 in Section V.K.3.c.1.b.i is incorporated
7 herein by reference. The discussion related to Grimsgaard, Mori 2000 and/or Maki in Section
8 V.K.3.c.1.a.ii.a.iii is incorporated herein by reference. Defendants contend that “Grimsgaard and
9 Mori 2000 also disclose the administration of 4 g per day of highly purified EPA with no DHA.”
10 However, neither Grimsgaard nor Mori 2000 discloses the administration of 4g/day EPA to the
11 *very high TG patient population*. Neither Grimsgaard nor Mori 2000 provides motivation to
12 administer 4g/day EPA to the *very high TG patient population*. Defendants identify no other
13 basis upon which a person of ordinary skill would have sought to combine the composition
14 disclosed in Grimsgaard or Mori 2000.⁵¹³⁰

15 Defendants argue that it “would have been obvious to a person of ordinary skill in the art
16 to use EPA as described in WO ‘118, WO ‘900, Grimsgaard or Mori 2000 in the treatment
17 regimen used for Omacor/Lovaza as described in the Omacor PDR/Lovaza PDR,” but their
18

19 ⁵¹²⁹ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

20 ⁵¹³⁰ Defendants also argue that “[t]he administration of about 4 grams of ethyl eicosapentaenoate would have been
21 obvious to one of skill in the art based on the teaching of Kris-Etherton.” Defendants’ Joint Invalidity Contentions at
22 670. They are incorrect. Kris-Etherton teaches that patients in need of TG lowering should consume “two to four
23 grams of EPA+DHA per day.” Kris-Etherton at 9. Kris-Etherton does not distinguish between EPA and DHA and in
24 fact recommends the administration of EPA and DHA together. Kris-Etherton does not provide any teaching related
to the administration of EPA alone. In addition, Defendants have offered no specific combination of references that
includes Kris-Etherton and accordingly have not met the requirements of the Local Patent Rules and the law of
obviousness.

1 assertions fail to provide a motivation for combining the references.⁵¹³¹ Although Defendants
2 need not point to an explicit statement in the prior art motivating the combination of these
3 references, any assertion of an “apparent reason” to combine must find a basis in the factual
4 record.⁵¹³² Defendants’ assertions related to motivation are insufficient,⁵¹³³ and accordingly
5 Defendants fail to meet their burden to establish *prima facie* obviousness.

6 Defendants formulate an obviousness argument that relies on Katayama, Matsuzawa, or
7 Takaku. However, they’ve failed to provide any factual or legal basis as to why each reference
8 discloses a claim element, an “apparent reason” or motivation to combine the elements in the
9 manner claimed.⁵¹³⁴ Therefore, Defendants should be precluded from relying on this these
10 references.

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13 ⁵¹³¹ Defendants’ Joint Invalidity Contentions at 669-70.

14 ⁵¹³² See, e.g., *In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the
15 formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did
16 not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply
17 the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi*
18 *Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must
19 avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to
20 select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and
21 elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp.
22 2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie*
23 obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding
24 that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been
motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

⁵¹³³ For example, Defendants’ assertion that “WO ’118 may be combined with other prior art in the field of treating
hypertriglyceridemia” is nothing more than a statement that a reference can be combined but fails to provide any
basis for that statement. While the paragraph associated with that statement makes assertions regarding the
disclosure of certain other references, it does not provide a basis for the assertion of motivation to combine with WO
’118. See Defendants’ Joint Invalidity Contentions at 670.

⁵¹³⁴ *KSR*, 550 U.S. at 417–19; *TriMed, Inc. v. Stryker Corp.*, 608 F.3d 1333, 1341 (Fed. Cir. 2010). Hindsight may
not be employed to identify relevant prior art and relevant teachings therein: *Heidelberger Druckmaschinen AG v.*
Hantscho Comm. Prods., Inc., 21 F.3d 1068, 1071–72 (Fed. Cir. 1994); *Monarch Knitting Mach. Corp. v. Sulzer*
Morat GmbH, 139 F.3d 877, 881 (Fed. Cir. 1998).

1 As discussed above in Section V.K.3.c.1.a.i.a.i, Katayama and Matsuzawa were both only
2 designed to confirm the safety of long term treatment of Epadel and its ability to lower both
3 serum total cholesterol and triglyceride levels. They fail to provide motivation to administer
4 purified EPA to the very high TG patient population. As discussed above in Section
5 V.K.3.c.1.a.ii.a.i, Takaku candidly acknowledges that “only a few subjects were examined” and
6 cautions against drawing a conclusion “only from the results of the present study.”⁵¹³⁵ Further,
7 the study did not include any placebo control, therefore, a person of ordinary skill in the art
8 would understand these reports do not provide the ability to conclude that the observed lipid
9 effects would have occurred independent of the drug that is administered. In addition, the study
10 was conducted exclusively in Japanese patients, and a person of ordinary skill would not have
11 expected the results to be applicable to the general population.⁵¹³⁶

12 The proposed combination does not render the independent claims of the '929 patent
13 obvious and Defendants' burden to prove otherwise is especially difficult because the PTO
14 considered WO '118, WO '900, Grimsgaard, Mori 2000, Maki, Katayama, Matsuzawa and
15 Lovaza (both generally and the Lovaza package insert specifically) during prosecution.⁵¹³⁷

16 The analysis of the independent claims of the '929 patent is incorporated into all
17 asserted claims that depend from those Claims.

18 (a) Grimsgaard, Mori 2000 and/or Maki
19 Do Not Disclose Purported
20 Knowledge that DHA was

21 ⁵¹³⁵ Takaku at ICOSAPENT_DFNDT00006897.

22 ⁵¹³⁶ Yokoyama 2007 at 1097 (“[b]ecause our population was exclusively Japanese, we cannot generalise our results to other populations.”)

23 ⁵¹³⁷ See, e.g., *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012) (taking into account that “the examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention. Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear and convincing standard came into play”).

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3 Defendants contend that a “person of ordinary skill in the art would have been motivated
4 to administer pure EPA to hypertriglyceridemic patients according to Omacor/Lovaza’s known
5 regimen, Katayama, Matsuzawa or Takaku, particularly in light of the knowledge that DHA is
6 responsible for the increase in LDL-C levels as evidenced by Grimsgaard, Mori 2000 or
7 Maki.”⁵¹³⁸

8 Contrary to Defendants’ assertion, Grimsgaard, Mori 2000 and/or Maki do *not* disclose
9 that DHA is responsible for the increase in LDL-C level. The discussion related to Grimsgaard,
10 Mori 2000 and/or Maki in Section V.K.3.c.1.a.ii.a.iii is incorporated herein by reference. A
11 person of ordinary skill would understand that the results of Grimsgaard demonstrated that EPA
12 and DHA’s impact on LDL-C were the same as the effect of the placebo corn oil group; that is,
13 there was no difference between EPA, DHA, or placebo’s effect on LDL-C levels. Although
14 Mori 2000 discloses an increase in LDL-C for patients administered DHA, the reference does not
15 disclose administration of DHA to the requisite patient population and teaches that DHA is
16 preferable to EPA—thus teaching away from the claimed invention. Engaging in hindsight bias,
17 Defendants ignore, without explanation, the other effects of DHA that a person of ordinary skill
18 would consider. Most controlled studies in patients with normal to high baseline TG levels
19 indicated that DHA had little or no effect on LDL-C.⁵¹³⁹ Therefore, a person of ordinary skill
20 would not have concluded that DHA increases LDL-C in patients with normal to high baseline
21 TG levels. Maki demonstrated that when 1.52 g/day DHA and 0.84 g/day palmitic acid is

22 ⁵¹³⁸ Defendants’ Joint Invalidity Contentions at 670.

23 ⁵¹³⁹ Mori 2006 at 98. Moreover, Mori 2000, the only study which compared EPA versus DHA, and is placebo
24 controlled, found an increase in LDL-C after DHA administration.

1 administered to patients with below-average levels of HDL-C levels and borderline-high TG
2 levels, a significant increase in LDL-C is observed.⁵¹⁴⁰ However, one of ordinary skill in the art
3 knew that saturated fatty acids, such as palmitate, may contributed to the elevation in LDL-C.⁵¹⁴¹
4 Therefore, the results of Maki are inconclusive as to DHA's effect alone on LDL-C levels.

5 Therefore, Grimsgaard, Mori 2000 and/or Maki fail to substantiate Defendants' assertion
6 that it was known that DHA was responsible for the increase in LDL-C levels. Further,
7 Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or
8 has little effect on LDL-C levels.⁵¹⁴² Defendants identify no other basis upon which a person of
9 ordinary skill would have sought to combine WO '118, WO '900, Grimsgaard, Mori 2000, Maki,
10 the Omacor PDR/the Lovaza PDR, Katayama, Matsuzawa and/or Takaku.

11 (iii) A Person of Ordinary Skill Would Not Have
12 Been Motivated to Administer Purified EPA
13 in the Treatment Regimen Recited in the
14 Claims

15 For an invention to be obvious, there must have been an "apparent reason" to make it.
16 Defendants assert that a "person of ordinary skill in the art would have been motivated to
17 administer 4 grams of highly-purified EPA to patients with triglycerides greater than or equal to
18 500 mg/dL, with a reasonable expectation of success in lowering triglycerides."⁵¹⁴³ However, as
19 set forth below, Defendants fail to address why a person of ordinary skill in the art would have

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⁵¹⁴⁰ Maki at 195.

21 ⁵¹⁴¹ Maki at 197; Yu et al., *Plasma Cholesterol-Predictive Equations Demonstrate that Stearic Acid is Neutral and*
22 *Monounsaturated Fatty Acids are Hypocholesterlemic*, 61 AM J CLIN NUTR 1129, 1136 (1995); Weber 2000 ("A
23 number of the earlier-formulated (older) omega-3 fatty acid supplements contained significant amounts of saturated
24 fat and cholesterol, both of which are known to elevate LDL-C.").

⁵¹⁴² See e.g., Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

⁵¹⁴³ Defendants' Joint Invalidity Contentions at 670.

1 been motivated to administer 4 grams of highly-purified EPA to patients with triglycerides
2 greater than or equal to 500 mg/dL.

3 A person of ordinary skill in the art would have understood that omega 3-fatty acids,
4 including DHA and EPA, and fibrates cause an increase in LDL-C among very high TG patients,
5 as reflected in the prior art. Accordingly, a person of ordinary skill in the art would not have been
6 motivated to look to omega 3-fatty acids in order to obtain a reduction in TGs without increasing
7 LDL-C in very high TG patients:

	LDL-C Effect	
	Borderline-High or High TG Patients	Very-High TG Patients
Fibrate ⁵¹⁴⁴	-20%	+45%
Lovaza/Omacor ⁵¹⁴⁵	-6%	+45%

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12 That Epadel has been approved for decades but not approved for use in the very high TG
13 patient population prior to the invention of the asserted patents is a real-world reflection of the
14 lack of motivation. Research into the pharmaceutical uses of EPA started as early as the 1970s.
15 In 1990, Mochida Pharmaceutical, began to market Epadel, a high purity EPA drug. There have
16 been countless studies conducted which administer Epadel and report the effects observed.
17 Although a few studies administer Epadel to a patient population which included a few patients
18 with TG levels > 500 mg/dL, Defendants fail to identify a single reference directed to the
19 administration of Epadel to patients with very-high TG levels, reflecting a lack of motivation.

20 Defendants further argue that the disclosure in WO '118 would combine with the prior art
21 concerning Lovaza for at least two reasons; first, "products containing DHA were reported to

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23 ⁵¹⁴⁴ Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

24 ⁵¹⁴⁵ Chan 2002 I at 2381 (Table 3).

1 increase LDL-C levels while products containing only EPA did not,” and second, “WO ‘118
2 reports a reduction in cardiovascular events in hypertriglyceridemic patients administered highly-
3 purified ethyl-EPA.”⁵¹⁴⁶ Both of the “reasons” identified by Defendants are false.

4 Regarding Defendants’ first reason, that “products containing DHA were reported to
5 increase LDL-C levels while products containing only EPA did not,” most controlled studies in
6 patients with normal to high baseline TG levels indicated that DHA had little or no effect on
7 LDL-C.⁵¹⁴⁷ Therefore, a person of ordinary skill would not have concluded that DHA increases
8 LDL-C in patients with normal to high baseline TG levels. Specifically, Leigh-Firbank, Kelley,
9 and Theobald does *not* disclose that “DHA raises LDL-C, an effect associated with heart disease,
10 while EPA does not.”⁵¹⁴⁸ First, Leigh-Firbank cannot comment on the effect of EPA and DHA
11 alone because it did not administer EPA and DHA separately.⁵¹⁴⁹ A person of ordinary skill
12 would similarly understand that Leigh-Firbank does not offer any disclosure regarding the effect
13 of EPA and DHA separately or gain any understanding of the separate impact of DHA or EPA
14 on lipid parameters. Second, Kelley administered DHA-rich oil that was contaminated with
15 other saturated and polyunsaturated fatty acids.⁵¹⁵⁰ Therefore, a person of ordinary skill would
16 have known it is unsuitable for evaluating the independent effects of DHA because it is not clear
17 how much of the supplement’s effects can be attributed to DHA.⁵¹⁵¹ Kelley does not show that

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19 _____
⁵¹⁴⁶ Defendants’ Joint Invalidity Contentions at 671.

20 ⁵¹⁴⁷ Mori 2006 at 98. Moreover, Mori 2000, the only study which compared EPA versus DHA, and is placebo
21 controlled, found an increase in LDL-C after DHA administration.

22 ⁵¹⁴⁸ Defendants’ Joint Invalidity Contentions at 676.

23 ⁵¹⁴⁹ The discussion related to Leigh-Firbank in Section V.K.3.c.1.a.i.a.iii is incorporated herein by reference.

24 ⁵¹⁵⁰ The discussion related to Kelley in Section V.K.3.c.1.a.iii.a.ii is incorporated herein by reference.

⁵¹⁵¹ See Mori 2006 at 96.

1 DHA is responsible for the increase in LDL-C. Kelley suggests that increase in LDL-C is a
2 general phenomenon associated with triglyceride-lowering drugs, stating that a similar increase
3 was induced by fibrate therapy.⁵¹⁵² Kelley specifically teaches that the increase in LDL-C
4 caused by DHA supplementation is unlikely to be “detrimental” because there was not a parallel
5 increase in overall LDL particle number. Rather than concluding that DHA was uniquely
6 responsible for a rise in LDL-C levels, a person of ordinary skill would understand Kelley to
7 disclose that DHA had uniquely beneficial cardioprotective effects.⁵¹⁵³ Finally, Theobald also
8 does not teach that DHA increases LDL-C. In Theobald, 0.7 g/day of DHA was administered for
9 3 months in patients with normal baseline TG levels. Theobald found that LDL-C increased by
10 7% when compared to placebo. However, the DHA composition that was administered in
11 Theobald contained significant amounts of other fatty acids, such as myristic acid, palmitic acid,
12 and oleic acid. Therefore, a person of ordinary skill would have known that the DHA
13 administered by Theobald is unsuitable for evaluating the independent effects of DHA because it
14 impossible to determine whether or how much of the supplement’s effects can be attributed to
15 DHA.⁵¹⁵⁴ Contrary to Defendants’ assertion that there was “a reported advantage to using EPA
16 vs. DHA in hypertriglyceridemic subjects,”⁵¹⁵⁵ there was no known advantage to using EPA vs.
17 DHA. In fact, a number of the references Defendants cite in their contentions ultimately
18 conclude that DHA supplementation “may represent a more favorable lipid profile than after
19

20 ⁵¹⁵² Kelley at 329.

21 ⁵¹⁵³ Kelley at 324, 332 (Kelley’s ultimate conclusion is that “[o]verall, DHA supplementation reduced the
22 concentrations of atherogenic lipids and lipoproteins and increased concentrations of cardioprotective lipoproteins”
and that “DHA supplementation may improve cardiovascular health.”)

23 ⁵¹⁵⁴ See Mori 2006 at 96.

24 ⁵¹⁵⁵ Defendants’ Joint Invalidity Contentions at 671.

1 EPA supplementation.”⁵¹⁵⁶ In addition, a person of ordinary skill would have recognized any
2 impact of DHA reported by the study to be applicable to EPA because they would have
3 understood these substances to function by the same mechanism. Furthermore, as discussed
4 above in Section III, a person of ordinary skill would not expect the same LDL-C effect in
5 patients with lower baseline TG levels, including healthy patients, as in very-high TG patients
6 because patients with higher TG levels had different lipid responses compared to patients with
7 lower TG levels.

8 Defendants contend, without support, that the recited reduction in TG represents
9 therapeutic efficacy, and that a person of ordinary skill would naturally seek to reduce TG to
10 therapeutic efficacy. Defendants further contend that it would have been obvious to a person of
11 ordinary skill to seek to reduce TG by the recited amount because there is no significance
12 attached to the amount. Defendants conclude, without support, that there was a reasonable
13 expectation of success without identifying any combination of references and without explaining
14 how each reference relates to the claimed invention.⁵¹⁵⁷ These contentions: 1) do not assert
15 what the prior art discloses to a person of ordinary skill in the art; 2) are irrelevant to an obvious
16 analysis; 3) fail to address whether the specific combination of claim elements were all present in
17 the prior art references that would have been combined by a person of ordinary skill in the art to
18 produce the claimed invention with a reasonable expectation of success; and 4) fail to establish
19 *prima facie* obviousness. Defendants do not offer an obvious analysis, but trivialize the claim
20 element to the point of reading the element out of the claim. Although convenient and expedient,

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22 ⁵¹⁵⁶ Mori 2000 at 1092.

23 ⁵¹⁵⁷ Ando, Calabresi, Contacos, Grimsgaard, Harris, Hayashi, Katayama, Kris_Etherton 2002, Kurabayashi, Leigh-
24 Firbank, Lovaza 2007 Label, Lovaza PDR, Omacor 2004 Label, Omacor PDR, Lovegrove, Matsuzawa, McKenney
2003, McKenney 2007, Mori 2000, Mori 2006, Nakamura, Nestel, Nozaki, Pownall, Sanders, Shinozaki, Takaku,
von Schacky, Wojenski, Yokoyama 2003, and/or Yokoyama 2007.

1 Defendants' approach does not conform with the Local Patent Rules of this District, the law of
2 claim construction, or the law of obviousness.

3 Defendants further contend, without support, that it would have been obvious to a person
4 of ordinary skill "to use a composition comprising 4 grams of ethyl eicosapentaenoate and not
5 more than about 4% docosahexaenoic acid to lower triglycerides without increasing LDL-C,"
6 and that "using compositions comprising pure EPA would have been obvious to one of skill in
7 the art because such a composition comprising pure EPA would have been obvious to one of
8 skill because such a composition would remove the negative impacts associated with their
9 impurities, such as DHA."⁵¹⁵⁸ These contentions: 1) do not assert what the prior art discloses to
10 a person of ordinary skill in the art; 2) fail to address whether the specific combination of claim
11 elements were all present in the prior art references that would have been combined by a person
12 of ordinary skill in the art to produce the claimed invention with a reasonable expectation of
13 success; and 3) fail to establish *prima facie* obviousness. Defendants do not offer an obvious
14 analysis, but trivialize the claim element to the point of reading the element out of the claim.
15 Although convenient and expedient, Defendants' approach does not conform with the Local
16 Patent Rules of this District, the law of claim construction, or the law of obviousness.

17 Defendants do not identify any combination of references and simply provide a list of
18 references that purportedly disclose disparate elements without explaining how they can be
19 combined.⁵¹⁵⁹ As such, Defendants discuss the claim elements in isolation, and fail to address
20

21 ⁵¹⁵⁸ Defendants rely on Leigh-Firbank, Kelley and Theobald in support of this statement. For the reasons discussed
22 above, these references do not provide motivation to one of ordinary skill to use compositions comprising pure EPA.

23 ⁵¹⁵⁹ *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int'l Co. v.*
24 *Teleflex Inc.*, 550 U.S. 398, 418 (2007)) ("[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").

1 the claimed invention as a whole.⁵¹⁶⁰ Defendants selectively cite to an unspecified isolated
2 disclosure within a reference without considering other disclosures or even the reference as a
3 whole. Each reference, however, must be evaluated for all that it teaches.⁵¹⁶¹ Defendants'
4 unsupported cobbling of selective disclosures represents hindsight reconstruction.⁵¹⁶²

5 Because Defendants do not identify any combination of references, they necessarily fail
6 to offer any evidence that a person of skill in the art would be motivated to combine those
7 references in order to achieve the invention of the claim as a whole. Defendants offers
8 conclusory statements without providing a reason that would have prompted a person of ordinary
9 skill to reduce triglycerides without increasing LDL-C by the recited amount.⁵¹⁶³ Defendants'
10 burden to establish *prima facie* obviousness is not discharged because there is allegedly "no
11 significance" attached to the recited TG reduction amount.⁵¹⁶⁴ Defendants have not met the
12 burden with the naked assertion that it would have been obvious to seek the claim element.

14 ⁵¹⁶⁰ *Sanofi Syntheolabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008) ("The determination of obviousness is
15 made with respect to the subject matter as a whole, not separate pieces of the claim").

16 ⁵¹⁶¹ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

17 ⁵¹⁶² See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under
18 *KSR*, "[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention
19 without any explanation as to how or why the references would be combined to produce the claimed invention").

20 ⁵¹⁶³ *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) ("Rejections on obviousness grounds cannot be
21 sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational
22 underpinning to support the legal conclusion of obviousness.") (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir.
23 2006)) (internal quotation marks omitted); *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350,
24 1356-57 (Fed. Cir. 2007) ("While the *KSR* Court rejected a rigid application of the teaching, suggestion, or
motivation ('TSM') test in an obviousness inquiry, the Court acknowledged the importance of identifying 'a reason
that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the
claimed new invention does' in an obviousness determination.") (quoting *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S.
398, 418 (2007)).

⁵¹⁶⁴ Plaintiffs do not have to show that a claimed range is critical unless a *prima facie* case of obviousness has been
established. See *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003) ("An applicant may overcome a *prima facie*
case of obviousness by establishing that the claimed range is critical . . .") (internal quotation marks omitted).

1 Similarly, without the disclosure of a combination of references and a motivation/reason
2 to combine or modify the references, Defendants necessarily fail to offer any evidence that a
3 person of ordinary skill in the art would have had a reasonable expectation of success in
4 achieving the claimed invention. Defendants make a conclusory statement that there was a
5 reasonable expectation of success, without providing a support other than merely identifying
6 prior art references that purportedly disclose disparate elements.⁵¹⁶⁵

7 Regarding Defendants' second reason, that "WO '118 reports a reduction in
8 cardiovascular events in hypertriglyceridemic patients administered highly-purified ethyl-EPA,"
9 the cardioprotective effects of omega-3 fatty acids, including both EPA and DHA, have been
10 well documented.⁵¹⁶⁶ Lovaza/Omacor has been shown to reduce the risk for cardiovascular
11 death plus nonfatal myocardial infarction and nonfatal stroke.⁵¹⁶⁷ Omega-3 fatty acids have been
12 shown to exert cardioprotective effects in both primary and secondary coronary heart disease
13 prevention trials.⁵¹⁶⁸ Omega-3 fatty acids were known to reduce TG concentration, have
14 antiarrhythmic effects, decrease platelet aggregation, stabilize plaque, reduce blood pressure
15 and/or reduce heart rate.⁵¹⁶⁹

17 ⁵¹⁶⁵ *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) ("Rejections on obviousness grounds cannot be
18 sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational
19 underpinning to support the legal conclusion of obviousness.") (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir.
2006)) (internal quotation marks omitted).

20 ⁵¹⁶⁶ Harris et al., *Tissue n-3 and n-6 Fatty Acids and Risk for Coronary Heart Disease Events*, 193
ATHEROSCLEROSIS, 1, 8 (2007) ("Overall, these findings confirm the well-known relationship between the n-3 FA
and CHD risk.") ("Harris 2007"); Bays 2008 II at 229-230.

21 ⁵¹⁶⁷ See Bays, *Clinical Overview of Omacor: A Concentrated Formulation of Omega-3 Polyunsaturated Fatty Acids*,
98 AM. J. CARDIOL 71i (2006) ("Bays 2006").

22 ⁵¹⁶⁸ Harris et al., *Omega-3 Fatty Acids and Coronary Heart Disease Risk: Clinical and Mechanistic Perspectives*,
197 ATHEROSCLEROSIS 12, 13 (2008) ("Harris 2008").

23 ⁵¹⁶⁹ Harris 2008 at 13.

1 Defendants argue that a “person of ordinary skill in the art would have appreciated the
2 fact that highly-purified ethyl-EPA, and not Lovaza, had been demonstrated to reduce
3 cardiovascular events in high-risk hypertriglyceridemic patients, and understood the benefits of
4 replacing the EPA+DHA of Lovaza with the highly purified ethyl-EPA of WO ‘118.”⁵¹⁷⁰ As
5 discussed above, the cardioprotective effects of omega-3 fatty acids, including both EPA, DHA
6 and Lovaza/Omacor have been well documented.⁵¹⁷¹

7 In fact, a meta-analysis of twenty-five studies which examined the risk of coronary heart
8 disease endpoints as a function of tissue FA composition found that the evidence suggested that
9 DHA is *more* cardioprotective than EPA.⁵¹⁷² This study found that “depressed levels of long-
10 chain *n*-3 FA (especially DHA) in tissues is a consistent marker of increased risk for coronary
11 heart disease events.”⁵¹⁷³ Further, the study found that DHA levels, with or without EPA, were
12 significantly lower in fatal endpoints.⁵¹⁷⁴ This study suggests that DHA is preferable to EPA—
13 thus teaching away from the claimed invention.⁵¹⁷⁵ Defendants rely on hindsight bias to argue
14 that a person of ordinary skill would have been motivated to use purified EPA, when both EPA
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17 ⁵¹⁷⁰ Defendants’ Joint Invalidation Contentions at 671-72.

18 ⁵¹⁷¹ Harris et al., *Tissue n-3 and n-6 Fatty Acids and Risk for Coronary Heart Disease Events*, 193
ATHEROSCLEROSIS, 1, 8 (2007) (“Overall, these findings confirm the well-known relationship between the *n*-3 FA
and CHD risk.”) (“Harris 2007”).

19 ⁵¹⁷² Harris 2007 at 8.

20 ⁵¹⁷³ *Id.*

21 ⁵¹⁷⁴ Harris 2007 at 7, Table 5; *see also* Harris 2007 at 8 (“Low DHA was the most common finding across all
studies, suggesting that this FA was perhaps more cardioprotective than EPA as others have suggested.”).

22 ⁵¹⁷⁵ *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994) (A reference may be said to teach away when a person of
ordinary skill, upon [examining] the reference, would be discouraged from following the path set out in the
reference, or would be led in a direction divergent from the path that was taken by the applicant.”); *see also*
23 *Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012) (quoting *Gurley*); *W.L. Gore & Assocs.,*
Inc. v. Garlock, Inc., 721 F.2d 1540, 1552 (Fed. Cir. 1983) (“[P]roceed[ing] contrary to the accepted wisdom of the
24 prior art ... is strong evidence of nonobviousness.”).

1 and DHA were known to have cardioprotective effects, and there were studies suggesting DHA
2 was *more* cardioprotective than EPA.

3 Defendants argue that the following claim elements were known: the administration of
4 highly-purified EPA-E to reduce TG levels in patients with normal to high TG levels, the
5 administration of purified EPA to patients with TG levels > 500 mg/dL, to administer EPA-E to
6 patients with high and very high TG levels who were not receiving concurrent lipid altering
7 therapy, and the dose of 4g/day and 12-week regimen. Defendants then argue that the “only
8 question is whether one skilled in the art would have been motivated to use the DHA-free,
9 highly-purified EPA-E of the prior art for the treatment of patients with triglyceride levels of at
10 least 500 mg/dL as part of the claimed dosage regimen.”⁵¹⁷⁶

11 Defendants’ contentions are no more than a recitation that certain claim elements were
12 known in the prior art. Defendants’ assertions to the contrary represent hindsight
13 reconstruction.⁵¹⁷⁷ Notably, Defendants *do not* assert that a person of ordinary skill would have
14 known that purified EPA, when administered to patients with very-high TG levels (≥ 500 mg/dL),
15 *would not substantially increase LDL-C*. Further, Defendants point to three Japanese studies,⁵¹⁷⁸
16 which included a small minority of patients with baseline TG levels > 500 mg/dL to argue that “a
17 number of prior art references disclosed the administration of purified EPA to patients with TG
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21 ⁵¹⁷⁶ Defendants’ Joint Invalidation Contentions at 673.

22 ⁵¹⁷⁷ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that even under
23 KSR, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention
without any explanation as to how or why the references would be combined to produce the claimed invention.”).

24 ⁵¹⁷⁸ Nakamura, Matsuzawa, and Takaku.

1 levels > 500 mg/dL.”^{5179, 5180} The disclosures of Nakamura (one patient), Matsuzawa (disclosure
2 of three patients with TG between 400 and 1000 mg/dL, with no evidence or support for the
3 assertion that the patients had very high TGs), and Takaku (three patients) reflect that a person of
4 ordinary skill in the art would *not* understand these references to relate to the use of EPA in
5 patients with very high TGs, nor would a person of ordinary skill in the art draw any conclusions
6 regarding these references in terms of the very high TG patient population. In Nakamura, one
7 patient had a baseline TG level > 500 mg/dL.⁵¹⁸¹ However, the mean baseline TG for all patients
8 was 2.07 mmol/l (183 mg/dL), indicating that the baseline TG values for the other patients was
9 well below 500 mg/dL.⁵¹⁸² In Matsuzawa, three patients had TG levels between 400 and 1000
10 mg/dL and one patient had TG levels > 1,000 mg/dL.⁵¹⁸³ Based on this disclosure, only one
11 patient definitively had a baseline TG level \geq 500 mg/dL. Further, this one patient was excluded
12 when analyzing the lipid impact because he was a “heavy drinker” and the “effect of alcohol
13 made it impossible to assess triglyceride levels.”⁵¹⁸⁴ In Takaku, three patients had baseline TG
14 levels above 500 mg/dL.⁵¹⁸⁵ However, the mean baseline TG level for all patients was 245
15 mg/dL.⁵¹⁸⁶ Indeed, the mean baseline TG level of the patients in all three studies was well below
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17 ⁵¹⁷⁹ Defendants’ Joint Invalidity Contentions at 672.

18 ⁵¹⁸⁰ Okumura and Hayashi also fail to disclose administration of purified EPA to patients with TG levels > 500
19 mg/dL. Hayashi states that the baseline TG level was 300 +/- 233 mg/dL. However, the standard error is unusually
20 high and there is no specific disclosure of a single subject with TG levels > 500 mg/dL. Okumuara specifically
21 states that its hypertriglyceridemia patients had baseline TG levels between 150 and 500 mg/dL.

22 ⁵¹⁸¹ Nakamura at 23, Table 1.

23 ⁵¹⁸² Nakamura at 23, Tables 1 and 2.

24 ⁵¹⁸³ *Id.* at 23.

⁵¹⁸⁴ *Id.* at 10.

⁵¹⁸⁵ Takaku at ICOSAPENT_DFNDTS00006895.

⁵¹⁸⁶ Takaku at ICOSAPENT_DFNDTS00006875.

1 500 mg/dL; therefore, a person of ordinary skill would not have expected the results to be
2 applicable to patients with triglycerides above 500 mg/dL. Further, in each of these studies,
3 patients with >500 mg/dL were most likely excluded from the LDL-C calculations because the
4 Friedewald's Equation cannot be used for patients with triglyceride levels ≥ 400 mg/dL.⁵¹⁸⁷
5 Defendants have failed to identify all of the claimed elements and fail to provide motivation to
6 use the DHA-free, highly-purified EPA-E of the prior art for the treatment of patients with
7 triglyceride levels of at least 500 mg/dL as part of the claimed dosage regimen.

8 Defendants contend that a "person of ordinary skill in the art would have been motivated
9 to administer highly-purified EPA-E capsules or those with not more than about 4% DHA for at
10 least 12 weeks . . . in order to achieve the known TG-lowering effects of highly-purified EPA-
11 E."⁵¹⁸⁸ This argument is flawed. The prior art demonstrates a wide range of administration
12 periods utilized in different clinical studies. For example, EPA was administered for 4 weeks in
13 Park, for 7 weeks in Grimsgaard, for 8 weeks in Hayashi, for 1 year in Takaku, for 2 years in
14 Katayama, and for 5 years in Yokoyama 2007. Given the large number of choices of
15 administration periods disclosed in prior art, Defendants have not shown that a person of
16 ordinary skill would not have been motivated to administer highly-purified EPA-E capsules for
17 12 weeks and offer no basis for their assertions.

18 Moreover, a person of ordinary skill would not have been motivated to administer highly-
19 purified *EPA-E* capsules, as opposed to DHA or a combination of EPA and DHA (such as
20 Lovaza), for 12 weeks. It was well known that both EPA and DHA reduced blood

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23 ⁵¹⁸⁷ See Matsuzawa at ICOSAPENT_DFNDTS00006450.

24 ⁵¹⁸⁸ Defendants' Joint Invalidity Contentions at 673.

1 triglycerides.⁵¹⁸⁹ In fact, Defendants acknowledge in their Joint Invalidation Contentions that
2 “DHA and EPA were both known to comparably reduce triglycerides, independently of one
3 another.”⁵¹⁹⁰ Data from some studies even suggested that DHA or fish oil may reduce
4 triglyceride more effectively than EPA.⁵¹⁹¹ Therefore, a person of ordinary skill would not have
5 been motivated to administer highly-purified *EPA-E* capsules instead of DHA or a combination
6 of EPA and DHA (such as Lovaza) for 12 weeks.

7 Defendants argue that a “person of ordinary skill in the art also would have been
8 motivated to administer 4 g/day highly-pure ethyl EPA . . . because of the observed significant
9 reduction in TG that was achieved in six weeks of treatment,” citing Mori 2000.⁵¹⁹² This
10 argument is incorrect. The administration of 4 g/day of highly-pure ethyl EPA to patients with
11 *mild* hypertriglyceridemia for *six* weeks does not provide a person of ordinary skill motivation to
12 administer the same dose to patients with *severe* hypertriglyceridemia for *twelve* weeks.

13 Defendants also, once again, fail to demonstrate that a person of ordinary skill would have
14 chosen to administer 4g/day EPA as opposed to DHA or a combination of EPA and DHA (such
15 as Lovaza).

16 Defendants further argue that “because Katayama and Saito 1998 teach that higher doses
17 of highly-purified EPA-E reduce TG level to a greater extent than lower doses . . . a person of
18 ordinary skill in the art would have been motivated to administer highly-purified EPA-E at a
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20 ⁵¹⁸⁹ Mori 2006 at 98.

21 ⁵¹⁹⁰ Defendants’ Joint Invalidation Contentions at 678.

22 ⁵¹⁹¹ Mori 2000 (showing that EPA reduced triglyceride by 18% while DHA reduced triglyceride by 20%); Rambjor
23 (showing that fish oil reduced triglyceride more than EPA); Grimsgaard (showing that decrease in triglyceride was
greater with DHA supplementation than EPA supplementation).

24 ⁵¹⁹² Defendants’ Joint Invalidation Contentions at 673.

1 dose of 4 g/day rather than a lower dose.”⁵¹⁹³ A person of ordinary skill would not have relied
2 on either reference to determine the EPA dosage required to treat severe hypertriglyceridemia,
3 because these studies were not designed to determine the effect of dose on the degree of TG
4 reduction. Second, Katayama and Saito do not suggest that 4 g/day of EPA, rather than a lower
5 dose or a higher dose, would be the right dosage to treat severe hypertriglyceridemia.

6 Moreover, as discussed above, it was well known that both EPA and DHA reduced blood
7 triglycerides.⁵¹⁹⁴ Therefore, a person of ordinary skill would not have been motivated to
8 administer 4 g/day of highly-purified *EPA-E* capsules, as opposed to DHA or a combination of
9 EPA and DHA (such as Lovaza).

10 Defendants further argue that a “person of ordinary skill in the art would have also been
11 motivated to treat subjects having baseline TG levels of 500 mg/dl to about 1500 mg/dl with
12 highly-purified EPA-E, as suggested by Yokoyama’s teaching that TG was reduced to a much
13 greater extent in subjects having higher baseline TG levels . . . and because Katayama and Saito
14 treated subjects having baseline triglyceride levels greater than 500 mg/dl.”⁵¹⁹⁵ This argument is
15 incorrect. It was well known that any TG-reducing therapy will reduce TG to a greater extent in a
16 patient having higher baseline TG levels. Therefore, a person of ordinary skill would not have
17 been motivated to administer highly-purified *EPA-E* capsules as opposed to any other omega-3
18 fatty acid composition, fibrate, or other TG-lowering therapy, to treat subjects having baseline
19 TG levels above 500mg/dL. Further, a person of ordinary skill would have expected that a
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⁵¹⁹³ Defendants’ Joint Invalidity Contentions at 673-74.

23 ⁵¹⁹⁴ See Section III.

24 ⁵¹⁹⁵ Defendants’ Joint Invalidity Contentions at 674.

1 greater decrease in TG levels, in the very high TG patient population, would lead to a greater
2 increase in LDL-C levels.

3 Defendants contend that a “person of ordinary skill in the art would have been motivated
4 to administer highly-purified EPA-E—either on its own or with statin therapy—to effect a
5 reduction in TG levels without affecting LDL-C if treatment was without statin therapy, or to
6 effect a reduction in TG and LDL-C, if treatment was with statin therapy.”⁵¹⁹⁶ Defendants first
7 support this argument by asserting that a person of ordinary skill in the art would have known
8 that EPA could lower TG levels without increasing LDL-C in very high TG patients. That is
9 incorrect. As discussed above, a person of ordinary skill in the art would not have expected EPA
10 to raise LDL-C levels in very high TG patients. Defendants’ broadly cite to “Yokoyama 2003,
11 Yokoyama 2007, Mori 2000, Mori 2006, Saito 1998, and the other references discussed in
12 V.B.4. and 5” to support this proposition,⁵¹⁹⁷ however these references do not disclose or suggest
13 to a person of ordinary skill that EPA could lower TG levels without increasing LDL-C in very
14 high TG patients.⁵¹⁹⁸

15 Defendants next argue again that DHA was known to be responsible for the increase in
16 LDL-C levels in very high TG patients, but as discussed above, *see* Section III, a person of
17 ordinary skill would understand that both EPA and DHA function similarly, and that both would
18 have little to no impact on borderline-high TG patients in terms of LDL-C levels and would
19 increase LDL-C levels in patients with very high TGs.

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22 ⁵¹⁹⁶ Defendants’ Joint Invalidity Contentions at 675.

23 ⁵¹⁹⁷ Defendants’ Joint Invalidity Contentions at 675.

24 ⁵¹⁹⁸ *See* Section IV.

1 Defendants argue that a person of ordinary skill in the art “would have known that an
2 increase in LDL-C was an adverse health effect to be avoided.”⁵¹⁹⁹ While an increase in LDL-C
3 was seen as a *possible* adverse health effect, a person of ordinary skill in the art understood that
4 the increase in LDL-C seen in the very-high TG patient population with Lovaza, and omega-3
5 fatty acids generally, was related to increased conversion of VLDL to LDL particles.⁵²⁰⁰

6 Defendants rely on Kelley and the Lovaza label to argue that one of ordinary skill in the
7 art would have been motivated, with a reasonable expectation of success, to administer a highly-
8 purified EPA-E dosage form, with little to no DHA, in order to avoid the expected increase in
9 LDL-C with DHA.”⁵²⁰¹ However, a person of ordinary skill in the art expected an increase in
10 LDL-C in the very high TG population, with both EPA and DHA. It was well known at the time
11 of the invention that omega-3 fatty acids, including both EPA and DHA, caused significant
12 decrease in the production of VLDL particles and a significant increase in the conversion of
13 VLDL to IDL and LDL, supporting the theory that omega-3 fatty acids worked in part by
14 inhibiting VLDL production and improving the conversion of VLDL particles to LDL.⁵²⁰² A
15 person of ordinary skill in the art understood that EPA and DHA had the *same* TG-lowering
16 mechanism and did not differentiate between EPA and DHA when discussing the TG-lowering
17 mechanism of omega-3 fatty acids.⁵²⁰³ The discussion related to the TG-lowering mechanism of

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19 ⁵¹⁹⁹ Defendants’ Joint Invalidation Contentions at 677.

20 ⁵²⁰⁰ See Bays 2008 I at 402; McKenny 2007 at 720 (finding that “[t]hese results illustrate that with prescription
21 omega-3, fewer VLDL particles are secreted into the systemic circulation, and secreted VLDL particles are rapidly
22 converted to LDL particle, thus explaining why LDL levels may increase in patients with very-high triglyceride
23 levels when given prescription omega-3 therapy”); Chan 2003.

22 ⁵²⁰¹ Defendants’ Joint Invalidation Contentions at 678.

23 ⁵²⁰² Chan 202 at 2378-84; see also Westphal at 917 (stating “our data confirm the well-known and pronounced
24 decrease in VLDLs after n-3 fatty acid treatment”).

⁵²⁰³ Bays 2008 I, at 398; Bay in Kwiterovich at 247.

1 omega-3 fatty acids is discussed above in Section III and incorporated herein by reference.
2 Further, a person of ordinary skill in the art would have understood that EPA therapy would *not*
3 reduce Apo-B⁵²⁰⁴ (which is a reflection of total atherogenic lipoproteins)⁵²⁰⁵ in very high TG
4 patients, and accordingly would not have been motivated to administer the claimed EPA
5 composition to the very high TG patient population.

6 Accordingly, a person of ordinary skill would not have been motivated to combine WO
7 '118, WO '900, Grimsgaard, Mori 2000 and/or Maki in with the Omacor PDR/Lovaza PDR, and
8 Katayama, Matsuzawa and/or Takaku. A person of ordinary skill in the art further would not
9 have been motivated to combine WO '118 or WO '900, with the Lovaza PDR, or with Leigh-
10 Firbank and/or Mori 2000.

11 (2) Dependent Claims

12 (a) Defendants Have Not Shown that Claim 2 of the
13 '929 Patent Would Have Been Obvious

14 Plaintiffs incorporate by reference the discussion related to the Independent Claim in
15 Section V.K.3. Because Defendants have not shown the obviousness of the Independent Claim
16 by clear and convincing evidence, they also have not adequately proven the obviousness of
17 Claim 2.

18 Defendants contend that it would be obvious that a person receiving the claimed EPA
19 compositions would have a fasting baseline LDL-C from 50 mg/dL to about 300 mg/dL because
20 hypertriglyceridemic patients in the Lovaza label had a mean LDL-C level of 100 mg/dL. These
21 contentions: 1) fail to address whether the specific combination of claim elements were all
22 present in the prior art references that would have been combined by a person of ordinary skill in

23 ⁵²⁰⁴ *see* Section V.O.

24 ⁵²⁰⁵ *see* Section III.

1 the art to produce the claimed invention with a reasonable expectation of success; and 2) fail to
2 establish *prima facie* obviousness. Defendants do not offer an obvious analysis, but trivialize the
3 claim element to the point of reading the element out of the claim. Although convenient and
4 expedient, Defendants' approach does not conform with the Local Patent Rules of this District,
5 the law of claim construction, or the law of obviousness.

6 Defendants do not identify any combination of references. Because Defendants do not
7 identify any combination of references, they necessarily fail to offer any evidence that a person
8 of skill in the art would be motivated to combine those references in order to achieve the
9 invention of the claim as a whole. Further, Defendants do not discuss at all whether a person of
10 ordinary skill would have been motivated to combine the elements, other than stating that a
11 patient with LDL-C levels of 50 mg/dL to about 300 mg/dL would benefit from receiving the
12 claimed fish oil treatment. Defendants also state erroneously that a patient with LDL-C levels of
13 50 mg/dL to about 300 mg/dL would be considered hypertriglyceridemic. Defendants do not
14 establish that a person of ordinary skill would have been motivated to combine the elements to
15 achieve the claimed invention.⁵²⁰⁶

16 Similarly, without the disclosure of a combination of references and a motivation/reason
17 to combine or modify the references, Defendants necessarily fail to offer any evidence that a
18 person of ordinary skill in the art would have had a reasonable expectation of success in
19 achieving the claimed invention. Defendants do not even discuss whether a person of ordinary
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22 ⁵²⁰⁶ *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the *KSR*
23 Court rejected a rigid application of the teaching, suggestion, or motivation (‘TSM’) test in an obviousness inquiry,
24 the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill
in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness
determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

1 skill would have expected that the combination to work for its intended purpose for treating the
2 recited patient population.⁵²⁰⁷ As such, Defendants fail to demonstrate reasonable expectation of
3 success of the claimed invention.

4 (b) Defendants Have Not Shown that Claim 3 of the
5 '929 Patent Would Have Been Obvious

6 Plaintiffs incorporate by reference the discussion related to the Independent Claim in
7 Section V.K.3. Because Defendants have not shown the obviousness of the Independent Claim
8 by clear and convincing evidence, they also have not adequately proven the obviousness of
9 Claim 3.

10 Defendants do not identify any combination of references and simply provide a laundry
11 list of references without explaining how each reference relates to the claimed invention.
12 Defendants further contend, without any support, that a person of ordinary skill would have been
13 able to determine the patient population in need of the claimed methods of treatment, would seek
14 to measure the HDL-C, VLDL-C and cholesterol baselines of a patient, and would seek to treat
15 those patients having very high triglycerides regardless of the baseline values of these lipids.⁵²⁰⁸
16 These contentions: 1) do not assert what the prior art discloses to a person of ordinary skill in
17 the art; 2) are irrelevant to an obvious analysis; 3) fail to address whether the specific
18 combination of claim elements were all present in the prior art references that would have been
19 combined by a person of ordinary skill in the art to produce the claimed invention with a
20 reasonable expectation of success; and 4) fail to establish *prima facie* obviousness. Defendants
21 do not offer an obvious analysis, but trivialize the claim element to the point of reading the

22 ⁵²⁰⁷ *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable
23 result’ discussed in KSR refers not only to the expectation that prior art elements are capable of being physically
24 combined, but also that the combination would have worked for its intended purpose.”)

⁵²⁰⁸ *Id.*

1 element out of the claim. Although convenient and expedient, Defendants’ approach does not
2 conform with the Local Patent Rules of this District, the law of claim construction, or the law of
3 obviousness.

4 Defendants fail to show a specific combination of references that discloses each element
5 of the claimed invention. Defendants merely list references, without reference to a specific page
6 or section, that purportedly disclose disparate elements without explaining how they can be
7 combined.⁵²⁰⁹ As such, Defendants discuss the claim elements in isolation, and fail to address
8 the claimed invention as a whole.⁵²¹⁰ Moreover, by simply identifying prior art references
9 without discussing the specific teachings of each reference, Defendants fail to consider each
10 prior art reference as a whole.⁵²¹¹ Each reference must be evaluated for all that it teaches.
11 Defendants’ unsupported cobbling of selective disclosures represents hindsight
12 reconstruction.⁵²¹²

13 Because Defendants do not identify any combination of references, they necessarily fail
14 to offer any evidence that a person of skill in the art would be motivated to combine those
15 references in order to achieve the invention of the claim as a whole. Defendants make a
16 conclusory statement that a person of ordinary skill “would indeed seek” to perform the claimed
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18 ⁵²⁰⁹ *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int’l Co. v.*
19 *Teleflex Inc.*, 550 U.S. 398, 418 (2007)) (“[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”).

20 ⁵²¹⁰ *Sanofi Syntheolabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008) (“The determination of obviousness is
made with respect to the subject matter as a whole, not separate pieces of the claim”).

21 ⁵²¹¹ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011) (“A prior
22 patent must be considered in its entirety, i.e., as a whole, including portions that would lead away from the invention
in suit.”) (internal citation and quotation marks omitted).

23 ⁵²¹² See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under
24 *KSR*, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention
without any explanation as to how or why the references would be combined to produce the claimed invention”).

1 methods of treatment, without providing a reason that would have prompted a person of ordinary
2 skill to combine the elements.⁵²¹³ Such a naked assertion does not show why a person of
3 ordinary skill would have been motivated to treat the recited patient population using the claimed
4 methods of treatment.⁵²¹⁴

5 Similarly, without the disclosure of a combination of references and a motivation/reason
6 to combine or modify the references, Defendants necessarily fail to offer any evidence that a
7 person of ordinary skill in the art would have had a reasonable expectation of success in
8 achieving the claimed invention. In fact, other than simply identifying prior art references that
9 purportedly disclose disparate elements, Defendants do not even discuss whether a person of
10 ordinary skill would have expected that the combination to work for its intended purpose for
11 treating the recited patient population.⁵²¹⁵ As such, Defendants fail to demonstrate reasonable
12 expectation of success of the claimed invention.

13 (c) Defendants Have Not Shown that Claim 4 of the
14 '929 Patent Would Have Been Obvious

15 Plaintiffs incorporate by reference the discussion related to the Independent Claim in
16 Section V.K.3. Because Defendants have not shown the obviousness of the Independent Claim
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18 ⁵²¹³ *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (“Rejections on obviousness grounds cannot be
19 sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational
20 underpinning to support the legal conclusion of obviousness.”) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir.
2006)) (internal quotation marks omitted)

21 ⁵²¹⁴ *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the *KSR*
22 Court rejected a rigid application of the teaching, suggestion, or motivation (‘TSM’) test in an obviousness inquiry,
the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill
in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness
determination.”) (quoting *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

23 ⁵²¹⁵ *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable
24 result’ discussed in *KSR* refers not only to the expectation that prior art elements are capable of being physically
combined, but also that the combination would have worked for its intended purpose.”)

1 by clear and convincing evidence, they also have not adequately proven the obviousness of
2 Claim 4.

3 Defendants contend, without support, that the recited reduction in TG represents
4 therapeutic efficacy, and that a person of ordinary skill would naturally seek to reduce TG to
5 therapeutic efficacy. Defendants further contend that it would have been obvious to a person of
6 ordinary skill to seek to reduce TG by the recited amount because there is no significance
7 attached to the amount. Defendants conclude, without support, that there was a reasonable
8 expectation of success without identifying any combination of references and without explaining
9 how each reference relates to the claimed invention.⁵²¹⁶ These contentions: 1) do not assert
10 what the prior art discloses to a person of ordinary skill in the art; 2) are irrelevant to an obvious
11 analysis; 3) fail to address whether the specific combination of claim elements were all present in
12 the prior art references that would have been combined by a person of ordinary skill in the art to
13 produce the claimed invention with a reasonable expectation of success; and 4) fail to establish
14 *prima facie* obviousness. Defendants do not offer an obvious analysis, but trivialize the claim
15 element to the point of reading the element out of the claim. Although convenient and expedient,
16 Defendants' approach does not conform with the Local Patent Rules of this District, the law of
17 claim construction, or the law of obviousness.

18 Defendants further contend, without support, that a person of ordinary skill would
19 "reasonably expect to see the same hypotriglyceridemic effect from a pure EPA formulation
20 containing no DHA," as a formulation containing both EPA and DHA. Defendants conclude,
21

22 ⁵²¹⁶ Ando, Calabresi, Contacos, Grimsgaard, Harris, Hayashi, Katayama, Kris_Etherton 2002, Kurabayashi, Leigh-
23 Firbank, Lovaza 2007 Label, Lovaza PDR, Omacor 2004 Label, Omacor PDR, Lovegrove, Matsuzawa, McKenney
24 2003, McKenney 2007, Mori 2000, Mori 2006, Nakamura, Nestel, Nozaki, Pownall, Sanders, Shinozaki, Takaku,
von Schacky, Wojenski, Yokoyama 2003, and/or Yokoyama 2007.

1 without support, that it would have been obvious to administer a composition containing EPA,
2 but containing no DHA, with a reasonable expectation of success in reducing triglycerides while
3 avoiding an increase in LDL. These contentions: 1) do not assert what the prior art discloses to
4 a person of ordinary skill in the art; 2) fail to address whether the specific combination of claim
5 elements were all present in the prior art references that would have been combined by a person
6 of ordinary skill in the art to produce the claimed invention with a reasonable expectation of
7 success; and 3) fail to establish *prima facie* obviousness. Defendants do not offer an obvious
8 analysis, but trivialize the claim element to the point of reading the element out of the claim.
9 Although convenient and expedient, Defendants' approach does not conform with the Local
10 Patent Rules of this District, the law of claim construction, or the law of obviousness.

11 Defendants do not identify any combination of references and simply provide a laundry
12 list of references that purportedly disclose disparate elements without explaining how they can
13 be combined.⁵²¹⁷ As such, Defendants discuss the claim elements in isolation, and fail to address
14 the claimed invention as a whole.⁵²¹⁸ Defendants selectively cite to an unspecified isolated
15 disclosure within a reference without considering other disclosures or even the reference as a
16 whole. Each reference, however, must be evaluated for all that it teaches.⁵²¹⁹ Defendants'
17 unsupported cobbling of selective disclosures represents hindsight reconstruction.⁵²²⁰

19 ⁵²¹⁷ *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)) (“[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”).

21 ⁵²¹⁸ *Sanofi Syntheolabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008) (“The determination of obviousness is made with respect to the subject matter as a whole, not separate pieces of the claim”).

22 ⁵²¹⁹ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

23 ⁵²²⁰ *See, e.g., Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under *KSR*, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention”).

1 Because Defendants do not identify any combination of references, they necessarily fail
2 to offer any evidence that a person of skill in the art would be motivated to combine those
3 references in order to achieve the invention of the claim as a whole. Defendants make a
4 conclusory statement that “it would have been obvious to the ordinarily skilled artisan to seek to
5 reduce triglycerides by 5% to 25%,” without providing a reason that would have prompted a
6 person of ordinary skill to reduce triglycerides by the recited amount.⁵²²¹ Defendants’ burden to
7 establish *prima facie* obviousness is not discharged because there is allegedly “no significance”
8 attached to the recited TG reduction amount.⁵²²² Defendants have not met the burden with the
9 naked assertion that it would have been obvious to seek the claim element.

10 Similarly, without the disclosure of a combination of references and a motivation/reason
11 to combine or modify the references, Defendants necessarily fail to offer any evidence that a
12 person of ordinary skill in the art would have had a reasonable expectation of success in
13 achieving the claimed invention. Defendants make a conclusory statement that there was a
14 reasonable expectation of success, without providing a support other than merely identifying
15 prior art references that purportedly disclose disparate elements.⁵²²³ The mere fact that elements
16

17 ⁵²²¹ *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (“Rejections on obviousness grounds cannot be
18 sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational
19 underpinning to support the legal conclusion of obviousness.”) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir.
20 2006)) (internal quotation marks omitted); *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350,
21 1356-57 (Fed. Cir. 2007) (“While the *KSR* Court rejected a rigid application of the teaching, suggestion, or
22 motivation (‘TSM’) test in an obviousness inquiry, the Court acknowledged the importance of identifying ‘a reason
23 that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the
24 claimed new invention does’ in an obviousness determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S.
398, 418 (2007)).

⁵²²² Plaintiffs do not have to show that a claimed range is critical unless a *prima facie* case of obviousness has been
established. See *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003) (“An applicant may overcome a *prima facie*
case of obviousness by establishing that the claimed range is critical . . .”) (internal quotation marks omitted).

⁵²²³ *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (“Rejections on obviousness grounds cannot be
sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational

1 are capable of being physically combined does not establish reasonable expectation of
2 success.⁵²²⁴

3 Defendants contend, without support, that the specific recitation of the effect on LDL-C
4 represents “a property inherent upon administering a formulation known in or rendered obvious
5 by the art,” and that “such inherent properties do not render the claimed methods obvious.”
6 Inherency may not supply a missing claim limitation in an obviousness analysis unless the
7 inherency would have been obvious to one of ordinary skill in the art.⁵²²⁵ Obviousness is based
8 on what is *known* in the art at the time of the invention.⁵²²⁶ It was not known or reasonably
9 expected at the time of the claimed invention that purified EPA, when administered to patients
10 with very-high TG levels (≥ 500 mg/dL), would not substantially increase LDL-C. Nor was
11 EPA’s effect on LDL-C necessarily present, or the natural result of the combination of elements
12 explicitly disclosed by the prior art.⁵²²⁷ Therefore, inherency does not supply the missing claim
13 elements in the prior art cited by Defendants.

14 These contentions: 1) do not assert what the prior art discloses to a person of ordinary
15 skill in the art; 2) fail to address whether the specific combination of claim elements were all

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17 underpinning to support the legal conclusion of obviousness.”) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)) (internal quotation marks omitted).

18 ⁵²²⁴ *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable
19 result’ discussed in *KSR* refers not only to the expectation that prior art elements are capable of being physically
combined, but also that the combination would have worked for its intended purpose.”).

20 ⁵²²⁵ *See, e.g., PAR Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1195–96 (Fed. Cir. 2014) (“A party must . . .
meet a high standard in order to rely on inherency to establish the existence of a claim limitation in the prior art in an
obviousness analysis—the limitation at issue necessarily must be present, or the natural result of the combination of
21 elements explicitly disclosed by the prior art.”); *In re Rijckaert*, 9 F.3d 1531, 1533–34 (Fed. Cir. 1993) (“The mere
fact that a certain thing may result from a given set of circumstances is not sufficient [to establish inherency].”) (internal quotation omitted).

22 ⁵²²⁶ *In re Spormann*, 363 F.2d 444, 448 (CCPA 1966) (“That which may be inherent is not necessarily known.
23 Obviousness cannot be predicated on what is unknown.”).

24 ⁵²²⁷ *See* discussions below for Grimsgaard, Park, Nozaki Kurabayashi and Hayashi.

1 present in the prior art references that would have been combined by a person of ordinary skill in
2 the art to produce the claimed invention with a reasonable expectation of success; and 3) fail to
3 establish *prima facie* obviousness. Defendants do not offer an obvious analysis, but trivialize the
4 claim element to the point of reading the element out of the claim. Although convenient and
5 expedient, Defendants' approach does not conform with the Local Patent Rules of this District,
6 the law of claim construction, or the law of obviousness.

7 Defendants do not identify any combination of references. Because Defendants do not
8 identify any combination of references, they necessarily fail to offer any evidence that a person
9 of skill in the art would be motivated to combine those references in order to achieve the
10 invention of the claim as a whole. Defendants have not met the burden to establish *prima facie*
11 obviousness with the naked assertion that it would have been obvious to seek the claim element.

12 Similarly, without the disclosure of a combination of references and a motivation/reason
13 to combine or modify the references, Defendants necessarily fail to offer any evidence that a
14 person of ordinary skill in the art would have had a reasonable expectation of success in
15 achieving the claimed invention. In fact, Defendants fail to make any statement related to the
16 reasonable expectation of success of achieving the claimed invention as a whole. As such,
17 Defendants fail to demonstrate reasonable expectation of success of the claimed invention.

18 (i) A Person of Ordinary Skill Would Not Have
19 Had a Reasonable Expectation of Success in
20 Replacing the Mixed Fish Oil Active
Ingredient in Lovaza with Pure EPA

21 Defendants provide no evidence that a person or ordinary skill would have had a
22 reasonable expectation of successfully obtaining the claimed invention—a method of reducing
23 triglycerides in a subject having very-high triglyceride levels by administering EPA of the
24 recited purity to effect a reduction in triglycerides *with the claimed LDL-C effect*—by combining

1 the references cited by defendants. For a particular combination of references, there must be a
2 reasonable expectation that the combination will produce the claimed invention. In this case, the
3 art taught that DHA and EPA have similar effects on LDL-C levels in patients with very-high
4 TG levels.⁵²²⁸ A person of ordinary skill would have expected EPA, like Lovaza/Omacor, to
5 raise LDL-C levels when administered to patients in the very-high TG patient population. As
6 discussed in Section III and above, it was well known that TG-lowering agents, specifically
7 fibrates and Lovaza/Omacor, and little or no effect on LDL-C levels for normal to high TG
8 patients, but caused significant increases in LDL-C levels for patients with very-high
9 triglycerides. The art cited by Defendants provides no basis for a person of ordinary skill to
10 expect anything to the contrary. A person of ordinary skill would have understood that omega 3-
11 fatty acids, including DHA and EPA, and fibrates cause an increase in LDL-C among very high
12 TG patients, as reflected in the prior art:

	LDL-C Effect	
	Borderline-High or High TG Patients	Very-High TG Patients
Fibrate ⁵²²⁹	-20%	+45%
Lovaza/Omacor ⁵²³⁰	-6%	+45%

20 ⁵²²⁸ As discussed above, see *supra* section III, a person of ordinary skill would have understood EPA and DHA to
21 have the same TG lowering mechanism and would have further understood that the increase in LDL-C
22 accompanying the TG-lowering effects of Lovaza was a product of that same mechanism. Accordingly, a person of
ordinary skill would have expected EPA to increase LDL-C levels in patients with very-high TG levels in similar
fashion to Lovaza or DHA alone.

23 ⁵²²⁹ Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

24 ⁵²³⁰ Chan 2002 I at 2381 (Table 3).

1 Accordingly, a person of ordinary skill would *not* have a reasonable expectation of
2 success in achieving a reduction in TG levels *with the claimed LDL-C effect* in patients with
3 very-high TG levels.⁵²³¹

4 Defendants’ position that a person of ordinary skill would have had a reasonable
5 expectation of success in administering purified EPA to patients with very high triglyceride
6 levels to achieve TG lowering *with the claimed LDL-C effect* is belied by the fact that
7 Defendants’ provide no evidence that anyone thought to administer Epadel.⁵²³² Epadel was
8 available for many years prior to the invention of the ’929 patent, to patients with very-high TGs
9 as a treatment. A person of ordinary skill did not expect Epadel, which consisted of mostly EPA,
10 to have superior qualities over a drug such as Lovaza/Omacor, which comprised a mixture of
11 EPA and DHA, in patients with very-high triglycerides. Indeed, none of clinical studies cited by
12 Defendants are directed to the use of purified EPA in the very-high TG population.

13 Research into the pharmaceutical uses of EPA started as early as the 1970s. In 1990,
14 Mochida Pharmaceutical, began to market Epadel, a high purity EPA drug. There have been
15 countless studies conducted which administer Epadel and report the effects observed. Although
16 a few studies administer Epadel to a patient population which included a few patients with TG
17 levels > 500 mg/dL, Defendants fail to identify a single reference directed to the administration
18 of Epadel to patients with very-high TG levels. The fact is, a person of ordinary skill did not
19 expect Epadel, which consisted of mostly EPA, to have superior qualities over a drug such as
20

21
22 _____
23 ⁵²³¹ Indeed, as discussed above, a person of ordinary skill would have understood that DHA had a better overall
effect on lipid parameters, teaching away from this combination.

24 ⁵²³² Although Epadel was available at different levels of purity, the fact that Epadel—at any level of purity—was not
examined in any study directed to the very-high TG patient population supports Amarin’s position.

1 Lovaza/Omacor, which comprised a mixture of EPA and DHA, in patients with very-high
 2 triglycerides.

3 Defendants argue that because Grimsgaard administered purified ethyl EPA to patients
 4 with borderline-high/high TG, it would have been obvious to try administering purified ethyl
 5 EPA to patients with very-high TG levels with a reasonable expectation of success. Defendants
 6 base this unsupported conclusion on Grimsgaard, Lovaza/Omacor, the known administration of
 7 2.7 grams of purified EPA to patients with greater than 500 mg/dL TG by Matsuzawa.

8 Defendants' contentions are no more than a demonstration that certain claim elements was
 9 known in the prior art and demonstrates impermissible hindsight reconstruction.⁵²³³ As is
 10 reflected in Table 4 of Grimsgaard, the study authors found no difference between the DHA,
 11 EPA, and control in terms of LDL-C levels. Defendants use hindsight to argue that, despite EPA
 12 and DHA showing the same effect on LDL-C, one would have chosen EPA and expected that
 13 administration to very-high TG would have resulted in little or no impact on LDL-C. Notably,
 14 none of these references would provide a person of ordinary skill in the art with a reasonable
 15 expectation of successfully obtaining the claimed invention even if there were reasons to
 16 combine disparate, independent elements found in the prior art, which there were not.

17 **TABLE 4**
 18 Serum lipids and apolipoproteins at baseline and change after 7 wk of supplementation with docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), or corn oil

	DHA (n = 72)		EPA (n = 75)		Corn oil (n = 77)		F test: P ¹	Contrasts between groups: P		
	Baseline	Change	Baseline	Change	Baseline	Change		DHA vs EPA	DHA vs corn oil	EPA vs corn oil
Triacylglycerols (mmol/L)	1.24 ± 0.58 ²	-0.22 ± 0.31 ²	1.23 ± 0.57	-0.15 ± 0.40 ²	1.22 ± 0.55	0.11 ± 0.34 ²	0.0001	0.14	0.0001	0.0001
Total cholesterol (mmol/L)	6.00 ± 0.95	0.03 ± 0.49	5.98 ± 0.94	-0.15 ± 0.55 ²	6.02 ± 1.08	0.10 ± 0.55	0.01	0.04	0.4	0.004
LDL cholesterol (mmol/L)	4.06 ± 0.86	0.07 ± 0.46	4.06 ± 0.83	-0.08 ± 0.48	4.04 ± 0.98	0.06 ± 0.48	0.10	—	—	—
HDL cholesterol (mmol/L)	1.36 ± 0.30	0.06 ± 0.13 ³	1.33 ± 0.31	0.01 ± 0.12	1.41 ± 0.28	-0.01 ± 0.11	0.001	0.009	0.0005	0.4
Apolipoprotein A-I (g/L)	1.38 ± 0.21	0.02 ± 0.13	1.38 ± 0.20	-0.04 ± 0.10 ³	1.46 ± 0.23	0.00 ± 0.12	0.003	0.0008	0.3	0.02
Apolipoprotein B (g/L)	1.00 ± 0.21	-0.01 ± 0.11	1.01 ± 0.23	-0.03 ± 0.11 ³	1.02 ± 0.28	0.02 ± 0.11	0.05	—	—	—
HDL:apolipoprotein A-I	0.97 ± 0.14	0.04 ± 0.07 ³	0.96 ± 0.13	0.04 ± 0.08 ³	0.97 ± 0.12	-0.01 ± 0.06	0.0001	0.8	0.0003	0.0001
Total:HDL cholesterol	4.62 ± 1.19	-0.19 ± 0.52 ²	4.70 ± 1.24	-0.13 ± 0.47 ²	4.43 ± 1.19	0.11 ± 0.62	0.002	0.4	0.0006	0.007

¹ ANOVA for between-group comparisons of change.

² x ± SD.

³⁻⁵ One-sample t test of difference between baseline and 7 wk: ² P < 0.001, ⁴ P < 0.01, ⁵ P < 0.05.

23 ⁵²³³ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that even under
 24 KSR, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention
 without any explanation as to how or why the references would be combined to produce the claimed invention.”).

1 In addition, Grimsgaard was conducted in patients with normal TG levels, so a person of
2 ordinary skill would have expected no difference between EPA and DHA in terms of LDL-C
3 level change and would have expected no significant increase (or decrease) in LDL-C, as
4 reported by that publication. A person of ordinary skill would further have understood that the
5 data reported by Grimsgaard to be consistent with the understanding that while LDL-C levels are
6 not significantly impacted in normal to high TG patient populations, LDL-C levels would
7 increase significantly in very-high TG patients.

8 Matsuzawa similarly provides no basis for a reasonable expectation of success in
9 achieving the claimed invention. The subjects of Matsuzawa had a wide range of baseline TG
10 levels and the study was not directed to the very-high TG patient population. Accordingly, just
11 as with Grimsgaard, Matsuzawa would not provide a reasonable expectation of success as a
12 person of ordinary skill would understand patients with very-high TG levels to be different in
13 terms of LDL-C effect than patients with lower TG levels.

14 To the extent that Defendants' arguments are based on results that are not statistically
15 significant and not reported by Grimsgaard as significant, a person of ordinary skill would not
16 draw conclusions from these statistically insignificant differences. Indeed, the standard
17 deviation for the changes reported is greater than the value of the change itself.

18 Defendants argue that it would have been obvious to try administering purified ethyl EPA
19 to patients with very-high TG levels with a reasonable expectation of success. However, the
20 Federal Circuit has often rejected the notion that showing something may have been "obvious-to-
21 try" proves that the claimed invention was obvious where the prior art did not suggest what to
22 try.⁵²³⁴ Rather than there being a limited number of options, the state of the art provided a

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24 ⁵²³⁴ See *Sanofi*, 748 F.3d at 1360–61.

1 plethora of compositions and administration protocols associated with multiple kinds of TG-
2 lowering therapies.⁵²³⁵ There were not a finite number of options for a person of ordinary skill
3 seeking to reduce TG levels without increasing LDL-C among the very-high TG patient
4 population.

5 Defendants argue that a person of ordinary skill at the time of the invention, based on
6 studies in normal, borderline-high and high TG patients, knew that administration of DHA alone
7 resulted in undesirable increased LDL-C levels while administration of EPA alone had little to
8 no impact on LDL-C levels. However, that statement does not conform with what was known
9 regarding the effect of Epadel and Lovaza/Omacor in normal, borderline-high and high TG
10 patients. Instead as Defendants' own prior art demonstrates, Epadel and Lovaza/Omacor were
11 both known to have little or no effect on LDL-C in patients with borderline-high/high TG levels.

12 With the lack of any reasonable expectation of success, Defendants argue that their
13 proposed combination amounts to a simple substitution of one known element for another, and
14 that that these changes yield predictable results. Such an argument, however, represents pure
15 and impermissible hindsight bias and further does not consider that reasons for which a person of
16 ordinary skill would not be motivated to combine these references and affirmatives ways in
17 which the art taught away from these combinations.

18 (ii) A Person of Ordinary Skill Would Not Have
19 Had a Reasonable Expectation of Success in
20 Administering the Purified EPA in the
Dosing Regimen Recited in the Claims

21 Defendants contend that a "person of ordinary skill in the art would have been motivated
22 to administer 4 grams of highly-purified EPA to patients with triglycerides greater than or equal

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24 ⁵²³⁵ See *supra* Section III.

1 to 500 mg/dL, with a reasonable expectation of success in lowering triglycerides.” Defendants
2 also argue that “[a]t least Katayama, Saito 1998, Yokoyama 2007, and Mori 2000 . . . would
3 have given a person of ordinary skill in the art a reasonable expectation of successfully
4 administering 4 g/day of highly-purified EPA-E for at least 12 weeks to lower triglycerides in
5 these subjects relative to baseline or placebo.” However, Defendants provide no evidence that a
6 person or ordinary skill would have had a reasonable expectation of success in a method of
7 reducing triglycerides in a subject having very-high triglyceride levels by administering purified
8 EPA to effect a reduction in triglycerides *with the claimed LDL-C effect*. Therefore, Defendants
9 fail to provide a reasonable expectation of success for the claimed invention.

10 Defendants further argue, that “because it was known that DHA and EPA were
11 comparably efficacious in reducing triglycerides . . . one of ordinary skill in the art would have
12 reasonably expected to see the same hypotriglyceridemic effect from a 4 g/day dose of purified
13 EPA-E as seen with 4 g/day of a combination of both EPA and DHA. Thus, it would have been
14 obvious to one of ordinary skill in the art to administer a highly-purified EPA-E composition
15 with a reasonable expectation of success that such administration would result in reducing
16 triglycerides while avoiding an increase in LDL.” Defendants argument is without any basis. To
17 the contrary, because a person of ordinary skill in the art would have understood DHA and EPA
18 to lower TGs via the same mechanism, the person of ordinary skill in the art would have
19 expected DHA and EPA to have the same impact on LDL-C levels. Defendants provide no
20 explanation and cite to no article to support their argument that the similar effects on TG levels is
21 a basis to differentiate the efficacy of DHA and EPA with respect to LDL-C impact. Based on
22 the hypotriglyceridemic effect alone, a person of ordinary skill would have reasonably expected
23
24

1 both EPA and DHA, whether administered alone or in combination, would cause an increase in
2 LDL-C when administered to the very high TG patient population.

3 The prior art taught that DHA and EPA have similar effects on LDL-C levels in patients
4 with very-high TG. A person of ordinary skill would have thus expected EPA, like
5 Lovaza/Omacor, to raise LDL-C levels when administered to the very-high TG patient
6 population. It was well known that TG-lowering agents, specifically fibrates and
7 Lovaza/Omacor, and little or no effect on LDL-C levels for normal to high TG patients, but
8 caused significant increases in LDL-C levels for patients with very-high triglycerides. The art
9 cited by Defendants provides no basis for a person of ordinary skill to expect anything to the
10 contrary. A person of ordinary skill would have understood that omega 3-fatty acids, including
11 DHA and EPA, and fibrates cause an increase in LDL-C among very high TG patients, as
12 reflected in the prior art:

	LDL-C Effect	
	Borderline-High or High TG Patients	Very-High TG Patients
Fibrate ⁵²³⁶	-20%	+45%
Lovaza/Omacor ⁵²³⁷	-6%	+45%

17 Accordingly, a person of ordinary skill would not have a reasonable expectation of
18 success in achieving a reduction in TG levels *with the claimed LDL-C effect* in patients with
19 very-high TG levels using EPA.

20 Defendants' position that a person of ordinary skill would have had a reasonable
21 expectation of success in administering purified EPA to the requisite patient population to
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23 ⁵²³⁶ Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

24 ⁵²³⁷ Chan 2002 I at 2381 (Table 3).

1 achieve a lowering in TG levels *with the claimed LDL-C effect* is belied by the fact that
2 Defendants' provide no evidence that anyone thought to administer Epadel, which was available
3 for many years prior to the invention of the '929 patent, to patients with very-high TGs as a
4 treatment. Indeed, none of clinical studies cited by Defendants are directed to the use of purified
5 EPA in the very-high TG population.

6 Research into the pharmaceutical uses of EPA started as early as the 1970s. In 1990,
7 Mochida Pharmaceutical, began to market Epadel, a high purity EPA drug. There have been
8 countless studies conducted which administer Epadel and report the effects observed. Although
9 a few studies administer Epadel to a patient population which included a few patients with TG
10 levels > 500 mg/dL, Defendants fail to identify a single reference directed to the administration
11 of Epadel to patients with very-high TG levels. The fact is, a person of ordinary skill did not
12 expect Epadel, which consisted of mostly EPA, to have superior qualities over a drug such as
13 Lovaza/Omacor, which comprised a mixture of EPA and DHA, in patients with very-high
14 triglycerides.

15 Accordingly, a person of ordinary skill would not have a reasonable expectation of
16 success in achieving the claimed invention.

17 (d) Defendants Have Not Shown that Claim 5 of the
18 '929 Patent Would Have Been Obvious

19 Plaintiffs incorporate by reference the discussion related to the Independent Claim in
20 Section V.K.3. Because Defendants have not shown the obviousness of the Independent Claim
21 by clear and convincing evidence, they also have not adequately proven the obviousness of
22 Claim 5.

23 Defendants offer no reference in support of their contention that this claim is obvious.
24 Defendants contend, without providing any support, that it would be obvious to one of skill in

1 the art to administer a composition containing EPA, but containing no DHA, with a reasonable
2 expectation of success in reducing Apo-B levels and thus also reduce LDL-C levels. These
3 contentions: 1) do not assert what the prior art discloses to a person of ordinary skill in the art;
4 2) are irrelevant to an obvious analysis; 3) fail to address whether the specific combination of
5 claim elements were all present in the prior art references that would have been combined by a
6 person of ordinary skill in the art to produce the claimed invention with a reasonable expectation
7 of success; and 4) fail to establish *prima facie* obviousness. Defendants do not offer an obvious
8 analysis, but trivialize the claim element to the point of reading the element out of the claim.
9 Although convenient and expedient, Defendants' approach does not conform with the Local
10 Patent Rules of this District, the law of claim construction, or the law of obviousness.

11 Defendants fail to show a specific combination of references that discloses each element
12 of the claimed invention. None of the cited references discloses administration of the claimed
13 EPA to very high TG patients. Defendants further fail to explain how the cited references can be
14 combined to teach the administration of the claimed EPA to very high TG patients.⁵²³⁸
15 Defendants selectively cite to an unspecified, isolated disclosure within a reference without
16 considering other disclosures or even the reference as a whole. Each reference, however, must
17 be evaluated for all that it teaches.⁵²³⁹ Defendants' unsupported cobbling of selective disclosures
18 represents hindsight reconstruction.⁵²⁴⁰

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20 ⁵²³⁸ *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)) (“[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”).

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22 ⁵²³⁹ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

23 ⁵²⁴⁰ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under *KSR*, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention”).

1 Defendants fail to show a motivation or reason to combine or modify the references
2 recited above. Defendants make a conclusory statement that the claimed methods of treatment
3 would have been obvious but such a naked assertion does not show why a person of ordinary
4 skill would have been motivated to combine the references to achieve the claimed invention.⁵²⁴¹

5 Defendants fail to show a reasonable expectation that a person of ordinary skill would
6 have successfully achieved the claimed invention. In fact, Defendants do not even discuss
7 whether a person of ordinary skill would have expected that the combination to work for its
8 intended purpose.⁵²⁴² As such, Defendants fail to demonstrate reasonable expectation of success
9 of the claimed invention.

10 Defendants rely on only one reference in their invalidity contentions with respect to this
11 claim, Theobald, and *not* for the proposition that the asserted claim is obvious. Instead,
12 Defendants cite Theobald for the proposition that “it was known that Apo-B is a component of
13 LDL-C.” Defendants cite to no passage or page of Theobald in connection with that argument
14 and no support for their argument that Theobald makes such a disclosure. Defendants appear to
15 suggest a correlation between Apo-B and LDL-C but ignore that Apo-B is present on all
16 atherogenic lipoproteins.⁵²⁴³

17 Defendants then make the unsupported assertion that “one of ordinary skill in the art
18 would reasonably expect that a pure EPA composition would reduce Apo-B, as it is known to

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20 ⁵²⁴¹*Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the *KSR*
21 Court rejected a rigid application of the teaching, suggestion, or motivation (‘TSM’) test in an obviousness inquiry,
22 the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill
23 in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness
24 determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

⁵²⁴² *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable
23 result’ discussed in *KSR* refers not only to the expectation that prior art elements are capable of being physically
24 combined, but also that the combination would have worked for its intended purpose.”)

⁵²⁴³ June 26, 2012 Bays Declaration; *see also* Section III.

1 reduce VLDL syntheses.” They are incorrect. Neither Defendants’ characterization of Theobald
 2 nor the disclosures of that reference teach that EPA compositions would reduce Apo-B or render
 3 this claim obvious. Defendants’ assertion that EPA was known to reduce VLDL synthesis
 4 ignores that, as discussed above, *see* Section III, DHA was also understood to reduce VLDL
 5 synthesis. Nor do defendants explain the relevance of VLDL synthesis to their arguments with
 6 respect to this claim or Apo-B levels.

7 As discussed above, *see* Section IV, Theobald discloses the administration of a
 8 triacylglycerol composition derived from *Cryptocodinium cohnii* to healthy subjects. While
 9 Defendants make an unexplained citation to Theobald regarding the proposition that Apo-B is a
 10 component of LDL-C, they fail to discuss the reference’s disclosures regarding the impact of
 11 administration of the triacylglycerol composition on Apo-B levels. In doing so, they fail to
 12 consider the reference for all that it teaches. Theobald discloses an *increase* in Apo-B following
 13 administration of the triacylglycerol composition of that reference.⁵²⁴⁴

14 **TABLE 3**
 15 Serum lipoproteins before treatment and after 3 mo of docosahexaenoic acid (DHA) and placebo treatment in all subjects

	DHA		Placebo		Treatment effect ¹
	Before treatment	After treatment	Before treatment	After treatment	
Total cholesterol (mmol/L)	5.15 ± 0.145 ²	5.44 ± 0.174	5.08 ± 0.168	5.22 ± 0.155	0.22 (0.01, 0.42) ³
LDL cholesterol (mmol/L)	3.16 ± 0.129	3.48 ± 0.152	3.16 ± 0.146	3.25 ± 0.131	0.23 (0.08, 0.38) ⁴
HDL cholesterol (mmol/L) ⁵	1.47 ± 0.052	1.55 ± 0.064	1.46 ± 0.062	1.48 ± 0.056	0.07 (0.005, 0.14)
Triacylglycerol (mmol/L) ⁶	1.03 ± 0.094	1.01 ± 0.089	1.06 ± 0.106	1.19 ± 0.103	-0.18 (-0.37, 0.05)
Apolipoprotein B (g/L)	0.84 ± 0.027	0.87 ± 0.026	0.83 ± 0.028	0.84 ± 0.028	0.03 (0.002, 0.055)⁷
LDL cholesterol:apo B (mmol/g)	3.75 ± 0.376	3.96 ± 0.462	3.74 ± 0.521	3.84 ± 0.409	0.12 (0.004, 0.24) ³
Weight (kg) ⁸	70.1 ± 2.04	70.6 ± 2.06	70.5 ± 2.01	70.6 ± 2.01	0 (-0.85, 0.24)

19 ¹ Mean difference between active treatment and placebo; 95% CI in parentheses.

20 ² $\bar{x} \pm \text{SEM}$ (all such values); $n = 38$.

21 ^{3,4,7} Paired t test: ³ $P = 0.04$, ⁴ $P = 0.004$, ⁷ $P = 0.03$.

22 ⁵ HDL increased in subjects receiving DHA first. Significant treatment \times order effect, $P = 0.005$.

23 ⁶ $n = 37$; data were log transformed before analysis by paired t test.

24 ⁸ Weight increased over the entire study period. Significant order \times time effect, $P = 0.001$.

⁵²⁴⁴ Theobald at 561, table 3.

1 As discussed above, *see* Section III, a person of skill in the art would not have
2 distinguished between the lipid effects of EPA and DHA therapy. To the extent, then that a
3 person of ordinary skill would have considered Theobald, they would not conclude from the
4 reference that EPA therapy decreases Apo-B levels in very high TG patients.

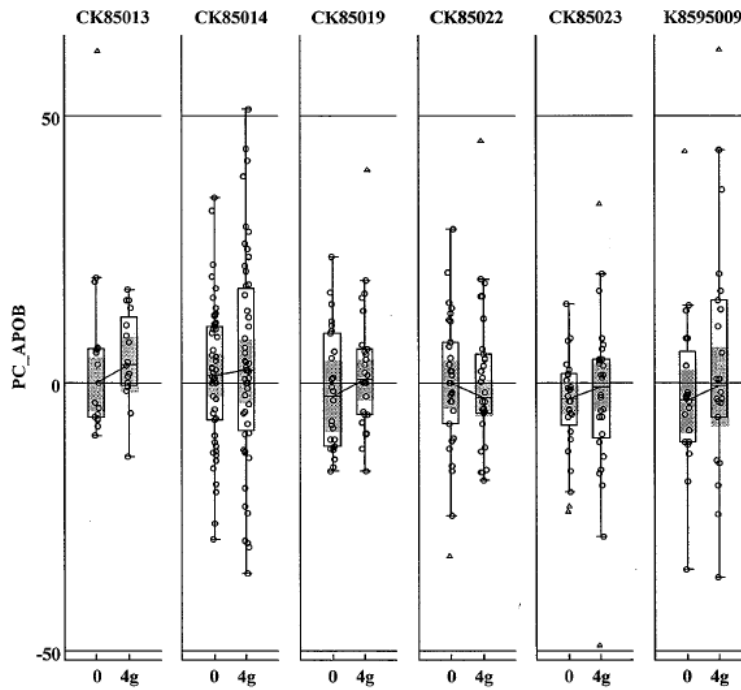
5 A person of skill in the art would *not* have understood that EPA therapy in very high TG
6 patients would yield a reduction in Apo-B levels. A person of ordinary skill would have looked
7 to the Lovaza clinical trials—the only clinical trial to study the effects of omega-3 fatty acids on
8 Apo-B levels in patients with very high TG levels.⁵²⁴⁵ The Lovaza clinical trial, which was a
9 large study conducted on patients with very high TG levels, shows no difference between a
10 placebo-control group and the treatment group with respect to Apo-B levels.⁵²⁴⁶

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⁵²⁴⁵ May 8, 2012 Bays Declaration.

24 ⁵²⁴⁶ Lovaza Approval Package at Table 14.

14. Box plot of individual Category I studies -% change of APOB

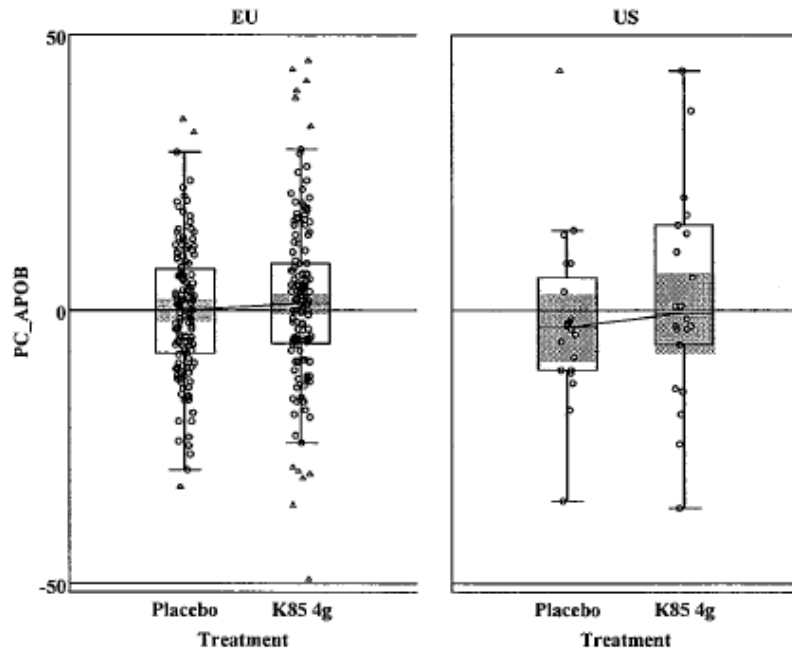


In each of these studies, including K8595009, where subjects had a median baseline TG level of 818 mg/dL,⁵²⁴⁷ there was no change in Apo-B between the control and treatment groups. Likewise, pooling the data from the different studies of Lovaza in the EU and US also reflected that treatment with Lovaza did not impact Apo-B compared to placebo.⁵²⁴⁸

⁵²⁴⁷ The parameters for each study reports can be located at page 4 of the Lovaza Approval Package.

⁵²⁴⁸ Lovaza Approval Package at Table 7.

7. Box plot of pooled Category I studies -% change of APOB



Indeed, none of the data reported in the Lovaza clinical trials reflects a decrease in Apo-B. In addition to the Lovaza studies, a person of ordinary skill would have understood that the literature reported, in a variety of clinical studies, that omega-3s do not impact Apo-B levels.⁵²⁴⁹ While Theobald does not even support Defendants' obviousness arguments, their selective citation of that reference represents impermissible hindsight bias. The examiner had before him a large number of prior art references reporting Apo-B effects and, even as defendants concede, agreed that the Apo-B effects reported by the claimed inventions were unexpected in light of

⁵²⁴⁹ See Grimsgaard, Okumura, Hayashi, Hayasaka 1995, and Aoki 1993.

1 those references, also reflecting a lack of motivation and no reasonable expectation of
2 success.⁵²⁵⁰

3 Further, a person of skill in the art would have understood Apo-B to be a surrogate for the
4 number of atherogenic lipoproteins (VLDL, IDL, LDL) present in the body.⁵²⁵¹ The person of
5 skill in the art would also have recognized that, as TG levels in patients with very high TG levels
6 rose, an increasing amount of TGs in those patients were contained within chylomicrons. As
7 discussed above, *see* Section III, the processing of chylomicrons would not yield atherogenic
8 lipoproteins, but instead smaller, denser particles referred to as remnant.⁵²⁵² Accordingly,
9 because very high TG patients had increasing levels of TGs stored in chylomicrons and because
10 chylomicron processing would not have been understood to yield changes in Apo-B, a person of
11 skill in the art would have believed that TG-lowering therapies directed to very high TG patients
12 would not significantly impact Apo-B.

13 Accordingly, a person of ordinary skill in the art would not have been motivated to
14 replace EPA with the composition of Lovaza, nor would the person of ordinary skill in the art
15 have been motivated to administer the EPA composition of the claimed invention to very high
16 TG patients. For the same reasons, a person of ordinary skill in the art would not have a
17 reasonable expectation of success in achieving the claimed invention.

18 (e) Defendants Have Not Shown that Claim 6 of the
19 '929 Patent Would Have Been Obvious

20 Plaintiffs incorporate by reference the discussion related to the Independent Claim in
21 Section V.K.3. Because Defendants have not shown the obviousness of the Independent Claim

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⁵²⁵⁰ Defendants' Contentions at 236.

23 ⁵²⁵¹ ATP-III at 3170; Bays 2008 I at 395.

24 ⁵²⁵² Kwiterovich in Kwiterovich at 4.

1 by clear and convincing evidence, they also have not adequately proven the obviousness of
2 Claim 6.

3 Defendants contend that it would have been obvious to use the claimed composition to
4 reduce VLDL-C levels, and that the recited VLDL-C reduction represents therapeutic efficacy.
5 These contentions: 1) do not assert what the prior art discloses to a person of ordinary skill in
6 the art; 2) are irrelevant to an obvious analysis; 3) fail to address whether the specific
7 combination of claim elements were all present in the prior art references that would have been
8 combined by a person of ordinary skill in the art to produce the claimed invention with a
9 reasonable expectation of success; and 4) fail to establish *prima facie* obviousness. Defendants
10 do not offer an obvious analysis, but trivialize the claim element to the point of reading the
11 element out of the claim. Although convenient and expedient, Defendants' approach does not
12 conform with the Local Patent Rules of this District, the law of claim construction, or the law of
13 obviousness.

14 Defendants do not identify any combination of references. Because Defendants do not
15 identify any combination of references, they necessarily fail to offer any evidence that a person
16 of skill in the art would be motivated to combine those references in order to achieve the
17 invention of the claim as a whole. In fact, Defendants do not discuss at all whether a person of
18 ordinary skill would have been motivated to combine the elements.⁵²⁵³ As such, Defendants fail
19 to demonstrate that there was no motivation to combine the references to achieve the claimed
20 invention.

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22 ⁵²⁵³ *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the *KSR*
23 Court rejected a rigid application of the teaching, suggestion, or motivation (‘TSM’) test in an obviousness inquiry,
24 the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill
in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness
determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

1 Similarly, without the disclosure of a combination of references and a motivation/reason
2 to combine or modify the references, Defendants necessarily fail to offer any evidence that a
3 person of ordinary skill in the art would have had a reasonable expectation of success in
4 achieving the claimed invention. Defendants make conclusory statements without providing any
5 support. What is more, Defendants do not even discuss the reasonable expectation of reducing
6 VLDL-C levels. As such, Defendants fail to demonstrate reasonable expectation of success of
7 reducing VLDL-C levels using the claimed methods.

8 (f) Defendants Have Not Shown that Claim 7 of the
9 '929 Patent Would Have Been Obvious

10 Plaintiffs incorporate by reference the discussion related to the Independent Claim in
11 Section V.K.3. Because Defendants have not shown the obviousness of the Independent Claim
12 by clear and convincing evidence, they also have not adequately proven the obviousness of
13 Claim 7.

14 Defendants do not identify any combination of references. Defendants contend, without
15 meaningful support, that a person of ordinary skill would have been able to determine the patient
16 population in need of the claimed methods of treatment, would seek to measure the fasting
17 baseline TG level of a patient, and would seek to treat those patients having very high
18 triglycerides. Defendants point to Lovaza and argue that it would have been obvious to one of
19 skill in the art to administer fish oil treatment to subjects with TG levels in the range of 500 to
20 1500 mg/dL. These contentions: 1) do not assert what the prior art discloses to a person of
21 ordinary skill in the art; 2) are irrelevant to an obvious analysis; 3) fail to address whether the
22 specific combination of claim elements were all present in the prior art references that would
23 have been combined by a person of ordinary skill in the art to produce the claimed invention
24 with a reasonable expectation of success; and 4) fail to establish *prima facie* obviousness.

1 Defendants do not offer an obvious analysis, but trivialize the claim element to the point of
2 reading the element out of the claim. Although convenient and expedient, Defendants' approach
3 does not conform with the Local Patent Rules of this District, the law of claim construction, or
4 the law of obviousness.

5 Defendants fail to show a specific combination of references that discloses each element
6 of the claimed invention. Because Defendants do not identify any combination of references,
7 they necessarily fail to offer any evidence that a person of skill in the art would be motivated to
8 combine those references in order to achieve the invention of the claim as a whole. Defendants
9 make conclusory statements without providing a reason that would have prompted a person of
10 ordinary skill to combine the elements.⁵²⁵⁴ Such a naked assertion does not show why a person
11 of ordinary skill would have been motivated to treat the recited patient population using the
12 claimed methods of treatment.⁵²⁵⁵

13 Similarly, without the disclosure of a combination of references and a motivation/reason
14 to combine or modify the references, Defendants necessarily fail to offer any evidence that a
15 person of ordinary skill in the art would have had a reasonable expectation of success in
16 achieving the claimed invention. Defendants do not even discuss whether a person of ordinary
17 skill would have expected that the combination to work for its intended purpose for treating the
18

19 ⁵²⁵⁴ *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (“Rejections on obviousness grounds cannot be
20 sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational
21 underpinning to support the legal conclusion of obviousness.”) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir.
2006)) (internal quotation marks omitted)

22 ⁵²⁵⁵ *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the *KSR*
23 Court rejected a rigid application of the teaching, suggestion, or motivation (‘TSM’) test in an obviousness inquiry,
24 the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill
in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness
determination.”) (quoting *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

1 recited patient population.⁵²⁵⁶ As such, Defendants fail to demonstrate reasonable expectation of
2 success of the claimed invention.

3 (g) Defendants Have Not Shown that Claims 8 and 9 of
4 the '929 Patent Would Have Been Obvious

5 Plaintiffs incorporate by reference the discussion related to the Independent Claim in
6 Section V.K.3. Because Defendants have not shown the obviousness of the Independent Claim
7 by clear and convincing evidence, they also have not adequately proven the obviousness of
8 Claims 8 and 9.

9 Defendants contend, without providing meaningful support, that the claim element was
10 well known in the art. These contentions: 1) do not assert what the prior art discloses to a
11 person of ordinary skill in the art; 2) are irrelevant to an obvious analysis; 3) fail to address
12 whether the specific combination of claim elements were all present in the prior art references
13 that would have been combined by a person of ordinary skill in the art to produce the claimed
14 invention with a reasonable expectation of success; and 4) fail to establish *prima facie*
15 obviousness. Defendants do not offer an obvious analysis, but trivialize the claim element to the
16 point of reading the element out of the claim. Although convenient and expedient, Defendants'
17 approach does not conform with the Local Patent Rules of this District, the law of claim
18 construction, or the law of obviousness.

19 Defendants fail to show a specific combination of references that discloses each element
20 of the claimed invention. Defendants make a conclusory statement that the claimed method of
21 treatment was well known in the art, but such a naked assertion does not show why a person of

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23 ⁵²⁵⁶ *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable
24 result’ discussed in KSR refers not only to the expectation that prior art elements are capable of being physically
combined, but also that the combination would have worked for its intended purpose.”)

1 ordinary skill would have been motivated to combine the references to achieve the claimed
2 invention.⁵²⁵⁷ Further Defendants cite to the “Lovaza product” without identifying the prior art
3 reference to which they refer. Such a reference is inadequate.

4 Defendants fail to show a reasonable expectation that a person of ordinary skill would
5 have successfully achieved the claimed invention. Defendants do not even discuss whether a
6 person of ordinary skill would have expected that the combination to work for its intended
7 purpose.⁵²⁵⁸ As such, Defendants fail to demonstrate reasonable expectation of success of the
8 claimed invention.

9 4. The ‘929 Patent is Not Invalid Under § 112

10 a) Defendants Have Not Demonstrated that the Claims of the ‘929 11 patent Are Invalid for Indefiniteness

12 35 U.S.C. ¶ 112(b) requires that a patentee “particularly point[] out and distinctly claim[]
13 the subject matter which the applicant regards as his invention.”⁵²⁵⁹ Patent claims are valid in
14 light of an indefiniteness challenge if they “inform, with reasonable certainty, those skilled in the
15 art about the scope of the invention” in light of the specification and the prosecution history.⁵²⁶⁰

16 _____
17 ⁵²⁵⁷*Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the *KSR*
18 Court rejected a rigid application of the teaching, suggestion, or motivation (‘TSM’) test in an obviousness inquiry,
the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill
in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness
determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

19 ⁵²⁵⁸*DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable
20 result’ discussed in *KSR* refers not only to the expectation that prior art elements are capable of being physically
combined, but also that the combination would have worked for its intended purpose.”)

21 ⁵²⁵⁹ Defendants were required to disclose the basis for their assertion of indefiniteness with respect to each term, and
they have not met that requirement. They simply make conclusory assertions regarding indefiniteness despite
22 bearing the burden of proof. Moreover, Defendants’ failure prevents Plaintiffs from responding to their assertions
other than by making conclusory assertions in return. Therefore, Defendants should be precluded from
23 supplementing their naked assertions with new basis in the course of the litigation.

24 ⁵²⁶⁰*Nautilus, Inc. v. Biosig Instruments, Inc.*, 134 S. Ct. 2120, 2124 (2014).

1 The Supreme Court has recognized that “absolute precision is unattainable” in claim language
2 and “the certainty which the law requires in patents is not greater than is reasonable.”⁵²⁶¹

3 Defendants allege that a number of terms containing the phrases “about” and
4 “substantially” are indefinite. Defendants do not provide any reason why these terms are
5 indefinite other than that they contain the phrases “about” and “substantially.” But, of course,
6 these terms are routinely used in patent claims, and are not *per se* indefinite.⁵²⁶² In particular,
7 courts have held repeatedly that claims that contain the words “about” and “substantially” are not
8 indefinite.⁵²⁶³ Here, a person of ordinary skill would understand with reasonable certainty what
9 is claimed when the claims are read in light of the specification and prosecution history.⁵²⁶⁴
10 Therefore, the terms that contain the words “about” and “substantially” are not invalid for being
11 indefinite.

12 Defendants further allege that the term “a pharmaceutical composition comprising ... not
13 more than about 4% docosahexaenoic acid, by weight of all fatty acid” is indefinite. They

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15 ⁵²⁶¹ *Id.* at 2129.

16 ⁵²⁶² *Interval Licensing LLC v. AOL, Inc.*, 766 F.3d 1364, 1370 (Fed. Cir. 2014) (“Claim language employing terms
17 of degree has long been found definite where it provided enough certainty to one of skill in the art when read in the
18 context of the invention.”); *see also BJ Servs. Co. v. Halliburton Energy Servs., Inc.*, 338 F.3d 1368, 1372 (Fed. Cir.
19 2003) (“The question becomes whether one of ordinary skill in the art would understand what is claimed when the
20 claim is read in light of the specification.”) (discussing the term “about”); *Verve, LLC v. Crane Cams, Inc.*, 311 F.3d
21 1116, 1120 (Fed. Cir. 2002) (“It is well established that when the term ‘substantially’ serves reasonably to describe
22 the subject matter so that its scope would be understood by persons in the field of the invention, and to distinguish
23 the claimed subject matter from the prior art, it is not indefinite.”).

20 ⁵²⁶³ *See, e.g., Deere & Co. v. Bush Hog, LLC*, 703 F.3d 1349, 1359 (Fed. Cir. 2012) (rejecting contention that claim
21 term “substantially planar” is indefinite); *Enzo Biochem, Inc. v. Applera Corp.*, 599 F.3d 1325, 1335 (Fed. Cir.
22 2010) (holding that the claim phrase “not interfering substantially” was not indefinite even though the construction
23 “define[d] the term without reference to a precise numerical measurement”); *BJ Services Co. v. Halliburton Energy
24 Services, Inc.*, 338 F.3d 1368, 1372–73 (Fed. Cir. 2003) (affirming jury’s verdict that claims reciting a concentration
as “about 0.06” were not invalid for being indefinite); *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540,
1557 (Fed. Cir. 1983) (ruling that the claim term “stretching ... at a rate exceeding about 10% per second” is not
indefinite).

⁵²⁶⁴ *See generally* the ’929 patent and its prosecution history.

1 contend that, because there is no indication of how much of the pharmaceutical composition is
2 composed of fatty acids, by extension it is indefinite how much of each fatty acid is present in
3 the composition. This is incorrect. A claim can use a ratio to define amounts of components in a
4 product, using terms such as “percent by weight.”⁵²⁶⁵ In light of the specification and
5 prosecution history, a person of ordinary skill would understand with reasonable certainty the
6 range of relative quantities of EPA, DHA and/or other fatty acids in the recited pharmaceutical
7 composition in relation to all fatty acids present.⁵²⁶⁶ Therefore, these terms are not indefinite and
8 do not render the claims indefinite.

9 Finally, Defendants contend that the asserted claims improperly mix methods and
10 formulations because Plaintiffs’ assertion of contributory infringement apparently suggests that
11 the scope of the claims includes formulations. This is a mistaken interpretation. Indefiniteness
12 analysis is based on what the claim language informs a person of ordinary skill in the art in light
13 of the specification and the prosecution history. Defendants do not identify any actual claim
14 language that mixes methods and formulations. Moreover, contributory infringement may be
15 asserted and proven when a party sells “a material or apparatus for use in *practicing a patented*
16 *process . . . knowing the same to be especially made or especially adapted for use in an*
17 *infringement of such patent.*”⁵²⁶⁷ Plaintiffs assert that Defendants’ ANDA products will be used
18 in practicing the claimed methods. Plaintiffs do not assert that the pharmaceutical compound
19 itself directly infringes. Therefore, Defendants’ interpretations of Plaintiffs’ assertions are

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21 ⁵²⁶⁵ *T.F.H. Publications, Inc. v. Doskocil Mfg. Co.*, No. CIV.A. 08-4805 FLW, 2012 WL 715628, at *5–6 (D.N.J.
22 Mar. 5, 2012) (construing “by weight” to mean the weight of a first component was in a ratio to the weight of a
23 second component); *Allergan, Inc. v. Sandoz Inc.*, No. 2:09-CV-182, 2011 WL 1599049, at *10 (E.D. Tex. Apr. 27,
24 2011) (construing percent by weight to mean “ratio of the weight of the ingredient in question divided by the total
volume of the solution, with this ratio expressed as a percentage”).

⁵²⁶⁶ See generally the ’929 patent and its prosecution history.

⁵²⁶⁷ 35 U.S.C. § 271(c) (emphasis added).

1 mistaken and the '929 patent claims are not indefinite for improperly mixing methods and
2 formulations.

3 b) Defendants Have Not Demonstrated that the Claims of the '929
4 patent Are Invalid for Insufficient Written Description

5 The first paragraph of 35 U.S.C. § 112 requires that a patent specification “contain a
6 written description of the invention.” This requires that the specification “reasonably convey” to
7 a skilled artisan that the applicant “invented” or “had possession” of the claimed subject matter
8 when the application was filed.⁵²⁶⁸ Support need not be literal⁵²⁶⁹—it may be implicit⁵²⁷⁰ or
9 inherent⁵²⁷¹ in the disclosure. In addition, it is unnecessary to include information that is already
10 known or available to persons of ordinary skill.⁵²⁷²

11 Defendants make two arguments regarding the written description requirement. First,
12 Defendants contend that elements reciting the baseline TG levels of the asserted claims lack
13 written description. This is incorrect. The specification of asserted patents literally discloses the
14 claimed invention.⁵²⁷³ Defendants do not contend that the patient population of the asserted
15 claims is not literally described by the specification. In fact, the specification at the time of filing
16 described these limitations. Therefore, Defendants have failed to explain whether and how an

17 ⁵²⁶⁸ *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010).

18 ⁵²⁶⁹ *Id.* at 1352; *Cordis Corp. v. Medtronic AVE, Inc.*, 339 F.3d 1352, 1365 (Fed. Cir. 2003); *In re Wright*, 866 F.2d
422, 425 (Fed. Cir. 1989); *In re Smith*, 481 F.2d 910, 914 (C.C.P.A. 1973).

19 ⁵²⁷⁰ *All Dental Prodx, LLC v. Advantage Dental Prods. Inc.*, 309 F.3d 774, 779 (Fed. Cir. 2002); *In re Wright*, 866
F.2d at 424–25.

20 ⁵²⁷¹ *In re Gay*, 309 F.2d 769, 771 (C.C.P.A. 1962).

21 ⁵²⁷² *Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1367–68 (Fed. Cir. 2006); *Capon v. Eshhar*, 418 F.3d 1349,
1357 (Fed. Cir. 2005); *In re Gay*, 309 F.2d at 774.

22 ⁵²⁷³ *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (“[T]he test requires an objective
23 inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art.”);
Snitzer v. Etzel, 465 F.2d 899, 902 (C.C.P.A. 1972) (“[T]he literal description of a species provides the requisite
24 legal foundation for claiming that species.”).

1 aspect of the claimed invention has not been described with sufficient particularity such that one
2 skilled in the art would recognize that the applicant had possession of the claimed invention.

3 Second, Defendants contend that “a person of skill in the art would not understand that
4 the inventor was in possession of a method incorporating [] specific dosages and quantities.”
5 Defendants’ assertion is incorrect. The specification of the asserted patents literally discloses the
6 dosages and quantities of the claimed methods.⁵²⁷⁴ Moreover, the dosages and quantities of the
7 method appear in the claims, as originally filed. Thus, there is a strong presumption that the
8 claimed invention is adequately described.⁵²⁷⁵ Defendants do not and cannot rebut this
9 presumption. For example, the dosage of the composition was originally claimed as “about 1 g
10 to about 4g.”⁵²⁷⁶ The asserted claims recite “4 g.” Defendants do not contend that dosages and
11 quantities of the asserted claims are not literally described by the specification and in the original
12 claims. In fact, the specification and the provisional patent application claims, at the time of
13 filing, described these limitations. Therefore, Defendants have failed to explain whether and
14 how an aspect of the claimed invention has not been described with sufficient particularity such
15 that one skilled in the art would recognize that the applicant had possession of the claimed
16 invention.

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20 ⁵²⁷⁴ *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (“[T]he test requires an objective
21 inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art.”);
Snitzer v. Etzel, 465 F.2d 899, 902 (C.C.P.A. 1972) (“[T]he literal description of a species provides the requisite
22 legal foundation for claiming that species.”).

23 ⁵²⁷⁵ *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976) (“we are of the opinion that the PTO has the
24 initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure
a description of the invention defined by the claims”).

⁵²⁷⁶ *See* U.S. Application No. 12/702,889.

1 In its 2010 *en banc* decision in *Ariad Pharmaceuticals, Inc. v. Eli Lilly Co.*,⁵²⁷⁷ the court
2 elaborated that “possession” means possession as evidenced by disclosure. In this case, the
3 specification of asserted patents literally disclose the claimed invention in the specification and
4 the claims as originally filed. Thus, an examination of the four corners of the specification from
5 the perspective of a person of ordinary skill in the art demonstrates that the inventors of the
6 asserted patents were in possession of the claimed invention.

7 Defendants conclude by alleging that the specification does not describe anything more
8 than what is obvious, and thus does not provide adequate support for any nonobvious claim.
9 That is incorrect and irrelevant. Nonobviousness does not have to be supported solely by the
10 specification; nonobviousness can be supported by post-filing date evidence for example.⁵²⁷⁸
11 Written description requires only that the specification reasonably conveys that the applicant had
12 possession of the claimed subject matter when the application was filed. Therefore, whether the
13 claims are obvious has no bearing on the adequacy of written description.

14 c) Defendants Have Not Demonstrated that the Claims of the ‘929
15 patent Are Invalid for Lack of Enablement

16 The first paragraph of 35 U.S.C. § 112 requires that the specification “enable any person
17 skilled in the art . . . to make and use [the claimed invention].” A claim is not enabled if it would
18 require undue experimentation for a person of ordinary skill to make or use the invention.

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⁵²⁷⁷ *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1343-48 (Fed. Cir. 2010).

20 ⁵²⁷⁸ See *Sanofi–Aventis Deutschland GmbH v. Glenmark Pharm., Inc.*, 748 F.3d 1354, 1360 (Fed. Cir. 2014)
21 (“Glenmark also argues that later-discovered benefits cannot be considered in an obviousness analysis.... That is
22 incorrect; patentability may consider all of the characteristics possessed by the claimed invention, whenever those
23 characteristics become manifest.”); *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291,
24 1307 (Fed. Cir. 2011) (“[E]vidence of unexpected results may be [considered] ... even if that evidence was obtained
after the patent's filing or issue date.”); *Knoll Pharm. Co. v. Teva Pharm. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir.
2004) (“Evidence developed after the patent grant is not excluded from consideration, for understanding of the full
range of an invention is not always achieved at the time of filing the patent application.”).

1 Factors that may be considered include the quantity of experimentation necessary, the amount of
2 direction or guidance presented, the presence or absence of working examples, the nature of the
3 invention, the state of the prior art, the relative skill of those in the art, the predictability or
4 unpredictability of the art, and the breadth of the claims.⁵²⁷⁹ The enablement requirement is
5 separate and distinct from the written description requirement,⁵²⁸⁰ and as such a claim does not
6 require descriptive support in the disclosure as originally filed for it to be enabled.⁵²⁸¹

7 Defendants make two specific arguments regarding the enablement requirement. First,
8 Defendants contend that “[i]t would take undue experimentation to obtain the actual amounts of
9 the composition found in the ultimate claims.” This is incorrect. As Defendants admit, the
10 claims disclose amounts of the composition to be administered. Therefore, a person of ordinary
11 skill would be able to determine the amounts of the components in the pharmaceutical
12 composition without any experimentation, much less undue experimentation.

13 Second, Defendants contend that it would take undue experimentation to obtain the
14 claimed required results listed in the full scope of the patent claims, including the claimed lipid
15 effects. This is incorrect. The asserted claims require no experimentation to practice the claimed
16 method and certainly not undue experimentation. Administration of a recited amount of a recited
17 composition, for a recited duration, to a specific, recited patient population produces the recited
18 results. No additional experimentation is required, and Defendants do not explain their
19 allegation that undue experimentation would be required. Defendants also do not contend that
20 following the claimed method (each recited element) does not produce the recited results. The
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22 ⁵²⁷⁹ See, e.g., *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

23 ⁵²⁸⁰ *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991)

24 ⁵²⁸¹ MPEP § 2164.

1 clinical studies included in the VASCEPA® label and submitted to the USPTO clearly
2 demonstrate that administration of EPA of the recited composition, when administered to
3 patients with very high TG levels for at least 12 weeks, as specified, produces the recited
4 results.⁵²⁸² Therefore, the claims are not invalid for lack of enablement.

5 Defendants conclude by alleging that the specification does not enable anything more
6 than what is obvious over the prior art or was known to a person of skill in the art. First,
7 Defendants do not cite any case or present a legal theory to support this assertion. As such, they
8 do not allow Plaintiffs to adequately respond to the assertion. Therefore, Defendants should be
9 precluded in the future from raising any new legal theory to support this assertion. Moreover,
10 while the '929 patent's specification enables a person of ordinary skill to obtain the claimed
11 limitations without undue experiment, the claimed limitations would not have been obvious to a
12 person of ordinary skill, as discussed in Section V.K.3. Furthermore, Plaintiffs have initiated
13 human clinical trials and submitted the trial results to the USPTO to substantiate the utility of its
14 claimed methods.^{5283, 5284} Therefore, a person of ordinary skill would have concluded that the
15 claims possessed credible therapeutic utility, and the full scope of the claims was enabled.

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⁵²⁸² See VASCEPA® Prescribing Information at Table 2.

21 ⁵²⁸³ *In re Brana*, 51 F.3d 1560, 1567 n.19 (Fed. Cir. 1995) (Post-filing evidence “can be used to substantiate any
22 doubts as to the asserted utility.”); MPEP § 2107.03 (“[A]s a general rule, if an applicant has initiated human clinical
23 trials for a therapeutic product or process, Office personnel should presume that the applicant has established that
the subject matter of that trial is reasonably predictive of having the asserted therapeutic utility.”).

24 ⁵²⁸⁴ See May 16, 2011 Bays Declaration at Appendix B.

1 L. The '698 Patent

2 1. The '698 Patent Claims Eligible Subject Matter Under § 101

3 Defendants' allegation that the asserted claims of the '698 patent relate to ineligible
4 subject matter under Section 101 is without merit. Defendants do not establish a *prima facie*
5 case under Section 101 or provide a legal or factual basis to support their allegations.

6 As an initial matter, Defendants' disclosure is also insufficient under the Nevada Local
7 Patent Rules as the grounds for any allegation of invalidity under Section 101 must be
8 provided.⁵²⁸⁵ The bare assertion of invalidity under Section 101 without providing the grounds
9 for such an allegation and examining the elements of the asserted claims of the '698 patent does
10 not meet this requirement and thwarts the purpose of the Rules.⁵²⁸⁶

11 The inquiry under Section 101 involves a two-step test: first, a court must determine
12 whether the claim at issue is directed to a patent-ineligible concept: a law of nature, physical
13 phenomenon, or abstract idea.⁵²⁸⁷ Second, even if the claim is directed to one of these concepts,
14 it still may be patent eligible and the court must determine what else is part of the claim.⁵²⁸⁸

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17 ⁵²⁸⁵ See Nevada Local Patent Rule 1.8(e) (“[E]ach party opposing a claim of patent infringement, shall serve on all
18 other parties Non-Infringement, Invalidity, and Unenforceability Contentions that must include . . . A detailed
statement of any grounds of invalidity based on 35 U.S.C. § 101.”).

19 ⁵²⁸⁶ Nor does the preceding paragraph, which provides only a purported summary of the claims of the '698 patent, or
20 subsequent paragraph, which makes what appears to be an argument entirely unrelated to Section 101, provide the
21 grounds for Defendants' allegation of invalidity under 35 U.S.C. § 101. See, e.g., *Silver State Intellectual Techs.,
Inc. v. Garmin Int'l, Inc.*, 32 F. Supp. 3d 1155, 1161–62 (D. Nev. 2014) (“The District of Nevada’s Local Patent
Rules, like the local patent rules for the Northern District of California, are designed to require the parties to provide
early notice of their infringement and invalidity contentions, and to proceed with diligence in amending those
contentions when new information comes to light in the course of discovery”) (internal quotation marks omitted).

22 ⁵²⁸⁷ *Alice Corp. Pty. v. CLS Bank Int'l*, 134 S. Ct. 2347, 2355 (2014) (“First, we determine whether the claims at
23 issue are directed to one of those patent-ineligible concepts.”).

24 ⁵²⁸⁸ *Id.* (quoting *Mayo*, 132 S. Ct. at 1294) (“If so, we then ask, ‘[w]hat else is there in the claims before us?’”).

1 The sole Section 101 case identified by Defendants, *Mayo Collaborative Services v.*
2 *Prometheus Laboratories, Inc.*, 132 S. Ct. 1289 (2012), is inapplicable to the asserted claims of
3 the '698 patent. In *Mayo*, the claims were directed to “well-understood, routine, [and]
4 conventional” steps, and the only novel element related to administering the proper dosage based
5 on a natural law observation.⁵²⁸⁹ However, the claims merely recited this natural law without
6 reciting any novel application of it.⁵²⁹⁰ The Court found that providing protection to such
7 claims would result in pre-empting “a broad range of potential uses” and excluding others from
8 using “the basic tools of scientific and technical work.”⁵²⁹¹ A method of treatment claim,
9 specifying the subjects, dosage levels, composition, and time course does not raise the concerns
10 of *Mayo* and instead is akin to the typical claims which *Mayo* acknowledges are entitled to patent
11 protection.⁵²⁹²

12 Defendants suggest that the recited EPA composition of each asserted claim is a naturally
13 occurring substance. It is not. Even references contained within Defendants’ own contentions
14 make clear that EPA of the requisite purity and characteristics is not found in nature.⁵²⁹³ As
15 expressed by the patents cited in Defendants’ contentions and well-established precedent, for
16 decades it has been accepted that compositions isolated from nature or purified beyond their

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18 ⁵²⁸⁹ *Mayo*, 132 S. Ct. at 1294.

19 ⁵²⁹⁰ *Id.* at 1301.

20 ⁵²⁹¹ *Id.*

21 ⁵²⁹² *Id.* at 1302 (contrasting the patent-ineligible claims of that case to “a typical patent on a new drug or a new way
22 of using an existing drug); *see also Diamond v. Diehr*, 450 U.S. 175, 177, 191-193 (1981) (upholding patentability
23 for “a process for curing synthetic rubber which includes in several of its steps the use of a mathematical formula
24 and a programmed digital computer” under Section 101); *Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc.*, 827 F.3d
1042, 1048-49 (Fed. Cir. 2016) (finding claims patent eligible because by holding otherwise, a host of other patent
eligible claims, such as method of treatment claims, would also be necessarily ineligible).

⁵²⁹³ *See, e.g.*, U.S. Patent No. 5,215,630, “Method of Purifying Eicosapentaenoic Acid or the Ester Derivative
Thereof by Fractional Distillation” (cited in Defendants’ Joint Invalidity Contentions, *e.g.*, at 26–27).

1 natural state are patent-eligible.⁵²⁹⁴ Moreover, Defendants’ assertions are immaterial to a Section
2 101 defense because method of treatment claims like the ones asserted in this case are patent
3 eligible even if they are directed to administration of a naturally occurring substance.⁵²⁹⁵

4 To the extent Defendants are arguing that a law of nature both underlies the claims and
5 renders them ineligible, that argument is unsupported and incorrect. Defendants allege that “the
6 claimed effects are the natural result of ingesting a naturally-occurring substance.”⁵²⁹⁶ Since the
7 composition that is the subject of the claims is not naturally occurring, Defendants appear to
8 suggest that all method of treatment claims involve a law of nature. That is not what *Mayo* states
9 or even suggests, and indeed the Federal Circuit has refused to adopt Defendants’ overbroad
10 characterization of laws of nature.⁵²⁹⁷ To say that the claims of the ’698 patent claim a law of
11 nature is to suggest that all patents claim such laws and engage in an infinitely regressive mode
12 of analysis that the Supreme Court did not adopt in which “all inventions can be reduced to
13 underlying principles of nature” that would “make all inventions unpatentable.”⁵²⁹⁸ Indeed, even
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18 ⁵²⁹⁴ See, e.g., *In re Bergy*, 596 F.2d 952; *In re Kratz*, 592 F.2d 1169 (CCPA 1979); *In re Bergstrom*, 427 F.2d 1394
(CCPA 1970); *Parke-Davis & Co. v. H.K. Mulford Co.*, 189 F.95 (S.D.N.Y. 1911).

19 ⁵²⁹⁵ *Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc.*, 827 F.3d 1042, 1048-49 (Fed. Cir. 2016).

20 ⁵²⁹⁶ See Defendants’ Joint Invalidation Contentions at 698.

21 ⁵²⁹⁷ See *CellzDirect*, 827 F.3d at 1048-49 (“The [asserted] claims are like thousands of others that recite processes
22 to achieve a desired outcome That one way of describing the process is to describe the natural ability of the
subject matter to *undergo* the process does not make the claim ‘directed to’ that natural ability. If that were so, we
would find patent-ineligible methods of . . . treating cancer with chemotherapy (as directed to cancer cells’ inability
to survive chemotherapy), or treating headaches with aspirin (as directed to the human body’s natural response to
aspirin).”).

23 ⁵²⁹⁸ See *Mayo*, 132 S. Ct. at 1034 (quoting *Diamond v. Diehr*, 450 U.S. 175, 188 (1981)).
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1 those concerned about the implications of *Mayo* on future patents were focused on diagnostic
2 claims not treatment claims of the type that *Mayo* stated were typical and patentable.⁵²⁹⁹

3 Even if there is some underlying law of nature in the asserted claims, the subject matter
4 of the '698 patent remains eligible for protection under Section 101. As articulated by *Mayo* and
5 *Diehr*, patents claiming a law of nature, such as a mathematical equation, are entitled to
6 protection where claims “did not ‘seek to pre-empt the use of [the] equation,’ but sought ‘only to
7 foreclose from others the use of that equation in conjunction with all of the other steps in their
8 claimed process.’”⁵³⁰⁰ As discussed above, the asserted claims of the '698 patent contain a
9 novel, unconventional, and specific method of treatment comprising a particularized application
10 of a nonnaturally occurring substance and does not preempt the use of a law of nature.⁵³⁰¹

11 Defendants also argue that any argument by Amarin in response to Defendants’ § 112
12 arguments are further evidence of invalidity under § 101. This argument is without merit. The
13 claims are enabled and written description is satisfied for the reasons discussed below. In
14 addition, as discussed above, the asserted claims are not merely a naturally-occurring
15 phenomena, and thus satisfy the requirements of § 101.

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20 ⁵²⁹⁹ See *Mayo*, 132 S. Ct. at 1034 (“Prometheus, supported by several *amici*, argues that a principle of law denying
21 patent coverage here will interfere significantly with the ability of medical researchers to make valuable discoveries,
particularly in the area of diagnostic research.”).

22 ⁵³⁰⁰ See *Mayo*, 132 S. Ct. at 1299 (quoting *Diehr*, 450 U.S. at 187).

23 ⁵³⁰¹ See, e.g., *Tannas Electronics v. Luxell Technologies, Inc.*, 2012 WL 3800822, at *4 (C.D. Cal. July 24, 2012)
24 (rejecting a challenge to the patentability of a claim under Section 101 where the alleged natural phenomenon was
“just one step in the whole process” claimed by the invention).

1 **2. The Asserted Claims of the ‘698 Patent Are Not Anticipated by WO**
2 **‘118**

3 To anticipate, a single prior art reference must sufficiently describe a claimed
4 invention so that the public is in “possession” of that invention.⁵³⁰² Therefore, to anticipate, a
5 reference must set forth every element of the claim, either expressly or inherently, in as complete
6 detail as is contained in the claim.⁵³⁰³ The claim elements must also be “arranged” in the prior
7 art reference, just as they are in the claim,⁵³⁰⁴ rather than as “multiple, distinct teachings that the
8 artisan might somehow combine to achieve the claimed invention.”⁵³⁰⁵ In addition, public
9 “possession” requires that the prior art enable a person of ordinary skill to make and use the
10 invention without undue experimentation.⁵³⁰⁶ Factors that may be included in this analysis
11 include the quantity of experimentation necessary, the amount of direction or guidance
12 presented, the presence or absence of working examples, the nature of the invention, the state of
13 the prior art, the relative skill of those in the art, the predictability or unpredictability of the art,
14 and the breadth of the claims.⁵³⁰⁷ This inquiry is objective, and thus evidence of undue
15 experimentation need not be prior art.⁵³⁰⁸

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⁵³⁰² *Akzo N.V. v. U.S. Int’l Trade Com’n*, 808 F.2d 1471, 1479 (Fed. Cir. 1986).

17 ⁵³⁰³ *Id.*; *In re Bond*, 910 F.2d 831, 832 (Fed. Cir. 1990); *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed.
18 Cir. 1989).

⁵³⁰⁴ *Bond*, 910 F.2d at 833; *Akzo*, 808 F.2d at 1479.

19 ⁵³⁰⁵ *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369–71 (Fed. Cir. 2008); *In re Arkley*, 455 F.2d 586, 587
(C.C.P.A. 1972); *In re Ruschig*, 343 F.2d 965, 974 (C.C.P.A. 1965).

20 ⁵³⁰⁶ *Akzo*, 808 F.2d at 1479; *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1085 (Fed. Cir. 2008); *Forest Labs.,*
21 *Inc. v. Ivax Pharms., Inc.*, 501 F.3d 1263, 1268–69 (Fed. Cir. 2007).

⁵³⁰⁷ *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

22 ⁵³⁰⁸ *Plant Genetic Sys., N.V. v. DeKalb Genetics Corp.*, 315 F.3d 1335, 1344 (Fed. Cir. 2003); *In re Wright*, 999
23 F.2d 1557, 1562 (Fed. Cir. 1993); *Liquid Dynamics Corp. v. Vaughan Co., Inc.*, 449 F.3d 1209, 1224–25 (Fed. Cir.
24 2006); *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1336 (Fed. Cir. 2003); *Gould v. Quigg*, 822
F.2d 1074, 1078 (Fed. Cir. 1987).

1 Defendants assert that Claims 1-8 of the '698 Patent are anticipated by the WO '118
2 reference.⁵³⁰⁹

3 A element-by-element analysis, identifying each element of each asserted claim that is
4 absent from WO '118, is provided below. The contentions below are incorporated by reference
5 into Exhibit L, and vice-versa. WO '118 does not anticipate the claims of the '698 patent
6 because it does not describe, properly arrange, or enable the '698 patent claims.

7 a) WO '118 Does Not Teach Every Element of the Claims of the
8 '698 Patent

9 (1) WO '118 Does Not Describe the Claimed Lipid Effects

10 It is well established that, for a prior art reference to anticipate, “every element of the
11 claimed invention must be identically shown in a single reference.”⁵³¹⁰ Moreover, the elements
12 of the claimed invention must have “strict identity” with the elements of the reference; “minimal
13 and obvious” differences are sufficient to prevent anticipation.⁵³¹¹ Here, WO '118 entirely fails
14 to disclose the following elements of Claim 1 of the '698 Patent: *effective to reduce a median*
15 *triglyceride level in the first patient population by at least about 25% compared to a median*
16 *triglyceride level observed in a second patient population having said baseline triglyceride level*
17 *who has not received the pharmaceutical composition.* Defendants appear to concede that WO
18 '118 does not expressly teach these elements, as they fail to set forth any basis for concluding
19 that WO '118 teaches this element.⁵³¹² Indeed, Defendants could not set forth any basis for

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21 ⁵³⁰⁹ References to “WO '118” are to the English translation that was filed with the European application. Plaintiffs
reserve their right to obtain a certified translation of WO '118.

22 ⁵³¹⁰ *Diversitech Corp. v. Century Steps, Inc.*, 850 F.2d 675, 677 (Fed. Cir. 1988); *see also Hybritech Inc. v.*
Monoclonal Antibodies, Inc., 802 F.2d 1367 (Fed. Cir. 1986).

23 ⁵³¹¹ *Trintech Industries, Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1296 (Fed. Cir. 2002).

24 ⁵³¹² Defendants' Invalidation Contentions at 202-204.

1 concluding that WO '118 teaches this element because WO '118 does not.

2 Instead, Defendants argue that these elements express the intended result of a method that
3 is positively recited, and therefore is inherently anticipated. However, for the reasons set forth
4 below, WO '118 fails to disclose each element of the independent claim of the '698 Patent, either
5 expressly or inherently. Therefore, WO '118 cannot anticipate the claimed method. Defendants
6 also argue that these elements represent inherent, natural properties of EPA, and are entitled to
7 no patentable weight. This conclusion is incorrect and inconsistent with the law of anticipation
8 and claim construction. Further, while Defendants argue that the inherent properties are
9 exemplified in the prior art, they fail to identify even a single prior art reference that makes such
10 a disclosure. Defendants cannot point to a single, specific prior art reference because the
11 claimed pharmaceutical composition has never been administered in the manner claimed to the
12 claimed patient population. Also, these elements are positively recited in the body of the claim
13 and therefore cannot be construed as a non-limiting preamble and must be given patentable
14 weight.

15 Further, Defendants entirely fail to prove that inherently discloses the claimed lipid
16 effects. A prior art reference that “only ‘probably’ or ‘possibly’ meets the claims cannot
17 inherently anticipate as a matter of law.”⁵³¹³ “[A]nticipation by inherent disclosure is appropriate
18 only when the reference discloses prior art that must *necessarily* include the unstated
19 limitation.”⁵³¹⁴ “It is not sufficient if a material element or limitation is ‘merely probably or
20 possibly present’ in the prior art.”⁵³¹⁵ WO '118 fails to provide any data related to the lipid
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⁵³¹³ *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

23 ⁵³¹⁴ *Transclean Corp. v. Bridgewood Servs., Inc.*, 290 F.3d 1364, 1373 (Fed. Cir. 2002) (emphasis in original).

24 ⁵³¹⁵ *In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1378 (Fed. Cir. 2007).

1 effects of the disclosed invention on patients described in the publication. Therefore, Defendants
2 fail to prove by clear and convincing evidence that the composition disclosed by WO '118 meets
3 the elements of the independent claim every time it is administered.

4 Defendants fail to demonstrate that administration of the claimed EPA compositions
5 “necessarily” yields the claimed lipid effects. For example, one study cited by Defendants
6 suggests that EPA administration may increase LDL-C.⁵³¹⁶ Rambjor is a clinical study which
7 administered EPA, DHA, fish oil or placebo to human subjects. Rambjor showed that both EPA
8 and fish oil caused a significant increase in LDL-C. On the other hand, DHA effected only a
9 non-significant increase in LDL-C. As reflected by the disclosure of Rambjor, EPA does *not*
10 decrease TG without increasing LDL-C *every time it is administered*.

11 Therefore, WO '118 cannot anticipate the independent claim of the '698 patent. Because
12 the dependent claims include all of the claim elements of the independent claim, WO' 118
13 cannot anticipate any of the dependent claims as well.

14 (2) WO '118 Does Not Disclose Methods of Treating The
15 Claimed Patient Population

16 In addition, WO '118 fails to disclose or suggest the claimed pharmaceutical composition
17 be administered in the manner claimed to the claimed patient population. Defendants attempt to
18 eliminate these important elements by arguing that the preamble is non-limiting. A preamble is
19 the introductory clause of a patent claim and includes everything from the beginning of the claim
20 until a transitional phrase, such as “comprising.” Defendants improperly attempt to truncate the
21 preamble.

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⁵³¹⁶ See, e.g., Rambjor.

1 A claim preamble has patentable weight if, “when read in the context of the entire claim,
2 [it] recites limitations of the claim, or, if the claim preamble is ‘necessary to give life, meaning,
3 and vitality’ to the claim.”⁵³¹⁷ Additionally, the preamble constitutes a claim element when the
4 claim depends on it for antecedent basis because “it indicates reliance on both the preamble and
5 claim body to define the claimed limitation.”⁵³¹⁸

6 The preamble of the asserted claims is limiting for several reasons. The term “subject” in
7 the preamble of the independent claim defines and provides antecedent basis for the “subject”
8 recited in the body of the claims. When reading the claim, one must rely on both the preamble
9 and the claim body to define the claimed invention.

10 If the preamble states “a fundamental characteristic of the claimed invention,” then it “is
11 properly construed as a limitation of the claim itself.”⁵³¹⁹ The recitation of a “method of
12 reducing triglycerides” in the preamble provides antecedent basis for the effect of reducing
13 triglycerides in the body of the claim and emphasizes the intentional purpose for which the
14 method must be performed - to reduce triglycerides.

15 It is clear that “the claim drafter chose to use both the preamble and the body of the claim
16 to define the subject matter of the claimed invention.”⁵³²⁰ Thus, the entire preamble in the
17 independent claim of the ‘698 must contain patentable weight.

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20 ⁵³¹⁷ *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305 (Fed. Cir. 1999) (citation omitted).

21 ⁵³¹⁸ *Catalina Marketing Int’l v. Coolsavings.com, Inc.*, 289 F.3d 801, 808 (Fed. Cir. 2002) (citation omitted).

22 ⁵³¹⁹ *Poly-Am. L.P. v. GSE Lining Tech., Inc.*, 383 F.3d 1303, 1309 (Fed. Cir. 2004); *see also e.g., Computer*
Docking Station Corp. v. Dell, Inc., 519 F.3d 1366, 1375 (Fed. Cir. 2008) (concluding the preamble phrases
23 “portable computer” and “portable computer microprocessing system” limit the claims because they “clearly recite a
necessary and defining aspect of the invention, specifically its portability,” and because the specification and
prosecution history “emphasize this feature of the invention”).

24 ⁵³²⁰ *Bicon, Inc. v. Straumann Co.*, 441 F.3d 945, 953 (Fed. Cir. 2006).

1 WO '118 fails to disclose the patentable elements of the preamble of the asserted claims.
2 WO '118 does not describe or suggest that the claimed pharmaceutical composition be
3 administered in the manner claimed to the claimed patient population.

4 First, WO '118 fails to expressly disclose “a method of reducing triglycerides.” In fact,
5 the invention disclosed by WO '118 relates to a composition for **preventing occurrence of**
6 **cardiovascular events**, as evidenced by the title which reads “Composition for Preventing the
7 Occurrence of Cardiovascular Event in Multiple Risk Patient.” The prevention of the occurrence
8 of cardiovascular events is defined in WO '118 as “all cases of primary prevention, and
9 exemplary cases include prevention of cardiovascular death, fatal myocardial infarction, sudden
10 cardiac death, nonfatal myocardial infarction, cardiovascular angioplasty, new occurrence of rest
11 angina and exercise-induced angina, and destabilization of the angina.”⁵³²¹ The invention of WO
12 '118 is intended to be administered to any person in need of prevention of the occurrence of
13 cardiovascular events, who are typically hypercholesterolemia patients.⁵³²² WO '118 does not
14 expressly describe its invention as a “method of reducing triglycerides,” therefore it cannot
15 anticipate the independent claim.

16 Second, WO '118 fails to disclose the subject as described in the claims. Defendants fail
17 to prove that these elements of the claimed invention have “strict identity” with the elements of
18 the reference.⁵³²³ WO '118 fails to anticipate this claim element because the broad disclosure
19 fails to anticipate the narrow claimed range, and the specific patient population defined in the
20 claims is an essential part of the claimed invention.

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22 _____
⁵³²¹ WO '118 at 12.

23 ⁵³²² *Id.*

24 ⁵³²³ *Trintech Industries, Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1296 (Fed. Cir. 2002).

1 There is no evidence in that subject as described in the claims were ever treated. In fact,
2 WO '118 fails to disclose baseline lipid levels of a single subject. Defendants rely on the
3 definition of "hypertriglyceridemia" in WO '118 to argue that WO '118 discloses treatment of
4 the subject as described in the claims. It does not. Defendants' argument rests on the definition
5 in WO '118 of "hypertriglyceridemia" as "fasting serum triglyceride levels of at least 150
6 mg/dL." WO '118's definition is not tied to a specific subject and there are no working
7 examples, data or other reference in WO '118 indicating that any subject with fasting TG levels
8 of at least 500 mg/dL received an EPA composition as claimed in the asserted patents, or any
9 EPA at all. In addition, Defendants rely on a reference to "Omacor" in WO '118 (at 32) as
10 evidence that a "person of ordinary skill in the art would have understood that the term
11 'hypertriglyceridemia' when used in the WO '118 includes patients with triglyceride levels of
12 500 mg/dL to about 1500 mg/dL." The cited section states that "soft capsules" are preferable
13 and then merely provides examples of commercially available "soft capsules," such as Omacor.
14 The passage does not define "hypertriglyceridemia" as used in WO '118 as referring to patients
15 with triglyceride levels over 500 mg/dL. Nor does it suggest that the claimed EPA should be
16 used in the over 500 mg/dL TG patient population. A prior art reference that "only 'probably'
17 or 'possibly' meets the claims cannot inherently anticipate as a matter of law."⁵³²⁴ Therefore,
18 Defendants fail to prove by clear and convincing evidence that the composition disclosed by WO
19 '118 meets the claim elements of the independent claim every time it is administered.

20 Further, the broad range disclosed by WO '118 is insufficient to anticipate the ranges
21 claimed by the '698 patent. In *Atofina*, the prior art disclosed a temperature range of 100 to 500
22 degrees and a preferred range of 150 to 350 degrees; the patent at issue claimed a range between
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24 ⁵³²⁴ *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

1 330 and 450 degrees. The court found that the broader prior art range could not anticipate the
2 claimed temperature range, “[g]iven the considerable difference between the claimed range and
3 the range in the prior art, no reasonable fact finder could conclude that the prior art describes the
4 claimed range with sufficient specificity to anticipate this element of the claim.”⁵³²⁵ A prior art’s
5 teaching of a broad genus does not necessarily disclose every species within that genus. The
6 court explained the slightly overlapping range between the preferred range and claimed range “is
7 not disclosed as . . . a species of the claimed generic range of 330 to 450 °C,”⁵³²⁶ and therefore
8 failed to anticipate the claimed range. Likewise, WO ‘118’s broad disclosure of
9 hypertriglyceridemia as a “fasting serum triglyceride levels of at least 150 mg/dL” does not
10 anticipate the subject as described in the claims because it fails to described the claimed TG
11 range with sufficient specificity.

12 The court in *Atofina* ruled on an additional question of anticipation that also involved a
13 range of numbers. A prior art reference had disclosed a range of 0.001 to 1.0 percent, as
14 compared to the patent’s claimed range of 0.1 to 5.0 percent.⁵³²⁷ The court explained that
15 “although there is a slight overlap, no reasonable fact finder could determine that this overlap
16 describes the entire claimed range with sufficient specificity to anticipate this limitation of the
17 claim. The ranges are different, not the same. . . . Thus, there is no anticipation.”⁵³²⁸ Similarly,
18 although there may be overlap between the definition of hypertriglyceridemia taught by WO
19 ‘118 and the TG range recited by the claims of the asserted patents, WO ‘118 does not
20 specifically discuss, highlight or otherwise suggest treating patients with TG values above 500

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22 ⁵³²⁵ *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006).

23 ⁵³²⁶ *Atofina*, 441 F.3d at 1000.

24 ⁵³²⁷ *Id.*

⁵³²⁸ *Id.*

1 mg/dL. In fact, WO '118 is directed to compositions and methods for preventing occurrence of
2 cardiovascular events, suggesting that the treatment was envisioned for patients with TG levels
3 below 500 mg/dL (the patient population the ATP III identifies the prevention of atherogenic
4 events as the primary clinical objective),⁵³²⁹ WO '118, therefore, does not expressly disclose the
5 specific patient population that is an essential element of the claims of the asserted patents.
6 Therefore, WO '118 cannot anticipate the claims of the asserted patents.

7 The treatment of a patient with elevated TG levels varies depending on their serum
8 triglyceride levels. Identification of the patient population with very high TG levels (at least 500
9 mg/dL) is central to the claimed invention. In the 2000s, physicians treating lipid disorders,
10 including hypertriglyceridemia, relied on the ATP-III for authoritative guidance on the treatment
11 of lipid disorders.⁵³³⁰ The ATP-III divided hypertriglyceridemia patients into three classes based
12 on the levels of TG in their blood—borderline-high (150-199 mg/dL), high (200-499 mg/dL),
13 and very-high TGs (\geq 500 mg/dL)—and recommended substantially different treatment
14 strategies for patients depending on classification.⁵³³¹ For the borderline-high and high TG
15 groups (150-499 mg/dL), the primary goal was to reduce risk of coronary heart disease.⁵³³²
16 Accordingly, in these populations, physicians focused on lowering LDL-C.⁵³³³ In this patient
17 population, lowering of TG and non-HDL-C levels were considered secondary treatment goals.
18 In contrast, the primary goal for very-high TG patients (\geq 500 mg/dL) was to reduce the risk of
19 pancreatitis—a potentially life threatening condition expected to be precipitated by elevated

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21 ⁵³²⁹ See Section III.

22 ⁵³³⁰ *Id.*

23 ⁵³³¹ ATP III at 3335; *See also* Section III.

24 ⁵³³² *Id.*

⁵³³³ *Id.*

1 TGs— by lowering TG levels. In very high TG patients, lowering LDL-C is a secondary
2 treatment goal.⁵³³⁴ Therefore, as evidenced by the ATP-III, patients with very-high TG levels
3 were considered fundamentally different from patients with borderline-high or high TGs from a
4 lipid chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint.

5 Therefore, WO ‘118’s definition of “hypertriglyceridemia” as “fasting serum triglyceride
6 levels of at least 150 mg/dL” fails to anticipate the claimed subject with very high TG levels. In
7 fact, as described above, WO ‘118 is not directed toward patients with the claimed TG levels at
8 all. WO 118’s disclosure is clearly directed towards preventing the occurrence of cardiovascular
9 risk, which is the primary aim for treatment of patients with high triglycerides (200-499 mg/dL).
10 Thus, WO ‘118’s disclosure is *not* directed towards patients with very high triglyceride levels
11 (where the primary goal is to prevent acute pancreatitis and damage to the pancreas by
12 decreasing triglycerides), as required by the independent claims of the asserted patents, and
13 therefore cannot anticipate the independent claim of the ‘698 Patent.

14 (3) WO ‘118 Does Not Describe the Claimed Pharmaceutical
15 Composition or its Specific Administration

16 WO ‘118 further does not anticipate the claims of the ‘698 patent because it does not
17 disclose “administering orally to the subject.” As WO ‘118 fails to disclose the subject as
18 claimed, it cannot anticipate oral administration to the claimed “subject.”

19 WO ‘118 additionally cannot anticipate the claims of the ‘698 patent because it does not
20 disclose administering the pharmaceutical composition at a dose of about 4g per day.

21 Defendants argue that this element is disclosed by WO ‘118’s teaching that the daily dose is
22 “typically 0.3 to 6 g/day.” Defendants fail to provide the entire disclosure of WO ‘118, which

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⁵³³⁴ *Id.*

1 states that the daily dose is “typically 0.3 to 6 g/day, preferably 0.9 to 3.6 g/day, and still more
2 preferably 1.8 to 2.7 g/day. Another preferable daily dose is 0.3 to 2.7 g/day, and 0.3 to 1.8
3 g.day. Another preferable fatty acid included is DHA-E.” WO ‘118 teaches that the dosage is
4 not particularly limited as long as the intended effect, preventing the occurrence of
5 cardiovascular events, is attained. However, Defendants fail to provide any evidence that a dose
6 that is effective to prevent the occurrence of cardiovascular event, is also a dose that would be
7 effective to reduce triglycerides in the claimed patient population. Furthermore, there are no
8 working examples, data or other reference in WO ‘118 indicating that any subject (much less
9 one with fasting TG levels of at least 500 mg/dL) received an EPA composition as claimed in the
10 asserted patents or any EPA at all, much less at the claimed dose of 4 grams/day.

11 As discussed above, in *Atofina*, the prior art disclosed a preferred temperature range of
12 150 to 350 degrees, and the patent at issue claimed a range between 330 and 450 degrees. The
13 court explained that this slight overlap “is not disclosed as . . . a species of the claimed generic
14 range of 330 to 450 °C,”⁵³³⁵ and therefore failed to anticipate the claimed range. The court in
15 *Atofina* also found that a prior art disclosure of a range of 0.001 to 1.0 percent failed to anticipate
16 the patent’s claimed range of 0.1 to 5.0 percent.⁵³³⁶ The court explained that “although there is a
17 slight overlap, no reasonable fact finder could determine that this overlap describes the entire
18 claimed range with sufficient specificity to anticipate this limitation of the claim. The ranges are
19 different, not the same. . . . Thus, there is no anticipation.”⁵³³⁷ Similarly, although there may be
20 some overlap between the daily dose disclosed by WO ‘118 and the dose claimed by the ‘698

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⁵³³⁵ *Atofina*, 441 F.3d at 1000.

23 ⁵³³⁶ *Id.*

24 ⁵³³⁷ *Id.*

1 patent, WO '118 does not specifically highlight the overlapping area and, moreover, the range
2 claimed by the '698 patent does not fall within WO '118's preferred range. Defendants
3 conveniently omit the preferred range and mischaracterize the teaching of WO '118. Notably,
4 the example indicates that up to 900 mg of the EPA composition could be used three times per
5 day (2.7 g). Thus, WO '118 does not expressly disclose the 4 g per day dose claimed by the '698
6 patent and cannot anticipate the independent claim of the '698 Patent.

7 WO '118 further does not anticipate the claims of the '698 patent because it does not
8 disclose the claimed EPA pharmaceutical composition. Defendants once again cite only a
9 portion of the disclosure and exclude sections that show the breadth of WO '118's teachings.
10 WO '118's full disclosure recites that "the EPA-E used is preferably the one having a high
11 purity, for example, the one having the proportion of the EPA-E in the total fatty acid and
12 derivatives thereof of preferably 40% by weight or higher, more preferably 90% by weight or
13 higher, and still more preferably 96.5% by weight or higher."⁵³³⁸ Therefore, WO '118 discloses
14 EPA-E with "high purity" is a composition which contains EPA-E of 40% by weight, of total
15 fatty acid and derivatives, or higher. This non-specific disclosure is not a species of the claimed
16 generic range for the EPA composition in the claimed pharmaceutical composition.

17 The Federal Circuit has explained that "a preferred . . . range . . . that slightly overlaps the
18 . . . range claimed in the" patent is insufficient for anticipation.⁵³³⁹ In *Atofina*, the prior art
19 disclosed a preferred temperature range of 150 to 350 degrees, and the patent at issue claimed a
20 range between 330 and 450 degrees. The court explained that this slight overlap "is not
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23 ⁵³³⁸ WO '118 at 22.

24 ⁵³³⁹ *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 1000 (Fed. Cir. 2006).

1 disclosed as . . . a species of the claimed generic range of 330 to 450 °C,⁵³⁴⁰ and therefore failed
2 to anticipate the claimed range.⁵³⁴¹ The court in *Atofina* also found that a prior art disclosure of a
3 range of 0.001 to 1.0 percent failed to anticipate the patent’s claimed range of 0.1 to 5.0
4 percent.⁵³⁴² The court explained that “although there is a slight overlap, no reasonable fact finder
5 could determine that this overlap describes the entire claimed range with sufficient specificity to
6 anticipate this element of the claim. The ranges are different, not the same. . . . Thus, there is no
7 anticipation.”⁵³⁴³

8 Similarly, although there may be some overlap between the E-EPA content disclosed by
9 WO ‘118 and the ranges claimed by the ‘698 patent, WO ‘118 does not specifically highlight the
10 overlapping area. The high content of E-EPA in the claimed pharmaceutical composition is a
11 critical factor of the invention disclosed in the ‘698 patent. Therefore, WO ‘118’s broad
12 disclosure of the E-EPA content in its invention does not describe the claimed range with
13 sufficient specificity and cannot anticipate the independent claim of the ‘698 patent.

14 WO ‘118 is additionally insufficient for anticipation because it does not expressly
15 disclose the recited DHA content of the claimed pharmaceutical composition. In fact, WO ‘118
16 makes no distinction between EPA and DHA, stating that “[a]nother preferable fatty acid is
17 DHA-E.”⁵³⁴⁴ The disclosure goes on to state that the composition of the invention is preferably
18 one having high purity of EPA-E and DHA-E. The recited DHA content of the claimed
19 pharmaceutical composition is a critical factor of the invention disclosed in the ‘698 patent.

21 ⁵³⁴⁰ *Atofina*, 441 F.3d at 1000.

22 ⁵³⁴¹ *Atofina*, 441 F.3d at 1000.

23 ⁵³⁴² *Id.*

23 ⁵³⁴³ *Id.*

24 ⁵³⁴⁴ WO ‘118 at 22.

1 The disclosure of WO '118 treats DHA and EPA interchangeably. The disclosed
2 concentrations of EPA and DHA may range from 0 to 100% and every concentration in between.
3 There is no express teaching or guidance directing the person of ordinary skill in the art to the
4 claimed EPA compositions, Therefore, WO '118's broad disclosure, which indicates no
5 difference between the use of EPA or DHA in its invention, cannot anticipate the independent
6 claim of the '698 patent.

7 Defendants contend that Plaintiffs are estopped from arguing there is any material
8 difference between "not more than about 4% DHA" and "substantially no DHA." Defendants
9 provide no legal basis for their argument of estoppel. Defendants appear to suggest that testing
10 data obtained by Plaintiffs constitutes the basis for their assertion of estoppel. That argument is
11 without merit. Plaintiffs' clinical data cannot form the basis for an estoppel argument and
12 Defendants have cited no authority to support their position suggesting the contrary. The
13 language of "not more than about 4% DHA" and "substantially no DHA" are different phrases
14 and are not co-extensive. Accordingly, plaintiffs are not estopped.

15 In the same paragraph containing their allegation of estoppel, Defendants also quote from
16 Amarin's 2011 10-K. It is unclear whether these quotations are associated with their
17 unexplained estoppel arguments. To the extent that they are, Plaintiffs disagree that these
18 statements form the basis for any theory of estoppel. To the extent that Defendants quote
19 Amarin's post-invention 10-K to make any invalidity argument, that is also unavailing. The
20 quoted statements do not identify any recited claim element, including the specific
21 pharmaceutical composition, the recited patient population, administration in the manner
22 claimed, and recited lipid effects. Nor can these elements of the asserted claims be inferred from
23 the quoted statements.

24

1 (4) WO '118 Does Not Describe the Dependent Claims

2 Defendants fail to address any of the claim elements of the dependent claims.

3 Defendants appear to concede that WO '118 does not expressly teach these elements, as they fail
4 to set forth any meaningful basis for concluding that WO '118 teaches these elements.

5 Defendants further argue that “aspects of the claims relating to effects that are to be achieved by
6 practicing the claimed method represent inherent, natural properties of EPA, and are entitled to
7 no patentable weight.” To the extent the recited claim elements relate to the administration step,
8 the dosage form or characteristics of the treated subject and the specific effect produced by the
9 claimed method, Defendants’ contentions that the claim limitations are inherent properties of
10 EPA are unavailing. While Defendants assert that the inherent properties are exemplified in WO
11 '118, they fail to identify any basis, explanation, or even supporting argument for that assertion.
12 Defendants have not met the burden to establish anticipation with the naked assertion that the
13 effects are inherent, natural properties of EPA.

14 Further, Defendants entirely fail to prove that inherently discloses the recited claim
15 limitations. A prior art reference that “only ‘probably’ or ‘possibly’ meets the claims cannot
16 inherently anticipate as a matter of law.”⁵³⁴⁵ “[A]nticipation by inherent disclosure is appropriate
17 only when the reference discloses prior art that must *necessarily* include the unstated
18 limitation.”⁵³⁴⁶ “It is not sufficient if a material element or limitation is ‘merely probably or
19 possibly present’ in the prior art.”⁵³⁴⁷ Defendants fail to show that WO '118 “*necessarily*” meets
20 the recited claim elements relating to the administration step, the dosage form or characteristics

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⁵³⁴⁵ *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

23 ⁵³⁴⁶ *Transclean Corp. v. Bridgewood Servs., Inc.*, 290 F.3d 1364, 1373 (Fed. Cir. 2002) (emphasis in original).

24 ⁵³⁴⁷ *In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1378 (Fed. Cir. 2007).

1 of the treated subject and the specific effect produced by the claimed method *every time*. WO
2 '118 fails to provide any data related to the TG, LDL-C, VLDL-C, non-HDL-C, Lp-PLA2, total
3 cholesterol, Apo-B, or any other lipid effect of the disclosed invention on patients described in
4 the publication. Further, WO '118 is a translated Japanese disclosure that makes no reference to,
5 let alone a disclosure of, a Western diet. Therefore, Defendants fail to prove by clear and
6 convincing evidence that the composition disclosed by WO '118 meets any dependent claim
7 elements.

8 **3. The Claims of the '698 Patent Would Not Have Been Obvious In**
9 **Light of the Asserted References**

10 Defendants identify 77 separate references that it asserts somehow render the claims of
11 the '698 patent obvious.⁵³⁴⁸ Defendants fail to demonstrate by clear and convincing evidence
12 that any of these references, alone or in combination, would render obvious any claims of the
13 '698 patent. Defendants' arguments rely on hindsight by impermissibly using the blueprint of
14 the '698 patent itself to guide its combination of references.⁵³⁴⁹ Defendants chart a laundry list
15 of 77 separate references, without explanation. Defendants' disclosures do not comply with
16 Local Patent Rule 1-8(d) and fail to put Plaintiffs on notice of how these references allegedly
17 establish that the asserted claims are allegedly *prima facie* obviousness. Consequently, Plaintiffs
18 cannot respond to undisclosed combinations and arguments.⁵³⁵⁰

19 ⁵³⁴⁸ Defendants' Joint Invalidation Contentions at 13-25.

20 ⁵³⁴⁹ *In re Suong-Hyu Hyon*, 679 F.3d 1363, 1371 (Fed. Cir. 2012) ("It is impermissible to use the claimed invention
21 as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is
22 obvious." (citing *In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992))).

23 ⁵³⁵⁰ This includes Defendants' improper attempt to incorporate by reference any alleged prior art or argument,
24 including Defendants' attempt to incorporate by reference "the reasons set forth in the opposition proceedings for
EP 2 395 991 B1" in the European Patent Office. Such wholesale incorporation by reference does not satisfy the
Defendants' obligations or burden of proof and is contrary to the Nevada Local Patent Rules, which require that
each prior art be identified specifically. *See* Local Pat. R. 1-8. Plaintiffs reserve the right to strike any attempt to
rely on undisclosed or insufficiently disclosed references or argument.

1 Despite the general, non-limiting nature of Defendants’ Joint Invalidity Contentions,
2 Plaintiffs have discerned and will specifically respond to the following alleged prior art
3 combinations:

- 4 • 1) “. . .the asserted claims of the ’698 patent would have been obvious over the
5 Omacor PDR/Lovaza PDR in combination with the known clinical benefits of
6 administering pure EPA as evidenced by Katayama and/or Matsuzawa, further in
7 view of Nozaki and/or Hayashi, and further in view of Leigh-Firbank and/or Mori
8 2000.”
- 9 • 2) “. . .the asserted claims of the ’698 patent would have been obvious over the
10 Omacor PDR/Lovaza PDR in combination with the known clinical benefits of
11 administering purified EPA as evidenced by Katayama, Matsuzawa and/or Takaku,
12 further in view of Nozaki and/or Hayashi, and further in view of Grimsgaard, Mori
13 2000 and/or Maki.”
- 14 • 3) “. . .the asserted claims of the ’698 patent would have been obvious over the
15 Omacor PDR/Lovaza PDR in combination with the known clinical benefits of
16 administering pure EPA as evidenced by Katayama in view of Satoh and/or in view
17 of Satoh or Shinozaki in further view of Contacos.”
- 18 • 4) “. . . the asserted claims of the ’698 patent would have been obvious over WO ’118
19 or WO ’900 in combination with treatment regimen of Lovaza as evidenced by the
20 Lovaza PDR, and further in view of Leigh-Firbank and/or Mori 2000.”
- 21 • 5) “. . . the asserted claims of the ’698 patent would have been obvious over WO
22 ’118, WO ’900, Grimsgaard, Mori 2000 and/or Maki in combination with treatment
23 regimen of Omacor/Lovaza as evidenced by the Omacor PDR/Lovaza PDR, and
24 further in view of Katayama, Matsuzawa and/or Takaku.”

18 A patent claim is invalid “if the differences between the subject matter sought to be
19 patented and the prior art are such that the subject matter as a whole would have been obvious at
20 the time the invention was made to a person having ordinary skill in the art.”⁵³⁵¹ Obviousness is
21 a legal determination, but it turns on factual inquiries into (1) the level of ordinary skill in the art,

23 ⁵³⁵¹ 35 U.S.C. § 103(a).

1 (2) the scope and content of the prior art, and (3) the differences between the prior art and the
2 claims at issue.⁵³⁵²

3 In evaluating obviousness, each prior art reference must be evaluated for all that it
4 teaches, including the portions that would lead away from the claimed invention.⁵³⁵³ Indeed, any
5 teaching in the art that points away from the claimed invention must be considered.⁵³⁵⁴ A
6 reference teaches away if a person of ordinary skill, upon reading the reference, would be
7 discouraged from following the path set out in the reference, or would be led in a direction
8 divergent from the path that was taken by the applicant.⁵³⁵⁵ For instance, a reference teaches
9 away if it suggests that the line of development flowing from the reference’s disclosure is
10 unlikely to be productive of the result sought by the applicant.⁵³⁵⁶

11 In order to find obviousness based on a combination of references, there must be some
12 rationale for combining the references in the way claimed that is separate and apart from the
13 hindsight provided by the patented invention itself.⁵³⁵⁷ The law prohibits an obviousness
14 challenge based on a hindsight reconstruction of the claimed invention from isolated prior art
15 references. It is improper for “the claims [to be] used as a frame, and individual, naked parts of
16 separate prior art references [to be] employed as a mosaic to recreate a facsimile of the claimed
17 invention.”⁵³⁵⁸ “The invention must be viewed not after the blueprint has been drawn by the
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19 ⁵³⁵² *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966); *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007).

20 ⁵³⁵³ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

21 ⁵³⁵⁴ *Tec Air, Inc. v. Denso Mfg. Mich. Inc.*, 192 F.3d 1353, 1359-60 (Fed. Cir. 1999)

22 ⁵³⁵⁵ *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994)

23 ⁵³⁵⁶ *Id.*

24 ⁵³⁵⁷ *Immogenetics, N.V. v. Abbott Labs*, 512 F.3d 1363, 1373–74 (Fed. Cir. 2008)

⁵³⁵⁸ *See W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1552 (Fed. Cir. 1983)

1 inventor, but as it would have been perceived in the state of the art that existed at the time the
2 invention was made.”⁵³⁵⁹

3 “The determination of obviousness is made with respect to the subject matter as a whole,
4 not separate pieces of the claim.”⁵³⁶⁰ “[A] patent composed of several elements is not proved
5 obvious merely by demonstrating that each of its elements was, independently, known in the
6 prior art.”⁵³⁶¹ “This is so because inventions in most, if not all, instances rely upon building
7 blocks long since uncovered, and claimed discoveries almost of necessity will be combinations
8 of what, in some sense, is already known.”⁵³⁶²

9 Accordingly, it is improper to pick and choose isolated elements from the prior art and
10 combine them so as to yield the invention⁵³⁶³ or to modify a prior art reference in a way that
11 “would destroy the fundamental characteristics of that reference.”⁵³⁶⁴ Moreover, a combination
12 is not obvious where “it would be impossible to apply these teachings [of the secondary
13 reference] to the [primary reference] without entirely changing the basic mechanism and
14 procedure thereof,”⁵³⁶⁵ or where the proposed combination requires “material and radical
15 modification in order to conform to [the patentee’s] claims” or a “total reconstruction” of the
16
17
18

19 ⁵³⁵⁹ *Sensonics, Inc. v. Aerosonic Corp.*, 81 F.3d 1566, 1570 (Fed. Cir. 1996)

20 ⁵³⁶⁰ *Sanofi Syntheolabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008)

21 ⁵³⁶¹ *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007))

22 ⁵³⁶² *KSR*, 550 U.S. at 418-419.

23 ⁵³⁶³ *Abbott Labs v. Sandoz, Inc.*, 544 F.3d 1341, 1348 (Fed. Cir. 2008)

24 ⁵³⁶⁴ *Apple, Inc. v. Samsung Elec. Co., Ltd.*, 678 F.3d 1314, 1331 (Fed. Cir. 2012)

⁵³⁶⁵ *In re Irmischer*, 262 F.2d 85, 87 (CCPA 1958)

1 prior art device.⁵³⁶⁶ Furthermore, it is improper “to modify the secondary reference before it is
2 employed to modify the primary reference” in assessing obviousness.⁵³⁶⁷

3 Further, a party asserting obviousness in view of a combination of prior art disclosures
4 must show that a person of ordinary skill in the relevant field had an “apparent reason” to
5 combine the elements in the manner claimed⁵³⁶⁸ and “a reasonable expectation of success.”⁵³⁶⁹

6 For chemical compounds, there must have been a reason both to select the prior art
7 compound “most promising to modify” and to make the necessary changes to arrive at the
8 claimed compound.⁵³⁷⁰ This protects against the use of hindsight to pick through the prior art
9 based solely on structural similarity to the claimed compound.⁵³⁷¹ Any assertion of an “apparent
10 reason” must find a basis in the factual record.⁵³⁷²

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12 ⁵³⁶⁶ *Id.* at 88.

13 ⁵³⁶⁷ *In re Hummer*, 241 F.2d 742, 745 (CCPA 1957)

14 ⁵³⁶⁸ *KSR*, 550 U.S. at 417–19; *TriMed, Inc. v. Stryker Corp.*, 608 F.3d 1333, 1341 (Fed. Cir. 2010). Hindsight may
15 not be employed to identify relevant prior art and relevant teachings therein: *Heidelberger Druckmaschinen AG v.*
16 *Hantscho Comm. Prods., Inc.*, 21 F.3d 1068, 1071–72 (Fed. Cir. 1994); *Monarch Knitting Mach. Corp. v. Sulzer*
17 *Morat GmbH*, 139 F.3d 877, 881 (Fed. Cir. 1998).

18 ⁵³⁶⁹ *Proctor & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (henceforth, “P&G”);
19 *Takeda Chem. Indus. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1361 (Fed. Cir. 2007); *KSR*, 550 U.S. at 416 (a
20 combination of elements “must do more than yield a predictable result;” combining elements that work together “in
21 an unexpected and fruitful manner” would not have been obvious).

22 ⁵³⁷⁰ *Daiichi Sankyo Co. v. Matrix Labs. Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010); *Takeda*, 492 F.3d at 1355, 1359–
23 60; P&G, 566 F.3d at 994–95; *Eisai Co. Ltd. v. Dr. Reddy’s Labs., Ltd.*, 533 F.3d 1533, 1358 (Fed. Cir. 2008); *Eli*
24 *Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 471 F.3d 1369, 1378–80 (Fed. Cir. 2006).

25 ⁵³⁷¹ *Daiichi Sankyo*, 619 F.3d at 1354; *Pfizer*, 2010 WL 339042, at *14. *Accord In re Vaidyanathan*, 381. 985, 994
(Fed. Cir. 2010) (nonprecedential); *Processing Corp. v. Am. Maize-Products Co.*, 840 F.2d 902, 907 (Fed. Cir.
1988); *Power-One*, 599 F.3d at 1351–52; *Crown Ops. Int’l, Ltd. v. Solutia, Inc.*, 289 F.3d 1367, 1376 (Fed. Cir.
2002).

26 ⁵³⁷² *See, e.g., Vaidyanathan*, 381. at 993–94 (“[W]hile *KSR* relaxed some of the formalism of earlier decisions
27 requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did not remove the need to
28 anchor the analysis in explanation of how a person of ordinary skill would select and apply the teachings of the
29 references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi Sankyo*, 619 F.3d at
30 1354 (The assertion of a starting point “must avoid hindsight bias; it must look at the state of the art *at the time the*
31 *invention was made* to find a motivation to select and then modify a lead compound to arrive at the claimed

1 The “reasonable expectation of success” for a chemical compound must be of all of a
2 claimed compound’s relevant properties,⁵³⁷³ including those discovered after the patent was filed
3 or even issued.⁵³⁷⁴ “The basic principle behind this rule is straight-forward—that which would
4 have been surprising to a person of ordinary skill in a particular art would not have been
5 obvious.”⁵³⁷⁵ Any assertion of a “reasonable expectation of success” must find a basis in the
6 factual record.⁵³⁷⁶

7 In an obviousness determination, any objective indicia of nonobviousness must be taken
8 into account.⁵³⁷⁷ An objective indicium is any “event[] proved to have actually happened in the
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11 invention.” This turns on the known “properties and elements of the prior art compounds.”; *Forest Labs.*, 438
12 F.Supp.2d at 492–93 (rejecting defendants’ contention that claims to (+)-citalopram were “prima facie obvious in
13 light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding that
14 defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been
15 motivated to resolve citalopram in June 1988”).

16 ⁵³⁷³ *Yamanouchi Pharm. Co., Ltd. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1345 (Fed. Cir. 2000) (“The success
17 of discovering famotidine . . . was finding a compound that had high activity, few side effects, and lacked toxicity. . .
18 . [T]he ordinary medicinal chemist would not have expected famotidine to have the ‘most desirable combination of
19 pharmacological properties’ that it possesses.”); *Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 364 F.Supp.2d
20 820, 908 (S.D. Ind. 2005) (“[S]uccess was not simply finding a compound as active as clozapine . . . Here, the
21 ordinary medicinal chemist . . . would not have expected olanzapine to have the highly desirable combination of
22 pharmacological properties that it possesses.”).

23 ⁵³⁷⁴ *Knoll Pharm. Inc. v. Teva Pharms. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004); *Eli Lilly*, 364 F.Supp.2d at
24 908.

⁵³⁷⁵ *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995) (“The principle applies most often to the less predictable fields,
such as chemistry, where minor changes in a product or process may yield substantially different results.”).

⁵³⁷⁶ See, e.g., *Sanofi-Synthelabo*, 550 F.3d at 1089 (“Apotex argues that the district court applied an incorrect
inquiry, and that the correct inquiry is not whether the results obtained with the separated enantiomer were
unexpected, but whether it would have been obvious to separate and test the enantiomers, based on the general
knowledge that enantiomers can exhibit different properties. Apotex refers to *In re Adamson*, 275 F.2d [952,] 955
[(C.C.P.A. 1960)], where the CCPA held that an enantiomer would have been obvious in view of its racemate.
However, the scientific facts differed from these herein, for in *Adamson* the court found that it was ‘particularly
expected’ that the specific enantiomer would have the observed properties. In contrast, as Sanofi points out, in *In re
May*, 574 F.2d at 1095, the CCPA held, as to the enantiomer claimed therein, that the appellant ‘established a
substantial record of unpredictability vis-à-vis a highly significant combination of properties.’”).

⁵³⁷⁷ *Graham*, 383 U.S. at 17–18; *KSR*, 550 U.S. at 406; *Jones v. Hardy*, 727 F.2d 1524, 1530–31 (Fed. Cir. 1984).

1 real world” that evidences the nonobvious nature of the invention.⁵³⁷⁸ The existence of an
2 enduring, unmet need, difficulties encountered by those skilled in the field, unexpected or
3 surprising results, expressions of skepticism, industry praise, commercial success, and copying
4 are classical indicia of nonobviousness.⁵³⁷⁹ These factual inquiries “guard against slipping into
5 use of hindsight,”⁵³⁸⁰ and “may often be the most probative and cogent evidence of
6 nonobviousness.”⁵³⁸¹

7 Also, as with assertions of anticipation, in order for an invention to be obvious, it must
8 have been fully “in possession” of the public—which requires that the claimed invention have
9 been enabled.⁵³⁸²

10 A element-by-element analysis, identifying each limitation of each asserted claim that is
11 absent from the prior art, is provided below, and also provided at Exhibit L. The contentions
12 below are incorporated by reference into Exhibit L, and vice-versa.

13 a) General Overview

14 Defendants fail to provide a single prior art reference that discloses administration of the
15 recited composition of EPA ethyl (in the recited purity) to the very-high TG patient population
16 (≥ 500 mg/dL) and the resulting lipid effects. Instead, they rely on a large number of studies,

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18 ⁵³⁷⁸ *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1569 (Fed. Cir. 1987).

19 ⁵³⁷⁹ *Graham*, 383 U.S. at 17–18; *KSR*, 550 U.S. at 406; *U.S. v. Adams*, 383 U.S. 39, 52 (1966); *Merck & Co. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1376 (Fed. Cir. 2005); *Panduit*, 810 F.2d at 1569; *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995); *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988); *Janissen*, 456 F.Supp.2d at 669–72.

20 ⁵³⁸⁰ *Graham*, 383 U.S. at 36.

21 ⁵³⁸¹ *Ortho-McNeil Pharm. Inc. v. Mylan Labs. Inc.*, 520 F.3d 1358, 1365 (Fed. Cir. 2008) (quoting *Catalina Lighting Inc. v. Lamps Plus, Inc.*, 295 F.3d 1277, 1288 (Fed. Cir. 2002)).

22 ⁵³⁸² *In re Kumar*, 418 F.3d 1361, 1368 (Fed. Cir. 2005) (“[I]n order to render an invention unpatentable for
23 obviousness, the prior art must enable a person of ordinary skill to make and use the invention.”); *In re Hoeksema*,
24 399 F.2d 269, 274 (C.C.P.A. 1968) (“[I]f the prior art of record fails to disclose or render obvious a method for
making a claimed compound, at the time the invention was made, it may not be legally concluded that the compound
itself is in the possession of the public.”).

1 many of which are not placebo controlled, which administer EPA, DHA, or both, in varying
2 degrees of purity, in a wide range of doses and administration periods, to subjects who have
3 baseline TG levels lower than 500 mg/dL and in many cases significantly lower. The importance
4 of a placebo-controlled study cannot be overstated. Randomized, double-blind placebo
5 controlled studies are considered the “gold standard” of clinical studies. Studies involving the
6 administration of fish oils or omega-3 fatty acids which are not placebo controlled cannot
7 distinguish between the effect of the placebo from that of the active agent. Studies which
8 administer mixtures enriched for either EPA or DHA are not suitable for evaluating the
9 independent effects of EPA and DHA.⁵³⁸³ Inconsistency in dosages and administration periods
10 and variations in the administered fatty acid compositions also complicate the interpretation of
11 the results and limit the application of these studies.

12 Defendants also rely on the ANCHOR study to argue that Amarin’s use of “patients with
13 very high TGs together with patients with high and borderline high TGs indicates that there is no
14 medical difference in responsiveness to treatment among the groups of people.”⁵³⁸⁴ Defendants
15 mischaracterize the ANCHOR study. The ANCHOR study was a multi-center, placebo-
16 controlled, randomized, double-blind, 12-week pivotal Phase 3 study on the effects of Vascepa in
17 patients with high triglycerides (≥ 200 mg/dL and < 500 mg/dL) who were also on statin therapy.
18 Defendants point to the reported “Min-max” TG levels, 157-782 mg/dL, for the AMR101 4g
19 daily group to argue that Amarin used very-high TG patients with high and borderline-high TG
20 patients. However, the mean TG level for this same group, 281.1 mg/dL, makes it clear that

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23 ⁵³⁸³ Mori 2006 at 96.

24 ⁵³⁸⁴ Defendants’ Joint Invalidity Contentions at 710 (*see* FN 136).

1 almost all of the 233 patients in this group had baseline TG values well below 500 mg/dL.⁵³⁸⁵ In
2 addition, the mean baseline TG values for the Placebo and AMR101 2g daily groups were
3 reported as 270.6 mg/dL and 270.2 mg/dL, respectively. Further, Amarin did *not* attempt to use
4 the results of ANCHOR to predict lipid effects in the very high TG patient population. Neither a
5 person of ordinary skill, nor the FDA, would attempt to draw conclusions or gain insight into the
6 very high TG patient population from the ANCHOR trial. In fact, Amarin simultaneously (to
7 ANCHOR) conducted an independent study with Vascepa in patients with very high TG levels.
8 Contrary to Defendants' assertion, the ANCHOR study does *not* indicate that there is no medical
9 difference in responsiveness to treatment between the very-high TG patient population and lower
10 TG patient populations merely because there was possibly one patient with baseline TG levels of
11 at least 500 mg/dL.

12 As discussed above in Section III, patients with very-high TG levels were considered
13 fundamentally different from patients with borderline-high or high TGs from a clinical,
14 regulatory, and therapeutic perspective.⁵³⁸⁶ Clinically, the authoritative guidance to physicians
15 on the treatment of lipid disorders throughout the last decade, the Adult Treatment Panel III
16 (ATP-III) divided hypertriglyceridemic patients into three groups: normal/borderline high TG;
17 high TG; and very high TG. The primary risk faced by borderline-high and high TG patients
18 was atherosclerosis, while the primary risk faced by very-high TG patients was acute
19 pancreatitis. Therefore, the primary focus of treatment, as described by the ATP III, for
20 borderline-high and high TG patients was to lower LDL-C levels. In contrast, the priority for

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22 ⁵³⁸⁵ FDA Briefing Document, Oct. 16, 2013 at pg. 26 (The mean baseline TG value for the placebo group was 270.6
23 mg/dL, AMR101 2g group was 270.2 mg/dL, and AMR101 4g group was 281.1 mg/dL. While there may have been
a few patients with TG > 500mg/dL in the AMR101 4g group, it is clear that the overwhelming majority had baseline
TG values < 500 mg/dL).

24 ⁵³⁸⁶ See Bays Jan. 8, 2012 Decl., ¶ 20.

1 very-high TG patients was TG reduction. This distinction between patients with borderline-
2 high/high TG levels and patients with very high TG levels is also observed on the regulatory
3 level. The FDA recognized the different clinical status of the very-high TG population by
4 approving some drugs specifically for the very-high TG group without granting treatment
5 indications for the borderline-high or high TG populations (i.e. Lovaza/Omacor).⁵³⁸⁷

6 Finally, from a therapeutic standpoint, a person of ordinary skill understood that the
7 effects of lipid-lowering therapies on lipid parameters, such as LDL-C, varied depending on the
8 patient's baseline TG level. Fibrates and prescription omega-3 therapies (two well-known
9 classes of drugs used to treat patient with very-high TGs to lower TG levels at the time of the
10 invention), for example, exhibit different effects on LDL-C levels, depending on the baseline TG
11 level of the patient receiving treatment.

12 Fibrates lower both TGs and LDL-C in normal and borderline-high TG patients, but
13 *increase* LDL-C in very-high TG patients.⁵³⁸⁸ The fibrate, Tricor (fenofibrate), for example,
14 decreased LDL-C significantly in both patients with normal baseline TG values (about 31%)⁵³⁸⁹
15 and high baseline TG values (mean baseline TG value of 231.9 mg/dL) (about 20%).⁵³⁹⁰ In
16 patients approaching very-high TGs levels (mean baseline TG value of 432 mg/dL), a non-
17 significant increase in LDL-C was observed.⁵³⁹¹ In patients with very-high TGs (mean baseline
18 TG = 726 mg/dL), a significant increase in LDL-C was observed (about 45%).⁵³⁹² Similar

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20 ⁵³⁸⁷ See Bays Jan. 8, 2012 Decl., ¶ 22.

21 ⁵³⁸⁸ See Bays 2008 II, at 214-15 (noting that a fibrate caused LDL-C to go down in borderline-high group, remain
roughly the same in high TG group, and increase by around 50% in the very-high TG group).

22 ⁵³⁸⁹ Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

23 ⁵³⁹⁰ *Id.*

24 ⁵³⁹¹ *Id.* See also, Trilipix Label at 27.

⁵³⁹² *Id.* See also, Trilipix Label at 27.

1 results were seen with the administration of Lopid (gemfibrozil).⁵³⁹³ The differing effects of
 2 fibrates, such as Tricor, on TG, LDL-C , HDL-C and Total-C based on baseline TG values
 3 demonstrates how a person of ordinary skill at the time of the invention would have understood
 4 that one could not simply assume that an observed effect of a TG-lowering agent on lipid
 5 parameters in patients with normal, borderline-high or high TG levels would be the same in
 6 patients with very-high TG levels (at least 500 mg/dL) compared to a patient with high or
 7 borderline-high TG levels (150-499 mg/dL). As illustrated in the table, below, patients with
 8 normal or high baseline TG levels experience reduced LDL-C levels upon treatment with a TG-
 9 reducing agent such as the fibrate, Tricor. Patients approaching very high TG levels (mean
 10 baseline TG level of 432 mg/dL) and patients with very high TG levels (mean baseline TG level
 11 of 726 mg/dL) experience significantly increased LDL-C levels.

Fibrate	Mean Baseline TG Value	TG	LDL-C	HDL-C	Total-C
Tricor (fenofibrate) ⁵³⁹⁴	101.7 mg/dL	-23.5%*	-31.4%*	+9.8%*	-22.4%*
	231.9 mg/dL	-35.9%*	-20.1%*	+14.6%*	-16.8%*
	432 mg/dL	-46.2*	+14.5	+19.6*	-9.1*
	726 mg/dL	-54.5*	+45.0*	+22.9*	-13.8*

* = p < 0.05 vs. Placebo

17 Lovaza/Omacor was (and is) a prescription omega-3 therapy known to have differing
 18 lipid effects depending on the patient's baseline TG level. When administered to patients with
 19 borderline-high baseline TG levels, Lovaza/Omacor significantly reduced TGs and raised HDL-
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21 ⁵³⁹³ See Otvos at 1558 (showing administration of Gemfibrozil to patients with borderline-high baseline TG levels
 22 had no impact on LDL-C levels); Manttari at 14 and 16 (stating that the effect of gemfibrozil on LDL-C was
 23 dependent on initial TG levels, no change was observed for LDL-C in subjects with high baseline TG levels while
 24 subjects with normal or borderline-high baseline TG levels showed significant decreases in LDL-C).

⁵³⁹⁴ Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

1 C.⁵³⁹⁵ It had no significant effect on other lipid-related variable, including LDL-C and Apo-
2 B.⁵³⁹⁶ However, when administered to patients with very-high baseline TG levels, TGs were
3 reduced significantly by nearly 50% while LDL-C increased sharply by nearly 50%.⁵³⁹⁷
4 Although the increase in LDL-C was concerning, it was understood that the overall lipid effect of
5 Lovaza/Omacor was beneficial.⁵³⁹⁸

6 Fibrates and prescription Omega-3 therapies demonstrate that one could not simply
7 assume that a lipid lowering agent would have the same effect in a patient with very-high TG
8 levels (≥ 500 mg/dL) as a patient with borderline-high or high TG levels (150-499 mg/dL). They
9 also demonstrate that one of ordinary skill would not expect to see an increase in LDL-C when
10 the normal, borderline-high or high TG patient populations were administered omega-3 fatty
11 acids. As discussed in Section III, the increase in LDL-C for very-high TG patients was
12 expected as a natural consequence of lowering TGs. A person of ordinary skill would have
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14 ⁵³⁹⁵ Chan 2002 I at 2379-81.

15 ⁵³⁹⁶ *Id.*; See also, Westphal at 918.

16 ⁵³⁹⁷ See Weintraub Sept. 7, 2011 Decl., ¶ 23 (citing Lovaza package insert); Bays May 16, 2011 Decl., ¶ 10; see also, Lovaza PDR and Omacor PDR.

17 ⁵³⁹⁸ See Pownall *et al.*, *Correlation of serum triglyceride and its reduction by ω -3 fatty acids with lipid transfer activity and the neutral lipid compositions of high-density and low-density lipoproteins*, 143 *Atherosclerosis* 285, 295 (1999) (“Treatment with ω -3 fatty acids appear to change the lipid profile of individuals with elevated TG to one that may be less atherogenic by changing LDL structure; lowering serum [cholesterol ester transfer activity], serum TG and VLDL-C; and increasing serum HDL-C.”); Stalenhoef at 134 (stating that “Omacor . . . adversely raise LDL cholesterol concentration but the increase in LDL cholesterol concentration reflects a less atherogenic light LDL subfraction profile that may be favorable”); Harris 1997 at 389 (“The increase in LDL, which was substantial on a percentage basis, has been a common finding in past studies in [very-high TG] patients. It may not be as problematic as it appears, however.” And “the use of omega-3 fatty acids for the treatment of severe hypertriglyceridemia may be beneficial not only for the short-term prevention of acute pancreatitis, but also for the long-term prevention of CHD”); Bays III at 248 (“No clinical trial data exist that this rise in LDL-C represents harm or potential “toxicity” to patients. In fact, most evidence supports that omega-3 fatty acids reduce cardiovascular risk as do fibrates. Importantly, clinical trials mostly support that even with increases in LDL-C, omega-3 fatty acids decrease the total cholesterol (TC) carried by atherogenic lipoproteins, as reflected by decreased non-HDL-C levels (TC minus HDL-C.)”

1 considered the rise in LDL-C to be a direct consequence of TG lowering through increased
2 VLDL particle conversion.⁵³⁹⁹ Because normal to high TG patients did not have the large
3 backlog of VLDL particles that very high TG patients have, a person of ordinary skill did not
4 expect LDL-C to increase in normal to high TG patients. It was also well known that the degree
5 of LDL-C elevation observed with prescription omega-3 fatty acids, such as Lovaza/Omacor,
6 was linked to baseline TG levels; that LDL-C levels increased the most in patients with the
7 highest baseline TG levels⁵⁴⁰⁰ and did not increase for patients with lower TG levels. Therefore,
8 the prior art defendants rely upon to show that EPA did *not* increase LDL-C levels in normal,
9 borderline-high or high TG patients was *expected*.

10 Defendants contend that “a composition and its properties are inseparable, and therefore
11 do not impart any additional patentability,” and that “all of the limitations regarding the
12 pharmacologic properties of the ethyl EPA compound identified in the claims of the ’698 patent
13 are inherent to the compound when administered to a human subject.”⁵⁴⁰¹ Inherency may not
14 supply a missing claim limitation in an obviousness analysis unless the inherency would have
15 been obvious to one of ordinary skill in the art.⁵⁴⁰² Obviousness is based on what is *known* in the

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17 ⁵³⁹⁹ Bays May 16, 2011 Decl., ¶ 11 (noting the “general knowledge in the art that omega-3 fatty acids as a class
18 increase LDL-C” in very-high TG patients); McKenney 2007, at 724 (“Because of the increase in LDL levels
19 observed in some patients treated with prescription omega-3, LDL levels also should be periodically assessed during
20 treatment.”); Bays in Kwiterovich at 247 (noting that increased LPL activity caused by fish oil “helps explain some
21 of the seemingly paradoxical lipid effects found with their clinical use, for example, the rise in LDL-C with the
22 decrease in VLDL.”).

20 ⁵⁴⁰⁰ Bays 2008 I at 400-402.

21 ⁵⁴⁰¹ Defendants’ Joint Invalidity Contentions at 711.

22 ⁵⁴⁰² See, e.g., *PAR Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1195–96 (Fed. Cir. 2014) (“A party must . . .
23 meet a high standard in order to rely on inherency to establish the existence of a claim limitation in the prior art in an
24 obviousness analysis—the limitation at issue necessarily must be present, or the natural result of the combination of
elements explicitly disclosed by the prior art.”); *In re Rijckaert*, 9 F.3d 1531, 1533–34 (Fed. Cir. 1993) (“The mere
fact that a certain thing may result from a given set of circumstances is not sufficient [to establish inherency].”) (internal quotation omitted).

1 art at the time of the invention.⁵⁴⁰³ It was not known or reasonably expected at the time of the
2 claimed invention that purified EPA, when administered to patients with very-high TG levels
3 (≥ 500 mg/dL), would not substantially increase LDL-C or would reduce Apo-B. Nor was EPA's
4 effect on LDL-C and Apo-B necessarily present, or the natural result of the combination of
5 elements explicitly disclosed by the prior art.⁵⁴⁰⁴ Therefore, inherency does not supply the
6 missing claim elements in the prior art cited by Defendants.

7 Defendants argue that the claims of the '698 patent which contain "a limiting clause, such
8 as 'to effect' or 'is effective to,'" simply express the intended result of a process step positively
9 recited and therefore are not elements.⁵⁴⁰⁵ This is incorrect. "There is nothing inherently wrong
10 with defining some part of an invention in functional terms."⁵⁴⁰⁶ When a clause "states a
11 condition that is material to patentability, it cannot be ignored in order to change the substance of
12 the invention."⁵⁴⁰⁷ The claim term "to effect" acts as a positive limitation if the term represents
13 "unexpected and improved effects of administration of the claimed compound."⁵⁴⁰⁸ In addition,
14 the elements represent unexpected and improved effects of administration of purified EPA,
15 because a person of ordinary skill would not have expected no substantial increase in LDL-C or
16 reduction in Apo-B when administering EPA to treat severe hypertriglyceridemia. Therefore, the

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20 ⁵⁴⁰³ *In re Spormann*, 363 F.2d 444, 448 (CCPA 1966) ("That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown.").

21 ⁵⁴⁰⁴ See discussions below for Grimsgaard, Park, Nozaki Kurabayashi and Hayashi.

22 ⁵⁴⁰⁵ Defendants' Joint Invalidity Contentions at 711.

23 ⁵⁴⁰⁶ See MPEP 2173.05(g) (citing *In re Swinehart*, 439 F.2d 210 (CCPA 1971)).

24 ⁵⁴⁰⁷ *Hoffer v. Microsoft Corp.*, 405 F.3d 1326, 1329 (Fed. Cir. 2005).

⁵⁴⁰⁸ *AstraZeneca AB v. Dr. Reddy's Labs., Ltd.*, No. CIV.A.05-5553 JAP, 2010 WL 1981790, at *11-12 (D.N.J. May 18, 2010).

1 requirements for no substantial increase in LDL-C and reduction in Apo-B must be accorded
2 patentable weight.

3 b) Identification of Claim Elements Absent from Each Item of Prior
4 Art

5 Plaintiffs identify each limitation of each asserted claim that Plaintiffs believe is absent.
6 Where a limitation is absent from any Independent Claim, that limitation is absent from all
7 asserted claims, and that analysis is incorporated by reference into each dependent claim. For
8 any reference, the fact that Plaintiffs do not list a particular limitation as absent from the asserted
9 claims is not a concession that such limitation is present in the reference. By discussing
10 Defendants' analysis of the "limitations" in the claims, Plaintiffs do not concede that Defendants
11 have appropriately divided the claim language for any purpose.

12 (1) WO '118

13 WO '118 discloses a composition containing EPA-E for preventing the occurrence of
14 cardiovascular events in multiple risk patients.

15 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of WO
16 '118 disclose or suggest elements of the '698 Claims. The cited portions of WO '118 do not
17 disclose or suggest these elements at least because they do not disclose or suggest administration
18 of EPA with the recited purity to a subject with the recited very high TG levels. The cited
19 portions of WO '118 further do not disclose or suggest the claimed pharmaceutical composition
20 with the recited fatty acid compositions or dosage. The cited portions of WO '118 further do not
21 disclose or suggest the claimed pharmaceutical composition, when administered for twelve
22 weeks to a first patient population with the recited very high TG levels is effective to reduce a
23 median triglyceride level in the first patient population by at least about 25% compared to a
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1 median triglyceride level observed in a second patient population with the recited very high TG
2 levels who has not received the pharmaceutical composition.

3 With respect to Claim 1 of the '698 Patent (and therefore all asserted claims), WO '118
4 does not disclose or suggest a subject with the recited very high TG level. WO '118 also does
5 not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid
6 composition or dosage. The cited portions of WO '118 further do not disclose or suggest the
7 claimed pharmaceutical composition, when administered for twelve weeks to a first patient
8 population with the recited very high TG levels is effective to reduce a median triglyceride level
9 in the first patient population by at least about 25% compared to a median triglyceride level
10 observed in a second patient population with the recited very high TG levels who has not
11 received the pharmaceutical composition.

12 Further, with respect to Claim 2, this reference fails to disclose or suggest the subject
13 having the recited baseline LDL-C levels. With respect to Claim 4, this reference fails to
14 disclose or suggest the recited reduction in Apolipoprotein B in the subject with the claimed TG
15 level. With respect to Claim 5, this reference fails to disclose or suggest the recited reduction in
16 VLDL-C in the subject with the claimed TG level. With respect to Claim 6, this reference fails
17 to disclose or suggest the subject with the recited very high TG level.

18 (2) WO '900

19 WO '900 describes methods for obtaining EPA-rich compositions.

20 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of WO
21 '900 disclose or suggest elements of the '698 Claims. The cited portions of WO '900 do not
22 disclose or suggest these elements at least because they do not disclose or suggest administration
23 of EPA with the recited purity to a subject with the recited very high TG levels. The cited
24 portions of WO '900 further do not disclose or suggest the claimed pharmaceutical composition

1 with the recited fatty acid dosage or administration period. The cited portions of WO '900
2 further do not disclose or suggest the claimed pharmaceutical composition, when administered
3 for twelve weeks to a first patient population with the recited very high TG levels is effective to
4 reduce a median triglyceride level in the first patient population by at least about 25% compared
5 to a median triglyceride level observed in a second patient population with the recited very high
6 TG levels who has not received the pharmaceutical composition.

7 With respect to Claim 1 of the '698 Patent (and therefore all asserted claims), WO '900
8 does not disclose or suggest a subject with the recited very high TG level. WO '900 also does
9 not disclose or suggest the claimed pharmaceutical composition with the recited fatty acids
10 dosage or administration period. WO '900 further does not disclose or suggest do not disclose or
11 suggest the claimed pharmaceutical composition, when administered for twelve weeks to a first
12 patient population with the recited very high TG levels is effective to reduce a median
13 triglyceride level in the first patient population by at least about 25% compared to a median
14 triglyceride level observed in a second patient population with the recited very high TG levels
15 who has not received the pharmaceutical composition.

16 Further, with respect to Claim 2, this reference fails to disclose or suggest the subject
17 having the recited baseline LDL-C levels. With respect to Claim 3, this reference fails to
18 disclose or suggest the subject with the recited baseline lipid levels. With respect to Claim 4,
19 this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in the subject
20 with the claimed TG level. With respect to Claim 5, this reference fails to disclose or suggest the
21 recited reduction in VLDL-C in the subject with the claimed TG level. With respect to Claim 6,
22 this reference fails to disclose or suggest the subject with the recited very high TG level.

1 (3) Contacos

2 Contacos describes a study designed to determine the safety and efficacy of a statin
3 (pravastatin) combined with fish oil either alone or in combination, for the management of
4 patients with mixed hyperlipidemia.

5 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of
6 Contacos disclose or suggest elements of the '698 Claims. The cited portions of Contacos do not
7 disclose or suggest these elements at least because they do not disclose or suggest administration
8 of EPA with the recited purity to a subject with the recited very high TG levels. The cited
9 portions of Contacos further do not disclose or suggest the claimed pharmaceutical composition
10 with the recited fatty acid compositions, dosage, or administration period. The cited portions of
11 Contacos further do not disclose or suggest the claimed pharmaceutical composition, when
12 administered for twelve weeks to a first patient population with the recited very high TG levels is
13 effective to reduce a median triglyceride level in the first patient population by at least about
14 25% compared to a median triglyceride level observed in a second patient population with the
15 recited very high TG levels who has not received the pharmaceutical composition.

16 With respect to Claim 1 of the '698 Patent (and therefore all asserted claims), Contacos
17 does not disclose or suggest a subject with the recited very high TG level. Contacos also does
18 not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid
19 compositions, dosage, or administration period. Contacos further does not disclose or suggest do
20 not disclose or suggest the claimed pharmaceutical composition, when administered for twelve
21 weeks to a first patient population with the recited very high TG levels is effective to reduce a
22 median triglyceride level in the first patient population by at least about 25% compared to a
23 median triglyceride level observed in a second patient population with the recited very high TG
24 levels who has not received the pharmaceutical composition.

1 Further, with respect to Claim 4, this reference fails to disclose or suggest the
2 administration of the claimed pharmaceutical composition to effect the recited reduction in
3 Apolipoprotein B. With respect to Claim 5, this reference fails to disclose or suggest the
4 administration of the claimed pharmaceutical composition to effect the recited reduction in
5 VLDL-C. With respect to Claim 6, this reference fails to disclose or suggest the subject with the
6 recited very high TG level.

7 (4) Grimsgaard

8 Grimsgaard conducted a double-blind, randomized, placebo-controlled, parallel design
9 intervention study to evaluate the dietary supplementation with EPA or DHA on serum lipids,
10 apolipoproteins, and serum phospholipid fatty acid composition in subjects with normal TG
11 levels.

12 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of
13 Grimsgaard disclose or suggest elements of the '698 Claims. The cited portions of Grimsgaard
14 do not disclose or suggest these elements at least because they do not disclose or suggest
15 administration of EPA with the recited purity to a subject with the recited very high TG levels.
16 The cited portions of Grimsgaard further do not disclose or suggest the claimed pharmaceutical
17 composition with the recited administration period. The cited portions of Grimsgaard further do
18 not disclose or suggest the claimed pharmaceutical composition, when administered for twelve
19 weeks to a first patient population with the recited very high TG levels is effective to reduce a
20 median triglyceride level in the first patient population by at least about 25% compared to a
21 median triglyceride level observed in a second patient population with the recited very high TG
22 levels who has not received the pharmaceutical composition.

23 With respect to Claim 1 of the '698 Patent (and therefore all asserted claims), Grimsgaard
24 does not disclose or suggest a subject with the recited very high TG level. Grimsgaard also does

1 not disclose or suggest the claimed pharmaceutical composition with the recited administration
2 period. The cited portions of Grimsgaard further do not disclose or suggest the claimed
3 pharmaceutical composition, when administered for twelve weeks to a first patient population
4 with the recited very high TG levels is effective to reduce a median triglyceride level in the first
5 patient population by at least about 25% compared to a median triglyceride level observed in a
6 second patient population with the recited very high TG levels who has not received the
7 pharmaceutical composition.

8 Further, with respect to Claim 4, this reference fails to disclose or suggest the recited
9 reduction in Apolipoprotein B in the subject with the claimed TG level. With respect to Claim 5,
10 this reference fails to disclose or suggest the recited reduction in VLDL-C in the subject with the
11 claimed TG level. With respect to Claim 6, this reference fails to disclose or suggest the subject
12 with the recited very high TG level.

13 (5) Hayashi

14 Hayashi is directed to administration of ethyl icosapentate 1800mg (6 capsules) daily for
15 8 weeks. The purity of the composition is not reported. The study was not placebo controlled
16 and was conducted in 28 patients with familial combined hyperlipidemia and a serum trygliceride
17 concentration higher than 150 mg/dl or serum total cholestorol concentration higher than 220
18 mg/dl.

19 The portions of Hayashi cited by Defendants do not disclose or suggest elements of the
20 '698 patent claims. For example, the cited portions of Hayashi do not disclose or suggest
21 administration of EPA with the recited purity to a subject with the recited very high TG levels
22 who does not receive concurrent lipid altering therapy. Figure 2 demonstrates that no subject
23 had a TG level above 400 mg/dl. The cited portions of Hayahsi further do not disclose or
24 suggest the claimed pharmaceutical composition with the recited fatty acid compositions or

1 dosage. The cited portions of Hayashi further do not disclose or suggest a method to effect the
2 recited TG reduction without substantially increasing LDL-C in a subject with the recited very
3 high TG levels.

4 With respect to Claim 1 of the '698 Patent (and therefore all asserted claims), Hayashi
5 does not disclose or suggest a subject with the recited very high TG level. Hayashi also does not
6 disclose or suggest the claimed pharmaceutical composition with the recited fatty acids
7 compositions or dosage. Hayashi further does not disclose or suggest do not disclose or suggest
8 the claimed pharmaceutical composition, when administered for twelve weeks to a first patient
9 population with the recited very high TG levels is effective to reduce a median triglyceride level
10 in the first patient population by at least about 25% compared to a median triglyceride level
11 observed in a second patient population with the recited very high TG levels who has not
12 received the pharmaceutical composition.

13 Further, with respect to Claim 2, this reference fails to disclose or suggest the subject
14 having the recited baseline LDL-C levels. With respect to Claim 4, this reference fails to
15 disclose or suggest the recited reduction in Apolipoprotein B in the subject with the claimed TG
16 level. With respect to Claim 5, this reference fails to disclose or suggest the recited reduction in
17 VLDL-C in the subject with the claimed TG level. With respect to Claim 6, this reference fails
18 to disclose or suggest the subject with the recited very high TG levels in the subject with the
19 claimed TG level.

20 (6) Katayama

21 Katayama was directed to an investigation of the safety and efficacy of Epadel during
22 long term treatment in patients with hyperlipidemia that was not placebo controlled. Notably,
23 Katayama did not disclose or suggest any LDL-C related data or describe any LDL-C effects and
24 was not placebo controlled.

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1 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of
2 Katayama disclose or suggest elements of the '698 Claims. The cited portions of Katayama do
3 not disclose or suggest these elements at least because they do not disclose or suggest
4 administration of EPA with the recited purity to a subject with the recited very high TG levels.
5 The cited portions of Katayama further do not disclose or suggest the claimed pharmaceutical
6 composition with the recited fatty acid compositions or dosage. The cited portions of Katayama
7 further do not disclose or suggest the claimed pharmaceutical composition, when administered
8 for twelve weeks to a first patient population with the recited very high TG levels is effective to
9 reduce a median triglyceride level in the first patient population by at least about 25% compared
10 to a median triglyceride level observed in a second patient population with the recited very high
11 TG levels who has not received the pharmaceutical composition.

12 With respect to Claim 1 of the '698 Patent (and therefore all asserted claims), Katayama
13 does not disclose or suggest a subject with the recited very high TG level. Katayama also does
14 not disclose or suggest the claimed pharmaceutical composition with the recited fatty acids
15 compositions or dosage. Katayama further does not disclose or suggest do not disclose or
16 suggest the claimed pharmaceutical composition, when administered for twelve weeks to a first
17 patient population with the recited very high TG levels is effective to reduce a median
18 triglyceride level in the first patient population by at least about 25% compared to a median
19 triglyceride level observed in a second patient population with the recited very high TG levels
20 who has not received the pharmaceutical composition.

21 Further, with respect to Claim 2, this reference fails to disclose or suggest the subject
22 having the recited baseline LDL-C levels. With respect to Claim 4, this reference fails to
23 disclose or suggest the recited reduction in Apolipoprotein B in the subject with the claimed TG
24

1 level. With respect to Claim 5, this reference fails to disclose or suggest the recited reduction in
2 VLDL-C in the subject with the claimed TG level. With respect to Claim 6, this reference fails
3 to disclose or suggest the subject with the recited very high TG levels in the subject with the
4 claimed TG level.

5 (7) Leigh-Firbank

6 Leigh-Firbank studied the impact of fish-oil intervention on LDL oxidation, particle
7 density and concentration in subjects with an atherogenic lipoprotein phenotype. Leigh-Firbank
8 does not administer EPA of the purity recited in the claims.

9 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of
10 Leigh-Firbank disclose or suggest elements of the '698 Claims. The cited portions of Leigh-
11 Firbank do not disclose or suggest these elements at least because they do not disclose or suggest
12 administration of EPA with the recited purity to a subject with the recited very high TG levels.
13 The cited portions of Leigh-Firbank further do not disclose or suggest the claimed
14 pharmaceutical composition with the recited fatty acid compositions, dosage, or administration
15 period. The cited portions of Leigh-Firbank further do not disclose or suggest the claimed
16 pharmaceutical composition, when administered for twelve weeks to a first patient population
17 with the recited very high TG levels is effective to reduce a median triglyceride level in the first
18 patient population by at least about 25% compared to a median triglyceride level observed in a
19 second patient population with the recited very high TG levels who has not received the
20 pharmaceutical composition.

21 With respect to Claim 1 of the '698 Patent (and therefore all asserted claims), Leigh-
22 Firbank does not disclose or suggest a subject with the recited very high TG level. Leigh-
23 Firbank also does not disclose or suggest the claimed pharmaceutical composition with the
24 recited fatty acid compositions, dosage, or administration period. Leigh-Firbank further does not

1 disclose or suggest the claimed pharmaceutical composition, when administered for twelve
2 weeks to a first patient population with the recited very high TG levels is effective to reduce a
3 median triglyceride level in the first patient population by at least about 25% compared to a
4 median triglyceride level observed in a second patient population with the recited very high TG
5 levels who has not received the pharmaceutical composition.

6 Further, with respect to Claim 4, this reference fails to disclose or suggest the
7 administration of the claimed pharmaceutical composition to effect the recited reduction in
8 Apolipoprotein B. With respect to Claim 5, this reference fails to disclose or suggest the
9 administration of the claimed pharmaceutical composition to effect the recited reduction in
10 VLDL-C. With respect to Claim 6, this reference fails to disclose or suggest the subject with the
11 recited very high TG level.

12 (8) Lovaza PDR

13 The Lovaza PDR is the Physicians' Desk Reference describing Lovaza.

14 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of the
15 Lovaza PDR disclose or suggest elements of the '698 Claims. The cited portions of the Lovaza
16 PDR do not disclose or suggest these elements at least because they do not disclose or suggest
17 administration of EPA with the recited purity to a subject with the recited very high TG levels.
18 The cited portions of the Lovaza PDR further do not disclose or suggest the claimed
19 pharmaceutical composition with the recited fatty acid compositions or administration period.
20 The cited portions of the Lovaza PDR further do not disclose or suggest the claimed
21 pharmaceutical composition, when administered for twelve weeks to a first patient population
22 with the recited very high TG levels is effective to reduce a median triglyceride level in the first
23 patient population by at least about 25% compared to a median triglyceride level observed in a
24

1 second patient population with the recited very high TG levels who has not received the claimed
2 pharmaceutical composition.

3 With respect to Claim 1 of the '698 Patent (and therefore all asserted claims), the Lovaza
4 PDR does not disclose or suggest the claimed pharmaceutical composition with the recited fatty
5 acid compositions or administration period. The Lovaza PDR further does not disclose or
6 suggest the claimed pharmaceutical composition, when administered for twelve weeks to a first
7 patient population with the recited very high TG levels is effective to reduce a median
8 triglyceride level in the first patient population by at least about 25% compared to a median
9 triglyceride level observed in a second patient population with the recited very high TG levels
10 who has not received the claimed pharmaceutical composition.

11 Further, with respect to Claim 4, this reference fails to disclose or suggest the
12 administration of the claimed pharmaceutical composition to effect the recited reduction in
13 Apolipoprotein B. With respect to Claim 5, this reference fails to disclose or suggest the
14 administration of the claimed pharmaceutical composition to effect the recited reduction in
15 VLDL-C.

16 (9) Maki

17 Maki administered 1.52g/day DHA supplements to patients with below-average levels of
18 HDL-C. Maki does not administer EPA of the purity recited in the claims.

19 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Maki
20 disclose or suggest elements of the '698 Claims. The cited portions of Maki do not disclose or
21 suggest these elements at least because they do not disclose or suggest administration of EPA
22 with the recited purity to a subject with the recited very high TG levels. The cited portions of
23 Maki further do not disclose or suggest the claimed pharmaceutical composition with the recited
24 fatty acid compositions, dosage, or administration period. The cited portions of Maki further do

1 not disclose or suggest the claimed pharmaceutical composition, when administered for twelve
2 weeks to a first patient population with the recited very high TG levels is effective to reduce a
3 median triglyceride level in the first patient population by at least about 25% compared to a
4 median triglyceride level observed in a second patient population with the recited very high TG
5 levels who has not received the pharmaceutical composition.

6 With respect to Claim 1 of the '698 Patent (and therefore all asserted claims), Maki does
7 not disclose or suggest a subject with the recited very high TG level. Maki also does not disclose
8 or suggest the claimed pharmaceutical composition with the recited fatty acid compositions,
9 dosage, or administration period. Maki further does not disclose or suggest the claimed
10 pharmaceutical composition, when administered for twelve weeks to a first patient population
11 with the recited very high TG levels is effective to reduce a median triglyceride level in the first
12 patient population by at least about 25% compared to a median triglyceride level observed in a
13 second patient population with the recited very high TG levels who has not received the
14 pharmaceutical composition.

15 Further, with respect to Claim 4, this reference fails to disclose or suggest the
16 administration of the claimed pharmaceutical composition to effect the recited reduction in
17 Apolipoprotein B. With respect to Claim 5, this reference fails to disclose or suggest the
18 administration of the claimed pharmaceutical composition to effect the recited reduction in
19 VLDL-C. With respect to Claim 6, this reference fails to disclose or suggest the subject with the
20 recited very high TG level.

21 (10) Matsuzawa

22 Matsuzawa administered Epadel to patients with hyperlipaemia in order to study its long-
23 term use in the treatment of the disease and was not placebo controlled.

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1 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of
2 Matsuzawa disclose or suggest elements of the '698 Claims. The cited portions of Matsuzawa
3 do not disclose or suggest these elements at least because they do not disclose or suggest
4 administration of EPA with the recited purity to a subject with the recited very high TG levels.
5 The cited portions of Matsuzawa further do not disclose or suggest the claimed pharmaceutical
6 composition with the recited fatty acid compositions or dosage. The cited portions of
7 Matsuzawa further do not disclose or suggest the claimed pharmaceutical composition, when
8 administered for twelve weeks to a first patient population with the recited very high TG levels is
9 effective to reduce a median triglyceride level in the first patient population by at least about
10 25% compared to a median triglyceride level observed in a second patient population with the
11 recited very high TG levels who has not received the pharmaceutical composition.

12 With respect to Claim 1 of the '698 Patent (and therefore all asserted claims), Matsuzawa
13 does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acids
14 compositions or dosage. Matsuzawa further does not disclose or suggest do not disclose or
15 suggest the claimed pharmaceutical composition, when administered for twelve weeks to a first
16 patient population with the recited very high TG levels is effective to reduce a median
17 triglyceride level in the first patient population by at least about 25% compared to a median
18 triglyceride level observed in a second patient population with the recited very high TG levels
19 who has not received the pharmaceutical composition.

20 Further, with respect to Claim 4, this reference fails to disclose or suggest the
21 administration of the claimed pharmaceutical composition to effect the recited reduction in
22 Apolipoprotein B in the subject with the claimed TG level. With respect to Claim 5, this
23 reference fails to disclose or suggest the administration of the claimed pharmaceutical
24

1 composition to effect the recited reduction in VLDL-C in the subject with the claimed TG level.
2 With respect to Claim 6, this reference fails to disclose or suggest the subject with the recited
3 very high TG levels in the subject with the claimed TG level.

4 (11) Mori 2000

5 Mori 2000 aimed to determine whether EPA and DHA have differential effects on serum
6 lipids and lipoproteins, glucose and insulin in humans.

7 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Mori
8 2000 disclose or suggest elements of the '698 Claims. The cited portions of Mori 2000 do not
9 disclose or suggest these elements at least because they do not disclose or suggest administration
10 of EPA with the recited purity to a subject with the recited very high TG levels. The cited
11 portions of Mori 2000 further do not disclose or suggest the claimed pharmaceutical composition
12 with the recited administration period. The cited portions of Mori 2000 further do not disclose or
13 suggest the claimed pharmaceutical composition, when administered for twelve weeks to a first
14 patient population with the recited very high TG levels is effective to reduce a median
15 triglyceride level in the first patient population by at least about 25% compared to a median
16 triglyceride level observed in a second patient population with the recited very high TG levels
17 who has not received the pharmaceutical composition.

18 With respect to Claim 1 of the '698 Patent (and therefore all asserted claims), Mori 2000
19 does not disclose or suggest a subject with the recited very high TG level. Mori 2000 also does
20 not disclose or suggest the claimed pharmaceutical composition with the recited administration
21 period. The cited portions of Mori 2000 further do not disclose or suggest the claimed
22 pharmaceutical composition, when administered for twelve weeks to a first patient population
23 with the recited very high TG levels is effective to reduce a median triglyceride level in the first
24 patient population by at least about 25% compared to a median triglyceride level observed in a

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1 second patient population with the recited very high TG levels who has not received the
2 pharmaceutical composition.

3 Further, with respect to Claim 4, this reference fails to disclose or suggest the recited
4 reduction in Apolipoprotein B in the subject with the claimed TG level. With respect to Claim 5,
5 this reference fails to disclose or suggest the recited reduction in VLDL-C in the subject with the
6 claimed TG level. With respect to Claim 6, this reference fails to disclose or suggest the subject
7 with the recited very high TG level.

8 (12) Mori 2006

9 Mori 2006 is a review which reports data from clinical trials which compared the
10 independent effects of EPA and DHA in individuals at increased risk of cardiovascular disease.

11 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Mori
12 2006 disclose or suggest elements of the '698 Claims. The cited portions of Mori 2006 do not
13 disclose or suggest these elements at least because they do not disclose or suggest administration
14 of EPA with the recited purity to a subject with the recited very high TG levels. The cited
15 portions of Mori 2006 further do not disclose or suggest the claimed pharmaceutical composition
16 with the recited fatty acid dosage or administration period. The cited portions of Mori 2006
17 further do not disclose or suggest the claimed pharmaceutical composition, when administered
18 for twelve weeks to a first patient population with the recited very high TG levels is effective to
19 reduce a median triglyceride level in the first patient population by at least about 25% compared
20 to a median triglyceride level observed in a second patient population with the recited very high
21 TG levels who has not received the pharmaceutical composition.

22 With respect to Claim 1 of the '698 Patent (and therefore all asserted claims), Mori 2006
23 does not disclose or suggest a subject with the recited very high TG level. Mori 2006 also does
24 not disclose or suggest the claimed pharmaceutical composition with the recited fatty acids

1 dosage or administration period. Mori 2006 further does not disclose or suggest do not disclose
2 or suggest the claimed pharmaceutical composition, when administered for twelve weeks to a
3 first patient population with the recited very high TG levels is effective to reduce a median
4 triglyceride level in the first patient population by at least about 25% compared to a median
5 triglyceride level observed in a second patient population with the recited very high TG levels
6 who has not received the pharmaceutical composition.

7 Further, with respect to Claim 2, this reference fails to disclose or suggest the subject
8 having the recited baseline LDL-C levels. With respect to Claim 3, this reference fails to
9 disclose or suggest the subject with the recited baseline lipid levels. With respect to Claim 4,
10 this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in the subject
11 with the claimed TG level. With respect to Claim 5, this reference fails to disclose or suggest the
12 recited reduction in VLDL-C in the subject with the claimed TG level. With respect to Claim 6,
13 this reference fails to disclose or suggest the subject with the recited very high TG level.

14 (13) Nozaki

15 Nozaki is directed to administration of 2.7 g ethyl icosapentate per day for 6 months. The
16 purity of the composition is reported as 90%. The study was not placebo controlled and was
17 conducted in 14 hypercholesterolemic subjects. The average baseline TG level was only 165
18 mg/dL, while the baseline LDL-C level was 185 mg/dL, which is unusually high for this TG
19 patient population.

20 The portions of Nozaki cited by Defendants do not disclose or suggest elements of the
21 '698 patent claims. For example, the cited portions of Nozaki do not disclose or suggest
22 administration of EPA with the recited purity to a subject with the recited very high TG levels
23 who does not receive concurrent lipid altering therapy. The cited portions of Nozaki further do
24 not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid

1 compositions or dosage. The cited portions of Nozaki further do not disclose or suggest a
2 method to effect the recited TG reduction without substantially increasing LDL-C in a subject
3 with the recited very high TG levels.

4 Defendants assert that certain cited sections of Nozaki disclose or suggest elements of the
5 '698 Claims. The cited portions of Nozaki do not disclose or suggest these elements at least
6 because they do not disclose or suggest administration of EPA with the recited purity to a subject
7 with the recited very high TG levels who does not receive concurrent lipid altering therapy. The
8 cited portions of Nozaki further do not disclose or suggest the claimed pharmaceutical
9 composition with the recited fatty acid compositions or dosage. The cited portions of Nozaki
10 further do not disclose or suggest a method to effect the recited TG reduction without
11 substantially increasing LDL-C.

12 With respect to Claim 1 of the '698 Patent (and therefore all asserted claims), Nozaki
13 does not disclose or suggest a subject with the recited very high TG level. Nozaki also does not
14 disclose or suggest the claimed pharmaceutical composition with the recited fatty acids
15 compositions or dosage. Nozaki further does not disclose or suggest do not disclose or suggest
16 the claimed pharmaceutical composition, when administered for twelve weeks to a first patient
17 population with the recited very high TG levels is effective to reduce a median triglyceride level
18 in the first patient population by at least about 25% compared to a median triglyceride level
19 observed in a second patient population with the recited very high TG levels who has not
20 received the pharmaceutical composition.

21 Further, with respect to Claim 2, this reference fails to disclose or suggest the subject
22 having the recited baseline LDL-C levels. With respect to Claim 4, this reference fails to
23 disclose or suggest the recited reduction in Apolipoprotein B in the subject with the claimed TG
24

1 level. With respect to Claim 5, this reference fails to disclose or suggest the recited reduction in
2 VLDL-C in the subject with the claimed TG level. With respect to Claim 6, this reference fails
3 to disclose or suggest the subject with the recited very high TG levels in the subject with the
4 claimed TG level.

5 (14) Omacor PDR

6 The Omacor PDR is the Physicians' Desk Reference describing Omacor.

7 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of the
8 Omacor PDR disclose or suggest elements of the '698 Claims. The cited portions of the Omacor
9 PDR do not disclose or suggest these elements at least because they do not disclose or suggest
10 administration of EPA with the recited purity to a subject with the recited very high TG levels.
11 The cited portions of the Omacor PDR further do not disclose or suggest the claimed
12 pharmaceutical composition with the recited fatty acid compositions or administration period.
13 The cited portions of the Omacor PDR further do not disclose or suggest the claimed
14 pharmaceutical composition, when administered for twelve weeks to a first patient population
15 with the recited very high TG levels is effective to reduce a median triglyceride level in the first
16 patient population by at least about 25% compared to a median triglyceride level observed in a
17 second patient population with the recited very high TG levels who has not received the claimed
18 pharmaceutical composition.

19 With respect to Claim 1 of the '698 Patent (and therefore all asserted claims), the Omacor
20 PDR does not disclose or suggest the claimed pharmaceutical composition with the recited fatty
21 acid compositions or administration period. The Omacor PDR further does not disclose or
22 suggest the claimed pharmaceutical composition, when administered for twelve weeks to a first
23 patient population with the recited very high TG levels is effective to reduce a median
24 triglyceride level in the first patient population by at least about 25% compared to a median

1 triglyceride level observed in a second patient population with the recited very high TG levels
2 who has not received the claimed pharmaceutical composition.

3 Further, with respect to Claim 4, this reference fails to disclose or suggest the
4 administration of the claimed pharmaceutical composition to effect the recited reduction in
5 Apolipoprotein B. With respect to Claim 5, this reference fails to disclose or suggest the
6 administration of the claimed pharmaceutical composition to effect the recited reduction in
7 VLDL-C.

8 (15) Satoh

9 Satoh administered 1.8g/day of >98% EPA to patients in order to measure the effects of
10 PEA on C-reactive protein and examine how alteration of lipoprotein profile by EPA affects
11 systemic inflammation.

12 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of
13 Satoh disclose or suggest elements of the '698 Claims. The cited portions of Satoh do not
14 disclose or suggest these elements at least because they do not disclose or suggest administration
15 of EPA with the recited purity to a subject with the recited very high TG levels. The cited
16 portions of Satoh further do not disclose or suggest the claimed pharmaceutical composition with
17 the recited fatty acid dosage. The cited portions of Satoh further do not disclose or suggest the
18 claimed pharmaceutical composition, when administered for twelve weeks to a first patient
19 population with the recited very high TG levels is effective to reduce a median triglyceride level
20 in the first patient population by at least about 25% compared to a median triglyceride level
21 observed in a second patient population with the recited very high TG levels who has not
22 received the pharmaceutical composition.

23 With respect to Claim 1 of the '698 Patent (and therefore all asserted claims), Satoh does
24 not disclose or suggest a subject with the recited very high TG level. Satoh also does not

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1 disclose or suggest the claimed pharmaceutical composition with the recited fatty acid dosage.
2 The cited portions of Satoh further do not disclose or suggest the claimed pharmaceutical
3 composition, when administered for twelve weeks to a first patient population with the recited
4 very high TG levels is effective to reduce a median triglyceride level in the first patient
5 population by at least about 25% compared to a median triglyceride level observed in a second
6 patient population with the recited very high TG levels who has not received the pharmaceutical
7 composition.

8 Further, with respect to Claim 4, this reference fails to disclose or suggest the recited
9 reduction in Apolipoprotein B in the subject with the claimed TG level. With respect to Claim 5,
10 this reference fails to disclose or suggest the recited reduction in VLDL-C in the subject with the
11 claimed TG level. With respect to Claim 6, this reference fails to disclose or suggest the subject
12 with the recited very high TG level.

13 (16) Shinozaki

14 Shinozaki studied the long-term effect of EPA on serum levels of Lipoprotein (a) and
15 lipids such as triglycerides, total cholesterol, and low density lipoprotein particles.

16 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of
17 Satoh disclose or suggest elements of the '698 Claims. The cited portions of Shinozaki do not
18 disclose or suggest these elements at least because they do not disclose or suggest administration
19 of EPA with the recited purity to a subject with the recited very high TG levels. The cited
20 portions of Shinozaki further do not disclose or suggest the claimed pharmaceutical composition
21 with the recited fatty acid dosage. The cited portions of Shinozaki further do not disclose or
22 suggest the claimed pharmaceutical composition, when administered for twelve weeks to a first
23 patient population with the recited very high TG levels is effective to reduce a median
24 triglyceride level in the first patient population by at least about 25% compared to a median

1 triglyceride level observed in a second patient population with the recited very high TG levels
2 who has not received the pharmaceutical composition.

3 With respect to Claim 1 of the '698 Patent (and therefore all asserted claims), Shinozaki
4 does not disclose or suggest a subject with the recited very high TG level. Satoh also does not
5 disclose or suggest the claimed pharmaceutical composition with the recited fatty acid dosage.
6 The cited portions of Shinozaki further do not disclose or suggest the claimed pharmaceutical
7 composition, when administered for twelve weeks to a first patient population with the recited
8 very high TG levels is effective to reduce a median triglyceride level in the first patient
9 population by at least about 25% compared to a median triglyceride level observed in a second
10 patient population with the recited very high TG levels who has not received the pharmaceutical
11 composition.

12 Further, with respect to Claim 2, this reference fails to disclose or suggest the subject
13 having the recited baseline LDL-C levels. With respect to Claim 3, this reference fails to
14 disclose or suggest the subject with the recited baseline lipid levels. With respect to Claim 4,
15 this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in the subject
16 with the claimed TG level. With respect to Claim 5, this reference fails to disclose or suggest the
17 recited reduction in VLDL-C in the subject with the claimed TG level. With respect to Claim 6,
18 this reference fails to disclose or suggest the subject with the recited very high TG level.

19 (17) Takaku

20 Takaku administered Epadel to patients with hyperlipaemia in order to study its long-
21 term use and was not placebo controlled.

22 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of
23 Takaku disclose or suggest elements of the '698 Claims. The cited portions of Takaku do not
24 disclose or suggest these elements at least because they do not disclose or suggest administration

1 of EPA with the recited purity to a subject with the recited very high TG levels. The cited
2 portions of Takaku further do not disclose or suggest the claimed pharmaceutical composition
3 with the recited fatty acid compositions or dosage. The cited portions of Takaku further do not
4 disclose or suggest the claimed pharmaceutical composition, when administered for twelve
5 weeks to a first patient population with the recited very high TG levels is effective to reduce a
6 median triglyceride level in the first patient population by at least about 25% compared to a
7 median triglyceride level observed in a second patient population with the recited very high TG
8 levels who has not received the pharmaceutical composition.

9 With respect to Claim 1 of the '698 Patent (and therefore all asserted claims), Takaku
10 does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acids
11 compositions or dosage. Takaku further does not disclose or suggest do not disclose or suggest
12 the claimed pharmaceutical composition, when administered for twelve weeks to a first patient
13 population with the recited very high TG levels is effective to reduce a median triglyceride level
14 in the first patient population by at least about 25% compared to a median triglyceride level
15 observed in a second patient population with the recited very high TG levels who has not
16 received the pharmaceutical composition.

17 Further, with respect to Claim 2, this reference fails to disclose or suggest the subject
18 having the recited baseline LDL-C levels. With respect to Claim 3, this reference fails to
19 disclose or suggest the subject with the recited baseline lipid levels. With respect to Claim 4,
20 this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in the subject
21 with the claimed TG level. With respect to Claim 5, this reference fails to disclose or suggest the
22 recited reduction in VLDL-C in the subject with the claimed TG level.

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c) The Prior Art Does Not Render the Claims Obvious

Defendants have not identified by clear and convincing evidence that the asserted claims of the '698 patent would have been *prima facie* obvious in light of the references cited, either alone or in combination. As described above, none of the references discloses all of the elements in any of the asserted claims. Defendants chart a laundry list of 66 separate references, without explanation, and argue they somehow must be combined to render obvious the asserted claims. Where Defendants have failed to make disclosures with the specificity required by Local Patent Rule 1-8(d), it has failed to put Plaintiffs on notice of how these references allegedly disclose the claim elements at issue.

Defendants' contentions fail to disclose each and every element of the claims of the '698 patent. Specifically, Defendants do not contend that the relied upon references disclose the following elements of Claim 1 (and therefore its dependent claims as well): administering the claimed pharmaceutical composition to the recited patient population effective to reduce a median triglyceride level in the first patient population by at least about 25% based on a comparison to a median triglyceride level observed in a second patient population having said baseline triglyceride level who has not received the pharmaceutical composition. Therefore, Defendants' prior art combinations cannot render the claims *prima facie* obvious.

Facts supporting the non-obviousness of the claims of the '698 patent are discussed in detail below. The objective indicia discussed in Section V.O further demonstrate that the '698 patent is not obvious. In short, Defendants have not met their burden of showing that the claims would have been obvious.

- (1) Defendants Do Not Demonstrate that the Independent Claims of the '698 patent Would Have Been Obvious
 - (a) Defendants Do Not Demonstrate that a Person of Ordinary Skill in the Art Would Have Had Any

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CONFIDENTIAL

Reason to Replace the Mixed Fish Oil Active Ingredient in Lovaza with Pure EPA

- (i) The '698 Patent is not Obvious Over the Omacor PDR/Lovaza PDR, in Combination with Katayama and/or Matsuzawa, Further in View of Nozaki and/or Hayashi and Further in View of Leigh-Firbank and/or Mori 2000

With respect to the '698 patent, Defendants present a combination of seven references:

“the Omacor PDR/Lovaza PDR in combination with the known clinical benefits of administering pure EPA as evidenced by Katayama and/or Matsuzawa, further in view of Nozaki and/or Hayashi, and further in view of Leigh-Firbank and/or Mori 2000.”⁵⁴⁰⁹ Defendants also present charts purporting to assert that an additional 61 references may be combined in order to render the Claims obvious. Not only do Defendants ignore the improbability that a person of ordinary skill would combine 61 separate references, they additionally do not identify any motivation for combining these references.^{5410, 5411} Although Defendants need not point to an explicit statement in the prior art motivating the combination of these references, any assertion of an “apparent

⁵⁴⁰⁹ Defendants’ Joint Invalidity Contentions at 705.

⁵⁴¹⁰ Defendants’ bare assertion that the asserted claims are obvious “in view of one or more of Omacor or Lovaza (as described in the references cited above in Section V.B.2 in view of, at least, the references cited in V.B.3 and 4, including, the '954 publication, WO '900, WO '118, Ando, Grimsgaard, Hayashi, Katayama, Matsuzawa, Matak, Mori 2000, Nakamura, Nozaki, Okumura, Park, Saito 1998, Saito 2008 Satoh, Shinozaki, Takaku, Yokoyama 2003, Yokoyama 2007, Calabresi, Chan 2002, Chan 2003, Contacos, Geppert, Kelley, Leigh-Firbank, Maki, Mori 2006, Rambjør, Sanders or Theobald,” similarly fails to meet the disclosure requirements of the Nevada Local Patent Rules, and fails to provide any motivation to combine these references. *See* Defendants’ Joint Invalidity Contentions at 704.

⁵⁴¹¹ Defendants’ bare assertion that “the motivation or reason to combine or modify the prior art to create invalidating combinations under 35 U.S.C. §103 can be found in the references identified above in Section III.C,” and that “[c]ommon sense, design incentives, market forces, and the background knowledge possessed by a person having ordinary skill in the art provide the reasons or rationales for combining the teachings of multiple references or modifying references to render obvious the claimed inventions of the asserted claims,” fails to meet the disclosure requirements of the Nevada Local Patent Rules. *See* Defendants’ Joint Invalidity Contentions at 703-04.

1 reason” to combine must find a basis in the factual record.⁵⁴¹² Defendants’ unsupported cobbling
2 of selective disclosures represents hindsight reconstruction.⁵⁴¹³ Defendants’ contentions are no
3 more than an assertion that certain claim elements were known in the prior art. Throughout their
4 contentions, Defendants’ selectively cite to data points in a reference without considering other
5 disclosures or even the reference as a whole. Each reference, however, must be evaluated for all
6 that it teaches.⁵⁴¹⁴ Accordingly, Defendants fail to meet their burden to establish *prima facie*
7 obviousness.

8 The Lovaza PDR fails to disclose or even suggest the claimed method of reducing
9 triglycerides in a subject with the claimed pharmaceutical composition containing the claimed
10 fatty acid compositions or administration period. The Lovaza PDR further does not disclose a
11 method to effect the specified TG reduction without substantially increasing LDL-C. Indeed, the
12 Lovaza PDR discloses the exact opposite. The EPA/DHA composition of Lovaza causes a
13 significant increase in LDL-C levels in the very high TG patient population, for whom the
14 product is indicated. At most, the Lovaza PDR discloses administration of a prescription fish oil,
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16 ⁵⁴¹² See, e.g., *In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the
17 formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did
18 not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply
19 the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi*
20 *Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must
21 avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to
22 select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and
23 elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp.
24 2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie*
obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding
that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been
motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

⁵⁴¹³ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under
KSR, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention
without any explanation as to how or why the references would be combined to produce the claimed invention”).

⁵⁴¹⁴ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

1 a combination of approximately 465 mg EPA and 375 mg DHA, as an adjunct to diet to reduce
2 TG levels in adult patients with very-high (≥ 500 mg/dL) TG levels.

3 The proposed combinations do not render the independent claims of the '698 patent
4 obvious and Defendants' burden to prove otherwise is especially difficult because the PTO
5 considered Matsuzawa, Katayama, Mori 2000, and Lovaza (both generally and the Lovaza
6 package insert specifically) during prosecution.⁵⁴¹⁵

7 The analysis of the independent claim of the '698 patent is incorporated into all asserted
8 claims that depend from those Claims.

9 (a) A Person of Ordinary Skill Would
10 Not Have Been Motivated to
11 Replace the Mixed Fish Oil Active
12 **Ingredient in Lovaza with Pure
13 EPA**

12 For an invention to be obvious, there must have been an "apparent reason" to make it.
13 The subject matter of the '698 patent claims would not have been obvious in light of these
14 references because a person of ordinary skill would not have been motivated to purify EPA or
15 been able to reasonably expect that the claimed pharmaceutical composition would reduce TG
16 levels without an increase in LDL-C levels.

17 (i) Katayama and/or Matsuzawa
18 Do Not Disclose Purported
19 Known Clinical Benefits of
20 Administering Pure EPA

20 Both Katayama and Matsuzawa are long term studies directed to an investigation of the
21 safety and efficacy of Epadel in patients with a wide range of baseline TG levels. These studies

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23 ⁵⁴¹⁵ See, e.g., *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012)(taking into account that "the
24 examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention.
Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear
and convincing standard came into play").

1 were not placebo controlled. A person of ordinary skill in the art understood that a placebo may
2 itself cause an effect. Without accounting for the placebo effect, a person of ordinary skill in the
3 art would not and could not attribute any observed effect (and the magnitude of that effect) to
4 that of the drug. Any observed effect could be placebo dependent.⁵⁴¹⁶ As discussed above in
5 Section III, a person of ordinary skill would not expect the same LDL-C effect in patients with
6 lower baseline TG levels—the subjects of Katayama and Matsuzawa—as in very-high TG
7 patients because patients with higher TG levels had different lipid responses compared to
8 patients with lower TG levels. Patients with very-high TG levels were considered fundamentally
9 different from patients with borderline-high or high TGs from a lipid chemistry, medical, clinical
10 guideline, regulatory, and therapeutic standpoint. As previously discussed, a person of ordinary
11 skill in the art would expect to see an increase in LDL-C levels when omega-3 fatty acids were
12 administered to patients with normal, borderline-high or high TG levels. Therefore, the prior art
13 Defendants rely upon to show that EPA did not increase LDL-C levels in normal, borderline-
14 high or high TG patients, was expected. At the priority date of the ‘698 patent, a person of
15 ordinary skill in the art would have expected an *increase* in LDL-C for very-high TG patients
16 receiving a TG-lowering agent, as a natural consequence of lowering TGs. This pattern had been
17 demonstrated for both fibrates and fish oils and was understood as a direct consequence of TG
18 lowering through increased VLDL particle conversion.

19 Defendants argue that these studies disclose known “clinical benefits” of administering
20 pure EPA, lowering triglycerides without raising LDL-C.⁵⁴¹⁷ This is an incorrect characterization

22 ⁵⁴¹⁶See Grimsgaard at 652 (Although administration of EPA reduced Apo-B compared to baseline, it was not a
23 statistically significant effect when compared to placebo. Grimsgaard’s disclosure highlights the importance of a
24 placebo-controlled study and why results compared only to baseline may be misleading.)

⁵⁴¹⁷ Defendants’ Joint Invalidation Contentions at 705, 706.

1 of these two studies. Katayama and Matsuzawa both were only designed to confirm the safety of
2 long term treatment of Epadel and its ability to lower both serum total cholesterol and TG levels.
3 They do just that. They do not discuss any purported “benefits” observed related to LDL-C.
4 Defendants’ selective citation of LDL-C data from these references represents the improper use
5 of hindsight bias. A person of ordinary skill would understand the focus of Katayama and
6 Matsuzawa to be TG and total cholesterol effects and not LDL-C levels, and would not draw
7 conclusions regarding LDL-C from these studies. Indeed, Katayama does not mention LDL-C
8 levels at all. Defendants’ characterization of Katayama and Matsuzawa as disclosing the
9 lowering of TG levels without increasing LDL-C to be “clinical benefits” is incorrect.⁵⁴¹⁸ The
10 references don’t disclose or suggest that the LDL-C results obtained were a clinical benefit, nor
11 would a person of ordinary skill view these references as teaching such a benefit for very-high
12 TG patients.

13 Further, both Katayama and Matsuzawa administered only EPA and studied its lipid
14 effects. These studies fail to provide a head to head comparison of EPA versus DHA.
15 Therefore, a person of ordinary skill in the art would not rely on Katayama or Matsuzawa to
16 draw any conclusions related to possible differences between the lipid effects of EPA and DHA.

17 In addition, Katayama and Matsuzawa do not disclose the purity of the Epadel used. The
18 purity of Epadel has varied over time and across different formulations of the product, therefore
19 it is difficult to determine the purity of the version of Epadel used unless it is specified by the
20 disclosure. One cannot simply rely on the fact that Epadel was administered and assume that the
21 composition comprised at least about 96%, by weight of all fatty acids present, EPA, and
22 substantially no DHA, as required by the asserted claims. Defendants fail to provide a reference
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24 ⁵⁴¹⁸ Defendants’ Joint Invalidity Contentions at 705, 706.

1 disclosing the purity of the form of Epadel used in the Katayama and Matsuzawa studies.
2 Nishikawa,⁵⁴¹⁹ published in 1997, discloses a form of Epadel that was a 91% E-EPA preparation.
3 Nishikawa reflects that versions of Epadel used in some clinical studies do not have the requisite
4 purity.⁵⁴²⁰

5 Further, Katayama and Matsuzawa were small studies conducted in only Japanese
6 patients. These studies would not have been extrapolated to Western populations because the
7 Japanese diet contains much more fish and has a number of other different attributes. The
8 Japanese consume a higher amount of EPA and DHA in their diets than Western populations. In
9 fact, Yokoyama 2007 (cited in Defendants' contentions) states that the results from studies where
10 the patient population is exclusively Japanese cannot be generalized to other populations.⁵⁴²¹
11 The Japanese diet comprises between 8 and 15 times more EPA and DHA than the typical
12 Western Diet. The Western diet typically consists of higher amounts of polyunsaturated omega-
13 6 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand
14 that the Japanese respond differently to lipid lowering agents than Westerners.

15 Defendants rely on Katayama to demonstrate the "known clinical benefits of
16 administering pure EPA - lowering triglycerides without raising LDL-C."⁵⁴²² However,
17 Katayama was directed to an investigation of the safety and efficacy of Epadel during long-term
18 treatment in patients with hyperlipidemia.⁵⁴²³ Katayama does not disclose *any* LDL-C related

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20 ⁵⁴¹⁹ Nishikawa et al., *Effects of Eicosapentaenoic Acid (EPA) on Prostacyclin Production in Diabetics: GC/MS Analysis of PGI₂ and PGI₃ Levels*, 19 METHODS FIND EXP CLIN PHARMACOL. 429 (1997).

21 ⁵⁴²⁰ See also, Ando at 2177 (Epadel with purity greater than 91%), Nakamura at 23 (Epadel with purity > 90%).

22 ⁵⁴²¹ Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to other populations.").

23 ⁵⁴²² Defendants' Joint Invalidity Contentions at 706.

24 ⁵⁴²³ Katayama at 2.

1 data or describe *any* LDL-C effects, and a person of ordinary skill would not understand that
2 reference to provide any such disclosure. The only results disclosed by Katayama were a
3 significant reduction in TGs and total cholesterol when Epadel (EPA of undisclosed purity) was
4 administered to patients with borderline-high to high TG levels, and its safety for long term use
5 in this patient population.⁵⁴²⁴ In addition to Katayama’s lack of disclosure regarding LDL-C,
6 Defendants identify no other basis upon which a person of ordinary skill would have sought to
7 combine the composition disclosed in Katayama with the Lovaza PDR.

8 Defendants similarly rely on Matsuzawa to demonstrate the “known clinical benefits of
9 administering pure EPA - lowering triglycerides without raising LDL-C.”⁵⁴²⁵ However,
10 Matsuzawa included 26 participants, of whom 23 were adopted for the evaluation of overall
11 safety, 22 were adopted for the evaluation of usefulness, 20 were adopted for evaluation of
12 general improvement, 15 were adopted for improvement in serum total cholesterol levels, and 13
13 were evaluated for improvement in serum triglycerides levels.⁵⁴²⁶ It is unclear which of the 26
14 patients were included in each separate evaluation; therefore one cannot determine the baseline
15 lipid characteristics for each subset of patients evaluated. Further, the small sample size and lack
16 of a placebo control makes it less likely that the results of this study can be generalized as an
17 effect on any population as a whole and provides no insight with respect to the very-high TG
18 patient population.

22 ⁵⁴²⁴ *Id.* at 16.

23 ⁵⁴²⁵ Defendants’ Joint Invalidation Contentions at 706.

24 ⁵⁴²⁶ Matsuzawa at 7 and 19.

1 Matsuzawa discloses that 3 of the 26 participants had 400 mg/dL < TG < 1000 mg/dL,
2 and one participant with TG levels > 1,000 mg/dL.⁵⁴²⁷ However, when analyzing the lipid
3 impact of Epadel, Matsuzawa excluded the patient with a TG level greater than 1,000 mg/dL
4 because he was a “heavy drinker” and the “effect of alcohol made it impossible to assess
5 triglyceride levels.”⁵⁴²⁸ Fig. 4, which depicts the changes in serum triglycerides, shows that the
6 mean triglycerides of the 12 patients with TG greater than 150 mg/dL was well below 500
7 mg/dL. Furthermore, as shown in Table 4, patients with TG levels above 500 mg/dL (other than
8 the excluded patient who had TG above 1,000 mg/dL) were not treated in the study with EPA (of
9 undisclosed purity). The identification of three patients with TG levels between 400 and less
10 than 1,000 mg/dL does not disclose a patient with TG levels above 500 mg/dl, and a person of
11 ordinary skill would not understand that the reference makes any such disclosure. As discussed
12 above, one of ordinary skill in the art would not expect LDL-C to increase in a patient with TG
13 less than 500 mg/dL upon treatment with a TG-lowering agent. Matsuzawa provides no
14 evidence to the contrary.

15 Matsuzawa demonstrated mixed results related to LDL-C over time, at first showing a
16 2% decrease, and then a 1% increase in LDL-C by the end of 52 weeks.⁵⁴²⁹ The disclosure
17 further reflects that the 4 patients with serum triglyceride levels of at least 400 mg/dL were
18 excluded from the LDL-C results because the Friedewald’s Equation was used to calculate LDL-
19 C levels. The Friedewald’s Equation cannot be used for patients with triglyceride levels of at
20 least 400 mg/dL. Therefore, the LDL-C results only reflect the LDL-C changes in patients with

22 ⁵⁴²⁷ *Id.* at 23.

23 ⁵⁴²⁸ *Id.* at 10.

24 ⁵⁴²⁹ *Id.* at 11.

1 triglyceride levels below 400 mg/dL. Matsuzawa fails to provide any information to a person of
2 ordinary skill regarding the LDL-C effect in the very-high TG population. A person of ordinary
3 skill in the art, however, would have expected the same treatment in patients with very high TG
4 levels to produce a substantial increase in LDL-C. In addition, Matsuzawa acknowledges that
5 there have been conflicting results related to the LDL-C impact of EPA preparations that lowered
6 triglyceride levels.⁵⁴³⁰ At best, Matsuzawa demonstrates the uncertainty and confusion related to
7 the LDL-C effect EPA had on patients with hyperlipidemia. Further, Defendants fail to identify
8 any other basis upon which a person of ordinary skill would have sought to combine the
9 composition disclosed in Matsuzawa with the Lovaza PDR.

10 Therefore, Katayama and Matsuzawa fail to substantiate Defendants' assertion that
11 compositions comprising EPA as recited in the asserted claims lowers triglycerides without
12 substantially increasing LDL-C. Further, other studies cited by Defendants suggest that EPA
13 increases LDL-C.⁵⁴³¹ Defendants identify no other basis upon which a person of ordinary skill
14 would have sought to combine the Lovaza PDR with Katayama, Matsuzawa, Leigh-Firbank
15 and/or Mori 2000 or reasonably expected that such a combination would successfully yield the
16 asserted claims of the '698 patent.

17 (ii) Nozaki and/or Hayashi
18 Would Not Have Rendered
19 the Asserted Claims Obvious

20 Defendants contend that the asserted claims of the '698 patent would have been obvious
21 in view Nozaki and/or Hayashi in combination with other references, but they do not explain

22 ⁵⁴³⁰ *Id.* at 15. Matsuzawa suggests the conflicting results are due to differences in the EPA content of the EPA
23 preparation administered. However, Matsuzawa fails to identify the specific conflicting studies, disclose the specific
24 compositions used, or identify the patient populations were observed.

⁵⁴³¹ *See, e.g.,* Rambjor.

1 why Nozaki and/or Hayashi render the asserted claims obvious or what element of the asserted
2 claims is found in Nozaki or Hayashi. Nozaki and Hayashi do not disclose or suggest a
3 reduction in triglycerides without increasing LDL-C when purified EPA is administered to the
4 very high TG patient population.

5 Nozaki administered 2.7 g/day of 90% EPA (DHA < 1%) to 14 primary
6 hypercholesterolemia subjects. A person of ordinary skill would not have found the results of
7 Nozaki reliable. Nozaki was not placebo-controlled, nor did the study compare lipid effect of
8 EPA to that of DHA. The average baseline TG level was only 165 mg/dL, while the baseline
9 LDL-C level was 185 mg/dL, which is unusually high for this TG patient population. A person
10 of skill in the art would not look to a study consisting of patients with baseline TG levels of 165
11 mg/dL in order to understand the impact of EPA therapy on the very high TG patient population.
12 Further, a person of ordinary skill would understand that the baseline LDL-C level in this small
13 patient population were abnormally high and would not have relied upon these results. Further,
14 the person of skill in the art would not have looked to this patient population to predict the Apo-
15 B or LDL-C effect of EPA therapy on very high TG patients. Nozaki acknowledges that as of
16 1991, “[t]here is still controversy concerning the effects of fish oil” on LDL and HDL cholesterol
17 levels.⁵⁴³² Nozaki does not provide a motivation or reasonable expectation of success for
18 administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA and
19 substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL, to
20 effect a reduction in triglycerides without increasing LDL-C when purified EPA is administered
21 to the very high TG patient population.

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⁵⁴³² Nozaki at 256.

1 In Hayashi, 1.8 g/day of EPA was administered to 28 patients for 8 weeks. The purity of
2 the EPA and the DHA content in the composition that was administered is unknown. A person
3 of ordinary skill would not have found the results of Hayashi reliable. The study involved 28
4 patients and it was conducted for only 8 weeks. Hayashi shows that changes in Apo-B and LDL-
5 C were not statistically significant.⁵⁴³³ Further, the person of skill in the art would not have
6 looked to this patient population to predict the Apo-B or LDL-C effect of EPA therapy on very
7 high TG patients. Hayashi does not provide a motivation or reasonable expectation of success
8 for administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA
9 and substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL,
10 to effect a reduction in triglycerides without increasing LDL-C when purified EPA is
11 administered to the very high TG patient population.

12 Further, Hayashi was a small study conducted in only Japanese patients and was not
13 placebo controlled. This study would not have been extrapolated to Western populations
14 because the Japanese diet contains much more fish and has a number of other different attributes.
15 The Japanese consume a higher amount of EPA and DHA in their diets than Western
16 populations. In fact, Defendants' own reference states that the results from studies where the
17 patient population is exclusively Japanese cannot be generalized to other populations.⁵⁴³⁴ The
18 Japanese diet comprises between 8 and 15 times more EPA and DHA than typical the typical
19 Western diet. The Western diet typically consists of higher amounts of polyunsaturated omega-6
20 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand that
21 the Japanese respond differently to lipid lowering agents than Westerners.

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23 ⁵⁴³³ Hayashi at 26, Table I.

24 ⁵⁴³⁴ Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to other populations.").

1 Further, Defendants have failed to offer a purported combination of references as part of
2 their obviousness contentions that include Nozaki and Hayashi. Similarly, they fail to offer any
3 motivation to combine Nozaki and Hayashi with the other references of their purported
4 obviousness combinations. Therefore, Defendants should be precluded from relying on these
5 references.

6 (iii) Leigh-Firbank and/or Mori
7 2000 Do Not Disclose
8 Purported Knowledge that
9 DHA was Responsible for the
10 Increase in LDL-C

9 Defendants assert, incorrectly, that “it was known in the art as of February 2009 that
10 administration of DHA (alone or in a mixture) resulted in the negative effect of increasing LDL-
11 C levels.”⁵⁴³⁵ Defendants’ caveat of DHA being “alone or in a mixture” is telling that it was *not*
12 known that DHA alone resulted in an increase in LDL-C levels. Further, the prior art Defendants
13 rely upon to support this statement does not categorize the increase in LDL-C as a “negative
14 effect” in light of the overall impact of the disclosed composition on all lipid parameters.
15 Further, the patients in Leigh Firbank and Mori 2000 had normal to high baseline TG levels. As
16 discussed above in Section III, a person of ordinary skill would not expect the same LDL-C
17 effect in patients with lower baseline TG levels—the subjects of Leigh-Firbank and Mori 2000—
18 as in very-high TG patients because patients with higher TG levels had different lipid responses
19 compared to patients with lower TG levels. Patients with very-high TG levels were considered
20 fundamentally different from patients with borderline-high or high triglycerides from a lipid
21 chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint. Instead, a person
22 of ordinary skill in the art would have expected that fish oils (and other TG lowering agents)

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24 ⁵⁴³⁵ Defendants’ Joint Invalidity Contentions at 708.

1 would not increase LDL-C substantially in patients with normal to borderline high TG levels, but
2 would substantially increase LDL-C in patients with very high TG levels.

3 Defendants rely upon Leigh-Firbank to demonstrate that it was known that “DHA was
4 responsible for the increase in LDL-C levels.” Leigh-Firbank, however, administered fish oil,
5 comprising 1.67 g of EPA and 1.34 g of DHA per day, for six weeks, to patients with triglyceride
6 levels between 133 mg/dL and 354 mg/dL. Leigh-Firbank does not evaluate the effect of either
7 EPA or DHA alone because it did not disclose the administration of EPA or DHA alone. A
8 person of ordinary skill would similarly understand that Leigh-Firbank does not offer any
9 disclosure regarding the effect of EPA and DHA separately or gain any understanding of the
10 separate impact of DHA or EPA on any lipid parameter. Mori 2006 (also cited by defendants)
11 acknowledges that EPA- and DHA-enriched oils, which are contaminated with other saturated
12 and polyunsaturated fatty acids, are not suitable for evaluating the independent effects of EPA
13 and DHA.⁵⁴³⁶ A person of ordinary skill would understand that studies directed to EPA and
14 DHA-enriched oils are not indicative or predictive of the impact of the EPA or DHA alone on
15 lipid parameters. Defendants’ own prior art refutes the validity of the results disclosed by Leigh-
16 Firbank, because purified EPA and DHA were not administered separately.

17 Leigh-Firbank is a poor quality study. Leigh-Firbank makes conclusion on independent
18 effects of EPA and DHA individually, even though it administered a combination of EPA and
19 DHA, not EPA alone and DHA alone. The error in this approach is evident from the conclusions
20 of Leigh-Firbank itself. For example, Leigh-Firbank concludes that changes in platelet
21 phospholipid EPA were *independently* associated with the decrease in fasting TGs,⁵⁴³⁷ and DHA

23 ⁵⁴³⁶ Mori 2006 at 96.

24 ⁵⁴³⁷ Leigh-Firbank at 440.

1 is *not* associated with decreases in fasting TGs. This is incorrect and inconsistent with the state
2 of the art and numerous publications cited by Defendants.⁵⁴³⁸ It is widely accepted that DHA
3 also has a hypotriglyceridemic effect.

4 Mori 2000 compared the administration of 4g daily of EPA, DHA, or olive oil to patients
5 with borderline-high TG levels for 6 weeks. Although Mori 2000 discloses an increase in LDL-
6 C for patients administered DHA, it also teaches that DHA is preferable to EPA—thus teaching
7 away from the claimed invention. “A reference may be said to teach away when a person of
8 ordinary skill, upon [examining] the reference, would be discouraged from following the path set
9 out in the reference, or would be led in a direction divergent from the path that was taken by the
10 applicant.”⁵⁴³⁹ Although teaching away is fact-dependent, “in general, a reference will teach
11 away if it suggests that the line of development flowing from the reference’s disclosures is
12 unlikely to be productive of the result sought by the applicant.”⁵⁴⁴⁰

13 Mori 2000 concludes that the changes effected by DHA supplementation “may represent
14 a more favorable lipid profile than after EPA supplementation.”⁵⁴⁴¹ For example, it states that
15 “DHA, but not EPA, improved serum lipid status, in particular a small increase in HDL
16 cholesterol and a significant increase in the HDL₂-cholesterol subfraction, without adverse
17 effects on fasting glucose concentrations.”⁵⁴⁴² Mori 2000 also states that “[d]espite an increase
18 in LDL cholesterol after DHA supplementation, LDL particle size increased—a finding that may

19 ⁵⁴³⁸ See, e.g. Grimsgaard at 654.

20 ⁵⁴³⁹ *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994).

21 ⁵⁴⁴⁰ *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994); see also *Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354
22 (Fed. Cir. 2012) (quoting *Gurley*); *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1552 (Fed. Cir. 1983)
23 (“[P]roceed[ing] contrary to the accepted wisdom of the prior art ... is strong evidence of nonobviousness.”).

24 ⁵⁴⁴¹ Mori 2000 at 1092.

⁵⁴⁴² Mori 2000 at 1088.

1 be favorable.”⁵⁴⁴³ Therefore, based on the “favorable lipid profile” of DHA over EPA in Mori
2 2000, a person of ordinary skill would *not* have been motivated to use EPA to treat patients, the
3 exact opposite of what Defendants argue in their contentions. Therefore, the art taught away
4 from using purified EPA. At a minimum, the teachings of Mori 2000 provide reasons for
5 favoring or selecting DHA over EPA and highlight Defendants’ hindsight-driven focus on EPA,
6 despite disclosed advantages of DHA. A person of ordinary skill would take into consideration
7 the entire disclosure, including lipid effects other than LDL-C. Engaging in hindsight bias,
8 Defendants ignore, without explanation, the other effects of DHA that a person of ordinary skill
9 would consider. Defendants fail to identify any other basis upon which a person of ordinary skill
10 would have sought to combine Mori 2000 with the Lovaza PDR.

11 Therefore, Leigh-Firbank and Mori 2000 fail to substantiate Defendants’ assertion that it
12 was known that DHA alone was responsible for the increase in LDL-C levels. Further,
13 Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or
14 has little effect on LDL-C levels.⁵⁴⁴⁴ Defendants identify no other basis upon which a person of
15 ordinary skill would have sought to combine the Lovaza PDR with Katayama, Matsuzawa,
16 Leigh-Firbank and/or Mori 2000.

17 (ii) The ‘698 Patent is not Obvious Over the
18 Omacor PDR/Lovaza PDR, in Combination
19 with Katayama and/or Matsuzawa, and/or
20 Takaku, Further in View of Nozaki and/or
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22 _____
23 ⁵⁴⁴³ Mori 2000 at 1092.

24 ⁵⁴⁴⁴ See e.g., Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

With respect to the '698 patent, Defendants present a combination of nine references:

“the Omacor PDR/Lovaza PDR, in combination with the known clinical benefits of administering pure EPA as evidenced by Katayama, Matsuzawa, and/or Takaku, further in view of Nozaki and/or Hayashi, and further in view of Grimsgaard, Mori 2000 and/or Maki.”⁵⁴⁴⁵

Defendants also present charts purporting to assert that an additional 58 references may be combined in order to render the Claims obvious. Not only do Defendants ignore the improbability that a person of ordinary skill would combine 58 separate references, they additionally do not identify any motivation for combining these references. Although Defendants need not point to an explicit statement in the prior art motivating the combination of these references, any assertion of an “apparent reason” to combine must find a basis in the factual record.⁵⁴⁴⁶ Defendants’ unsupported cobbling of selective disclosures represents hindsight reconstruction.⁵⁴⁴⁷ Defendants’ contentions are no more than an assertion that certain

⁵⁴⁴⁵ Defendants’ Joint Invalidity Contentions at 705.

⁵⁴⁴⁶ See, e.g., *In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp. 2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie* obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

⁵⁴⁴⁷ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under KSR, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention”).

1 claim elements were known in the prior art. Throughout their contentions, Defendants’
2 selectively cite to data points in a reference without considering other disclosures or even the
3 reference as a whole. Each reference, however, must be evaluated for all that it teaches.⁵⁴⁴⁸
4 Accordingly, Defendants fail to meet their burden to establish *prima facie* obviousness.

5 The Omacor PDR and Lovaza PDR fail to disclose or even suggest the claimed method
6 of reducing triglycerides in a subject with the claimed pharmaceutical composition with the
7 recited fatty acid compositions or administration period. The Omacor PDR and Lovaza PDR
8 further do not disclose a method to effect the claimed TG reduction without substantially
9 increasing LDL-C. Indeed, the Omacor PDR and Lovaza PDR disclose the opposite: EPA/DHA
10 causes a significant increase in LDL-C levels in a very high TG patient population, for whom the
11 product (Lovaza/Omacor) is indicated. At most, the Omacor PDR and Lovaza PDR disclose
12 administration of a prescription fish oil, a combination of approximately 465 mg EPA and 375
13 mg DHA, as an adjunct to diet to reduce TG levels in adult patients with very-high (at least 500
14 mg/dL) TG levels. The proposed combinations do not render the independent claims of the ’698
15 patent obvious and Defendants’ burden to prove otherwise is especially difficult because the
16 PTO considered Matsuzawa, Katayama, and Mori 2000, Grimsgaard, Maki, and Lovaza (both
17 generally and the Lovaza package insert specifically) during prosecution.⁵⁴⁴⁹

18 The analysis of the independent claims of the ’698 patent is incorporated into all asserted
19 claims that depend from those Claims.

20 (a) A Person of Ordinary Skill Would
21 Not Have Been Motivated to

22 ⁵⁴⁴⁸ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

23 ⁵⁴⁴⁹ *See, e.g., Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012)(taking into account that “the
24 examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention.
Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear
and convincing standard came into play”).

3 For an invention to be obvious, there must have been an “apparent reason” to make it.
4 The subject matter of the ‘698 patent claims would not have been obvious in light of these
5 references because a person of ordinary skill would not have been motivated to purify EPA or
6 been able to reasonably expect that the claimed pharmaceutical composition would reduce TG
7 levels without an increase in LDL-C levels.

8 (i) Grimsgaard, Katayama,
9 Matsuzawa and/or Takaku
10 Do Not Disclose Purported
Known Clinical Benefits of
Administering Pure EPA

11 Defendants rely on Grimsgaard, Katayama, Matsuzawa and/or Takaku to demonstrate the
12 “known clinical benefits of administering pure EPA - lowering triglycerides without raising
13 LDL-C.” As discussed in Section V.L.3.c.1.a.i.a.i, incorporated herein by reference, Katayama
14 and Matsuzawa merely confirm the safety of long term treatment of Epadel and its ability to
15 lower both serum total cholesterol and triglyceride levels. They do not discuss any purported
16 “benefits” observed related to LDL-C. Katayama and Matsuzawa do not disclose or suggest that
17 the LDL-C results obtained were a clinical benefit.

18 Defendants also rely on Grimsgaard to support their assertion that “administration of
19 purified EPA-E reduced TG levels while minimally impacting the LDL-C levels.”⁵⁴⁵⁰ However,
20 the results of Grimsgaard demonstrate that both EPA and DHA had no measureable impact on
21 LDL-C levels, and in fact were indistinguishable from the control (placebo) group.

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23 _____
⁵⁴⁵⁰ Defendants’ Joint Invalidity Contentions at 708.

1 Grimsgaard examined the effect of 3.8g/day of EPA versus 3.6g/day of DHA
2 administered to people with normal triglyceride levels for 7 weeks.⁵⁴⁵¹ The results from the
3 Grimsgaard study show that both DHA and EPA reduce triglycerides. The authors state that the
4 net decrease in triglycerides was consistently greater for DHA. Grimsgaard also concludes that
5 DHA may be responsible for the beneficial increase in HDL-C observed with some n-3 fatty acid
6 supplements, which is consistent with previous studies which “suggested that serum HDL-C is
7 better maintained with oil rich in DHA than oil rich in EPA.”⁵⁴⁵² Although Grimsgaard states
8 that EPA may produce a small decrease in serum total cholesterol, it does not specifically
9 comment on EPA’s effect on LDL-C.

10 Defendants completely misconstrue the results of Grimsgaard. Defendants attempt to
11 characterize a non-significant increase in LDL-C by DHA and a non-significant decrease in
12 LDL-C by EPA, as confirmation “that administration of purified DHA results in increased LDL-
13 C levels while administration of purified EPA resulted in a decrease in LDL-C levels.”⁵⁴⁵³ The
14 results of Grimsgaard, reproduced below, show that EPA and DHA’s impact on LDL-C were the
15 same as placebo (corn oil); that is, there was no difference between EPA, DHA, or placebo’s
16 effect on LDL-C levels. Further, although administration of EPA reduced Apo-B compared to
17 baseline, it was not a statistically significant effect when compared to placebo. Grimsgaard’s
18 disclosure highlights the importance of a placebo-controlled study and why results compared
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22 ⁵⁴⁵¹ Defendants state in their Joint Invalidation Contentions at 211 that Grimsgaard was conducted in patients with TG
23 levels in the borderline-high/high ranges. This is incorrect; Grimsgaard was conducted in patients with normal TG
24 levels. (See Grimsgaard at Abstract (describing participants as “healthy”) and Table 4).

⁵⁴⁵² Grimsgaard at 654.

⁵⁴⁵³ Defendants’ Joint Invalidation Contentions at 708 n.133.

only to baseline may be misleading. This type of exaggeration and misinterpretation of the results published in the prior art is seen throughout the Defendants' Joint Invalidity Contentions.

TABLE 4
Serum lipids and apolipoproteins at baseline and change after 7 wk of supplementation with docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), or corn oil

	DHA (n = 72)		EPA (n = 75)		Corn oil (n = 77)		F test: P ¹	Contrasts between groups: P		
	Baseline	Change	Baseline	Change	Baseline	Change		DHA vs EPA	DHA vs corn oil	EPA vs corn oil
Triacylglycerols (mmol/L)	1.24 ± 0.58 ²	-0.22 ± 0.31 ²	1.23 ± 0.57	-0.15 ± 0.40 ⁴	1.22 ± 0.55	0.11 ± 0.34 ⁴	0.0001	0.14	0.0001	0.0001
Total cholesterol (mmol/L)	6.00 ± 0.95	0.03 ± 0.49	5.98 ± 0.94	-0.15 ± 0.55 ⁵	6.02 ± 1.08	0.10 ± 0.55	0.01	0.04	0.4	0.004
LDL cholesterol (mmol/L)	4.06 ± 0.86	0.07 ± 0.46	4.06 ± 0.83	-0.08 ± 0.48	4.04 ± 0.98	0.06 ± 0.48	0.10	—	—	—
HDL cholesterol (mmol/L)	1.36 ± 0.30	0.06 ± 0.13 ³	1.33 ± 0.31	0.01 ± 0.12	1.41 ± 0.28	-0.01 ± 0.11	0.001	0.009	0.0005	0.4
Apolipoprotein A-I (g/L)	1.38 ± 0.21	0.02 ± 0.13	1.38 ± 0.20	-0.04 ± 0.10 ³	1.46 ± 0.23	0.00 ± 0.12	0.003	0.0008	0.3	0.02
Apolipoprotein B (g/L)	1.00 ± 0.21	-0.01 ± 0.11	1.01 ± 0.23	-0.03 ± 0.11 ³	1.02 ± 0.28	0.02 ± 0.11	0.05	—	—	—
HDL:apolipoprotein A-I	0.97 ± 0.14	0.04 ± 0.07 ³	0.96 ± 0.13	0.04 ± 0.08 ³	0.97 ± 0.12	-0.01 ± 0.06	0.0001	0.8	0.0003	0.0001
Total:HDL cholesterol	4.62 ± 1.19	-0.19 ± 0.52 ⁴	4.70 ± 1.24	-0.13 ± 0.47 ⁵	4.43 ± 1.19	0.11 ± 0.62	0.002	0.4	0.0006	0.007

¹ ANOVA for between-group comparisons of change.

² $\bar{x} \pm$ SD.

³⁻⁵ One-sample t test of difference between baseline and 7 wk: ³ P < 0.001, ⁴ P < 0.01, ⁵ P < 0.05.

Grimsgaard concludes that both DHA and EPA lower TG levels but have “differential effects on lipoprotein and fatty acid metabolism.”⁵⁴⁵⁴ However, Grimsgaard does not conclude that DHA and EPA have differential effects on LDL-C because Table 4 clearly demonstrates that neither DHA nor EPA had a measurable impact on LDL-C. Table 4 demonstrates that EPA and DHA had the same effect on LDL-C. In fact, one of ordinary skill in the art, when reading Grimsgaard, may have been motivated to use purified DHA instead of EPA for the treatment of patients with very-high triglycerides, because net decrease in triglycerides was consistently greater for DHA and DHA caused a statistically significant increase in HDL-C when compared to placebo. Grimsgaard states that “DHA may be responsible for the increase in HDL cholesterol observed with some n-3 fatty acid supplements.”⁵⁴⁵⁵ Grimsgaard makes no such statement regarding LDL-C.

Defendants cherry-pick results, regardless of whether the effect is found to be statistically significant compared to placebo, in an attempt to force the studies to support their argument that

⁵⁴⁵⁴ Grimsgaard at 657.

⁵⁴⁵⁵ Grimsgaard at 654.

1 it was well known to one of ordinary skill in the art that DHA increases LDL-C while EPA did
2 not. This illustrates the hindsight reasoning driving Defendants’ analysis of the prior art and
3 proposed combinations of prior art. Defendants point to a non-significant increase in DHA and
4 non-significant decrease in EPA in Grimsgaard as confirmation “that administration of purified
5 DHA results in increased LDL-C levels while administration of purified EPA resulted in a
6 decrease in LDL-C levels.” The results from Grimsgaard clearly show that EPA and DHA did
7 not have statistically significantly effects on LDL-C compared to placebo.⁵⁴⁵⁶ A person of
8 ordinary skill would not draw conclusions regarding differences between EPA and DHA based
9 on statistically insignificant results.

10 Defendants also rely on Takaku to support their assertion that “clinical benefits of
11 administering purified EPA—lowering triglycerides without raising LDL-C” was known in the
12 art.⁵⁴⁵⁷ Similar to Katayama and Matsuzawa, Takaku was conducted to test the efficacy and
13 safety of Epadel (of undisclosed purity)⁵⁴⁵⁸ based on long-term administration.⁵⁴⁵⁹

14 A person of ordinary skill would not have concluded based on Takaku that EPA lowers
15 triglycerides without raising LDL-C, because of its unreliable study method. Takaku candidly
16 acknowledges that “only a few subjects were examined” and cautions against drawing a
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18 ⁵⁴⁵⁶In Mori 2000, EPA resulted in a non-significant 0.18 mmol/L increase in LDL-C, while DHA caused a
19 statistically significant 0.37 mmol/L increase in LDL-C compared to placebo. Applying the same logic used to
20 interpret Grimsgaard, that non-significant effects are nonetheless confirmation of an effect, Defendants should have
21 argued that Mori 2000 was confirmation that both EPA and DHA increases LDL-C. However, they do not make
22 such arguments for the obvious reason that it does not support their argument that EPA was known to have little or
23 no impact on LDL-C levels.

21 ⁵⁴⁵⁷ Defendants’ Joint Invalidation Contentions at 705.

22 ⁵⁴⁵⁸ It is possible that the version of Epadel used in the Katayama study fails to meet the purity limitation required by
23 the claims. See Nishikawa (91% E-EPA preparation), Ando at 2177 (Epadel with purity greater than 91%),
24 Nakamura at 23 (Epadel with purity > 90%).

⁵⁴⁵⁹ Takaku at ICOSAPENT_DFNDT00006834.

1 conclusion “only from the results of the present study.”⁵⁴⁶⁰ Because the study did not include
2 any placebo control, a person of ordinary skill in the art would understand these reports do not
3 provide the ability to conclude that the observed lipid effects would have occurred independent
4 of the drug that is administered. In addition, the study was conducted exclusively in Japanese
5 patients, and a person of ordinary skill would not have expected the results to be applicable to the
6 general population.⁵⁴⁶¹

7 The mean baseline triglyceride level of the patients in Takaku was 245 mg/dL, and a
8 person of ordinary skill would not have expected the results to be applicable to patients with
9 triglycerides above 500 mg/dL. Takaku also excluded 6 subjects from the LDL-C study because
10 measurement was not feasible due to “insufficient sample.”⁵⁴⁶² It is possible that patients with
11 triglycerides above 500 mg/dL were among those excluded because of the challenges involved in
12 calculating LDL-C levels when triglyceride level is above 400 mg/dL.⁵⁴⁶³ Moreover, the study
13 does not provide different LDL-C graphs based on the baseline triglyceride levels.⁵⁴⁶⁴ Therefore,
14 it is impossible to determine whether the patients with triglycerides above 500 mg/dL had
15 increased or decreased LDL-C after taking MND-21. In addition, the graph of the rate of LDL-C
16 change in patients with normal baseline LDL-C shows that the LDL-C change was volatile
17 throughout the study period, decreasing slightly at times but increasing by more than 8% at other
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⁵⁴⁶⁰ Takaku at ICOSAPENT_DFNDT00006897.

21 ⁵⁴⁶¹ Yokoyama 2007 at 1097 (“[b]ecause our population was exclusively Japanese, we cannot generalise our results
to other populations.”)

22 ⁵⁴⁶² Takaku at ICOSAPENT_DFNDT00006884.

23 ⁵⁴⁶³ See Matsuzawa at ICOSPENT_DFNDTS00006450.

24 ⁵⁴⁶⁴ Takaku at Fig. 13, ICOSAPENT_DFNDT00006882.

1 times.⁵⁴⁶⁵ Because of this volatility, a person of ordinary skill would not be able to conclude
2 what effect EPA has on LDL-C. Indeed, Takaku did not conclude that there was no increase in
3 LDL-C, stating only that the fluctuation in LDL-C was not significant.⁵⁴⁶⁶

4 A person of ordinary skill would not have concluded, based on Takaku, that purified EPA
5 had any advantage over fish oil in its effect on LDL-C. Takaku states that a previous study has
6 “confirmed a decrease in serum VLDL-cholesterol and serum LDL-cholesterol through the
7 administration of *fish oil* to hypercholesterolemia patients.”⁵⁴⁶⁷ In contrast, Takaku states merely
8 that the fluctuation in LDL-C was not significant in its study. Therefore, a person of ordinary
9 skill would have concluded based on Takaku that any favorable LDL-C effect seen in the study
10 was attributable to fish oil in general, not EPA specifically.

11 Therefore, Grimsgaard, Katayama, Matsuzawa and/or Takaku fail to substantiate
12 Defendants’ assertion that pure EPA lowers triglycerides without raising LDL-C. Further, other
13 studies cited by Defendants suggest that EPA increases LDL-C.⁵⁴⁶⁸ Defendants identify no other
14 basis upon which a person of ordinary skill would have sought to combine the Omacor
15 PDR/Lovaza PDR with Katayama, Matsuzawa, Takaku, Grimsgaard, Mori 2000 and/or Maki.

16 (ii) Nozaki and/or Hayashi
17 Would Not Have Rendered
18 the Asserted Claims Obvious

18 Defendants contend that the asserted claims of the ’698 patent would have been obvious
19 in view Nozaki and/or Hayashi in combination with other references, but they do not explain
20 why Nozaki and/or Hayashi render the asserted claims obvious or what element of the asserted
21

22 ⁵⁴⁶⁵ Takaku at Fig. 14, ICOSAPENT_DFNDT00006883.

23 ⁵⁴⁶⁶ Takaku at ICOSAPENT_DFNDT00006897.

24 ⁵⁴⁶⁷ Takaku at ICOSAPENT_DFNDT00006897.

⁵⁴⁶⁸ See, e.g., Rambjor.

1 claims is found in Nozaki or Hayashi. Nozaki and Hayashi do not disclose or suggest a
2 reduction in triglycerides without increasing LDL-C when purified EPA is administered to the
3 very high TG patient population.

4 Nozaki administered 2.7 g/day of 90% EPA (DHA < 1%) to 14 primary
5 hypercholesterolemia subjects. A person of ordinary skill would not have found the results of
6 Nozaki reliable. Nozaki was not placebo-controlled, nor did the study compare lipid effect of
7 EPA to that of DHA. The average baseline TG level was only 165 mg/dL, while the baseline
8 LDL-C level was 185 mg/dL, which is unusually high for this TG patient population. A person
9 of skill in the art would not look to a study consisting of patients with baseline TG levels of 165
10 mg/dL in order to understand the impact of EPA therapy on the very high TG patient population.
11 Further, a person of ordinary skill would understand that the baseline LDL-C level in this small
12 patient population were abnormally high and would not have relied upon these results. Further,
13 the person of skill in the art would not have looked to this patient population to predict the Apo-
14 B or LDL-C effect of EPA therapy on very high TG patients. Nozaki acknowledges that as of
15 1991, “[t]here is still controversy concerning the effects of fish oil” on LDL and HDL cholesterol
16 levels.⁵⁴⁶⁹ Nozaki does not provide a motivation or reasonable expectation of success for
17 administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA and
18 substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL, to
19 effect a reduction in triglycerides without increasing LDL-C when purified EPA is administered
20 to the very high TG patient population.

21 In Hayashi, 1.8 g/day of EPA was administered to 28 patients for 8 weeks. The purity of
22 the EPA and the DHA content in the composition that was administered is unknown. A person
23

24 ⁵⁴⁶⁹ Nozaki at 256.

1 of ordinary skill would not have found the results of Hayashi reliable. The study involved 28
2 patients and it was conducted for only 8 weeks. Hayashi shows that changes in Apo-B and LDL-
3 C were not statistically significant.⁵⁴⁷⁰ Further, the person of skill in the art would not have
4 looked to this patient population to predict the Apo-B or LDL-C effect of EPA therapy on very
5 high TG patients. Hayashi does not provide a motivation or reasonable expectation of success
6 for administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA
7 and substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL,
8 to effect a reduction in triglycerides without increasing LDL-C when purified EPA is
9 administered to the very high TG patient population.

10 Further, Hayashi was a small study conducted in only Japanese patients and was not
11 placebo controlled. This study would not have been extrapolated to Western populations
12 because the Japanese diet contains much more fish and has a number of other different attributes.
13 The Japanese consume a higher amount of EPA and DHA in their diets than Western
14 populations. In fact, Defendants' own reference states that the results from studies where the
15 patient population is exclusively Japanese cannot be generalized to other populations.⁵⁴⁷¹ The
16 Japanese diet comprises between 8 and 15 times more EPA and DHA than typical the typical
17 Western diet. The Western diet typically consists of higher amounts of polyunsaturated omega-6
18 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand that
19 the Japanese respond differently to lipid lowering agents than Westerners.

20 Further, Defendants have failed to offer a purported combination of references as part of
21 their obviousness contentions that include Nozaki and Hayashi. Similarly, they fail to offer any

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23 ⁵⁴⁷⁰ Hayashi at 26, Table I.

24 ⁵⁴⁷¹ Yokoyama 2007 at 1097 (“Because our population was exclusively Japanese, we cannot generalise our results to other populations.”).

1 motivation to combine Nozaki and Hayashi with the other references of their purported
2 obviousness combinations. Therefore, Defendants should be precluded from relying on these
3 references.

4 (iii) Grimsgaard, Mori 2000
5 and/or Maki Do Not Disclose
6 Purported Knowledge that
7 DHA was Responsible for the
8 Increase in LDL-C

9 Defendants assert, incorrectly, that “it was known in the art as of February 2009 that
10 administration of DHA (alone or in a mixture) resulted in the negative effect of increasing LDL-
11 C levels.”⁵⁴⁷² Defendants’ caveat of DHA being “alone or in a mixture” is telling that it was *not*
12 known that DHA alone resulted in an increase in LDL-C levels. Further, the prior art Defendants
13 rely on to support this statement does not categorize the increase in LDL-C as a “negative effect”
14 in light of the overall impact of the disclosed composition on all lipid parameters. Further, the
15 patients in Grimsgaard, Mori 2000 and Maki had normal to borderline-high baseline TG levels.
16 As discussed above in Section III, a person of ordinary skill would not expect the same LDL-C
17 effect in patients with lower baseline TG levels—the subjects of Grimsgaard, Mori 2000 and/or
18 Maki—as in very-high TG patients because patients with higher TG levels had different lipid
19 responses compared to patients with lower TG levels. Patients with very-high TG levels were
20 considered fundamentally different from patients with borderline-high or high triglycerides from
21 a lipid chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint. A person of
22 ordinary skill in the art would have expected that fish oils (and other TG lowering agents) would

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⁵⁴⁷² Defendants’ Joint Invalidity Contentions at 708.

1 not increase LDL-C substantially in patients with normal to borderline high TG levels, but would
2 substantially increase LDL-C in patients with very high TG levels.

3 Defendants rely on Grimsgaard, Mori 2000 and/or Maki to demonstrate that it was known
4 that “DHA was responsible for the increase in LDL-C levels.”⁵⁴⁷³ The discussion related to
5 Grimsgaard in Section V.L.3.c.1.a.ii.a.i and Mori 2000 in Section V.L.3.c.1.a.i.a.iii is
6 incorporated herein by reference.

7 Defendants argue that Maki discloses the administration of purified DHA resulted in the
8 desired reduction of TGs, but also significantly increased LDL-C levels.⁵⁴⁷⁴ Maki was designed
9 to assess the impact of 1.52g/day DHA supplements on the serum lipid profile of patients with
10 below-average levels of HDL-C levels.⁵⁴⁷⁵ The DHA supplemented group was administered
11 capsules containing 1.52 g/day DHA **and** 0.84 g/day palmitic acid, in addition to other saturated,
12 monounsaturated and polyunsaturated fatty acids.⁵⁴⁷⁶ Therefore, Maki demonstrated that when
13 1.52 g/day DHA **and** 0.84 g/day palmitic acid is administered to patients with below-average
14 levels of HDL-C levels and borderline-high TG levels, a significant increase in LDL-C is
15 observed.⁵⁴⁷⁷ However, one cannot attribute the rise in LDL-C solely to DHA, because the
16 authors admit that “changes in fatty acid intake other than DHA, particularly palmitate, may have
17 also contributed to the elevation in LDL cholesterol.”⁵⁴⁷⁸ Further, Maki admits that the
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⁵⁴⁷³ Defendants’ Joint Invalidity Contentions at 706.

20 ⁵⁴⁷⁴ Defendants’ Joint Invalidity Contentions at 708.

21 ⁵⁴⁷⁵ Maki at 190.

22 ⁵⁴⁷⁶ Maki at 191.

23 ⁵⁴⁷⁷ Maki at 195.

24 ⁵⁴⁷⁸ Maki at 197; Yu et al., *Plasma Cholesterol-Predictive Equations Demonstrate that Stearic Acid is Neutral and Monounsaturated Fatty Acids are Hypocholesterlemic*, 61 AM J CLIN NUTR 1129, 1136 (1995).

1 “mechanism(s) responsible for the changes in the lipid profile associated with DHA
2 supplementation are not fully understood.”⁵⁴⁷⁹ Therefore, the results of Maki are inconclusive as
3 to DHA’s effect alone on LDL-C levels.

4 Defendants mischaracterize the rise in LDL-C associated with the administration of
5 omega-3 fatty acids as being a “negative effect” because they incorrectly focus on only the LDL-
6 C effect and fail to look at the lipid effects as a whole. In fact, Maki does not find the increase in
7 LDL-C to be troublesome; Maki states that “the lack of increase in the total/HDL cholesterol
8 ratio, the decline in the triglyceride/HDL cholesterol ratio and the reduction in the proportion of
9 cholesterol carried by small, dense LDL particles render the changes in LDL cholesterol level
10 less worrisome.”⁵⁴⁸⁰ Therefore, when one of ordinary skill in the art reviewed all the lipid effects
11 of the DHA-rich algal triglycerides, they would have understood that the increase in LDL-C was
12 “less worrisome” because of the “potentially favorable effects on triglycerides, the
13 triglyceride/HDL cholesterol ratio and the fraction of LDL cholesterol carried by small, dense
14 particles.”⁵⁴⁸¹

15 Therefore, Grimsgaard, Mori 2000 and/or Maki fail to substantiate Defendants’ assertion
16 that it was known that DHA was responsible for the increase in LDL-C levels. Further,
17 Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or
18 has little effect on LDL-C levels.⁵⁴⁸² Defendants identify no other basis upon which a person of
19 ordinary skill would have sought to combine the Omacor PDR/Lovaza PDR with Katayama,
20 Matsuzawa, Takaku, Grimsgaard, Mori 2000 and/or Maki.

21 _____
22 ⁵⁴⁷⁹ Maki at 197.

23 ⁵⁴⁸⁰ Maki at 197.

24 ⁵⁴⁸¹ Maki at 197.

⁵⁴⁸² See e.g., Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

1 (iii) The '698 Patent is not Obvious Over the
2 Omacor PDR/Lovaza PDR, in Combination
3 with Katayama in View of Satoh and/or in
4 View of Satoh or Shinozaki in Further View
5 of Contacos

6 With respect to the '698 patent, Defendants present a combination of five references: "the
7 Omacor PDR/Lovaza PDR, in combination with the known clinical benefits of administering
8 pure EPA as evidenced by Katayama in view of Satoh and/or in view of Satoh or Shinozaki in
9 further view of Contacos."⁵⁴⁸³ Defendants also present charts purporting to assert that an
10 additional 60 references may be combined in order to render the Claims obvious. Not only do
11 Defendants ignore the improbability that a person of ordinary skill would combine 60 separate
12 references, they additionally do not suggest any identify for combining these references.
13 Although Defendants need not point to an explicit statement in the prior art motivating the
14 combination of these references, any assertion of an "apparent reason" to combine must find a
15 basis in the factual record.⁵⁴⁸⁴ Defendants' unsupported cobbling of selective disclosures
16 represents hindsight reconstruction.⁵⁴⁸⁵ Defendants' contentions are no more than an assertion

17 ⁵⁴⁸³ Defendants' Joint Invalidity Contentions at 706.

18 ⁵⁴⁸⁴ See, e.g., *In re Vaidyanathan*, 381 F. App'x 985, 993-94 (Fed. Cir. 2010) ("[W]hile KSR relaxed some of the
19 formalism of earlier decisions requiring a 'teaching, suggestion, or motivation' to combine prior art references, it did
20 not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply
21 the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight."); *Daiichi
22 Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point "must
23 avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to
24 select and then modify a lead compound to arrive at the claimed invention." This turns on the known "properties and
elements of the prior art compounds.") (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp.
2d 479, 492-93 (D. Del. 2006) (rejecting defendants' contention that claims to (+)-citalopram were "*prima facie*
obvious in light of . . . claims [to] racemic citalopram" despite its use to "treat the same condition," and concluding
that defendants "have not demonstrated by clear and convincing evidence that one skilled in the art would have been
motivated to resolve citalopram in June 1988."), *aff'd*, 501 F.3d 1263 (Fed. Cir. 2007).

⁵⁴⁸⁵ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under
KSR, "[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention
without any explanation as to how or why the references would be combined to produce the claimed invention").

1 that certain claim elements were known in the prior art. Throughout their contentions,
2 Defendants’ selectively cite to data points in a reference without considering other disclosures or
3 even the reference as a whole. Each reference, however, must be evaluated for all that it
4 teaches.⁵⁴⁸⁶ Accordingly, Defendants fail to meet their burden to establish *prima facie*
5 obviousness.

6 The Lovaza PDR fails to disclose or even suggest the claimed method of reducing
7 triglycerides in a subject with the claimed pharmaceutical composition with the specified fatty
8 acid compositions or administration period. The Lovaza PDR further does not disclose a method
9 to effect the specified TG reduction without substantially increasing LDL-C. Indeed, the Lovaza
10 PDR discloses the exact opposite, that the EPA/DHA composition contained within the reference
11 would cause a significant increase in LDL-C levels in the very high TG patient population, for
12 whom the product is indicated. At most, the Lovaza PDR discloses administration of a
13 prescription fish oil, a combination of approximately 465 mg EPA and 375 mg DHA, as an
14 adjunct to diet to reduce TG levels in adult patients with very-high (at least 500 mg/dL) TG
15 levels.

16 Defendants formulate an obviousness argument that relies on Contacos.⁵⁴⁸⁷ However,
17 Defendants fail to provide any factual or legal basis as to why Contacos discloses a claim
18 element or an “apparent reason” or motivation to combine the elements in the manner
19 claimed,⁵⁴⁸⁸.

21 ⁵⁴⁸⁶ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

22 ⁵⁴⁸⁷ *Id.*

23 ⁵⁴⁸⁸ *KSR*, 550 U.S. at 417–19; *TriMed, Inc. v. Stryker Corp.*, 608 F.3d 1333, 1341 (Fed. Cir. 2010). Hindsight may
24 not be employed to identify relevant prior art and relevant teachings therein: *Heidelberger Druckmaschinen AG v. Hantscho Comm. Prods., Inc.*, 21 F.3d 1068, 1071–72 (Fed. Cir. 1994); *Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 881 (Fed. Cir. 1998).

1 Contacos disclosed administration of fish oil, pravastatin, and combination of fish oil and
2 pravastatin, but it does not disclose administration of EPA of the recited composition. Therefore,
3 Contacos fails to provide motivation to administer purified EPA to a very high TG patient
4 population. Contacos also fails to provide motivation to administer purified EPA to a very high
5 TG patient population.

6 The proposed combinations do not render the independent claims of the '698 patent
7 obvious and Defendants' burden to prove otherwise is especially difficult because the PTO
8 considered Katayama, Satoh, Shinozaki, Contacos, Geppert, Kelley and Lovaza (both generally
9 and the Lovaza package insert specifically) during prosecution.⁵⁴⁸⁹

10 The analysis of the independent claims of the '698 patent is incorporated into all asserted
11 claims that depend from those Claims.

12 (a) A Person of Ordinary Skill Would
13 Not Have Been Motivated to
14 Replace the Mixed Fish Oil Active
Ingredient in Lovaza with EPA of
the Recited Composition

15 For an invention to be obvious, there must have been an "apparent reason" to make it.
16 The subject matter of the '698 patent claims would not have been obvious in light of these
17 references because a person of ordinary skill would not have been motivated to purify EPA or
18 been able to reasonably expect that the claimed pharmaceutical composition would reduce TG
19 levels without an increase in LDL-C levels.

20 (i) Katayama, Satoh and/or
21 Shinozaki Do Not Disclose
Purported Known Clinical

22 _____
23 ⁵⁴⁸⁹ See, e.g., *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012)(taking into account that "the
24 examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention.
Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear
and convincing standard came into play").

1
2
3 Defendants rely on Katayama, Satoh and/or Shinozaki to demonstrate the “known clinical
4 benefits of administering pure EPA - lowering triglycerides without raising LDL-C.” As
5 discussed in Section V.L.3.c.1.a.i.a.i, incorporated herein by reference, Katayama merely
6 confirms the safety of long term treatment of Epadel and its ability to lower both serum total
7 cholesterol and triglyceride levels. Katayama does not mention LDL-C levels at all, let alone
8 discuss any purported “benefits” observed related to LDL-C. Katayama does not disclose or
9 suggest that the LDL-C results obtained were a clinical benefit, nor would a person of ordinary
10 skill view these references as teaching such a benefit for very-high TG patients.

11 Satoh administered 1.8g/day of >98% EPA to patients in order to measure the effects of
12 EPA on C-reactive protein and examine how alteration of lipoprotein profile by EPA affects
13 systemic inflammation. Satoh reported a statistically significant reduction in LDL-C only when
14 compared to baseline, there was no significant effect when compared to placebo.⁵⁴⁹⁰

15 Defendants’ characterization of Satoh as disclosing the lowering of TG levels without increasing
16 LDL-C to be a “clinical benefit” is incorrect.⁵⁴⁹¹ Satoh does not disclose or suggest that the
17 LDL-C results obtained were a clinical benefit, nor would a person of ordinary skill view these
18 references as teaching such a benefit for very-high TG patients. As discussed above, one of
19 ordinary skill in the art would not expect LDL-C to increase in a patient with TG below 500
20 mg/dL and Satoh provides no evidence to the contrary. A person of ordinary skill in the art,
21 however, would have expected that fish oils (and other TG lowering agents) would substantially

22
23 ⁵⁴⁹⁰ Satoh at 145.

24 ⁵⁴⁹¹ Defendants’ Joint Invalidation Contentions at 705-706.

1 increase LDL-C in patients with very high TG levels. Satoh fails to provide motivation to
2 administer purified EPA to a very high TG patient population.

3 Further, Satoh was a small study conducted in only Japanese patients. This study would
4 not have been extrapolated to Western populations because the Japanese diet contains much
5 more fish and has a number of other different attributes. The Japanese consume a higher amount
6 of EPA and DHA in their diets than Western populations. In fact, Defendants' own reference
7 states that the results from studies where the patient population is exclusively Japanese cannot be
8 generalized to other populations.⁵⁴⁹² The Japanese diet comprises between 8 and 15 times more
9 EPA and DHA than typical the typical Western diet. The Western diet typically consists of
10 higher amounts of polyunsaturated omega-6 fatty acids and saturated fatty acids. Therefore, a
11 person of ordinary skill would understand that the Japanese respond differently to lipid lowering
12 agents than Westerners.

13 Shinozaki studied the long-term effect of EPA on serum levels of Lipoprotein (a) (Lp(a))
14 and lipids such as triglycerides, total cholesterol, and low density lipoprotein particles.
15 Defendants' characterization of Shinozaki as disclosing the lowering of TG levels without
16 increasing LDL-C to be a "clinical benefit" is incorrect.⁵⁴⁹³ Shinozaki says nothing about an
17 LDL-C effect because it measured LDL particle number, not LDL-C. The finding disclosed by
18 Shinozaki was that "long term administration of EPA may lower Lp(a) and serum lipids."⁵⁴⁹⁴ In
19 addition to Shinozaki's lack of disclosure regarding LDL-C, Defendants identify no other basis
20
21

22 ⁵⁴⁹² Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to
other populations.").

23 ⁵⁴⁹³ Defendants' Joint Invalidation Contentions at 705-706.

24 ⁵⁴⁹⁴ Shinozaki at 107-109.

1 upon which a person of ordinary skill would have sought to combine the composition disclosed
2 in Shinozaki.

3 Therefore, Katayama, Satoh and/or Shinozaki fail to substantiate Defendants' assertion
4 that pure EPA lowers triglycerides without raising LDL-C. Further, other studies cited by
5 Defendants suggest that EPA increases LDL-C.⁵⁴⁹⁵ Defendants identify no other basis upon
6 which a person of ordinary skill would have sought to combine the Lovaza PDR with Katayama,
7 Satoh, Shinozaki and/or Contacos.

8 (ii) Geppert and/or Kelley Do
9 Not Disclose Purported
10 Knowledge that DHA was
11 Responsible for the Increase
12 in LDL-C

11 Defendants assert, incorrectly, that “it was known in the art as of February 2009 that
12 administration of DHA (alone or in a mixture) resulted in the negative effect of increasing LDL-
13 C levels.”⁵⁴⁹⁶ Defendants' caveat of DHA being “alone or in a mixture” is telling that it was *not*
14 known that DHA alone resulted in an increase in LDL-C levels. Further, the prior art Defendants
15 rely on to support this statement do not categorize the increase in LDL-C as a “negative effect”
16 in light of the overall impact of the disclosed composition on all lipid parameters. Further, the
17 patients in Geppert and Kelley had normal and borderline-high/high baseline TG levels,
18 respectively. As discussed above in Section III, a person of ordinary skill would not expect the
19 same LDL-C effect in patients with lower baseline TG levels—the subjects of Geppert and/or
20 Kelley—as in very-high TG patients because patients with higher TG levels had different lipid
21 responses compared to patients with lower TG levels. Patients with very-high TG levels were
22

23 ⁵⁴⁹⁵ See, e.g., Rambjor.

24 ⁵⁴⁹⁶ Defendants' Joint Invalidity Contentions at 708.

1 considered fundamentally different from patients with borderline-high or high triglycerides from
2 a lipid chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint. Although a
3 person of ordinary skill in the art would have expected that fish oils (and other TG lowering
4 agents) would not increase LDL-C substantially in patients with normal to borderline high TG
5 levels, a person of ordinary skill in the art would expect a substantial increase in LDL-C in
6 patients with very high TG levels.

7 Defendants rely on Geppert and/or Kelley to demonstrate that it was known that “DHA
8 was responsible for the increase in LDL-C levels.”⁵⁴⁹⁷ Both Geppert and Kelley administer
9 DHA-rich oil that is contaminated with other saturated and polyunsaturated fatty acids.
10 Therefore, a person of ordinary skill would have known it is unsuitable for evaluating the
11 independent effects of DHA because it is not clear how much of the supplement’s effects can be
12 attributed to DHA.⁵⁴⁹⁸ For example, Defendants’ own prior art teaches that changes in fatty acid
13 intake other than DHA, particularly palmitate, may contribute to elevations in LDL-C.⁵⁴⁹⁹

14 In Geppert, 0.94 g/day of DHA derived from microalgae oil was administered to
15 normolipidaemic vegetarians for 8 weeks. A person of ordinary skill would not have been
16 convinced that DHA increases LDL-C based on Geppert. As Geppert acknowledges, prior
17 studies have shown “[i]nconsistent effects of DHA on LDL cholesterol.”⁵⁵⁰⁰ Rather than reading
18 Geppert in isolation, a person of ordinary skill would have read Geppert together with the prior
19 studies cited in Geppert. As such, a person of ordinary skill would have concluded that there
20 was confusion in the art and it was unclear whether DHA increased LDL-C.

21
22 ⁵⁴⁹⁷ Defendants’ Joint Invalidation Contentions at 706.

23 ⁵⁴⁹⁸ See Mori 2006 at 96.

24 ⁵⁴⁹⁹ Maki at 197.

⁵⁵⁰⁰ Geppert at 784.

1 A person of ordinary skill would have expected that Geppert's results would be
2 applicable to other components of fish oil such as EPA. Nothing in Geppert suggests that DHA
3 was the only component of fish oil to increase LDL-C. For example, there is no data comparing
4 DHA to fish oil or EPA. In fact, Geppert discusses DHA and fish oil together when trying
5 explain the mechanism of LDL-C increase.⁵⁵⁰¹ A person of ordinary skill would have not
6 expected that EPA and DHA would have different effects on LDL-C based on Geppert.

7 Defendants contend that Kelley shows that DHA was responsible for the increase in
8 LDL-C.⁵⁵⁰² In Kelley, patients fasting serum TG levels of 150 to 400 mg/dL received 7.5 g/day
9 of DHA oil containing 3 g of DHA for 90 days. Kelley does not show that DHA is responsible
10 for the increase in LDL-C. Kelley suggests that increase in LDL-C is a general phenomenon
11 associated with triglyceride-lowering drugs, stating that a similar increase was induced by fibrate
12 therapy.⁵⁵⁰³ Further, Kelley teaches that the increase in LDL-C is not harmful when viewed in
13 context with the other lipid effects reported in the study. Kelley states that:

14 DHA supplementation may lower the risk of CVD by reducing
15 plasma triacylglycerols; triacylglycerol:HDL; the number of small,
16 dense LDL particles; and mean diameter of VLDL particles. An
17 increase was observed in fasting LDL cholesterol, but it is unlikely
18 this increase is detrimental because no increase was observed in the
19 overall number of LDL particles; actually, there was an 11%
20 reduction that was statistically not significant. The reason LDL
21 cholesterol increased despite no change in LDL particle number was
22 that the LDL particles were made larger and hence more cholesterol
23 rich by DHA treatment.⁵⁵⁰⁴

22 ⁵⁵⁰¹ *Id.*

23 ⁵⁵⁰² Defendants' Joint Invalidity Contentions at 706.

24 ⁵⁵⁰³ Kelley at 329.

⁵⁵⁰⁴ Kelley at 329

1 Kelley specifically teaches that the increase in LDL-C caused by DHA supplementation
2 is unlikely to be “detrimental” because there was not a parallel increase in overall LDL particle
3 number. Kelley’s ultimate conclusion is that “[o]verall, DHA supplementation reduced the
4 concentrations of atherogenic lipids and lipoproteins and increased concentrations of
5 cardioprotective lipoproteins” and that “DHA supplementation may improve cardiovascular
6 health.”⁵⁵⁰⁵ Rather than concluding that DHA was uniquely responsible for a rise in LDL-C
7 levels, a person of ordinary skill would understand Kelley to disclose that DHA had uniquely
8 beneficial cardioprotective effects. Indeed, instead of identifying DHA as composition with
9 negative attributes, a person of ordinary skill would understand that the reference taught towards
10 the use of DHA. In addition, none of the study subjects in Kelley had a TG level above 400
11 mg/dL and, for the reasons previously discussed, a person of ordinary skill would understand the
12 very high TG patient population to be different in terms of their response to lipid therapy,
13 including administration of DHA. A person of ordinary skill in the art would have expected that
14 fish oils (and other TG lowering agents) would not increase LDL-C substantially in patients with
15 normal to borderline high TG levels, but a person of ordinary skill in the art would expect a
16 substantial increase in LDL-C in patients with very high TG levels.

17 Therefore, Geppert and/or Kelley fail to substantiate Defendants’ assertion that it was
18 known that DHA was responsible for the increase in LDL-C levels.

19 Throughout their contentions, Defendants’ selectively cite to data points in a reference
20 without considering other disclosures or even the reference as a whole. Each reference,
21 however, must be evaluated for all that it teaches.⁵⁵⁰⁶ As is the case with Kelley, Defendants use

22 _____
23 ⁵⁵⁰⁵ Kelley at 324, 332.

24 ⁵⁵⁰⁶ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

1 hindsight to characterize a reference based on LDL-C levels alone without considering the other
2 lipid effects studied, considered and reported.⁵⁵⁰⁷ The isolated manner in which Defendants
3 select such data points is not the approach that a person of ordinary skill would have taken at the
4 time of the invention. Defendants' approach represents the use of impermissible hindsight bias.
5 A person of ordinary skill would take into consideration the entire disclosure of a reference,
6 including lipid effects other than LDL-C. In pointing only to LDL-C, Defendants ignore,
7 without explanation, the other effects of DHA that a person of ordinary skill would consider.
8 With respect to Kelley, These effects would teach a person of ordinary skill that DHA has a
9 favorable effect in hypertriglyceridemic patients.

10 Therefore, Geppert and/or Kelley fail to substantiate Defendants' assertion that it was
11 known that DHA was responsible for the increase in LDL-C levels. Further, Defendants ignore,
12 without explanation, other studies that demonstrate that DHA decreases or has little effect on
13 LDL-C levels.⁵⁵⁰⁸ Defendants identify no other basis upon which a person of ordinary skill
14 would have sought to combine the Lovaza PDR with Katayama, Satoh, Shinozaki, Contacos,
15 Geppert and/or Kelley.

16 (iv) A Person of Ordinary Skill Would Not Have
17 Been Motivated to Find an Omega-3 Fatty
18 Acid "therapy that would reduce TG levels
in patients with TG levels ≥ 500 mg/dL"
without negatively impacting LDL-C levels.

19 Plaintiffs agree that although there was a *need* to find a therapy that would reduce TG
20 levels in patients with very-high TG levels, without negatively impacting LDL-C levels, there
21

22 ⁵⁵⁰⁷ Kelley at 324 (providing that the objectives of the study were to determine "the effects of DHA supplementation
23 on the concentrations of apoproteins; large, medium, and small VLDL, LDL, and HDL particles; and the mean
diameters of these particles in fasting and postprandial plasma.").

24 ⁵⁵⁰⁸ See e.g., Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

1 was no motivation to find an *omega-3 fatty acid* therapy, or to modify Lovaza/Omacor, to effect
2 a reduction in TG levels without increasing LDL-C levels for very-high TG patients at the time
3 of the invention. A person of ordinary skill in the art understood that the rise in LDL-C caused
4 by omega-3 fatty acids (or fibrates) and Lovaza/Omacor was a consequence of the TG-lowering
5 mechanism. The therapies that were available at the time of the invention to treat very-high TGs
6 were niacin, fibrates and prescription omega-3 fatty acids (Lovaza/Omacor). However, niacin
7 was associated with a highly undesirable side effects—including “flushing” (or reddening of the
8 face and other areas with a burning sensation) and dyspepsia—that limited their usefulness.⁵⁵⁰⁹
9 Fibrates were effective at reducing TGs, but they also caused an increase in LDL-C levels in
10 patients with very-high TG levels. To combat the rise of LDL-C, doctors often prescribed
11 fibrates in combination with an LDL-C lowering medication such as a statin.⁵⁵¹⁰ However, the
12 risk of rhabdomyolysis increased five-fold if fibrates were administered with a statin.⁵⁵¹¹
13 Therefore, physicians were reluctant to recommend, and patients were hesitant embrace, a
14 combination fibrate/statin course of treatment.⁵⁵¹² Finally, Lovaza/Omacor were also effective at
15 reducing TG levels, but, similar to fibrates, could cause a substantial increase in LDL-C levels
16 for very-high TG patients. However, Lovaza/Omacor could be safely administered with statins
17 in order to mitigate increased LDL-C.

20 ⁵⁵⁰⁹ See *id.* at 991-92; McKenney 2007, at 718; ATP-III at 3315 (noting that patients often could not tolerate higher
21 doses of niacin due to side effects).

22 ⁵⁵¹⁰ Bays May 16, 2011 Decl., ¶ 8; Topol, at 71 (noting that in high TG patients “the addition of a statin to a fibrate
is often required to achieve LDL-C and non-HDL-C goals”);

23 ⁵⁵¹¹ See *Id.*; McKenney 2007, at 719 (“[F]ibrates may cause rhabdomyolysis, especially when combined with
statins.”).

24 ⁵⁵¹² See *Id.*, ¶ 17

1 In any event, a person of ordinary skill in the art would have understood that omega 3-
2 fatty acids, including DHA and EPA, and fibrates cause an increase in LDL-C among very high
3 TG patients, as reflected in the prior art. Accordingly, a person of ordinary skill in the art would
4 not have been motivated to look to omega 3-fatty acids in order to obtain a reduction in TGs
5 without increasing LDL-C in very high TG patients:

	LDL-C Effect	
	Borderline-High or High TG Patients	Very-High TG Patients
Fibrate ⁵⁵¹³	-20%	+45%
Lovaza/Omacor ⁵⁵¹⁴	-6%	+45%

9
10 That Epadel has been approved for decades but not approved for use in the very high TG
11 patient population prior to the invention of the asserted patents is a real-world reflection of the
12 lack of motivation. Research into the pharmaceutical uses of EPA started as early as the 1970s.
13 In 1990, Mochida Pharmaceutical, began to market Epadel, a high purity EPA drug. There have
14 been countless studies conducted which administer Epadel and report the effects observed.
15 Although a few studies administer Epadel to a patient population which included a few patients
16 with TG levels > 500 mg/dL, Defendants fail to identify a single reference directed to the
17 administration of Epadel to patients with very-high TG levels, reflecting the lack of motivation.

18 Defendants offer no “apparent reason” to administer EPA as claimed to patients with
19 fasting baseline TG levels of 500 mg/dl to about 1500 mg/dl. Defendants rely on
20 Lovaza/Omacor as the starting point to “find a therapy that would reduce TG levels in patients

21
22 _____
23 ⁵⁵¹³ Tricor®, Physicians’ Desk Reference 502-505 (62d ed. 2008).

24 ⁵⁵¹⁴ Chan 2002 I at 2381 (Table 3).

1 with TG levels \geq 500 mg/dL” without negatively impacting LDL-C levels.⁵⁵¹⁵ Ironically,
2 Lovaza/Omacor significantly reduces TGs in patients with TG levels of at least 500 mg/dL but
3 significantly increases LDL-C--an effect understood to be a consequence of TG reduction and
4 the increased conversion of VLDL to LDL particles.⁵⁵¹⁶

5 It was well known at the time of the invention that omega-3 fatty acids, including both
6 EPA and DHA, caused significant decrease in the production of VLDL particles and a significant
7 increase in the conversion of VLDL to IDL and LDL, supporting the understanding that omega-3
8 fatty acids worked in part by inhibiting VLDL production and improving the conversion of
9 VLDL particles to LDL.⁵⁵¹⁷ A person of ordinary skill in the art understood that EPA and DHA
10 had the *same* TG-lowering mechanism and did not differentiate between EPA and DHA when
11 discussing the TG-lowering mechanism of omega-3 fatty acids.⁵⁵¹⁸ The discussion related to the
12 TG-lowering mechanism of omega-3 fatty acids is discussed above in Section III and
13 incorporated herein by reference.

14 In fact, it was well understood that the degree of LDL-C elevation observed with
15 prescription omega-3 therapy, such as Lovaza/Omacor, generally related to pretreatment TG
16 levels; that is, prescription omega-3 therapy, such as Lovaza/Omacor, increased LDL-C levels
17
18

19 ⁵⁵¹⁵ Defendants’ Joint Invalidity Contentions at 707.

20 ⁵⁵¹⁶ See Bays 2008 Rx Omega-3 p. 402; McKenny 2007 Role of Prescription Omega-3 at 720 (finding that “[t]hese
21 results illustrate that with prescription omega-3, fewer VLDL particles are secreted into the systemic circulation, and
22 secreted VLDL particles are rapidly converted to LDL particle, thus explaining why LDL levels may increase in
23 patients with very-high triglyceride levels when given prescription omega-3 therapy”); Chan 2003

22 ⁵⁵¹⁷ Chan 202 at 2378-84; see also Westphal at 917 (stating “our data confirm the well-known and pronounced
23 decrease in VLDLs after n-3 fatty acid treatment”)

23 ⁵⁵¹⁸ Bays I, at 398; Harold E. Bays, *Fish Oils in the Treatment of Dyslipidemia and Cardiovascular Disease*, in *The*
24 *Johns Hopkins Textbook of Dyslipidemia* 245, 247 (Peter O. Kwiterovich Jr. ed., 2009 (Bays III))

1 the most in patients with the highest pretreatment TG levels.⁵⁵¹⁹ Therefore, a person of ordinary
2 skill in the art would have viewed increased LDL-C levels caused by Lovaza/Omacor as a direct
3 consequence of lowering triglycerides in patients with TG levels ≥ 500 mg/dL. The rise in LDL-
4 C was often offset by concurrent treatment with statins.⁵⁵²⁰ The safety and efficacy of using
5 prescription omega-3 in combination with a statin has been well-established.⁵⁵²¹

6 Although an increase in LDL-C was generally observed when omega-3 fatty acids were
7 administered to patients with very-high TG levels, the increase in LDL-C was not necessarily a
8 cause for concern because LDL-C is often low in patients with severe hypertriglyceridemia.
9 Therefore, the final LDL-C concentration may still be in the normal range.⁵⁵²² Furthermore, it
10 was understood that the overall lipid effect of Lovaza/Omacor was beneficial.⁵⁵²³

11 In two pivotal studies in very-high TG patients, both of which used prospective,
12 randomized, double-blind, placebo-controlled study designs, Lovaza/Omacor increased HDL
13 levels from baseline 13% (p=0.014) and 5.9% (p=0.057).⁵⁵²⁴ Correspondingly, prescription
14

15 ⁵⁵¹⁹ See Bays 2008 Rx Omega-3 p. 402.

16 ⁵⁵²⁰ See Harris 2008 at 14, McKenney at 722.

17 ⁵⁵²¹ McKenney at 722-23.

18 ⁵⁵²² See Westphal at 918, Harris 1997 at 389.

19 ⁵⁵²³ See Pownall at 295 (stating that “[t]reatment with ω -3 fatty acids appear to change the lipid profile of individuals
20 with elevated TG to one that may be less atherogenic by changing LDL structure; lowering serum [cholesteryl ester
21 transfer activity], serum TG and VLDL-C; and increasing serum HDL-C”); Harris 1997 at 389 (stating that “[t]he
22 increase in LDL, which was substantial on a percentage basis, has been a common finding in past studies in [very-
23 high TG] patients. It may not be as problematic as it appears, however,” and “the use of omega-3 fatty acids for the
24 treatment of severe hypertriglyceridemia may be beneficial not only for the short-term prevention of acute
pancreatitis, but also for the long-term prevention of CHD”); Bays III at 248 (“No clinical trial data exist that this
rise in LDL-C represents harm or potential “toxicity” to patients. In fact, most evidence supports that omega-3 fatty
acids reduce cardiovascular risk as do fibrates. Importantly, clinical trials mostly support that even with increases in
LDL-C, omega-3 fatty acids decrease the total cholesterol (TC) carried by atherogenic lipoproteins, as reflected by
decreased non-HDL-C levels (TC minus HDL-C”).

⁵⁵²⁴ McKenney 2007 at 721 (citing Harris 1997 and Pownall).

1 | omega-3 fatty acids were known to have favorable effects on non-HDL-C levels.⁵⁵²⁵ Therefore,
2 | “[i]n patients with very-high triglyceride levels, prescription omega-3 fatty acids 4 g/day can
3 | substantially reduce triglycerides and VLDL levels and may increase LDL levels, but the net
4 | effect is a reduction in non-HDL levels. Modest increases in HDL level are also common in
5 | patients treated with prescription omega-3 fatty acids.” Prescription omega-3 therapy was also
6 | known to alter lipoprotein particle size and composition in a favorable manner by decreasing the
7 | number of small, dense LDL particles to larger LDL particles.⁵⁵²⁶ Lovaza/Omacor “adversely
8 | raise[d] LDL cholesterol concentration but the increase in LDL cholesterol concentration
9 | reflect[ed] a less atherogenic light LDL subfraction profile that may be favorable.”⁵⁵²⁷
10 | Therefore, one of ordinary skill in the art believed that the use of Lovaza/Omacor, and omega-3
11 | fatty acids generally, “for the treatment of severe hypertriglyceridemia may be beneficial not
12 | only for the short-term prevention of acute pancreatitis, but also for the longer-term prevention
13 | of [coronary heart disease].”⁵⁵²⁸

14 | Therefore, contrary to Defendants’ assertion that “a person of ordinary skill in the art at
15 | the time of the claimed inventions would have been motivated to find a therapy that would
16 | reduce TG levels in patients with TG levels \geq 500 mg/dL” without negatively impacting LDL-C
17 | levels,⁵⁵²⁹ one of ordinary skill in the art at the time of the invention understood that the rise in
18 | LDL-C caused by omega-3 fatty acids was a by-product of reducing TGs in patients with very-
19 | high TG levels. A person of ordinary skill in the art would have expected LDL-C to increase in
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21 | _____
⁵⁵²⁵ McKenney 2007 at 722 (*see* Fig. 1).

22 | ⁵⁵²⁶ McKenney 2007 at 722 (*citing* Calabresi and Stalenhoef).

23 | ⁵⁵²⁷ Stalenhoef at 134.

23 | ⁵⁵²⁸ Harris 1997 at 389.

24 | ⁵⁵²⁹ Defendants’ Joint Invalidity Contentions at 707.

1 very-high TG patients, and in some instances the rise was not concerning because LDL-C is
2 often low in patients with severe hypertriglyceridemia and therefore final concentration would
3 still be in the normal range. When LDL-C levels increased beyond what was recommended by
4 the ATP-III, prescribers often relied on statins to safely and effectively reduce LDL-C levels.
5 Furthermore, it was well known that the overall lipid effect of Lovaza/Omacor was beneficial
6 because non-HDL-C levels often increased. Defendants fail to identify any other basis upon
7 which a person of ordinary skill would have been motivated to find a therapy that would reduce
8 TG levels in patients with very-high TG levels without negatively impacting LDL-C levels.
9 Further, a person of ordinary skill in the art would have understood that EPA therapy would *not*
10 reduce Apo-B⁵⁵³⁰ (which is a reflection of total atherogenic lipoproteins)⁵⁵³¹ in very high TG
11 patients, and accordingly would not have been motivated to administer the claimed EPA
12 composition to the very high TG patient population.

13 Defendants make the conclusory allegation that “routine optimization” by a person of
14 ordinary skill would yield the claimed invention.⁵⁵³² Defendants, however, have offered no
15 explanation to support that allegation and they further fail to establish any of the required criteria
16 of “routine optimization” or the prerequisites to this argument. They also fail to provide any
17 factual detail to support their allegation and they fail to link the allegation to any particular claim
18 or claim element. Defendants mere allegation constitute an improper placeholder to later
19 advance arguments not disclosed in their contentions as required by the Local Rules. In addition,
20 for the reasons discussed herein, a person of ordinary skill would not be motivated to make the

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22 ⁵⁵³⁰ *see* Section V.O.

23 ⁵⁵³¹ *see* Section III.

24 ⁵⁵³² *See, e.g.*, Defendants’ Joint Invalidation Contentions at 703, 716, 731.

1 combinations alleged by Defendants and, for the same reasons, it would not be routine to
2 combine such references. Where, for example, defendants argue that it would be “obvious” to go
3 from the high TG patient population to the very high TG patient population,⁵⁵³³ they provide no
4 basis for that conclusory assertion and are incorrect. As discussed, a person of ordinary skill
5 would have understood these patient populations to be distinct with different impacts of lipid
6 therapy on blood-lipid chemistry for each group. Accordingly, a person of ordinary skill would
7 not have considered the dosage modification suggested by defendants to be routine; Defendants’
8 argument to the contrary represents hindsight bias.

9 In addition, a person of ordinary skill would have no motivation to combine these
10 references because EPA would have been expected to have same result as the mixture of EPA
11 and DHA used in Lovaza/Omacor.

12 (b) Defendants Have Not Shown It Would Have Been
13 Obvious to Administer Purified EPA in the Dosing
14 Regimen Recited in the Claims

14 (i) The ’698 Patent is not Obvious Over WO
15 ’118 or WO ’900, in Combination with the
16 Lovaza PDR, and Further in View of Leigh-
17 Firbank and/or Mori 2000

16 With respect to the ’698 patent, Defendants present a combination of five references:
17 “WO ’118 or WO ’900, in combination with treatment regimen of Lovaza as evidenced by the
18 Lovaza PDR, and further in view of Leigh-Firbank and/or Mori 2000.”⁵⁵³⁴ Defendants also
19 present charts arguing that an additional 61 references may be combined in order to render the
20 Claims obvious. Not only do Defendants ignore the improbability that a person of ordinary skill
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23 ⁵⁵³³Defendants’ Joint Invalidity Contentions at 710 & n.136.

24 ⁵⁵³⁴Defendants’ Joint Invalidity Contentions at 712.

1 would combine 61 separate references, they additionally do not identify any motivation for
2 combining these references.^{5535, 5536} Although Defendants need not point to an explicit statement
3 in the prior art motivating the combination of these references, any assertion of an “apparent
4 reason” to combine must find a basis in the factual record.⁵⁵³⁷ Defendants’ unsupported cobbling
5 of selective disclosures represents hindsight reconstruction.⁵⁵³⁸ Defendants’ contentions are no
6 more than an assertion that certain claim elements were known in the prior art. Throughout their
7 contentions, Defendants’ selectively cite to data points in a reference without considering other
8

9
10 ⁵⁵³⁵ Defendants’ bare assertion that the asserted claims are obvious “in view of one or more of the references cited in
11 V.B.3 and 4, including, the ’954 publication, WO ’900, WO ’118, Ando, Grimsgaard, Hayashi, Katayama,
12 Matsuzawa, Mataka, Mori 2000, Nakamura, Nozaki, Okumura, Park, Saito 1998, Saito 2008 Satoh, Shinozaki,
13 Takaku, Yokoyama 2003, Yokoyama 2007, Calabresi, Chan 2002, Chan 2003, Contacos, Geppert, Kelley, Leigh-
14 Firbank, Maki, Mori 2006, Rambjør, Sanders or Theobald in combination with the knowledge of a person of
15 ordinary skill in the art in light of the dosing regimen employed with Lovaza/Omacor” similarly fails to meet the
16 disclosure requirements of the Nevada Local Patent Rules, and fails to provide any motivation to combine these
17 references. *See* Defendants’ Joint Invalidity Contentions at 711-12.

18 ⁵⁵³⁶ Defendants’ bare assertion that “the motivation or reason to combine or modify prior art to create invalidating
19 combinations under 35 U.S.C. §103 can be found in the references identified above in Section III.C,” and that
20 “[c]ommon sense, design incentives, market forces, and the background knowledge possessed by a person having
21 ordinary skill in the art provide the reasons or rationales for combining the teachings of multiple references or
22 modifying references to render obvious the claimed inventions of the asserted claims,” fails to meet the disclosure
23 requirements of the Nevada Local Patent Rules. *See* Defendants’ Joint Invalidity Contentions at 703-04.

24 ⁵⁵³⁷ *See, e.g., In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the
formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did
not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply
the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi
Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (stating that the assertion of a starting point
“must avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation
to select and then modify a lead compound to arrive at the claimed invention,” which turns on the known “properties
and limitations of the prior art compounds”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F.
Supp. 2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima
facie* obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and
concluding that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art
would have been motivated to resolve citalopram in June 1988”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

⁵⁵³⁸ *See, e.g., Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under
KSR, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention
without any explanation as to how or why the references would be combined to produce the claimed invention”).

1 disclosures or even the reference as a whole. Each reference, however, must be evaluated for all
2 that it teaches.⁵⁵³⁹ Accordingly, Defendants fail to meet their burden to establish *prima facie*
3 obviousness.

4 WO '118 is directed at the composition containing EPA for the purpose of preventing the
5 occurrence of cardiovascular events in multiple risk patients. Further, the invention of WO '118
6 is directed, "in particular, [to] preventing occurrence of cardiovascular events in
7 hypercholesterolemia patients who have been treated with HMG-CoA RI but still suffer from the
8 risk of the cardiovascular events."⁵⁵⁴⁰ Contrary to Defendants' assertion that WO '118 discloses
9 "the administration of 4 g of pure EPA with no DHA,"⁵⁵⁴¹ WO '118 fails to disclose the claimed
10 subject with the specified very high TG levels (500-1500 mg/dL) who does not receive
11 concurrent lipid altering therapy, the claimed pharmaceutical composition with the specified
12 fatty acid compositions or dosage, or the claimed method to effect the specified TG reduction
13 without substantially increasing LDL-C. WO '118 discloses a composition with a wide range of
14 possible EPA content, dosages, and teaches that DHA is a "preferable fatty acid" to include in
15 the disclosed composition.⁵⁵⁴²

16 WO '118 does not disclose administration of highly-purified ethyl-EPA to the target
17 population of the claimed invention. The asserted claims are directed to persons with severe
18 hypertriglyceridemia (i.e. TG level above 500 mg/dL). WO '118 on the other hand only
19 discloses administration of EPA to persons with triglyceride of at least 150 mg/dL.⁵⁵⁴³ WO

20 ⁵⁵³⁹ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

21 ⁵⁵⁴⁰ WO '118 at 9.

22 ⁵⁵⁴¹ Defendants' Joint Invalidation Contentions at 712.

23 ⁵⁵⁴² WO '118 at 22-23.

24 ⁵⁵⁴³ WO '118 at 8.

1 '118's emphasis on reducing cardiovascular events suggests that its disclosure is directed to
2 patients with borderline-high to high TG levels, since the primary goal for patients with very-
3 high TG is to prevent acute pancreatitis by decreasing TG levels.⁵⁵⁴⁴

4 WO '118 also does not distinguish EPA from DHA in its disclosures regarding the
5 effectiveness of the substances for treating hypertriglyceridemia.⁵⁵⁴⁵ WO '118 states that
6 "[a]nother preferable fatty acid . . . is DHA-E," and that "the compositional ratio of EPA-
7 E/DHA-E, content of EPA-E and DHA-E . . . in the total fatty acid, and dosage of (EPA-E +
8 DHA-E) are not particularly limited as long as intended effects of the present invention are
9 attained."⁵⁵⁴⁶ It further states that "the composition is preferably the one having a high purity of
10 EPA-E and DHA-E."⁵⁵⁴⁷ Further, WO '118 does not disclose EPA's effect on LDL-C, VLDL-C,
11 Apo-B, or Lp-PLA2.

12 WO '900 is directed to a process for producing purified EPA from a culture of micro-
13 organisms. WO '900 fails to disclose the claimed subject with the specified very high TG levels
14 (500-1500 mg/dL) who does not receive concurrent lipid altering therapy, the claimed
15 pharmaceutical composition with the specified dosage or administration period, or the claimed
16 method to effect the specified TG reduction without substantially increasing LDL-C. WO '900
17 only discloses the method of producing purified EPA for therapeutic use, it does not teach
18 *administration* of pure EPA. WO '900 has no discussion, for example, regarding claimed patient
19 population or method of treatment.

21 ⁵⁵⁴⁴ See Section III.

22 ⁵⁵⁴⁵ WO '118 at 11, 13, 16-21 ("the composition containing at least EPA-E and/or DHA-E as its effective component").

23 ⁵⁵⁴⁶ WO '118 at 22-23.

24 ⁵⁵⁴⁷ WO '118 at 23.

1 WO '900 does not teach administration of pure EPA to treat hypertriglyceridemia. It lists
2 more than 30 diseases that can be treated with pure EPA, but hypertriglyceridemia is not one of
3 them.⁵⁵⁴⁸ Moreover, WO '900 does not teach the desired effect of EPA other than commenting
4 generally that it “may promote health and ameliorate or even reverse the effects of a range of
5 common diseases.”⁵⁵⁴⁹ It has no discussion, for example, on any TG-lowering effect of EPA.
6 Although WO '900 identifies DHA as an “undesired molecule”, it does not identify the *specific*
7 undesired effect of DHA or other impurities it is trying to prevent other than commenting
8 generally that “the desired effects of EPA may be limited or reversed” by them.⁵⁵⁵⁰ It has no
9 discussion related to any LDL-C effects caused by DHA.

10 The proposed combination does not render the independent claims of the '698 patent
11 obvious and Defendants' burden to prove otherwise is especially difficult because the PTO
12 considered WO '118, WO '900, Mori 2000, and Lovaza (both generally and the Lovaza package
13 insert specifically) during prosecution.⁵⁵⁵¹

14 The analysis of the independent claims of the '698 patent is incorporated into all asserted
15 claims that depend from those Claims.

16 (a) Leigh-Firbank and Mori 2000 Do
17 Not Disclose Purported Knowledge
18
19

20 ⁵⁵⁴⁸ See, e.g., '900 Pub. at 16-17.

21 ⁵⁵⁴⁹ '900 Pub. at 5.

22 ⁵⁵⁵⁰ '900 Pub. at 39.

23 ⁵⁵⁵¹ See, e.g., *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012)(taking into account that “the
24 examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention.
Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear
and convincing standard came into play”).

1 that DHA was Responsible for the
2 Increase in LDL-C

3 Defendants contend that a “person of ordinary skill in the art would have been motivated
4 to administer pure EPA to severely hypertriglyceridemic patients according to Lovaza’s known
5 regimen, particularly in light of the knowledge that DHA is responsible for the increase in LDL-
6 C levels as evidenced by Leigh-Firbank or Mori 2000.”⁵⁵⁵²

7 Defendants fail to identify a specific motivation to combine WO ‘118 or WO ‘900 with
8 the treatment regimen of Lovaza, as evidenced by the Lovaza PDR. Although Defendants need
9 not point to an explicit statement in the prior art motivating the combination of these references,
10 any assertion of an “apparent reason” to combine must find a basis in the factual record.⁵⁵⁵³

11 Defendants’ unsupported cobbling of selective disclosures represents hindsight
12 reconstruction.⁵⁵⁵⁴ Defendants’ contentions are no more than an assertion that certain claim
13 elements were known in the prior art. Accordingly, Defendants fail to meet their burden to
14 establish *prima facie* obviousness.

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⁵⁵⁵² Defendants’ Joint Invalidity Contentions at 713.

17 ⁵⁵⁵³ See, e.g., *In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the
18 formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did
19 not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply
20 the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi*
Sankyo Co. v. Matrix Labs., Ltd., 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must
21 avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to
22 select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and
23 elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp.
2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie*
24 obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding
that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been
motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

⁵⁵⁵⁴ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under
KSR, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention
without any explanation as to how or why the references would be combined to produce the claimed invention”).

1 Contrary to Defendants’ assertion, Leigh-Firbank and Mori 2000 do *not* disclose that
2 DHA is responsible for the increase in LDL-C level. The discussion regarding Leigh-Firbank
3 and Mori 2000 in Section V.L.3.c.1.a.i.a.iii is incorporated herein by reference. Leigh-Firbank
4 cannot comment on the effect of EPA and DHA alone because it did not administer EPA and
5 DHA separately. A person of ordinary skill would similarly understand that Leigh-Firbank does
6 not offer any disclosure regarding the effect of EPA and DHA separately or gain any
7 understanding of the separate impact of DHA or EPA on lipid parameters. Although Mori 2000
8 discloses an increase in LDL-C for patients administered DHA, it also teaches that DHA is
9 preferable to EPA—thus teaching away from the claimed invention and reflecting no motivation
10 to combine with WO ‘118 or WO ‘900. Engaging in hindsight bias, Defendants ignore, without
11 explanation, the other effects of DHA that a person of ordinary skill would consider. Defendants
12 fail to identify any other basis upon which a person of ordinary skill would have sought to
13 combine Mori 2000 with the Lovaza PDR.

14 Therefore, Leigh-Firbank and Mori 2000 fail to substantiate Defendants’ assertion that it
15 was known that DHA was responsible for the increase in LDL-C levels. Further, Defendants
16 ignore, without explanation, other studies that demonstrate that DHA decreases or has little
17 effect on LDL-C levels.⁵⁵⁵⁵ Defendants identify no other basis upon which a person of ordinary
18 skill would have sought to combine WO ‘118, WO ‘900, the Lovaza PDR, Leigh-Firbank and/or
19 Mori.

20 (ii) The ‘698 Patent is not Obvious Over WO
21 ‘118, WO ‘900, Grimsgaard, Mori 2000
22 and/or Maki in Combination with the
23 Omacor PDR/Lovaza PDR, and Further in

24 ⁵⁵⁵⁵ See *e.g.*, Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

With respect to the '698 patent, Defendants present a combination of nine references:

“WO '118, WO '900, Grimsgaard, Mori 2000 and/or Maki in combination with treatment regimen of Omacor/Lovaza as evidenced by the Omacor PDR/Lovaza PDR, and further in view of Katayama, Matsuzawa and/or Takaku.”⁵⁵⁵⁶ Defendants also present charts arguing that an additional 56 references may be combined in order to render the Claims obvious. Not only do Defendants ignore the improbability that a person of ordinary skill would combine 56 separate references, they additionally do not identify any motivation for combining these references. Although Defendants need not point to an explicit statement in the prior art motivating the combination of these references, any assertion of an “apparent reason” to combine must find a basis in the factual record.⁵⁵⁵⁷ Defendants’ unsupported cobbling of selective disclosures represents hindsight reconstruction.⁵⁵⁵⁸ Defendants’ contentions are no more than an assertion that certain claim elements were known in the prior art. Throughout their contentions,

⁵⁵⁵⁶ Defendants’ Joint Invalidity Contentions at 713.

⁵⁵⁵⁷ See, e.g., *In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp. 2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie* obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

⁵⁵⁵⁸ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under KSR, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention”).

1 Defendants’ selectively cite to data points in a reference without considering other disclosures or
2 even the reference as a whole. Each reference, however, must be evaluated for all that it
3 teaches.⁵⁵⁵⁹ Accordingly, Defendants fail to meet their burden to establish *prima facie*
4 obviousness.

5 The discussion related to WO ‘118 and WO ‘900 in Section V.L.3.c.1.b.i is incorporated
6 herein by reference. The discussion related to Grimsgaard, Mori 2000 and/or Maki in Section
7 V.L.3.c.1.a.ii.a.iii is incorporated herein by reference. Defendants contend that “Grimsgaard and
8 Mori 2000 also disclose the administration of 4 g per day of highly purified EPA with no DHA.”
9 However, neither Grimsgaard nor Mori 2000 discloses the administration of 4g/day EPA to the
10 *very high TG patient population*. Neither Grimsgaard nor Mori 2000 provides motivation to
11 administer 4g/day EPA to the *very high TG patient population*. Defendants identify no other
12 basis upon which a person of ordinary skill would have sought to combine the composition
13 disclosed in Grimsgaard or Mori 2000.

14 Defendants argue that it “would have been obvious to a person of ordinary skill in the art
15 to use EPA as described in WO ‘118, WO ‘900, Grimsgaard or Mori 2000 in the treatment
16 regimen used for Omacor/Lovaza as described in the Omacor PDR/Lovaza PDR,” but their
17 assertions fail to provide a motivation for combining the references.⁵⁵⁶⁰ Although Defendants
18 need not point to an explicit statement in the prior art motivating the combination of these
19 references, any assertion of an “apparent reason” to combine must find a basis in the factual
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23 ⁵⁵⁵⁹ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

24 ⁵⁵⁶⁰ Defendants’ Joint Invalidity Contentions at 713.

1 record.⁵⁵⁶¹ Defendants’ assertions related to motivation are insufficient,⁵⁵⁶² and accordingly
2 Defendants fail to meet their burden to establish *prima facie* obviousness.

3 Defendants formulate an obviousness argument that relies on Katayama, Matsuzawa, or
4 Takaku. However, they’ve failed to provide any factual or legal basis as to why each reference
5 discloses a claim element, an “apparent reason” or motivation to combine the elements in the
6 manner claimed.⁵⁵⁶³ Therefore, Defendants should be precluded from relying on this these
7 references.

8 As discussed above in Section V.L.3.c.1.a.i.a.i, Katayama and Matsuzawa were both only
9 designed to confirm the safety of long term treatment of Epadel and its ability to lower both
10 serum total cholesterol and triglyceride levels. They fail to provide motivation to administer
11 purified EPA to the very high TG patient population. As discussed above in Section
12

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14 ⁵⁵⁶¹ See, e.g., *In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the
15 formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did
16 not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply
17 the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi*
18 *Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must
19 avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to
20 select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and
21 elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp.
22 2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie*
23 obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding
24 that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been
motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

⁵⁵⁶² For example, Defendants’ assertion that “WO ’118 may be combined with other prior art in the field of treating
hypertriglyceridemia” is nothing more than a statement that a reference can be combined but fails to provide any
basis for that statement. While the paragraph associated with that statement makes assertions regarding the
disclosure of certain other references, it does not provide a basis for the assertion of motivation to combine with WO
’118. See Defendants’ Joint Invalidity Contentions at 713.

⁵⁵⁶³ *KSR*, 550 U.S. at 417–19; *TriMed, Inc. v. Stryker Corp.*, 608 F.3d 1333, 1341 (Fed. Cir. 2010). Hindsight may
not be employed to identify relevant prior art and relevant teachings therein: *Heidelberger Druckmaschinen AG v.*
Hantscho Comm. Prods., Inc., 21 F.3d 1068, 1071–72 (Fed. Cir. 1994); *Monarch Knitting Mach. Corp. v. Sulzer*
Morat GmbH, 139 F.3d 877, 881 (Fed. Cir. 1998).

1 V.L.3.c.1.a.ii.a.i, Takaku candidly acknowledges that “only a few subjects were examined” and
2 cautions against drawing a conclusion “only from the results of the present study.”⁵⁵⁶⁴ Further,
3 the study did not include any placebo control, therefore, a person of ordinary skill in the art
4 would understand these reports do not provide the ability to conclude that the observed lipid
5 effects would have occurred independent of the drug that is administered. In addition, the study
6 was conducted exclusively in Japanese patients, and a person of ordinary skill would not have
7 expected the results to be applicable to the general population.⁵⁵⁶⁵

8 The proposed combination does not render the independent claims of the ’698 patent
9 obvious and Defendants’ burden to prove otherwise is especially difficult because the PTO
10 considered WO ’118, WO ’900, Grimsgaard, Mori 2000, Maki, Katayama, Matsuzawa and
11 Lovaza (both generally and the Lovaza package insert specifically) during prosecution.⁵⁵⁶⁶

12 The analysis of the independent claims of the ’698 patent is incorporated into all asserted
13 claims that depend from those Claims.

- 14 (a) Grimsgaard, Mori 2000 and/or Maki
15 Do Not Disclose Purported
16 Knowledge that DHA was
17 Responsible for the Increase in LDL-
18 C

17 Defendants contend that a “person of ordinary skill in the art would have been motivated
18 to administer pure EPA to hypertriglyceridemic patients according to Omacor/Lovaza’s known
19

20 ⁵⁵⁶⁴ Takaku at ICOSAPENT_DFNDT00006897.

21 ⁵⁵⁶⁵ Yokoyama 2007 at 1097 (“[b]ecause our population was exclusively Japanese, we cannot generalise our results
to other populations.”)

22 ⁵⁵⁶⁶ See, e.g., *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012) (taking into account that “the
23 examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention.
Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear
24 and convincing standard came into play”).

1 regimen, Katayama, Matsuzawa or Takaku, particularly in light of the knowledge that DHA is
2 responsible for the increase in LDL-C levels as evidenced by Grimsgaard, Mori 2000 or
3 Maki.”⁵⁵⁶⁷

4 Contrary to Defendants’ assertion, Grimsgaard, Mori 2000 and/or Maki do *not* disclose
5 that DHA is responsible for the increase in LDL-C level. The discussion related to Grimsgaard,
6 Mori 2000 and/or Maki in Section V.L.3.c.1.a.ii.a.iii is incorporated herein by reference. A
7 person of ordinary skill would understand that the results of Grimsgaard demonstrated that EPA
8 and DHA’s impact on LDL-C were the same as the effect of the placebo corn oil group; that is,
9 there was no difference between EPA, DHA, or placebo’s effect on LDL-C levels. Although
10 Mori 2000 discloses an increase in LDL-C for patients administered DHA, the reference does not
11 disclose administration of DHA to the requisite patient population and teaches that DHA is
12 preferable to EPA—thus teaching away from the claimed invention. Engaging in hindsight bias,
13 Defendants ignore, without explanation, the other effects of DHA that a person of ordinary skill
14 would consider. Most controlled studies in patients with normal to high baseline TG levels
15 indicated that DHA had little or no effect on LDL-C.⁵⁵⁶⁸ Therefore, a person of ordinary skill
16 would not have concluded that DHA increases LDL-C in patients with normal to high baseline
17 TG levels. Maki demonstrated that when 1.52 g/day DHA **and** 0.84 g/day palmitic acid is
18 administered to patients with below-average levels of HDL-C levels and borderline-high TG
19 levels, a significant increase in LDL-C is observed.⁵⁵⁶⁹ However, one of ordinary skill in the art
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⁵⁵⁶⁷ Defendants’ Joint Invalidity Contentions at 713.

22 ⁵⁵⁶⁸ Mori 2000 at 98. Moreover, Mori 2000, the only study which compared EPA versus DHA, and is placebo
23 controlled, found an increase in LDL-C after DHA administration.

24 ⁵⁵⁶⁹ Maki at 195.

1 knew that saturated fatty acids, such as palmitate, may contributed to the elevation in LDL-C.⁵⁵⁷⁰
2 Therefore, the results of Maki are inconclusive as to DHA’s effect alone on LDL-C levels.

3 Therefore, Grimsgaard, Mori 2000 and/or Maki fail to substantiate Defendants’ assertion
4 that it was known that DHA was responsible for the increase in LDL-C levels. Further,
5 Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or
6 has little effect on LDL-C levels.⁵⁵⁷¹ Defendants identify no other basis upon which a person of
7 ordinary skill would have sought to combine WO ‘118, WO ‘900, Grimsgaard, Mori 2000, Maki,
8 the Omacor PDR/the Lovaza PDR, Katayama, Matsuzawa and/or Takaku.

9 (iii) A Person of Ordinary Skill Would Not Have
10 Been Motivated to Administer Purified EPA
11 in the Treatment Regimen Recited in the
12 Claims

12 For an invention to be obvious, there must have been an “apparent reason” to make it.
13 Defendants assert that a “person of ordinary skill in the art would have been motivated to
14 administer 4 grams of highly-purified EPA to patients with triglycerides greater than or equal to
15 500 mg/dL, with a reasonable expectation of success in lowering triglycerides.”⁵⁵⁷² However, as
16 set forth below, Defendants fail to address why a person of ordinary skill in the art would have
17 been motivated to administer 4 grams of highly-purified EPA to patients with triglycerides
18 greater than or equal to 500 mg/dL.

19 A person of ordinary skill in the art would have understood that omega 3-fatty acids,
20 including DHA and EPA, and fibrates cause an increase in LDL-C among very high TG patients,

21 ⁵⁵⁷⁰ Maki at 197; Yu et al., *Plasma Cholesterol-Predictive Equations Demonstrate that Stearic Acid is Neutral and*
22 *Monounsaturated Fatty Acids are Hypocholesterlemic*, 61 AM J CLIN NUTR 1129, 1136 (1995); Weber 2000 (“A
number of the earlier-formulated (older) omega-3 fatty acid supplements contained significant amounts of saturated
fat and cholesterol, both of which are known to elevate LDL-C.”).

23 ⁵⁵⁷¹ See e.g., Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

24 ⁵⁵⁷² Defendants’ Joint Invalidity Contentions at 714.

1 as reflected in the prior art. Accordingly, a person of ordinary skill in the art would not have been
2 motivated to look to omega 3-fatty acids in order to obtain a reduction in TGs without increasing
3 LDL-C in very high TG patients:

	LDL-C Effect	
	Borderline-High or High TG Patients	Very-High TG Patients
Fibrate ⁵⁵⁷³	-20%	+45%
Lovaza/Omacor ⁵⁵⁷⁴	-6%	+45%

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6
7
8 That Epadel has been approved for decades but not approved for use in the very high TG
9 patient population prior to the invention of the asserted patents is a real-world reflection of the
10 lack of motivation. Research into the pharmaceutical uses of EPA started as early as the 1970s.
11 In 1990, Mochida Pharmaceutical, began to market Epadel, a high purity EPA drug. There have
12 been countless studies conducted which administer Epadel and report the effects observed.
13 Although a few studies administer Epadel to a patient population which included a few patients
14 with TG levels > 500 mg/dL, Defendants fail to identify a single reference directed to the
15 administration of Epadel to patients with very-high TG levels, reflecting a lack of motivation.

16 Defendants further argue that the disclosure in WO '118 would combine with the prior art
17 concerning Lovaza for at least two reasons; first, "products containing DHA were reported to
18 increase LDL-C levels while products containing only EPA did not," and second, "WO '118
19 reports a reduction in cardiovascular events in hypertriglyceridemic patients administered highly-
20 purified ethyl-EPA."⁵⁵⁷⁵ Both of the "reasons" identified by Defendants are false.

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22 ⁵⁵⁷³ Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

23 ⁵⁵⁷⁴ Chan 2002 I at 2381 (Table 3).

24 ⁵⁵⁷⁵ Defendants' Joint Invalidity Contentions at 714.

1 Regarding Defendants’ first reason, that “products containing DHA were reported to
2 increase LDL-C levels while products containing only EPA did not,” most controlled studies in
3 patients with normal to high baseline TG levels indicated that DHA had little or no effect on
4 LDL-C.⁵⁵⁷⁶ Therefore, a person of ordinary skill would not have concluded that DHA increases
5 LDL-C in patients with normal to high baseline TG levels. Specifically, Leigh-Firbank, Kelley,
6 and Theobald does *not* disclose that “DHA raises LDL-C, an effect associated with heart disease,
7 while EPA does not.”⁵⁵⁷⁷ First, Leigh-Firbank cannot comment on the effect of EPA and DHA
8 alone because it did not administer EPA and DHA separately.⁵⁵⁷⁸ A person of ordinary skill
9 would similarly understand that Leigh-Firbank does not offer any disclosure regarding the effect
10 of EPA and DHA separately or gain any understanding of the separate impact of DHA or EPA
11 on lipid parameters. Second, Kelley administered DHA-rich oil that was contaminated with
12 other saturated and polyunsaturated fatty acids.⁵⁵⁷⁹ Therefore, a person of ordinary skill would
13 have known it is unsuitable for evaluating the independent effects of DHA because it is not clear
14 how much of the supplement’s effects can be attributed to DHA.⁵⁵⁸⁰ Kelley does not show that
15 DHA is responsible for the increase in LDL-C. Kelley suggests that increase in LDL-C is a
16 general phenomenon associated with triglyceride-lowering drugs, stating that a similar increase
17 was induced by fibrate therapy.⁵⁵⁸¹ Kelley specifically teaches that the increase in LDL-C

19 ⁵⁵⁷⁶ Mori 2006 at 98. Moreover, Mori 2000, the only study which compared EPA versus DHA, and is placebo
20 controlled, found an increase in LDL-C after DHA administration.

21 ⁵⁵⁷⁷ Defendants’ Joint Invalidation Contentions at 718.

22 ⁵⁵⁷⁸ The discussion related to Leigh-Firbank in Section V.L.3.c.1.a.i.a.iii is incorporated herein by reference.

23 ⁵⁵⁷⁹ The discussion related to Kelley in Section V.L.3.c.1.a.iii.a.ii is incorporated herein by reference.

24 ⁵⁵⁸⁰ See Mori 2006 at 96.

⁵⁵⁸¹ Kelley at 329.

1 caused by DHA supplementation is unlikely to be “detrimental” because there was not a parallel
2 increase in overall LDL particle number. Rather than concluding that DHA was uniquely
3 responsible for a rise in LDL-C levels, a person of ordinary skill would understand Kelley to
4 disclose that DHA had uniquely beneficial cardioprotective effects.⁵⁵⁸² Finally, Theobald also
5 does not teach that DHA increases LDL-C. In Theobald, 0.7 g/day of DHA was administered for
6 3 months in patients with normal baseline TG levels. Theobald found that LDL-C increased by
7 7% when compared to placebo. However, the DHA composition that was administered in
8 Theobald contained significant amounts of other fatty acids, such as myristic acid, palmitic acid,
9 and oleic acid. Therefore, a person of ordinary skill would have known that the DHA
10 administered by Theobald is unsuitable for evaluating the independent effects of DHA because it
11 impossible to determine whether or how much of the supplement’s effects can be attributed to
12 DHA.⁵⁵⁸³ Contrary to Defendants’ assertion that there was “a reported advantage to using EPA
13 vs. DHA in hypertriglyceridemic subjects,”⁵⁵⁸⁴ there was no known advantage to using EPA vs.
14 DHA. In fact, a number of the references Defendants cite in their contentions ultimately
15 conclude that DHA supplementation “may represent a more favorable lipid profile than after
16 EPA supplementation.”⁵⁵⁸⁵ In addition, a person of ordinary skill would have recognized any
17 impact of DHA reported by the study to be applicable to EPA because they would have
18 understood these substances to function by the same mechanism. Furthermore, as discussed
19 above in Section III, a person of ordinary skill would not expect the same LDL-C effect in
20

21 ⁵⁵⁸² Kelley at 324, 332 (Kelley’s ultimate conclusion is that “[o]verall, DHA supplementation reduced the
22 concentrations of atherogenic lipids and lipoproteins and increased concentrations of cardioprotective lipoproteins”
and that “DHA supplementation may improve cardiovascular health.”)

23 ⁵⁵⁸³ See Mori 2006 at 96.

24 ⁵⁵⁸⁴ Defendants’ Joint Invalidity Contentions at 714.

⁵⁵⁸⁵ Mori 2000 at 1092.

1 patients with lower baseline TG levels, including healthy patients, as in very-high TG patients
2 because patients with higher TG levels had different lipid responses compared to patients with
3 lower TG levels.

4 Regarding Defendants’ second reason, that “WO ‘118 reports a reduction in
5 cardiovascular events in hypertriglyceridemic patients administered highly-purified ethyl-EPA,”
6 the cardioprotective effects of omega-3 fatty acids, including both EPA and DHA, have been
7 well documented.⁵⁵⁸⁶ Lovaza/Omacor has been shown to reduce the risk for cardiovascular
8 death plus nonfatal myocardial infarction and nonfatal stroke.⁵⁵⁸⁷ Omega-3 fatty acids have been
9 shown to exert cardioprotective effects in both primary and secondary coronary heart disease
10 prevention trials.⁵⁵⁸⁸ Omega-3 fatty acids were known to reduce TG concentration, have
11 antiarrhythmic effects, decrease platelet aggregation, stabilize plaque, reduce blood pressure
12 and/or reduce heart rate.⁵⁵⁸⁹

13 Defendants argue that a “person of ordinary skill in the art would have appreciated the
14 fact that highly-purified ethyl-EPA, and not Lovaza, had been demonstrated to reduce
15 cardiovascular events in high-risk hypertriglyceridemic patients, and understood the benefits of
16 replacing the EPA+DHA of Lovaza with the highly purified ethyl-EPA of WO ‘118.”⁵⁵⁹⁰ As
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18

19 ⁵⁵⁸⁶ Harris et al., *Tissue n-3 and n-6 Fatty Acids and Risk for Coronary Heart Disease Events*, 193
20 *ATHEROSCLEROSIS*, 1, 8 (2007) (“Overall, these findings confirm the well-known relationship between the n-3 FA
and CHD risk.”) (“Harris 2007”); Bays 2008 II at 229-230.

21 ⁵⁵⁸⁷ See Bays, *Clinical Overview of Omacor: A Concentrated Formulation of Omega-3 Polyunsaturated Fatty Acids*,
98 *AM. J. CARDIOL* 71i (2006) (“Bays 2006”).

22 ⁵⁵⁸⁸ Harris et al., *Omega-3 Fatty Acids and Coronary Heart Disease Risk: Clinical and Mechanistic Perspectives*,
197 *ATHEROSCLEROSIS* 12, 13 (2008) (“Harris 2008”).

23 ⁵⁵⁸⁹ Harris 2008 at 13.

24 ⁵⁵⁹⁰ Defendants’ Joint Invalidity Contentions at 715.

1 discussed above, the cardioprotective effects of omega-3 fatty acids, including both EPA, DHA
2 and Lovaza/Omacor have been well documented.⁵⁵⁹¹

3 In fact, a meta-analysis of twenty-five studies which examined the risk of coronary heart
4 disease endpoints as a function of tissue FA composition found that the evidence suggested that
5 DHA is *more* cardioprotective than EPA.⁵⁵⁹² This study found that “depressed levels of long-
6 chain *n*-3 FA (especially DHA) in tissues is a consistent marker of increased risk for coronary
7 heart disease events.”⁵⁵⁹³ Further, the study found that DHA levels, with or without EPA, were
8 significantly lower in fatal endpoints.⁵⁵⁹⁴ This study suggests that DHA is preferable to EPA—
9 thus teaching away from the claimed invention.⁵⁵⁹⁵ Defendants rely on hindsight bias to argue
10 that a person of ordinary skill would have been motivated to use purified EPA, when both EPA
11 *and* DHA were known to have cardioprotective effects, and there were studies suggesting DHA
12 was *more* cardioprotective than EPA.

13 Defendants argue that the following claim elements were known: the administration of
14 highly-purified EPA-E to reduce TG levels in patients with normal to high TG levels, the
15 administration of purified EPA to patients with TG levels > 500 mg/dL, to administer EPA-E to
16

17 ⁵⁵⁹¹ Harris et al., *Tissue n-3 and n-6 Fatty Acids and Risk for Coronary Heart Disease Events*, 193
18 *ATHEROSCLEROSIS*, 1, 8 (2007) (“Overall, these findings confirm the well-known relationship between the *n*-3 FA
and CHD risk.”) (“Harris 2007”).

19 ⁵⁵⁹² Harris 2007 at 8.

20 ⁵⁵⁹³ *Id.*

21 ⁵⁵⁹⁴ Harris 2007 at 7, Table 5; *see also* Harris 2007 at 8 (“Low DHA was the most common finding across all
22 studies, suggesting that this FA was perhaps more cardioprotective than EPA as others have suggested.”).

23 ⁵⁵⁹⁵ *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994) (A reference may be said to teach away when a person of
24 ordinary skill, upon [examining] the reference, would be discouraged from following the path set out in the
reference, or would be led in a direction divergent from the path that was taken by the applicant.”); *see also*
Santarus, Inc. v. Par Pharm., Inc., 694 F.3d 1344, 1354 (Fed. Cir. 2012) (quoting Gurley); *W.L. Gore & Assocs.,
Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1552 (Fed. Cir. 1983) (“[P]roceed[ing] contrary to the accepted wisdom of the
prior art ... is strong evidence of nonobviousness.”).

1 patients with high and very high TG levels who were not receiving concurrent lipid altering
2 therapy, and the dose of 4g/day and 12-week regimen.⁵⁵⁹⁶ Defendants then argue that the “only
3 question is whether one skilled in the art would have been motivated to use the DHA-free,
4 highly-purified EPA-E of the prior art for the treatment of patients with triglyceride levels of at
5 least 500 mg/dL as part of the claimed dosage regimen.”⁵⁵⁹⁷

6 Defendants’ contentions are no more than a recitation that certain claim elements were
7 known in the prior art. Defendants’ assertions to the contrary represent hindsight
8 reconstruction.⁵⁵⁹⁸ Notably, Defendants *do not* assert that a person of ordinary skill would have
9 known that purified EPA, when administered to patients with very-high TG levels (≥ 500 mg/dL),
10 *would not substantially increase LDL-C*. Further, Defendants point to three Japanese studies,⁵⁵⁹⁹
11 which included a small minority of patients with baseline TG levels > 500 mg/dL to argue that “a
12 number of prior art references disclosed the administration of purified EPA to patients with
13 triglyceride levels > 500 mg/dL.”^{5600, 5601} The disclosures of Nakamura (one patient), Matsuzawa
14 (disclosure of three patients with TG between 400 and 1000 mg/dL, with no evidence or support
15 for the assertion that the patients had very high TGs), and Takaku (three patients) reflect that a

17 _____
18 ⁵⁵⁹⁶ Defendants’ Joint Invalidity Contentions at 716.

19 ⁵⁵⁹⁷ Defendants’ Joint Invalidity Contentions at 716.

20 ⁵⁵⁹⁸ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that even under KSR, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention.”).

21 ⁵⁵⁹⁹ Nakamura, Matsuzawa, and Takaku.

22 ⁵⁶⁰⁰ Defendants’ Joint Invalidity Contentions at 716.

23 ⁵⁶⁰¹ Okumura and Hayashi also fail to disclose administration of purified EPA to patients with TG levels > 500 mg/dL. Hayashi states that the baseline TG level was 300 ± 233 mg/dL. However, the standard error is unusually high and there is no specific disclosure of a single subject with TG levels > 500 mg/dL. Okumuara specifically states that its hypertriglyceridemia patients had baseline TG levels between 150 and 500 mg/dL.

1 person of ordinary skill in the art would *not* understand these references to relate to the use of
2 EPA in patients with very high TGs, nor would a person of ordinary skill in the art draw any
3 conclusions regarding these references in terms of the very high TG patient population. In
4 Nakamura, one patient had a baseline TG level > 500 mg/dL.⁵⁶⁰² However, the mean baseline
5 TG for all patients was 2.07 mmol/l (183 mg/dL), indicating that the baseline TG values for the
6 other patients was well below 500 mg/dL.⁵⁶⁰³ In Matsuzawa, three patients had TG levels
7 between 400 and 1000 mg/dL and one patient had TG levels > 1,000 mg/dL.⁵⁶⁰⁴ Based on this
8 disclosure, only one patient definitively had a baseline TG level \geq 500 mg/dL. Further, this one
9 patient was excluded when analyzing the lipid impact because he was a “heavy drinker” and the
10 “effect of alcohol made it impossible to assess triglyceride levels.”⁵⁶⁰⁵ In Takaku, three patients
11 had baseline TG levels above 500 mg/dL.⁵⁶⁰⁶ However, the mean baseline TG level for all
12 patients was 245 mg/dL.⁵⁶⁰⁷ Indeed, the mean baseline TG level of the patients in all three
13 studies was well below 500 mg/dL; therefore, a person of ordinary skill would not have expected
14 the results to be applicable to patients with triglycerides above 500 mg/dL. Further, in each of
15 these studies, patients with >500 mg/dL were most likely excluded from the LDL-C calculations
16 because the Friedewald’s Equation cannot be used for patients with triglyceride levels \geq 400
17 mg/dL.⁵⁶⁰⁸ Defendants have failed to identify all of the claimed elements and fail to provide

19 ⁵⁶⁰² Nakamura at 23, Table 1.

20 ⁵⁶⁰³ Nakamura at 23, Tables 1 and 2.

21 ⁵⁶⁰⁴ *Id.* at 23.

22 ⁵⁶⁰⁵ *Id.* at 10.

23 ⁵⁶⁰⁶ Takaku at ICOSAPENT_DFNDTS00006895.

24 ⁵⁶⁰⁷ Takaku at ICOSAPENT_DFNDTS00006875.

⁵⁶⁰⁸ *See* Matsuzawa at ICOSAPENT_DFNDTS00006450.

1 motivation to use the DHA-free, highly-purified EPA-E of the prior art for the treatment of
2 patients with triglyceride levels of at least 500 mg/dL as part of the claimed dosage regimen.

3 Defendants contend that a “person of ordinary skill in the art would have been motivated
4 to administer highly-purified EPA-E capsules, for at least 12 weeks . . . in order to achieve the
5 known TG-lowering effects of highly-purified EPA-E.”⁵⁶⁰⁹ This argument is flawed. The prior
6 art demonstrates a wide range of administration periods utilized in different clinical studies. For
7 example, EPA was administered for 4 weeks in Park, for 7 weeks in Grimsgaard, for 8 weeks in
8 Hayashi, for 1 year in Takaku, for 2 years in Katayama, and for 5 years in Yokoyama 2007.
9 Given the large number of choices of administration periods disclosed in prior art, Defendants
10 have not shown that a person of ordinary skill would not have been motivated to administer
11 highly-purified EPA-E capsules for 12 weeks and offer no basis for their assertions.

12 Moreover, a person of ordinary skill would not have been motivated to administer highly-
13 purified *EPA-E* capsules, as opposed to DHA or a combination of EPA and DHA (such as
14 Lovaza), for 12 weeks. It was well known that both EPA and DHA reduced blood
15 triglycerides.⁵⁶¹⁰ In fact, Defendants acknowledge in their Joint Invalidation Contentions that
16 “DHA and EPA were both known to comparably reduce triglycerides, independently of one
17 another.”⁵⁶¹¹ Data from some studies even suggested that DHA or fish oil may reduce
18 triglyceride more effectively than EPA.⁵⁶¹² Therefore, a person of ordinary skill would not have
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⁵⁶⁰⁹ Defendants’ Joint Invalidation Contentions at 716-17.

21 ⁵⁶¹⁰ Mori 2006 at 98.

22 ⁵⁶¹¹ Defendants’ Joint Invalidation Contentions at 720.

23 ⁵⁶¹² Mori 2000 (showing that EPA reduced triglyceride by 18% while DHA reduced triglyceride by 20%); Rambjor
24 (showing that fish oil reduced triglyceride more than EPA); Grimsgaard (showing that decrease in triglyceride was
grater with DHA supplementation than EPA supplementation).

1 | been motivated to administer highly-purified *EPA-E* capsules instead of DHA or a combination
2 | of EPA and DHA (such as Lovaza) for 12 weeks.

3 | Defendants argue that a “person of ordinary skill in the art also would have been
4 | motivated to administer 4 g/day highly-pure ethyl EPA . . . because of the observed significant
5 | reduction in TG . . . that was achieved in six weeks of treatment,” citing Mori 2000.⁵⁶¹³ This
6 | argument is incorrect. The administration of 4 g/day of highly-pure ethyl EPA to patients with
7 | *mild* hypertriglyceridemia for *six* weeks does not provide a person of ordinary skill motivation to
8 | administer the same dose to patients with *severe* hypertriglyceridemia for *twelve* weeks.

9 | Defendants also, once again, fail to demonstrate that a person of ordinary skill would have
10 | chosen to administer 4g/day EPA as opposed to DHA or a combination of EPA and DHA (such
11 | as Lovaza).

12 | Defendants further argue that “because Katayama and Saito 1998 teach that higher doses
13 | of highly-purified EPA-E reduce TG level to a greater extent than lower doses . . . a person of
14 | ordinary skill in the art would have been motivated to administer highly-purified EPA-E at a
15 | dose of 4 g/day rather than a lower dose.”⁵⁶¹⁴ A person of ordinary skill would not have relied
16 | on either reference to determine the EPA dosage required to treat severe hypertriglyceridemia,
17 | because these studies were not designed to determine the effect of dose on the degree of TG
18 | reduction. Second, Katayama and Saito do not suggest that 4 g/day of EPA, rather than a lower
19 | dose or a higher dose, would be the right dosage to treat severe hypertriglyceridemia.

20 |
21 |
22 | _____
23 | ⁵⁶¹³ Defendants’ Joint Invalidation Contentions at 717.

24 | ⁵⁶¹⁴ Defendants’ Joint Invalidation Contentions at 717.

1 Moreover, as discussed above, it was well known that both EPA and DHA reduced blood
2 triglycerides.⁵⁶¹⁵ Therefore, a person of ordinary skill would not have been motivated to
3 administer 4 g/day of highly-purified *EPA-E* capsules, as opposed to DHA or a combination of
4 EPA and DHA (such as Lovaza).

5 Defendants further argue that a “person of ordinary skill in the art would have also been
6 motivated to treat subjects having baseline TG levels of 500 mg/dl to about 1500 mg/dl with
7 highly-purified EPA-E, as suggested by Yokoyama’s teaching that TG was reduced to a much
8 greater extent in subjects having higher baseline TG levels . . . and because Katayama and Saito
9 treated subjects having baseline triglyceride levels greater than 500 mg/dl.”⁵⁶¹⁶ This argument is
10 incorrect. It was well known that any TG-reducing therapy will reduce TG to a greater extent in a
11 patient having higher baseline TG levels. Therefore, a person of ordinary skill would not have
12 been motivated to administer highly-purified *EPA-E* capsules as opposed to any other omega-3
13 fatty acid composition, fibrate, or other TG-lowering therapy, to treat subjects having baseline
14 TG levels above 500mg/dL. Further, a person of ordinary skill would have expected that a
15 greater decrease in TG levels, in the very high TG patient population, would lead to a greater
16 increase in LDL-C levels.

17 Defendants next argue again that DHA was known to be responsible for the increase in
18 LDL-C levels in very high TG patients, but as discussed above, *see* Section III, a person of
19 ordinary skill would understand that both EPA and DHA function similarly, and that both would
20 have little to no impact on borderline-high TG patients in terms of LDL-C levels and would
21 increase LDL-C levels in patients with very high TGs.

22 _____
23 ⁵⁶¹⁵ *See* Section III.

24 ⁵⁶¹⁶ Defendants’ Joint Invalidity Contentions at 717.

1 Defendants argue that a person of ordinary skill in the art “would have known that an
2 increase in LDL-C was an adverse health effect to be avoided.”⁵⁶¹⁷ While an increase in LDL-C
3 was seen as a *possible* adverse health effect, a person of ordinary skill in the art understood that
4 the increase in LDL-C seen in the very-high TG patient population with Lovaza, and omega-3
5 fatty acids generally, was related to increased conversion of VLDL to LDL particles.⁵⁶¹⁸

6 Defendants rely on Kelley and the Lovaza label to argue that “one of ordinary skill in the
7 art would have been motivated, with a reasonable expectation of success, to administer a highly-
8 purified EPA-E dosage form, with not more than about 4% to no DHA, in order to avoid the
9 expected increase in LDL-C with DHA.”⁵⁶¹⁹ However, a person of ordinary skill in the art
10 expected an increase in LDL-C in the very high TG population, with both EPA and DHA. It was
11 well known at the time of the invention that omega-3 fatty acids, including both EPA and DHA,
12 caused significant decrease in the production of VLDL particles and a significant increase in the
13 conversion of VLDL to IDL and LDL, supporting the theory that omega-3 fatty acids worked in
14 part by inhibiting VLDL production and improving the conversion of VLDL particles to
15 LDL.⁵⁶²⁰ A person of ordinary skill in the art understood that EPA and DHA had the *same* TG-
16 lowering mechanism and did not differentiate between EPA and DHA when discussing the TG-
17 lowering mechanism of omega-3 fatty acids.⁵⁶²¹ The discussion related to the TG-lowering

18 _____
19 ⁵⁶¹⁷ Defendants’ Joint Invalidity Contentions at 719.

20 ⁵⁶¹⁸ See Bays 2008 I at 402; McKenny 2007 at 720 (finding that “[t]hese results illustrate that with prescription
21 omega-3, fewer VLDL particles are secreted into the systemic circulation, and secreted VLDL particles are rapidly
22 converted to LDL particle, thus explaining why LDL levels may increase in patients with very-high triglyceride
23 levels when given prescription omega-3 therapy”); Chan 2003.

24 ⁵⁶¹⁹ Defendants’ Joint Invalidity Contentions at 720.

⁵⁶²⁰ Chan 202 at 2378-84; *see also* Westphal at 917 (stating “our data confirm the well-known and pronounced
decrease in VLDLs after n-3 fatty acid treatment”).

⁵⁶²¹ Bays 2008 I, at 398; Bay *in* Kwiterovich at 247.

1 mechanism of omega-3 fatty acids is discussed above in Section III and incorporated herein by
2 reference. Further, a person of ordinary skill in the art would have understood that EPA therapy
3 would *not* reduce Apo-B⁵⁶²² (which is a reflection of total atherogenic lipoproteins)⁵⁶²³ in very
4 high TG patients, and accordingly would not have been motivated to administer the claimed EPA
5 composition to the very high TG patient population.

6 Accordingly, a person of ordinary skill would not have been motivated to combine WO
7 '118, WO '900, Grimsgaard, Mori 2000 and/or Maki in with the Omacor PDR/Lovaza PDR, and
8 Katayama, Matsuzawa and/or Takaku. A person of ordinary skill in the art further would not
9 have been motivated to combine WO '118 or WO '900, with the Lovaza PDR, or with Leigh-
10 Firbank and/or Mori 2000.

11 (2) Dependent Claims

12 (a) Defendants Have Not Shown that Claim 2 of the
13 '698 Patent Would Have Been Obvious

14 Plaintiffs incorporate by reference the discussion related to the Independent Claim in
15 Section V.L.3. Because Defendants have not shown the obviousness of the Independent Claim
16 by clear and convincing evidence, they also have not adequately proven the obviousness of
17 Claim 2.

18 Defendants contend that it would be obvious that a person receiving the claimed EPA
19 compositions would have a fasting baseline LDL-C from 50 mg/dL to about 300 mg/dL because
20 hypertriglyceridemic patients in the Lovaza label had a mean LDL-C level of 100 mg/dL. These
21 contentions: 1) fail to address whether the specific combination of claim elements were all
22 present in the prior art references that would have been combined by a person of ordinary skill in

23 ⁵⁶²² *see* Section V.O.

24 ⁵⁶²³ *see* Section III.

1 the art to produce the claimed invention with a reasonable expectation of success; and 2) fail to
2 establish *prima facie* obviousness. Defendants do not offer an obvious analysis, but trivialize the
3 claim element to the point of reading the element out of the claim. Although convenient and
4 expedient, Defendants' approach does not conform with the Local Patent Rules of this District,
5 the law of claim construction, or the law of obviousness.

6 Defendants do not identify any combination of references. Because Defendants do not
7 identify any combination of references, they necessarily fail to offer any evidence that a person
8 of skill in the art would be motivated to combine those references in order to achieve the
9 invention of the claim as a whole. Further, Defendants do not discuss at all whether a person of
10 ordinary skill would have been motivated to combine the elements, other than stating that a
11 patient with LDL-C levels of 50 mg/dL to about 300 mg/dL would benefit from receiving the
12 claimed fish oil treatment. Defendants also state erroneously that a patient with LDL-C levels of
13 50 mg/dL to about 300 mg/dL would be considered hypertriglyceridemic. Defendants do not
14 establish that a person of ordinary skill would have been motivated to combine the elements to
15 achieve the claimed invention.⁵⁶²⁴

16 Similarly, without the disclosure of a combination of references and a motivation/reason
17 to combine or modify the references, Defendants necessarily fail to offer any evidence that a
18 person of ordinary skill in the art would have had a reasonable expectation of success in
19 achieving the claimed invention. Defendants do not even discuss whether a person of ordinary
20

21
22 ⁵⁶²⁴ *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the *KSR*
23 Court rejected a rigid application of the teaching, suggestion, or motivation (‘TSM’) test in an obviousness inquiry,
24 the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill
in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness
determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

1 skill would have expected that the combination to work for its intended purpose for treating the
2 recited patient population.⁵⁶²⁵ As such, Defendants fail to demonstrate reasonable expectation of
3 success of the claimed invention.

4 (b) Defendants Have Not Shown that Claim 3 of the
5 '698 Patent Would Have Been Obvious

6 Plaintiffs incorporate by reference the discussion related to the Independent Claim in
7 Section V.L.3. Because Defendants have not shown the obviousness of the Independent Claim
8 by clear and convincing evidence, they also have not adequately proven the obviousness of
9 Claim 3.

10 Defendants do not identify any combination of references and simply provide a laundry
11 list of references without explaining how each reference relates to the claimed invention.
12 Defendants further contend, without any support, that a person of ordinary skill would have been
13 able to determine the patient population in need of the claimed methods of treatment, would seek
14 to measure the HDL-C, VLDL-C and cholesterol baselines of a patient, and would seek to treat
15 those patients having very high triglycerides regardless of the baseline values of these lipids.⁵⁶²⁶
16 These contentions: 1) do not assert what the prior art discloses to a person of ordinary skill in
17 the art; 2) are irrelevant to an obvious analysis; 3) fail to address whether the specific
18 combination of claim elements were all present in the prior art references that would have been
19 combined by a person of ordinary skill in the art to produce the claimed invention with a
20 reasonable expectation of success; and 4) fail to establish *prima facie* obviousness. Defendants
21 do not offer an obvious analysis, but trivialize the claim element to the point of reading the

22 _____
23 ⁵⁶²⁵ *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable
24 result’ discussed in KSR refers not only to the expectation that prior art elements are capable of being physically
combined, but also that the combination would have worked for its intended purpose.”)

⁵⁶²⁶ *Id.*

1 element out of the claim. Although convenient and expedient, Defendants’ approach does not
2 conform with the Local Patent Rules of this District, the law of claim construction, or the law of
3 obviousness.

4 Defendants fail to show a specific combination of references that discloses each element
5 of the claimed invention. Defendants merely list references, without reference to a specific page
6 or section, that purportedly disclose disparate elements without explaining how they can be
7 combined.⁵⁶²⁷ As such, Defendants discuss the claim elements in isolation, and fail to address
8 the claimed invention as a whole.⁵⁶²⁸ Moreover, by simply identifying prior art references
9 without discussing the specific teachings of each reference, Defendants fail to consider each
10 prior art reference as a whole.⁵⁶²⁹ Each reference must be evaluated for all that it teaches.
11 Defendants’ unsupported cobbling of selective disclosures represents hindsight
12 reconstruction.⁵⁶³⁰

13 Because Defendants do not identify any combination of references, they necessarily fail
14 to offer any evidence that a person of skill in the art would be motivated to combine those
15 references in order to achieve the invention of the claim as a whole. Defendants make a
16 conclusory statement that a person of ordinary skill “would indeed seek” to perform the claimed
17

18 ⁵⁶²⁷ *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int’l Co. v.*
19 *Teleflex Inc.*, 550 U.S. 398, 418 (2007)) (“[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”).

20 ⁵⁶²⁸ *Sanofi Syntheolabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008) (“The determination of obviousness is
made with respect to the subject matter as a whole, not separate pieces of the claim”).

21 ⁵⁶²⁹ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011) (“A prior
22 patent must be considered in its entirety, i.e., as a whole, including portions that would lead away from the invention
in suit.”) (internal citation and quotation marks omitted).

23 ⁵⁶³⁰ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under
24 *KSR*, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention
without any explanation as to how or why the references would be combined to produce the claimed invention”).

1 methods of treatment, without providing a reason that would have prompted a person of ordinary
2 skill to combine the elements.⁵⁶³¹ Such a naked assertion does not show why a person of
3 ordinary skill would have been motivated to treat the recited patient population using the claimed
4 methods of treatment.⁵⁶³²

5 Similarly, without the disclosure of a combination of references and a motivation/reason
6 to combine or modify the references, Defendants necessarily fail to offer any evidence that a
7 person of ordinary skill in the art would have had a reasonable expectation of success in
8 achieving the claimed invention. In fact, other than simply identifying prior art references that
9 purportedly disclose disparate elements, Defendants do not even discuss whether a person of
10 ordinary skill would have expected that the combination to work for its intended purpose for
11 treating the recited patient population.⁵⁶³³ As such, Defendants fail to demonstrate reasonable
12 expectation of success of the claimed invention.

13 (c) Defendants Have Not Shown that Claim 4 of the
14 ‘698 Patent Would Have Been Obvious

15 Plaintiffs incorporate by reference the discussion related to the Independent Claim in
16 Section V.L.3. Because Defendants have not shown the obviousness of the Independent Claim
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18 ⁵⁶³¹ *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (“Rejections on obviousness grounds cannot be
19 sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational
20 underpinning to support the legal conclusion of obviousness.”) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir.
2006)) (internal quotation marks omitted)

21 ⁵⁶³² *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the *KSR*
22 Court rejected a rigid application of the teaching, suggestion, or motivation (‘TSM’) test in an obviousness inquiry,
the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill
in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness
determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

23 ⁵⁶³³ *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable
24 result’ discussed in *KSR* refers not only to the expectation that prior art elements are capable of being physically
combined, but also that the combination would have worked for its intended purpose.”)

1 by clear and convincing evidence, they also have not adequately proven the obviousness of
2 Claim 4.

3 Defendants contend, without providing any support, that it would be obvious to one of
4 skill in the art to administer a composition containing EPA, but containing no DHA, or not more
5 than 4% DHA, with a reasonable expectation of success in reducing Apo-B levels while avoiding
6 an increase in LDL-C associated with DHA. These contentions: 1) do not assert what the prior
7 art discloses to a person of ordinary skill in the art; 2) are irrelevant to an obvious analysis; 3)
8 fail to address whether the specific combination of claim elements were all present in the prior
9 art references that would have been combined by a person of ordinary skill in the art to produce
10 the claimed invention with a reasonable expectation of success; and 4) fail to establish *prima*
11 *facie* obviousness. Defendants do not offer an obvious analysis, but trivialize the claim element
12 to the point of reading the element out of the claim. Although convenient and expedient,
13 Defendants' approach does not conform with the Local Patent Rules of this District, the law of
14 claim construction, or the law of obviousness.

15 Defendants fail to show a specific combination of references that discloses each element
16 of the claimed invention. None of the cited references discloses administration of the claimed
17 EPA to very high TG patients. Defendants further fail to explain how the cited references can be
18 combined to teach the administration of the claimed EPA to very high TG patients.⁵⁶³⁴
19 Defendants selectively cite to an unspecified, isolated disclosure within a reference without
20 considering other disclosures or even the reference as a whole. Each reference, however, must
21

22 ⁵⁶³⁴ *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int'l Co. v.*
23 *Teleflex Inc.*, 550 U.S. 398, 418 (2007)) (“[A] patent composed of several elements is not proved obvious merely by
24 demonstrating that each of its elements was, independently, known in the prior art”).

1 be evaluated for all that it teaches.⁵⁶³⁵ Defendants’ unsupported cobbling of selective disclosures
2 represents hindsight reconstruction.⁵⁶³⁶

3 Defendants fail to show a motivation or reason to combine or modify the references
4 recited above. Defendants make a conclusory statement that the claimed methods of treatment
5 would have been obvious but such a naked assertion does not show why a person of ordinary
6 skill would have been motivated to combine the references to achieve the claimed invention.⁵⁶³⁷

7 Defendants fail to show a reasonable expectation that a person of ordinary skill would
8 have successfully achieved the claimed invention. In fact, Defendants do not even discuss
9 whether a person of ordinary skill would have expected that the combination to work for its
10 intended purpose.⁵⁶³⁸ As such, Defendants fail to demonstrate reasonable expectation of success
11 of the claimed invention.

12 Defendants cite to Kelley for the proposition that it was known that DHA
13 supplementation decreases VLDL diameter and increases the concentrations of small VLDL
14 particles.⁵⁶³⁹ Subsequently, they argue that because of the increase in small VLDL particles, a
15 person of skill in the art would expect that DHA therapy would increase Apo-B. That is

17 ⁵⁶³⁵ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

18 ⁵⁶³⁶ *See, e.g., Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under
19 *KSR*, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention
20 without any explanation as to how or why the references would be combined to produce the claimed invention”).

21 ⁵⁶³⁷ *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the *KSR*
22 Court rejected a rigid application of the teaching, suggestion, or motivation (“TSM”) test in an obviousness inquiry,
23 the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill
24 in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness
determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

⁵⁶³⁸ *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable
result’ discussed in *KSR* refers not only to the expectation that prior art elements are capable of being physically
combined, but also that the combination would have worked for its intended purpose.”)

⁵⁶³⁹ Similarly, citing Olofsson and Bays, they assert that Apo-B is a component of VLDL, ignoring the relationship
of Apo-B to all atherogenic lipoproteins. *See* Section III.

1 incorrect. As discussed above, *see* Section III, Apo-B is associated with all atherogenic
2 lipoproteins, not simply small VLDL particles. Citing Leigh-Firbank, Defendants also assert that
3 DHA was known to increase LDL-C levels, which is incorrect for the reasons discussed above
4 and in Sections III and IV. Further, as discussed below, the Lovaza clinical trials showed that
5 DHA supplementation in very high TG patients *did not* increase Apo-B levels. A person of skill
6 in the art would have been aware of these data and accordingly would not have expected DHA
7 therapy to increase Apo-B levels in very high TG patients.

8 Defendants rely on Theobald, but *not* for the proposition that the asserted claim is
9 obvious. Instead, Defendants cite Theobald for the proposition that it was known that Apo-B is a
10 component of LDL-C. Defendants cite to no passage or page of Theobald in connection with
11 that argument and no support for their argument that Theobald makes such a disclosure.
12 Defendants appear to suggest a correlation between Apo-B and LDL-C but ignore that Apo-B is
13 present on all atherogenic lipoproteins.⁵⁶⁴⁰

14 Defendants then make the unsupported assertion that “one of ordinary skill in the art
15 would reasonably expect that a pure EPA composition would reduce Apo-B, as it is known to
16 reduce VLDL syntheses.” They are incorrect. Neither Defendants’ characterization of the
17 references identified with respect to this claim, nor the disclosures of those references teach that
18 EPA compositions would reduce Apo-B or render this claim obvious. Defendants’ assertion that
19 EPA was known to reduce VLDL synthesis ignores that, as discussed above, *see* Section III,
20 DHA was also understood to reduce VLDL synthesis. Nor do defendants explain the relevance
21 of VLDL synthesis to their arguments with respect to this claim or Apo-B levels.

22
23
24 ⁵⁶⁴⁰ June 26, 2012 Bays Declaration; *see also* Section III.

As discussed above, *see* Section IV, Theobald discloses the administration of a triacylglycerol composition derived from *Cryptocodinium cohnii* to healthy subjects. While Defendants make an unexplained citation to Theobald regarding the proposition that Apo-B is a component of LDL-C, they fail to discuss the reference's disclosures regarding the impact of administration of the triacylglycerol composition on Apo-B levels. In doing so, they fail to consider the reference for all that it teaches. Theobald discloses an *increase* in Apo-B following administration of the triacylglycerol composition of that reference.⁵⁶⁴¹

TABLE 3
Serum lipoproteins before treatment and after 3 mo of docosahexaenoic acid (DHA) and placebo treatment in all subjects

	DHA		Placebo		Treatment effect ¹
	Before treatment	After treatment	Before treatment	After treatment	
Total cholesterol (mmol/L)	5.15 ± 0.145 ²	5.44 ± 0.174	5.08 ± 0.168	5.22 ± 0.155	0.22 (0.01, 0.42) ³
LDL cholesterol (mmol/L)	3.16 ± 0.129	3.48 ± 0.152	3.16 ± 0.146	3.25 ± 0.131	0.23 (0.08, 0.38) ⁴
HDL cholesterol (mmol/L) ⁵	1.47 ± 0.052	1.55 ± 0.064	1.46 ± 0.062	1.48 ± 0.056	0.07 (0.005, 0.14)
Triacylglycerol (mmol/L) ⁶	1.03 ± 0.094	1.01 ± 0.089	1.06 ± 0.106	1.19 ± 0.103	-0.18 (-0.37, 0.05)
Apolipoprotein B (g/L)	0.84 ± 0.027	0.87 ± 0.026	0.83 ± 0.028	0.84 ± 0.028	0.03 (0.002, 0.055)⁷
LDL cholesterol:apo B (mmol/g)	3.75 ± 0.376	3.96 ± 0.462	3.74 ± 0.521	3.84 ± 0.409	0.12 (0.004, 0.24) ³
Weight (kg) ⁸	70.1 ± 2.04	70.6 ± 2.06	70.5 ± 2.01	70.6 ± 2.01	0 (-0.85, 0.24)

¹ Mean difference between active treatment and placebo; 95% CI in parentheses.

² $\bar{x} \pm \text{SEM}$ (all such values); $n = 38$.

^{3,4,7} Paired t test: ³ $P = 0.04$, ⁴ $P = 0.004$, ⁷ $P = 0.03$.

⁵ HDL increased in subjects receiving DHA first. Significant treatment \times order effect, $P = 0.005$.

⁶ $n = 37$; data were log transformed before analysis by paired t test.

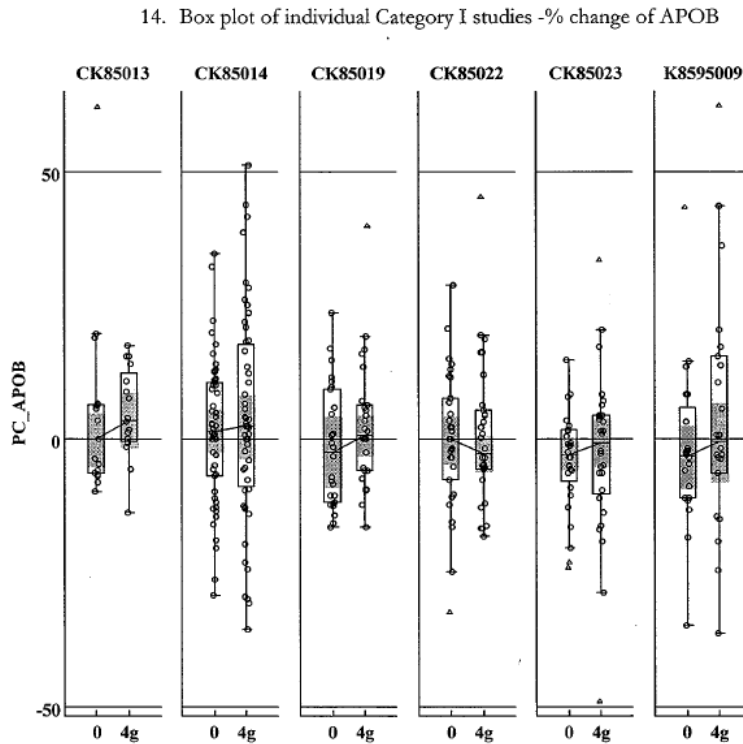
⁸ Weight increased over the entire study period. Significant order \times time effect, $P = 0.001$.

As discussed above, *see* Section III, a person of skill in the art would not have distinguished between the lipid effects of EPA and DHA therapy. To the extent, then that a person of ordinary skill would have considered Theobald, they would not conclude from the reference that EPA therapy decreases Apo-B levels in very high TG patients.

A person of skill in the art would *not* have understood that EPA therapy in very high TG patients would yield a reduction in Apo-B levels. A person of ordinary skill would have looked to the Lovaza clinical trials—the only clinical trial to study the effects of omega-3 fatty acids on

⁵⁶⁴¹ Theobald at 561, table 3.

1 Apo-B levels in patients with very high TG levels.⁵⁶⁴² The Lovaza clinical trial, which was a
 2 large study conducted on patients with very high TG levels, shows no difference between a
 3 placebo-control group and the treatment group with respect to Apo-B levels.⁵⁶⁴³



16 In each of these studies, including K8595009, where subjects had a median baseline TG
 17 level of 818 mg/dL,⁵⁶⁴⁴ there was no change in Apo-B between the control and treatment groups.
 18 Likewise, pooling the data from the different studies of Lovaza in the EU and US also reflected
 19 that treatment with Lovaza did not impact Apo-B compared to placebo.⁵⁶⁴⁵

20

21

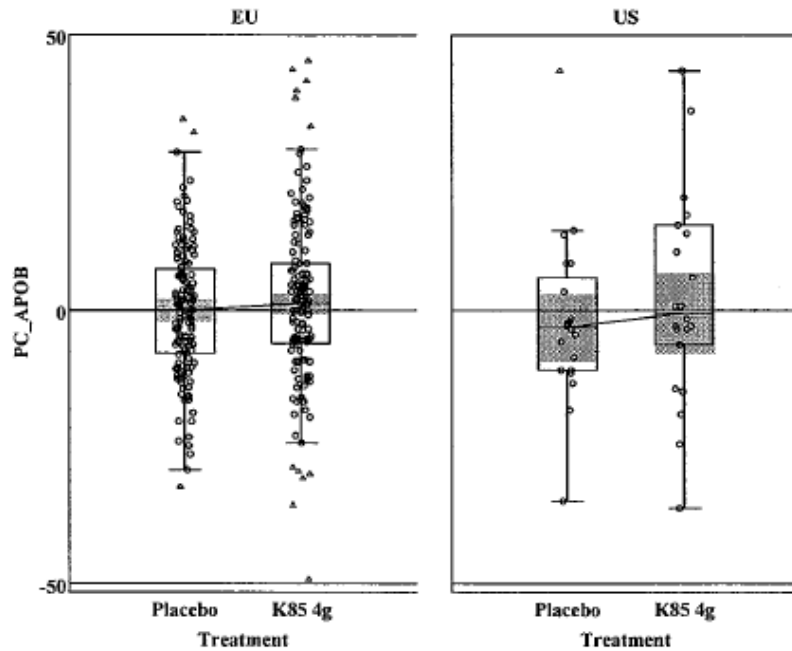
22 ⁵⁶⁴² May 8, 2012 Bays Declaration.

23 ⁵⁶⁴³ Lovaza Approval Package at Table 14.

24 ⁵⁶⁴⁴ The parameters for each study reports can be located at page 4 of the Lovaza Approval Package.

⁵⁶⁴⁵ Lovaza Approval Package at Table 7.

7. Box plot of pooled Category I studies -% change of APOB



Indeed, none of the data reported in the Lovaza clinical trials reflects a decrease in Apo-B. In addition to the Lovaza studies, a person of ordinary skill would have understood that the literature reported, in a variety of clinical studies, that omega-3s do not impact Apo-B levels.⁵⁶⁴⁶ While Theobald does not even support Defendants' obviousness arguments, their selective citation of that reference represents impermissible hindsight bias. The examiner had before him a large number of prior art references reporting Apo-B effects and, even as defendants concede, agreed that the Apo-B effects reported by the claimed inventions were unexpected in light of

⁵⁶⁴⁶ See Grimsgaard, Okumura, Hayashi, Hayasaka 1995, and Aoki 1993.

1 those references, also reflecting a lack of motivation and no reasonable expectation of
2 success.⁵⁶⁴⁷

3 Further, a person of skill in the art would have understood Apo-B to be a surrogate for the
4 number of atherogenic lipoproteins (VLDL, IDL, LDL) present in the body.⁵⁶⁴⁸ The person of
5 skill in the art would also have recognized that, as TG levels in patients with very high TG levels
6 rose, an increasing amount of TGs in those patients were contained within chylomicrons. As
7 discussed above, *see* Section III, the processing of chylomicrons would not yield atherogenic
8 lipoproteins, but instead smaller, denser particles referred to as remnant.⁵⁶⁴⁹ Accordingly,
9 because very high TG patients had increasing levels of TGs stored in chylomicrons and because
10 chylomicron processing would not have been understood to yield changes in Apo-B, a person of
11 skill in the art would have believed that TG-lowering therapies directed to very high TG patients
12 would not significantly impact Apo-B.

13 Accordingly, a person of ordinary skill in the art would not have been motivated to
14 replace EPA with the composition of Lovaza, nor would the person of ordinary skill in the art
15 have been motivated to administer the EPA composition of the claimed invention to very high
16 TG patients. For the same reasons, a person of ordinary skill in the art would not have a
17 reasonable expectation of success in achieving the claimed invention.

18
19 (d) Defendants Have Not Shown that Claim 5 of the
'698 Patent Would Have Been Obvious

20 Plaintiffs incorporate by reference the discussion related to the Independent Claim in
21 Section V.L.3. Because Defendants have not shown the obviousness of the Independent Claim

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⁵⁶⁴⁷ Defendants' Contentions at 236.

23 ⁵⁶⁴⁸ ATP-III at 3170; Bays 2008 I at 395.

24 ⁵⁶⁴⁹ Kwiterovich in Kwiterovich at 4.

1 by clear and convincing evidence, they also have not adequately proven the obviousness of
2 Claim 5.

3 Defendants contend that it would have been obvious to use the claimed composition to
4 reduce VLDL-C levels, and that the recited VLDL-C reduction represents therapeutic efficacy.
5 These contentions: 1) do not assert what the prior art discloses to a person of ordinary skill in
6 the art; 2) are irrelevant to an obvious analysis; 3) fail to address whether the specific
7 combination of claim elements were all present in the prior art references that would have been
8 combined by a person of ordinary skill in the art to produce the claimed invention with a
9 reasonable expectation of success; and 4) fail to establish *prima facie* obviousness. Defendants
10 do not offer an obvious analysis, but trivialize the claim element to the point of reading the
11 element out of the claim. Although convenient and expedient, Defendants' approach does not
12 conform with the Local Patent Rules of this District, the law of claim construction, or the law of
13 obviousness.

14 Defendants do not identify any combination of references. Because Defendants do not
15 identify any combination of references, they necessarily fail to offer any evidence that a person
16 of skill in the art would be motivated to combine those references in order to achieve the
17 invention of the claim as a whole. In fact, Defendants do not discuss at all whether a person of
18 ordinary skill would have been motivated to combine the elements.⁵⁶⁵⁰ As such, Defendants fail
19 to demonstrate that there was no motivation to combine the references to achieve the claimed
20 invention.

21
22 ⁵⁶⁵⁰ *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the *KSR*
23 Court rejected a rigid application of the teaching, suggestion, or motivation (‘TSM’) test in an obviousness inquiry,
24 the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill
in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness
determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

1 Similarly, without the disclosure of a combination of references and a motivation/reason
2 to combine or modify the references, Defendants necessarily fail to offer any evidence that a
3 person of ordinary skill in the art would have had a reasonable expectation of success in
4 achieving the claimed invention. Defendants make conclusory statements without providing any
5 support. What is more, Defendants do not even discuss the reasonable expectation of reducing
6 VLDL-C levels. As such, Defendants fail to demonstrate reasonable expectation of success of
7 reducing VLDL-C levels using the claimed methods.

8 (e) Defendants Have Not Shown that Claim 6 of the
9 '698 Patent Would Have Been Obvious

10 Plaintiffs incorporate by reference the discussion related to the Independent Claim in
11 Section V.L.3. Because Defendants have not shown the obviousness of the Independent Claim
12 by clear and convincing evidence, they also have not adequately proven the obviousness of
13 Claim 6.

14 Defendants do not identify any combination of references. Defendants contend, without
15 meaningful support, that a person of ordinary skill would have been able to determine the patient
16 population in need of the claimed methods of treatment, would seek to measure the fasting
17 baseline TG level of a patient, and would seek to treat those patients having very high
18 triglycerides. Defendants point to Lovaza and argue that it would have been obvious to one of
19 skill in the art to administer fish oil treatment to subjects with TG levels in the range of 500 to
20 1500 mg/dL. These contentions: 1) do not assert what the prior art discloses to a person of
21 ordinary skill in the art; 2) are irrelevant to an obvious analysis; 3) fail to address whether the
22 specific combination of claim elements were all present in the prior art references that would
23 have been combined by a person of ordinary skill in the art to produce the claimed invention
24 with a reasonable expectation of success; and 4) fail to establish *prima facie* obviousness.

1 Defendants do not offer an obvious analysis, but trivialize the claim element to the point of
2 reading the element out of the claim. Although convenient and expedient, Defendants' approach
3 does not conform with the Local Patent Rules of this District, the law of claim construction, or
4 the law of obviousness.

5 Defendants fail to show a specific combination of references that discloses each element
6 of the claimed invention. Because Defendants do not identify any combination of references,
7 they necessarily fail to offer any evidence that a person of skill in the art would be motivated to
8 combine those references in order to achieve the invention of the claim as a whole. Defendants
9 make conclusory statements without providing a reason that would have prompted a person of
10 ordinary skill to combine the elements.⁵⁶⁵¹ Such a naked assertion does not show why a person
11 of ordinary skill would have been motivated to treat the recited patient population using the
12 claimed methods of treatment.⁵⁶⁵²

13 Similarly, without the disclosure of a combination of references and a motivation/reason
14 to combine or modify the references, Defendants necessarily fail to offer any evidence that a
15 person of ordinary skill in the art would have had a reasonable expectation of success in
16 achieving the claimed invention. Defendants do not even discuss whether a person of ordinary
17 skill would have expected that the combination to work for its intended purpose for treating the
18

19 ⁵⁶⁵¹ *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (“Rejections on obviousness grounds cannot be
20 sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational
21 underpinning to support the legal conclusion of obviousness.”) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir.
2006)) (internal quotation marks omitted)

22 ⁵⁶⁵² *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the *KSR*
23 Court rejected a rigid application of the teaching, suggestion, or motivation (‘TSM’) test in an obviousness inquiry,
24 the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill
in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness
determination.”) (quoting *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

1 recited patient population.⁵⁶⁵³ As such, Defendants fail to demonstrate reasonable expectation of
2 success of the claimed invention.

3 (f) Defendants Have Not Shown that Claims 7 and 8 of
4 the '698 Patent Would Have Been Obvious

5 Plaintiffs incorporate by reference the discussion related to the Independent Claim in
6 Section V.L.3. Because Defendants have not shown the obviousness of the Independent Claim
7 by clear and convincing evidence, they also have not adequately proven the obviousness of
8 Claims 7 and 8.

9 Defendants contend, without providing meaningful support, that the claim element was
10 well known in the art. These contentions: 1) do not assert what the prior art discloses to a
11 person of ordinary skill in the art; 2) are irrelevant to an obvious analysis; 3) fail to address
12 whether the specific combination of claim elements were all present in the prior art references
13 that would have been combined by a person of ordinary skill in the art to produce the claimed
14 invention with a reasonable expectation of success; and 4) fail to establish *prima facie*
15 obviousness. Defendants do not offer an obvious analysis, but trivialize the claim element to the
16 point of reading the element out of the claim. Although convenient and expedient, Defendants'
17 approach does not conform with the Local Patent Rules of this District, the law of claim
18 construction, or the law of obviousness.

19 Defendants fail to show a specific combination of references that discloses each element
20 of the claimed invention. Defendants make a conclusory statement that the claimed method of
21 treatment was well known in the art, but such a naked assertion does not show why a person of

22 ⁵⁶⁵³ *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable
23 result’ discussed in KSR refers not only to the expectation that prior art elements are capable of being physically
24 combined, but also that the combination would have worked for its intended purpose.”)

1 ordinary skill would have been motivated to combine the references to achieve the claimed
2 invention.⁵⁶⁵⁴ Further Defendants cite to the “Lovaza product” without identifying the prior art
3 reference to which they refer. Such a reference is inadequate.

4 Defendants fail to show a reasonable expectation that a person of ordinary skill would
5 have successfully achieved the claimed invention. Defendants do not even discuss whether a
6 person of ordinary skill would have expected that the combination to work for its intended
7 purpose.⁵⁶⁵⁵ As such, Defendants fail to demonstrate reasonable expectation of success of the
8 claimed invention.

9 4. The '698 Patent is Not Invalid Under § 112

10 a) Defendants Have Not Demonstrated that the Claims of the '698 11 Patent Are Invalid for Indefiniteness

12 35 U.S.C. ¶ 112(b) requires that a patentee “particularly point[] out and distinctly claim[]
13 the subject matter which the applicant regards as his invention.”⁵⁶⁵⁶ Patent claims are valid in
14 light of an indefiniteness challenge if they “inform, with reasonable certainty, those skilled in the
15 art about the scope of the invention” in light of the specification and the prosecution history.⁵⁶⁵⁷

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17 ⁵⁶⁵⁴*Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the *KSR*
18 Court rejected a rigid application of the teaching, suggestion, or motivation (‘TSM’) test in an obviousness inquiry,
the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill
in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness
determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

19 ⁵⁶⁵⁵*DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable
20 result’ discussed in *KSR* refers not only to the expectation that prior art elements are capable of being physically
combined, but also that the combination would have worked for its intended purpose.”)

21 ⁵⁶⁵⁶ Defendants were required to disclose the basis for their assertion of indefiniteness with respect to each term, and
they have not met that requirement. They simply make conclusory assertions regarding indefiniteness despite
22 bearing the burden of proof. Moreover, Defendants’ failure prevents Plaintiffs from responding to their assertions
other than by making conclusory assertions in return. Therefore, Defendants should be precluded from
23 supplementing their naked assertions with new basis in the course of the litigation.

24 ⁵⁶⁵⁷*Nautilus, Inc. v. Biosig Instruments, Inc.*, 134 S. Ct. 2120, 2124 (2014).

1 The Supreme Court has recognized that “absolute precision is unattainable” in claim language
2 and “the certainty which the law requires in patents is not greater than is reasonable.”⁵⁶⁵⁸

3 Defendants allege that a number of terms containing the phrases “about” and
4 “substantially” are indefinite. Defendants do not provide any reason why these terms are
5 indefinite other than that they contain the phrases “about” and “substantially.” But, of course,
6 these terms are routinely used in patent claims, and are not *per se* indefinite.⁵⁶⁵⁹ In particular,
7 courts have held repeatedly that claims that contain the words “about” and “substantially” are not
8 indefinite.⁵⁶⁶⁰ Here, a person of ordinary skill would understand with reasonable certainty what
9 is claimed when the claims are read in light of the specification and prosecution history.⁵⁶⁶¹
10 Therefore, the terms that contain the words “about” and “substantially” are not invalid for being
11 indefinite.

12 Defendants further allege that the term “a pharmaceutical composition comprising... not
13 more than about 4% docosahexaenoic acid, by weight of all fatty acids” is indefinite. They

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15 ⁵⁶⁵⁸ *Id.* at 2129.

16 ⁵⁶⁵⁹ *Interval Licensing LLC v. AOL, Inc.*, 766 F.3d 1364, 1370 (Fed. Cir. 2014) (“Claim language employing terms
17 of degree has long been found definite where it provided enough certainty to one of skill in the art when read in the
18 context of the invention.”); *see also BJ Servs. Co. v. Halliburton Energy Servs., Inc.*, 338 F.3d 1368, 1372 (Fed. Cir.
19 2003) (“The question becomes whether one of ordinary skill in the art would understand what is claimed when the
20 claim is read in light of the specification.”) (discussing the term “about”); *Verve, LLC v. Crane Cams, Inc.*, 311 F.3d
21 1116, 1120 (Fed. Cir. 2002) (“It is well established that when the term ‘substantially’ serves reasonably to describe
22 the subject matter so that its scope would be understood by persons in the field of the invention, and to distinguish
23 the claimed subject matter from the prior art, it is not indefinite.”).

20 ⁵⁶⁶⁰ *See, e.g., Deere & Co. v. Bush Hog, LLC*, 703 F.3d 1349, 1359 (Fed. Cir. 2012) (rejecting contention that claim
21 term “substantially planar” is indefinite); *Enzo Biochem, Inc. v. Applera Corp.*, 599 F.3d 1325, 1335 (Fed. Cir.
22 2010) (holding that the claim phrase “not interfering substantially” was not indefinite even though the construction
23 “define[d] the term without reference to a precise numerical measurement”); *BJ Services Co. v. Halliburton Energy
24 Services, Inc.*, 338 F.3d 1368, 1372–73 (Fed. Cir. 2003) (affirming jury’s verdict that claims reciting a concentration
as “about 0.06” were not invalid for being indefinite); *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540,
1557 (Fed. Cir. 1983) (ruling that the claim term “stretching ... at a rate exceeding about 10% per second” is not
indefinite).

⁵⁶⁶¹ *See generally* the ’698 patent and its prosecution history.

1 contend that, because there is no indication of how much of the pharmaceutical composition is
2 composed of fatty acids, by extension it is indefinite how much of each fatty acid is present in
3 the composition. This is incorrect. A claim can use a ratio to define amounts of components in a
4 product, using terms such as “percent by weight.”⁵⁶⁶² In light of the specification and
5 prosecution history, a person of ordinary skill would understand with reasonable certainty the
6 range of relative quantities of EPA, DHA and/or other fatty acids in the recited pharmaceutical
7 composition in relation to all fatty acids present.⁵⁶⁶³ Therefore, the term is not indefinite and do
8 not render the claims indefinite.

9 Defendants also allege that it is impossible to ascertain the metes and bounds of “second
10 patient population ... who has not received the pharmaceutical composition.” A person of
11 ordinary skill, however, would understand the metes and bounds of the term in light of the
12 specification and the prosecution history.⁵⁶⁶⁴ Moreover, the method of comparing a subject to a
13 second patient population, such as a placebo controlled, randomized, double blind study, would
14 have been known to a person of ordinary skill at the time of the invention. Therefore, the term
15 does not render the claims indefinite.

16 Defendants further contend that claims 4 and 5 are indefinite because “claim 1 contains
17 no discussion of LDL-C levels and lacks antecedent basis.” Claims 4 and 5 of the ‘698 patent
18 have been corrected to dependent from claim 2. Therefore, Defendants’ allegations of
19 indefiniteness are misplaced.

20 ⁵⁶⁶² *T.F.H. Publications, Inc. v. Doskocil Mfg. Co.*, No. CIV.A. 08-4805 FLW, 2012 WL 715628, at *5–6 (D.N.J.
21 Mar. 5, 2012) (construing “by weight” to mean the weight of a first component was in a ratio to the weight of a
22 second component); *Allergan, Inc. v. Sandoz Inc.*, No. 2:09-CV-182, 2011 WL 1599049, at *10 (E.D. Tex. Apr. 27,
2011) (construing percent by weight to mean “ratio of the weight of the ingredient in question divided by the total
volume of the solution, with this ratio expressed as a percentage”).

23 ⁵⁶⁶³ See generally the ‘698 patent and its prosecution history.

24 ⁵⁶⁶⁴ See generally the ‘698 patent and its prosecution history.

1 Finally, Defendants contend that the asserted claims improperly mix methods and
2 formulations because Plaintiffs' assertion of contributory infringement apparently suggests that
3 the scope of the claims includes formulations. This is a mistaken interpretation. Indefiniteness
4 analysis is based on what the claim language informs a person of ordinary skill in the art in light
5 of the specification and the prosecution history. Defendants do not identify any actual claim
6 language that mixes methods and formulations. Moreover, contributory infringement may be
7 asserted and proven when a party sells "a material or apparatus for use in *practicing a patented*
8 *process . . . knowing the same to be especially made or especially adapted for use in an*
9 *infringement of such patent.*"⁵⁶⁶⁵ Plaintiffs assert that Defendants' ANDA products will be used
10 in practicing the claimed methods. Plaintiffs do not assert that the pharmaceutical compound
11 itself directly infringes. Therefore, Defendants' interpretations of Plaintiffs' assertions are
12 mistaken and the '698 patent claims are not indefinite for improperly mixing methods and
13 formulations.

14 b) Defendants Have Not Demonstrated that the Claims of the '698
15 Patent Are Invalid for Insufficient Written Description

16 The first paragraph of 35 U.S.C. § 112 requires that a patent specification "contain a
17 written description of the invention." This requires that the specification "reasonably convey"
18 that the applicant "invented" or "had possession" of the claimed subject matter when the
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24 ⁵⁶⁶⁵ 35 U.S.C. § 271(c) (emphasis added).

1 application was filed.⁵⁶⁶⁶ Support need not be literal⁵⁶⁶⁷—it may be implicit⁵⁶⁶⁸ or inherent⁵⁶⁶⁹ in
2 the disclosure. In addition, it is unnecessary to include information that is already known or
3 available to persons of ordinary skill.⁵⁶⁷⁰

4 Defendants make three arguments regarding the written description requirement. First,
5 Defendants contend that elements reciting the baseline TG levels of the asserted claims lack
6 written description. This is incorrect. The specification of asserted patents literally discloses the
7 claimed invention.⁵⁶⁷¹ Moreover, the recited baseline TG levels of the claimed invention appear
8 in the original claims of the application to which the asserted patent claims priority. Thus, there
9 is a strong presumption that the claimed invention is adequately described.⁵⁶⁷² Defendants do
10 not and cannot rebut this presumption. Specifically, the patient population is originally claimed
11 as “a subject having a fasting baseline triglyceride level of about 500 mg/dl to about 1500
12 mg/dl.”⁵⁶⁷³ The asserted claims recite the same patient population. Defendants do not contend
13 that the patient population of the asserted claims is not literally described by the specification
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15 ⁵⁶⁶⁶ *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010).

16 ⁵⁶⁶⁷ *Id.* at 1352; *Cordis Corp. v. Medtronic AVE, Inc.*, 339 F.3d 1352, 1365 (Fed. Cir. 2003); *In re Wright*, 866 F.2d
422, 425 (Fed. Cir. 1989); *In re Smith*, 481 F.2d 910, 914 (C.C.P.A. 1973).

17 ⁵⁶⁶⁸ *All Dental Prodx, LLC v. Advantage Dental Prods. Inc.*, 309 F.3d 774, 779 (Fed. Cir. 2002); *In re Wright*, 866
F.2d at 424–25.

18 ⁵⁶⁶⁹ *In re Gay*, 309 F.2d 769, 771 (C.C.P.A. 1962).

19 ⁵⁶⁷⁰ *Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1367–68 (Fed. Cir. 2006); *Capon v. Eshhar*, 418 F.3d 1349,
1357 (Fed. Cir. 2005); *In re Gay*, 309 F.2d at 774.

20 ⁵⁶⁷¹ *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (“[T]he test requires an objective
inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art.”);
21 *Snitzer v. Etzel*, 465 F.2d 899, 902 (C.C.P.A. 1972) (“[T]he literal description of a species provides the requisite
legal foundation for claiming that species.”).

22 ⁵⁶⁷² *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976) (“we are of the opinion that the PTO has the
initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure
23 a description of the invention defined by the claims”).

24 ⁵⁶⁷³ See U.S. Provisional Application No. 61/151,291.

1 and in the original claims of the application to which the asserted patent claims priority. In fact,
2 the specification and the provisional patent application claims at the time of filing described
3 these limitations. Therefore, Defendants have failed to explain whether and how an aspect of the
4 claimed invention has not been described with sufficient particularity such that one skilled in the
5 art would recognize that the applicant had possession of the claimed invention.

6 Second, Defendants contend that “a person of skill in the art would not understand that
7 the inventor was in possession of a method incorporating [] specific dosages and quantities.”
8 Defendants’ assertion is incorrect. The specification of the asserted patents literally discloses the
9 dosages and quantities of the claimed methods.⁵⁶⁷⁴ Moreover, the dosages and quantities of the
10 method appear in the claims, as originally filed. Thus, there is a strong presumption that the
11 claimed invention is adequately described.⁵⁶⁷⁵ Defendants do not and cannot rebut this
12 presumption. For example, the dosage of the composition was originally claimed as “about 1 g
13 to about 4g.”⁵⁶⁷⁶ The asserted claims recite “4 g.” Defendants do not contend that dosages and
14 quantities of the asserted claims are not literally described by the specification and in the original
15 claims. In fact, the specification and the provisional patent application claims, at the time of
16 filing, described these limitations. Therefore, Defendants have failed to explain whether and
17 how an aspect of the claimed invention has not been described with sufficient particularity such
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20 ⁵⁶⁷⁴ *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (“[T]he test requires an objective
21 inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art.”);
Snitzer v. Etzel, 465 F.2d 899, 902 (C.C.P.A. 1972) (“[T]he literal description of a species provides the requisite
22 legal foundation for claiming that species.”).

23 ⁵⁶⁷⁵ *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976) (“we are of the opinion that the PTO has the
24 initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure
a description of the invention defined by the claims”).

⁵⁶⁷⁶ *See* U.S. No. 12/702,889.

1 that one skilled in the art would recognize that the applicant had possession of the claimed
2 invention.

3 Third, Defendants contend that “a person of skill in the art would not understand that the
4 inventor was in possession of a method comprising a comparison against a second subject or
5 against a second population.” The specification demonstrates that the applicants were in
6 possession of the claimed inventions. For example, a person of ordinary skill would have
7 understood that the inventor was in possession of a method comprising administration of a
8 composition with the recited properties, based on a comparison of a patient population to a
9 second patient population.

10 In its 2010 *en banc* decision in *Ariad Pharmaceuticals, Inc. v. Eli Lilly Co.*,⁵⁶⁷⁷ the court
11 elaborated that “possession” means possession as evidenced by disclosure. In this case, the
12 specification of asserted patents literally disclose the claimed invention in the specification and
13 the claims as originally filed. Thus, an examination of the four corners of the specification from
14 the perspective of a person of ordinary skill in the art demonstrates that the inventors of the
15 asserted patents were in possession of the claimed invention.

16 Defendants conclude by alleging that the specification does not describe anything more
17 than what is obvious, and thus does not provide adequate support for any nonobvious claim.
18 That is incorrect and irrelevant. Nonobviousness does not have to be supported solely by the
19 specification; nonobviousness can be supported by post-filing date evidence for example.⁵⁶⁷⁸
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21 ⁵⁶⁷⁷ *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1343-48 (Fed. Cir. 2010).

22 ⁵⁶⁷⁸ See *Sanofi–Aventis Deutschland GmbH v. Glenmark Pharm., Inc.*, 748 F.3d 1354, 1360 (Fed. Cir. 2014)
23 (“Glenmark also argues that later-discovered benefits cannot be considered in an obviousness analysis.... That is
24 incorrect; patentability may consider all of the characteristics possessed by the claimed invention, whenever those
characteristics become manifest.”); *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291,
1307 (Fed. Cir. 2011) (“[E]vidence of unexpected results may be [considered] ... even if that evidence was obtained

1 Written description requires only that the specification reasonably conveys that the applicant had
2 possession of the claimed subject matter when the application was filed. Therefore, whether the
3 claims are obvious has no bearing on the adequacy of written description.

4 c) Defendants Have Not Demonstrated that the Claims of the '698
5 Patent Are Invalid for Lack of Enablement

6 The first paragraph of 35 U.S.C. § 112 requires that the specification “enable any person
7 skilled in the art . . . to make and use [the claimed invention].” A claim is not enabled if it would
8 require undue experimentation for a person of ordinary skill to make or use the invention.

9 Factors that may be considered include the quantity of experimentation necessary, the amount of
10 direction or guidance presented, the presence or absence of working examples, the nature of the
11 invention, the state of the prior art, the relative skill of those in the art, the predictability or
12 unpredictability of the art, and the breadth of the claims.⁵⁶⁷⁹ The enablement requirement is
13 separate and distinct from the written description requirement,⁵⁶⁸⁰ and as such a claim does not
14 require descriptive support in the disclosure as originally filed for it to be enabled.⁵⁶⁸¹

15 Defendants make two specific arguments regarding the enablement requirement. First,
16 Defendants contend that “[i]t would take undue experimentation to obtain the actual amounts of
17 the composition found in the ultimate claims.” This is incorrect. As Defendants admit, the
18 claims disclose amounts of the composition to be administered. Therefore, a person of ordinary
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22 after the patent's filing or issue date.”); *Knoll Pharm. Co. v. Teva Pharm. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004) (“Evidence developed after the patent grant is not excluded from consideration, for understanding of the full range of an invention is not always achieved at the time of filing the patent application.”).

23 ⁵⁶⁷⁹ See, e.g., *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

24 ⁵⁶⁸⁰ *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991)

⁵⁶⁸¹ MPEP § 2164.

1 skill would be able to determine the amounts of the components in the pharmaceutical
2 composition without any experimentation, much less undue experimentation.

3 Second, Defendants contend that it would take undue experimentation to obtain the
4 claimed required results listed in the full scope of the patent claims, including the claimed lipid
5 effects. This is incorrect. The asserted claims require no experimentation to practice the claimed
6 method and certainly not undue experimentation. Administration of a recited amount of a recited
7 composition, for a recited duration, to a specific, recited patient population produces the recited
8 results. No additional experimentation is required, and Defendants do not explain their
9 allegation that undue experimentation would be required. Defendants also do not contend that
10 following the claimed method (each recited element) does not produce the recited results. The
11 clinical studies included in the VASCEPA® label and submitted to the USPTO clearly
12 demonstrate that administration of EPA of the recited composition, when administered to
13 patients with very high TG levels for at least 12 weeks, as specified, produces the recited
14 results.⁵⁶⁸² Therefore, the claims are not invalid for lack of enablement.

15 Defendants conclude by alleging that the specification does not enable anything more
16 than what is obvious over the prior art or was known to a person of skill in the art. First,
17 Defendants do not cite any case or present a legal theory to support this assertion. As such, they
18 do not allow Plaintiffs to adequately respond to the assertion. Therefore, Defendants should be
19 precluded in the future from raising any new legal theory to support this assertion. Moreover,
20 while the '698 patent's specification enables a person of ordinary skill to obtain the claimed
21 limitations without undue experiment, the claimed limitations would not have been obvious to a
22 person of ordinary skill, as discussed in Section V.L.3. Furthermore, Plaintiffs have initiated

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⁵⁶⁸² See VASCEPA® Prescribing Information at Table 2.

1 human clinical trials and submitted the trial results to the USPTO to substantiate the utility of its
2 claimed methods.^{5683, 5684} Therefore, a person of ordinary skill would have concluded that the
3 claims possessed credible therapeutic utility, and the full scope of the claims was enabled.

4 **M. The '372 Patent**

5 **1. The '372 Patent Claims Eligible Subject Matter Under § 101**

6 Defendants' allegation that the asserted claims of the '372 patent relate to ineligible
7 subject matter under Section 101 is without merit. Defendants do not establish a *prima facie*
8 case under Section 101 or provide a legal or factual basis to support their allegations.

9 As an initial matter, Defendants' disclosure is also insufficient under the Nevada Local
10 Patent Rules as the grounds for any allegation of invalidity under Section 101 must be
11 provided.⁵⁶⁸⁵ The bare assertion of invalidity under Section 101 without providing the grounds
12 for such an allegation and examining the elements of the asserted claims of the '372 patent does
13 not meet this requirement and thwarts the purpose of the Rules.⁵⁶⁸⁶

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16 ⁵⁶⁸³ *In re Brana*, 51 F.3d 1560, 1567 n.19 (Fed. Cir. 1995) (Post-filing evidence “can be used to substantiate any
17 doubts as to the asserted utility.”); MPEP § 2107.03 (“[A]s a general rule, if an applicant has initiated human clinical
18 trials for a therapeutic product or process, Office personnel should presume that the applicant has established that
19 the subject matter of that trial is reasonably predictive of having the asserted therapeutic utility.”).

20 ⁵⁶⁸⁴ See May 16, 2011 Bays Declaration at Appendix B.

21 ⁵⁶⁸⁵ See Nevada Local Patent Rule 1.8(e) (“[E]ach party opposing a claim of patent infringement, shall serve on all
22 other parties Non-Infringement, Invalidity, and Unenforceability Contentions that must include . . . A detailed
23 statement of any grounds of invalidity based on 35 U.S.C. § 101.”).

24 ⁵⁶⁸⁶ Nor does the preceding paragraph, which provides only a purported summary of the claims of the '372 patent, or
subsequent paragraph, which makes what appears to be an argument entirely unrelated to Section 101, provide the
grounds for Defendants' allegation of invalidity under 35 U.S.C. § 101. See, e.g., *Silver State Intellectual Techs.,
Inc. v. Garmin Int'l, Inc.*, 32 F. Supp. 3d 1155, 1161–62 (D. Nev. 2014) (“The District of Nevada’s Local Patent
Rules, like the local patent rules for the Northern District of California, are designed to require the parties to provide
early notice of their infringement and invalidity contentions, and to proceed with diligence in amending those
contentions when new information comes to light in the course of discovery”) (internal quotation marks omitted).

1 The inquiry under Section 101 involves a two-step test: first, a court must determine
2 whether the claim at issue is directed to a patent-ineligible concept: a law of nature, physical
3 phenomenon, or abstract idea.⁵⁶⁸⁷ Second, even if the claim is directed to one of these concepts,
4 it still may be patent eligible and the court must determine what else is part of the claim.⁵⁶⁸⁸

5 The sole Section 101 case identified by Defendants, *Mayo Collaborative Services v.*
6 *Prometheus Laboratories, Inc.*, 132 S. Ct. 1289 (2012), is inapplicable to the asserted claims of
7 the '372 patent. In *Mayo*, the claims were directed to “well-understood, routine, [and]
8 conventional” steps, and the only novel element related to administering the proper dosage based
9 on a natural law observation.⁵⁶⁸⁹ However, the claims merely recited this natural law without
10 reciting any novel application of it.⁵⁶⁹⁰ The Court found that providing protection to such
11 claims would result in pre-empting “a broad range of potential uses” and excluding others from
12 using “the basic tools of scientific and technical work.”⁵⁶⁹¹ A method of treatment claim,
13 specifying the subjects, dosage levels, composition, and time course does not raise the concerns
14 of *Mayo* and instead is akin to the typical claims which *Mayo* acknowledges are entitled to patent
15 protection.⁵⁶⁹²

17 ⁵⁶⁸⁷ *Alice Corp. Pty. v. CLS Bank Int'l*, 134 S. Ct. 2347, 2355 (2014) (“First, we determine whether the claims at
18 issue are directed to one of those patent-ineligible concepts.”).

18 ⁵⁶⁸⁸ *Id.* (quoting *Mayo*, 132 S. Ct. at 1294) (“If so, we then ask, ‘[w]hat else is there in the claims before us?’”).

19 ⁵⁶⁸⁹ *Mayo*, 132 S. Ct. at 1294.

20 ⁵⁶⁹⁰ *Id.* at 1301.

20 ⁵⁶⁹¹ *Id.*

21 ⁵⁶⁹² *Id.* at 1302 (contrasting the patent-ineligible claims of that case to “a typical patent on a new drug or a new way
22 of using an existing drug); see also *Diamond v. Diehr*, 450 U.S. 175, 177, 191-193 (1981) (upholding patentability
23 for “a process for curing synthetic rubber which includes in several of its steps the use of a mathematical formula
24 and a programmed digital computer” under Section 101); *Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc.*, 827 F.3d
1042, 1048-49 (Fed. Cir. 2016) (finding claims patent eligible because by holding otherwise, a host of other patent
eligible claims, such as method of treatment claims, would also be necessarily ineligible).

1 Defendants suggest that the recited EPA composition of each asserted claim is a naturally
2 occurring substance. It is not. Even references contained within Defendants’ own contentions
3 make clear that EPA of the requisite purity and characteristics is not found in nature.⁵⁶⁹³ As
4 expressed by the patents cited in Defendants’ contentions and well-established precedent, for
5 decades it has been accepted that compositions isolated from nature or purified beyond their
6 natural state are patent-eligible.⁵⁶⁹⁴ Moreover, Defendants’ assertions are immaterial to a Section
7 101 defense because method of treatment claims like the ones asserted in this case are patent
8 eligible even if they are directed to administration of a naturally occurring substance.⁵⁶⁹⁵

9 To the extent Defendants are arguing that a law of nature both underlies the claims and
10 renders them ineligible, that argument is unsupported and incorrect. Defendants allege that “the
11 claimed effects are the natural result of ingesting a naturally-occurring substance.”⁵⁶⁹⁶ Since the
12 composition that is the subject of the claims is not naturally occurring, Defendants appear to
13 suggest that all method of treatment claims involve a law of nature. That is not what *Mayo* states
14 or even suggests, and indeed the Federal Circuit has refused to adopt Defendants’ overbroad
15 characterization of laws of nature.⁵⁶⁹⁷ To say that the claims of the ’372 patent claim a law of
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17 ⁵⁶⁹³ See, e.g., U.S. Patent No. 5,215,630, “Method of Purifying Eicosapentaenoic Acid or the Ester Derivative
18 Thereof by Fractional Distillation” (cited in Defendants’ Joint Invalidity Contentions, e.g., at 26–27).

19 ⁵⁶⁹⁴ See, e.g., *In re Bergy*, 596 F.2d 952; *In re Kratz*, 592 F.2d 1169 (CCPA 1979); *In re Bergstrom*, 427 F.2d 1394
(CCPA 1970); *Parke-Davis & Co. v. H.K. Mulford Co.*, 189 F.95 (S.D.N.Y. 1911).

20 ⁵⁶⁹⁵ *Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc.*, 827 F.3d 1042, 1048-49 (Fed. Cir. 2016).

21 ⁵⁶⁹⁶ See Defendants’ Joint Invalidity Contentions at 741.

22 ⁵⁶⁹⁷ See *CellzDirect*, 827 F.3d at 1048-49 (“The [asserted] claims are like thousands of others that recite processes
23 to achieve a desired outcome That one way of describing the process is to describe the natural ability of the
24 subject matter to *undergo* the process does not make the claim ‘directed to’ that natural ability. If that were so, we
would find patent-ineligible methods of . . . treating cancer with chemotherapy (as directed to cancer cells’ inability
to survive chemotherapy), or treating headaches with aspirin (as directed to the human body’s natural response to
aspirin).”).

1 nature is to suggest that all patents claim such laws and engage in an infinitely regressive mode
2 of analysis that the Supreme Court did not adopt in which “all inventions can be reduced to
3 underlying principles of nature” that would “make all inventions unpatentable.”⁵⁶⁹⁸ Indeed, even
4 those concerned about the implications of *Mayo* on future patents were focused on diagnostic
5 claims not treatment claims of the type that *Mayo* stated were typical and patentable.⁵⁶⁹⁹

6 Even if there is some underlying law of nature in the asserted claims, the subject matter
7 of the '372 patent remains eligible for protection under Section 101. As articulated by *Mayo* and
8 *Diehr*, patents claiming a law of nature, such as a mathematical equation, are entitled to
9 protection where claims “did not ‘seek to pre-empt the use of [the] equation,’ but sought ‘only to
10 foreclose from others the use of that equation in conjunction with all of the other steps in their
11 claimed process.’”⁵⁷⁰⁰ As discussed above, the asserted claims of the '372 patent contain a
12 novel, unconventional, and specific method of treatment comprising a particularized application
13 of a nonnaturally occurring substance and does not preempt the use of a law of nature.⁵⁷⁰¹

14 Defendants also argue that any argument by Amarin in response to Defendants’ § 112
15 arguments are further evidence of invalidity under § 101. This argument is without merit. The
16 claims are enabled and written description is satisfied for the reasons discussed below. In
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⁵⁶⁹⁸ See *Mayo*, 132 S. Ct. at 1034 (quoting *Diamond v. Diehr*, 450 U.S. 175, 188 (1981)).

20 ⁵⁶⁹⁹ See *Mayo*, 132 S. Ct. at 1034 (“Prometheus, supported by several *amici*, argues that a principle of law denying
21 patent coverage here will interfere significantly with the ability of medical researchers to make valuable discoveries,
particularly in the area of diagnostic research.”).

22 ⁵⁷⁰⁰ See *Mayo*, 132 S. Ct. at 1299 (quoting *Diehr*, 450 U.S. at 187).

23 ⁵⁷⁰¹ See, e.g., *Tannas Electronics v. Luxell Technologies, Inc.*, 2012 WL 3800822, at *4 (C.D. Cal. July 24, 2012)
24 (rejecting a challenge to the patentability of a claim under Section 101 where the alleged natural phenomenon was
“just one step in the whole process” claimed by the invention).

1 addition, as discussed above, the asserted claims are not merely a naturally-occurring
2 phenomena, and thus satisfy the requirements of § 101.

3 **2. The Asserted Claims of the ‘372 Patent Are Not Anticipated by WO**
4 **‘118**

5 To anticipate, a single prior art reference must sufficiently describe a claimed
6 invention so that the public is in “possession” of that invention.⁵⁷⁰² Therefore, to anticipate, a
7 reference must set forth every element of the claim, either expressly or inherently, in as complete
8 detail as is contained in the claim.⁵⁷⁰³ The claim elements must also be “arranged” in the prior
9 art reference, just as they are in the claim,⁵⁷⁰⁴ rather than as “multiple, distinct teachings that the
10 artisan might somehow combine to achieve the claimed invention.”⁵⁷⁰⁵ In addition, public
11 “possession” requires that the prior art enable a person of ordinary skill to make and use the
12 invention without undue experimentation.⁵⁷⁰⁶ Factors that may be included in this analysis
13 include the quantity of experimentation necessary, the amount of direction or guidance
14 presented, the presence or absence of working examples, the nature of the invention, the state of
15 the prior art, the relative skill of those in the art, the predictability or unpredictability of the art,

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⁵⁷⁰² *Akzo N.V. v. U.S. Int’l Trade Com’n*, 808 F.2d 1471, 1479 (Fed. Cir. 1986).

20 ⁵⁷⁰³ *Id.*; *In re Bond*, 910 F.2d 831, 832 (Fed. Cir. 1990); *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed.
21 Cir. 1989).

22 ⁵⁷⁰⁴ *Bond*, 910 F.2d at 833; *Akzo*, 808 F.2d at 1479.

23 ⁵⁷⁰⁵ *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369–71 (Fed. Cir. 2008); *In re Arkley*, 455 F.2d 586, 587
24 (C.C.P.A. 1972); *In re Ruschig*, 343 F.2d 965, 974 (C.C.P.A. 1965).

⁵⁷⁰⁶ *Akzo*, 808 F.2d at 1479; *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1085 (Fed. Cir. 2008); *Forest Labs.,
Inc. v. Ivax Pharms., Inc.*, 501 F.3d 1263, 1268–69 (Fed. Cir. 2007).

1 and the breadth of the claims.⁵⁷⁰⁷ This inquiry is objective, and thus evidence of undue
2 experimentation need not be prior art.⁵⁷⁰⁸

3 Defendants assert that Claims 1-25 of the '372 Patent are anticipated by the WO '118
4 reference.⁵⁷⁰⁹

5 A element-by-element analysis, identifying each element of each asserted claim that is
6 absent from WO '118, is provided below. The contentions below are incorporated by reference
7 into Exhibit M, and vice-versa. WO '118 does not anticipate the claims of the '372 patent
8 because it does not describe, properly arrange, or enable the '372 patent claims.

9 a) WO '118 Does Not Teach Every Element of the Claims of the
10 '372 Patent

11 (1) WO '118 Does Not Describe the Claimed Lipid Effects

12 It is well established that, for a prior art reference to anticipate, “every element of the
13 claimed invention must be identically shown in a single reference.”⁵⁷¹⁰ Moreover, the elements
14 of the claimed invention must have “strict identity” with the elements of the reference; “minimal
15 and obvious” differences are sufficient to prevent anticipation.⁵⁷¹¹ Here, WO '118 entirely fails
16 to disclose the following elements of Claim 1 of the '372 Patent: *to reduce fasting triglycerides*
17 *in the at least one subject*. WO '118 further entirely fails to disclose the following elements of

18 ⁵⁷⁰⁷ *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

19 ⁵⁷⁰⁸ *Plant Genetic Sys., N.V. v. DeKalb Genetics Corp.*, 315 F.3d 1335, 1344 (Fed. Cir. 2003); *In re Wright*, 999
20 F.2d 1557, 1562 (Fed. Cir. 1993); *Liquid Dynamics Corp. v. Vaughan Co., Inc.*, 449 F.3d 1209, 1224–25 (Fed. Cir.
2006); *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1336 (Fed. Cir. 2003); *Gould v. Quigg*, 822
F.2d 1074, 1078 (Fed. Cir. 1987).

21 ⁵⁷⁰⁹ References to “WO '118” are to the English translation that was filed with the European application. Plaintiffs
reserve their right to obtain a certified translation of WO '118.

22 ⁵⁷¹⁰ *Diversitech Corp. v. Century Steps, Inc.*, 850 F.2d 675, 677 (Fed. Cir. 1988); *see also Hybritech Inc. v.*
23 *Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986).

24 ⁵⁷¹¹ *Trintech Industries, Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1296 (Fed. Cir. 2002).

1 Claim 10 of the '372 Patent: *identifying a group of subjects having a median triglyceride level of*
2 *at least 500 mg/dl and to reduce fasting triglycerides in the at least one subject.* WO '118 also
3 entirely fails to disclose the following elements of Claim 17 of the '372 Patent: *identifying a*
4 *group of subjects having a median triglyceride level of at least 500 mg/dl and to reduce fasting*
5 *triglycerides in the at least one subject.* Defendants appear to concede that WO '118 does not
6 expressly teach these elements, as they fail to set forth any basis for concluding that WO '118
7 teaches this element.⁵⁷¹² Indeed, Defendants could not set forth any basis for concluding that
8 WO '118 teaches this element because WO '118 does not.

9 Instead, Defendants argue that these elements express the intended result of a method that
10 is positively recited, and therefore is inherently anticipated. However, for the reasons set forth
11 below, WO '118 fails to disclose each element of the independent claims of the '372 Patent,
12 either expressly or inherently. Therefore, WO '118 cannot anticipate the claimed method.
13 Defendants also argue that these elements represent inherent, natural properties of EPA, and are
14 entitled to no patentable weight. This conclusion is incorrect and inconsistent with the law of
15 anticipation and claim construction. Further, while Defendants argue that the inherent properties
16 are exemplified in the prior art, they fail to identify even a single prior art reference that makes
17 such a disclosure. Defendants cannot point to a single, specific prior art reference because the
18 claimed pharmaceutical composition has never been administered in the manner claimed to the
19 claimed patient population. Also, these elements are positively recited in the body of the claim
20 and therefore cannot be construed as a non-limiting preamble and must be given patentable
21 weight.

22 Further, Defendants entirely fail to prove that inherently discloses the claimed lipid
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24 ⁵⁷¹² Defendants' Invalidation Contentions at 202-204.

1 effects. A prior art reference that “only ‘probably’ or ‘possibly’ meets the claims cannot
2 inherently anticipate as a matter of law.”⁵⁷¹³ “[A]nticipation by inherent disclosure is appropriate
3 only when the reference discloses prior art that must *necessarily* include the unstated
4 limitation.”⁵⁷¹⁴ “It is not sufficient if a material element or limitation is ‘merely probably or
5 possibly present’ in the prior art.”⁵⁷¹⁵ WO ‘118 fails to provide any data related to the lipid
6 effects of the disclosed invention on patients described in the publication. Therefore, Defendants
7 fail to prove by clear and convincing evidence that the composition disclosed by WO ‘118 meets
8 the elements of the independent claims every time it is administered.

9 Defendants fail to demonstrate that administration of the claimed EPA compositions
10 “*necessarily*” yields the claimed lipid effects. For example, one study cited by Defendants
11 suggests that EPA administration may increase LDL-C.⁵⁷¹⁶ Rambjor is a clinical study which
12 administered EPA, DHA, fish oil or placebo to human subjects. Rambjor showed that both EPA
13 and fish oil caused a significant increase in LDL-C. On the other hand, DHA effected only a
14 non-significant increase in LDL-C. As reflected by the disclosure of Rambjor, EPA does *not*
15 decrease TG without increasing LDL-C *every time it is administered*.

16 Therefore, WO ‘118 cannot anticipate the independent claims of the ‘372 patent.
17 Because the dependent claims include all of the claim elements of the independent claims, WO’
18 118 cannot anticipate any of the dependent claims as well.

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22 ⁵⁷¹³ *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

23 ⁵⁷¹⁴ *Transclean Corp. v. Bridgewood Servs., Inc.*, 290 F.3d 1364, 1373 (Fed. Cir. 2002) (emphasis in original).

24 ⁵⁷¹⁵ *In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1378 (Fed. Cir. 2007).

⁵⁷¹⁶ *See, e.g., Rambjor*.

(2) WO '118 Does Not Disclose Methods of Treating The Claimed Patient Population

In addition, WO '118 fails to disclose or suggest the claimed pharmaceutical composition be administered in the manner claimed to the claimed patient population. Defendants attempt to eliminate these important elements by arguing that the preamble is non-limiting. A preamble is the introductory clause of a patent claim and includes everything from the beginning of the claim until a transitional phrase, such as “comprising.” Defendants improperly attempt to truncate the preamble.

A claim preamble has patentable weight if, “when read in the context of the entire claim, [it] recites limitations of the claim, or, if the claim preamble is ‘necessary to give life, meaning, and vitality’ to the claim.”⁵⁷¹⁷ Additionally, the preamble constitutes a claim element when the claim depends on it for antecedent basis because “it indicates reliance on both the preamble and claim body to define the claimed limitation.”⁵⁷¹⁸

The preamble of the asserted claims is limiting for several reasons. The term “subject” in the preamble of the independent claims defines and provides antecedent basis for the “subject” recited in the body of the claims. When reading the claim, one must rely on both the preamble and the claim body to define the claimed invention.

If the preamble states “a fundamental characteristic of the claimed invention,” then it “is properly construed as a limitation of the claim itself.”⁵⁷¹⁹ The recitation of a “method of

⁵⁷¹⁷ *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305 (Fed. Cir. 1999) (citation omitted).

⁵⁷¹⁸ *Catalina Marketing Int'l v. Coolsavings.com, Inc.*, 289 F.3d 801, 808 (Fed. Cir. 2002) (citation omitted).

⁵⁷¹⁹ *Poly-Am. L.P. v. GSE Lining Tech., Inc.*, 383 F.3d 1303, 1309 (Fed. Cor. 2004); *see also e.g., Computer Docking Station Corp. v. Dell, Inc.*, 519 F.3d 1366, 1375 (Fed. Cir. 2008) (concluding the preamble phrases “portable computer” and “portable computer microprocessing system” limit the claims because they “clearly recite a necessary and defining aspect of the invention, specifically its portability,” and because the specification and prosecution history “emphasize this feature of the invention”).

1 reducing triglycerides” in the preamble provides antecedent basis for the effect of reducing
2 triglycerides in the body of the claim and emphasizes the intentional purpose for which the
3 method must be performed - to reduce triglycerides.

4 It is clear that “the claim drafter chose to use both the preamble and the body of the claim
5 to define the subject matter of the claimed invention.”⁵⁷²⁰ Thus, the entire preamble in the
6 independent claims of the ‘372 must contain patentable weight.

7 WO ‘118 fails to disclose the patentable elements of the preamble of the asserted claims.
8 WO ‘118 does not describe or suggest that the claimed pharmaceutical composition be
9 administered in the manner claimed to the claimed patient population.

10 First, WO ‘118 fails to expressly disclose “a method of reducing triglycerides.” In fact,
11 the invention disclosed by WO ‘118 relates to a composition for **preventing occurrence of**
12 **cardiovascular events**, as evidenced by the title which reads “Composition for Preventing the
13 Occurrence of Cardiovascular Event in Multiple Risk Patient.” The prevention of the occurrence
14 of cardiovascular events is defined in WO ‘118 as “all cases of primary prevention, and
15 exemplary cases include prevention of cardiovascular death, fatal myocardial infarction, sudden
16 cardiac death, nonfatal myocardial infarction, cardiovascular angioplasty, new occurrence of rest
17 angina and exercise-induced angina, and destabilization of the angina.”⁵⁷²¹ The invention of WO
18 ‘118 is intended to be administered to any person in need of prevention of the occurrence of
19 cardiovascular events, who are typically hypercholesterolemia patients.⁵⁷²² WO ‘118 does not
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⁵⁷²⁰ *Bicon, Inc. v. Straumann Co.*, 441 F.3d 945, 953 (Fed. Cir. 2006).

23 ⁵⁷²¹ WO ‘118 at 12.

24 ⁵⁷²² *Id.*

1 expressly describe its invention as a “method of reducing triglycerides,” therefore it cannot
2 anticipate the independent claims.

3 Second, WO ‘118 fails to disclose the subject as described in the claims. Defendants fail
4 to prove that these elements of the claimed invention have “strict identity” with the elements of
5 the reference.⁵⁷²³ WO ‘118 fails to anticipate this claim element because the broad disclosure
6 fails to anticipate the narrow claimed range, and the specific patient population defined in the
7 claims is an essential part of the claimed invention.

8 There is no evidence in that subject as described in the claims were ever treated. In fact,
9 WO ‘118 fails to disclose baseline lipid levels of a single subject. Defendants rely on the
10 definition of “hypertriglyceridemia” in WO ‘118 to argue that WO ‘118 discloses treatment of
11 the subject as described in the claims. It does not. Defendants’ argument rests on the definition
12 in WO ‘118 of “hypertriglyceridemia” as “fasting serum triglyceride levels of at least 150
13 mg/dL.” WO ‘118’s definition is not tied to a specific subject and there are no working
14 examples, data or other reference in WO ‘118 indicating that any subject with fasting TG levels
15 of at least 500 mg/dL received an EPA composition as claimed in the asserted patents, or any
16 EPA at all. In addition, Defendants rely on a reference to “Omacor” in WO ‘118 (at 32) as
17 evidence that a “person of ordinary skill in the art would have understood that the term
18 ‘hypertriglyceridemia’ when used in the WO ‘118 includes patients with triglyceride levels of
19 500 mg/dL to about 1500 mg/dL.” The cited section states that “soft capsules” are preferable
20 and then merely provides examples of commercially available “soft capsules,” such as Omacor.
21 The passage does not define “hypertriglyceridemia” as used in WO ‘118 as referring to patients
22 with triglyceride levels over 500 mg/dL. Nor does it suggest that the claimed EPA should be

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24 ⁵⁷²³ *Trintech Industries, Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1296 (Fed. Cir. 2002).

1 used in the over 500 mg/dL TG patient population. A prior art reference that “only ‘probably’
2 or ‘possibly’ meets the claims cannot inherently anticipate as a matter of law.”⁵⁷²⁴ Therefore,
3 Defendants fail to prove by clear and convincing evidence that the composition disclosed by WO
4 ‘118 meets the claim elements of the independent claims every time it is administered.

5 Further, the broad range disclosed by WO ‘118 is insufficient to anticipate the ranges
6 claimed by the ‘372 patent. In *Atofina*, the prior art disclosed a temperature range of 100 to 500
7 degrees and a preferred range of 150 to 350 degrees; the patent at issue claimed a range between
8 330 and 450 degrees. The court found that the broader prior art range could not anticipate the
9 claimed temperature range, “[g]iven the considerable difference between the claimed range and
10 the range in the prior art, no reasonable fact finder could conclude that the prior art describes the
11 claimed range with sufficient specificity to anticipate this element of the claim.”⁵⁷²⁵ A prior art’s
12 teaching of a broad genus does not necessarily disclose every species within that genus. The
13 court explained the slightly overlapping range between the preferred range and claimed range “is
14 not disclosed as . . . a species of the claimed generic range of 330 to 450 °C,”⁵⁷²⁶ and therefore
15 failed to anticipate the claimed range. Likewise, WO ‘118’s broad disclosure of
16 hypertriglyceridemia as a “fasting serum triglyceride levels of at least 150 mg/dL” does not
17 anticipate the subject as described in the claims because it fails to described the claimed TG
18 range with sufficient specificity.

19 The court in *Atofina* ruled on an additional question of anticipation that also involved a
20 range of numbers. A prior art reference had disclosed a range of 0.001 to 1.0 percent, as

22 ⁵⁷²⁴ *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

23 ⁵⁷²⁵ *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006).

24 ⁵⁷²⁶ *Atofina*, 441 F.3d at 1000.

1 compared to the patent’s claimed range of 0.1 to 5.0 percent.⁵⁷²⁷ The court explained that
2 “although there is a slight overlap, no reasonable fact finder could determine that this overlap
3 describes the entire claimed range with sufficient specificity to anticipate this limitation of the
4 claim. The ranges are different, not the same. . . . Thus, there is no anticipation.”⁵⁷²⁸ Similarly,
5 although there may be overlap between the definition of hypertriglyceridemia taught by WO
6 ‘118 and the TG range recited by the claims of the asserted patents, WO ‘118 does not
7 specifically discuss, highlight or otherwise suggest treating patients with TG values above 500
8 mg/dL. In fact, WO ‘118 is directed to compositions and methods for preventing occurrence of
9 cardiovascular events, suggesting that the treatment was envisioned for patients with TG levels
10 below 500 mg/dL (the patient population the ATP III identifies the prevention of atherogenic
11 events as the primary clinical objective),⁵⁷²⁹ WO ‘118, therefore, does not expressly disclose the
12 specific patient population that is an essential element of the claims of the asserted patents.
13 Therefore, WO ‘118 cannot anticipate the claims of the asserted patents.

14 The treatment of a patient with elevated TG levels varies depending on their serum
15 triglyceride levels. Identification of the patient population with very high TG levels (at least 500
16 mg/dL) is central to the claimed invention. In the 2000s, physicians treating lipid disorders,
17 including hypertriglyceridemia, relied on the ATP-III for authoritative guidance on the treatment
18 of lipid disorders.⁵⁷³⁰ The ATP-III divided hypertriglyceridemia patients into three classes based
19 on the levels of TG in their blood—borderline-high (150-199 mg/dL), high (200-499 mg/dL),
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21 ⁵⁷²⁷ *Id.*

22 ⁵⁷²⁸ *Id.*

23 ⁵⁷²⁹ *See* Section III.

24 ⁵⁷³⁰ *Id.*

1 and very-high TGs (≥ 500 mg/dL)—and recommended substantially different treatment
2 strategies for patients depending on classification.⁵⁷³¹ For the borderline-high and high TG
3 groups (150-499 mg/dL), the primary goal was to reduce risk of coronary heart disease.⁵⁷³²
4 Accordingly, in these populations, physicians focused on lowering LDL-C.⁵⁷³³ In this patient
5 population, lowering of TG and non-HDL-C levels were considered secondary treatment goals.
6 In contrast, the primary goal for very-high TG patients (≥ 500 mg/dL) was to reduce the risk of
7 pancreatitis—a potentially life threatening condition expected to be precipitated by elevated
8 TGs— by lowering TG levels. In very high TG patients, lowering LDL-C is a secondary
9 treatment goal.⁵⁷³⁴ Therefore, as evidenced by the ATP-III, patients with very-high TG levels
10 were considered fundamentally different from patients with borderline-high or high TGs from a
11 lipid chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint.

12 Therefore, WO ‘118’s definition of “hypertriglyceridemia” as “fasting serum triglyceride
13 levels of at least 150 mg/dL” fails to anticipate the claimed subject with very high TG levels. In
14 fact, as described above, WO ‘118 is not directed toward patients with the claimed TG levels at
15 all. WO 118’s disclosure is clearly directed towards preventing the occurrence of cardiovascular
16 risk, which is the primary aim for treatment of patients with high triglycerides (200-499 mg/dL).
17 Thus, WO ‘118’s disclosure is *not* directed towards patients with very high triglyceride levels
18 (where the primary goal is to prevent acute pancreatitis and damage to the pancreas by
19 decreasing triglycerides), as required by the independent claims of the asserted patents, and
20 therefore cannot anticipate the independent claims of the ‘372 Patent.

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22 ⁵⁷³¹ ATP III at 3335; *See also* Section III.

23 ⁵⁷³² *Id.*

24 ⁵⁷³³ *Id.*

⁵⁷³⁴ *Id.*

1 (3) WO '118 Does Not Describe the Claimed Pharmaceutical
2 Composition or its Specific Administration

3 WO '118 further does not anticipate the claims of the '372 patent because it does not
4 disclose "administering orally to the subject." As WO '118 fails to disclose the subject as
5 claimed, it cannot anticipate oral administration to the claimed "subject."

6 WO '118 additionally cannot anticipate the claims of the '372 patent because it does not
7 disclose administering the pharmaceutical composition at a dose of about 4g per day.
8 Defendants argue that this element is disclosed by WO '118's teaching that the daily dose is
9 "typically 0.3 to 6 g/day." Defendants fail to provide the entire disclosure of WO '118, which
10 states that the daily dose is "typically 0.3 to 6 g/day, preferably 0.9 to 3.6 g/day, and still more
11 preferably 1.8 to 2.7 g/day. Another preferable daily dose is 0.3 to 2.7 g/day, and 0.3 to 1.8
12 g.day. Another preferable fatty acid included is DHA-E." WO '118 teaches that the dosage is
13 not particularly limited as long as the intended effect, preventing the occurrence of
14 cardiovascular events, is attained. However, Defendants fail to provide any evidence that a dose
15 that is effective to prevent the occurrence of cardiovascular event, is also a dose that would be
16 effective to reduce triglycerides in the claimed patient population. Furthermore, there are no
17 working examples, data or other reference in WO '118 indicating that any subject (much less
18 one with fasting TG levels of at least 500 mg/dL) received an EPA composition as claimed in the
19 asserted patents or any EPA at all, much less at the claimed dose of 4 grams/day.

20 As discussed above, in *Atofina*, the prior art disclosed a preferred temperature range of
21 150 to 350 degrees, and the patent at issue claimed a range between 330 and 450 degrees. The
22 court explained that this slight overlap "is not disclosed as . . . a species of the claimed generic
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1 range of 330 to 450 °C,”⁵⁷³⁵ and therefore failed to anticipate the claimed range. The court in
2 *Atofina* also found that a prior art disclosure of a range of 0.001 to 1.0 percent failed to anticipate
3 the patent’s claimed range of 0.1 to 5.0 percent.⁵⁷³⁶ The court explained that “although there is a
4 slight overlap, no reasonable fact finder could determine that this overlap describes the entire
5 claimed range with sufficient specificity to anticipate this limitation of the claim. The ranges are
6 different, not the same. . . . Thus, there is no anticipation.”⁵⁷³⁷ Similarly, although there may be
7 some overlap between the daily dose disclosed by WO ‘118 and the dose claimed by the ‘372
8 patent, WO ‘118 does not specifically highlight the overlapping area and, moreover, the range
9 claimed by the ‘372 patent does not fall within WO ‘118’s preferred range. Defendants
10 conveniently omit the preferred range and mischaracterize the teaching of WO ‘118. Notably,
11 the example indicates that up to 900 mg of the EPA composition could be used three times per
12 day (2.7 g). Thus, WO ‘118 does not expressly disclose the 4 g per day dose claimed by the ‘372
13 patent and cannot anticipate the independent claims of the ‘372 Patent.

14 WO ‘118 further does not anticipate the claims of the ‘372 patent because it does not
15 disclose the claimed EPA pharmaceutical composition. Defendants once again cite only a
16 portion of the disclosure and exclude sections that show the breadth of WO ‘118’s teachings.
17 WO ‘118’s full disclosure recites that “the EPA-E used is preferably the one having a high
18 purity, for example, the one having the proportion of the EPA-E in the total fatty acid and
19 derivatives thereof of preferably 40% by weight or higher, more preferably 90% by weight or
20 higher, and still more preferably 96.5% by weight or higher.”⁵⁷³⁸ Therefore, WO ‘118 discloses

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22 ⁵⁷³⁵ *Atofina*, 441 F.3d at 1000.

23 ⁵⁷³⁶ *Id.*

24 ⁵⁷³⁷ *Id.*

⁵⁷³⁸ WO ‘118 at 22.

1 EPA-E with “high purity” is a composition which contains EPA-E of 40% by weight, of total
2 fatty acid and derivatives, or higher. This non-specific disclosure is not a species of the claimed
3 generic range for the EPA composition in the claimed pharmaceutical composition.

4 The Federal Circuit has explained that “a preferred . . . range . . . that slightly overlaps the
5 . . . range claimed in the” patent is insufficient for anticipation.⁵⁷³⁹ In *Atofina*, the prior art
6 disclosed a preferred temperature range of 150 to 350 degrees, and the patent at issue claimed a
7 range between 330 and 450 degrees. The court explained that this slight overlap “is not
8 disclosed as . . . a species of the claimed generic range of 330 to 450 °C,”⁵⁷⁴⁰ and therefore failed
9 to anticipate the claimed range.⁵⁷⁴¹ The court in *Atofina* also found that a prior art disclosure of a
10 range of 0.001 to 1.0 percent failed to anticipate the patent’s claimed range of 0.1 to 5.0
11 percent.⁵⁷⁴² The court explained that “although there is a slight overlap, no reasonable fact finder
12 could determine that this overlap describes the entire claimed range with sufficient specificity to
13 anticipate this element of the claim. The ranges are different, not the same. . . . Thus, there is no
14 anticipation.”⁵⁷⁴³

15 Similarly, although there may be some overlap between the E-EPA content disclosed by
16 WO ‘118 and the ranges claimed by the ‘372 patent, WO ‘118 does not specifically highlight the
17 overlapping area. The high content of E-EPA in the claimed pharmaceutical composition is a
18 critical factor of the invention disclosed in the ‘372 patent. Therefore, WO ‘118’s broad
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21 ⁵⁷³⁹ *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 1000 (Fed. Cir. 2006).

22 ⁵⁷⁴⁰ *Atofina*, 441 F.3d at 1000.

23 ⁵⁷⁴¹ *Atofina*, 441 F.3d at 1000.

24 ⁵⁷⁴² *Id.*

⁵⁷⁴³ *Id.*

1 disclosure of the E-EPA content in its invention does not describe the claimed range with
2 sufficient specificity and cannot anticipate the independent claims of the '372 patent.

3 WO '118 is additionally insufficient for anticipation because it does not expressly
4 disclose the recited DHA content of the claimed pharmaceutical composition. In fact, WO '118
5 makes no distinction between EPA and DHA, stating that "[a]nother preferable fatty acid is
6 DHA-E."⁵⁷⁴⁴ The disclosure goes on to state that the composition of the invention is preferably
7 one having high purity of EPA-E and DHA-E. The recited DHA content of the claimed
8 pharmaceutical composition is a critical factor of the invention disclosed in the '372 patent.

9 The disclosure of WO '118 treats DHA and EPA interchangeably. The disclosed
10 concentrations of EPA and DHA may range from 0 to 100% and every concentration in between.
11 There is no express teaching or guidance directing the person of ordinary skill in the art to the
12 claimed EPA compositions, Therefore, WO '118's broad disclosure, which indicates no
13 difference between the use of EPA or DHA in its invention, cannot anticipate the independent
14 claims of the '372 patent.

15 Defendants contend that Plaintiffs are estopped from arguing there is any material
16 difference between "not more than about 4% DHA" and "substantially no DHA." Defendants
17 provide no legal basis for their argument of estoppel. Defendants appear to suggest that testing
18 data obtained by Plaintiffs constitutes the basis for their assertion of estoppel. That argument is
19 without merit. Plaintiffs' clinical data cannot form the basis for an estoppel argument and
20 Defendants have cited no authority to support their position suggesting the contrary. The
21 language of "not more than about 4% DHA" and "substantially no DHA" are different phrases
22 and are not co-extensive. Accordingly, plaintiffs are not estopped.

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⁵⁷⁴⁴ WO '118 at 22.

1 In the same paragraph containing their allegation of estoppel, Defendants also quote from
2 Amarin's 2011 10-K. It is unclear whether these quotations are associated with their
3 unexplained estoppel arguments. To the extent that they are, Plaintiffs disagree that these
4 statements form the basis for any theory of estoppel. To the extent that Defendants quote
5 Amarin's post-invention 10-K to make any invalidity argument, that is also unavailing. The
6 quoted statements do not identify any recited claim element, including the specific
7 pharmaceutical composition, the recited patient population, administration in the manner
8 claimed, and recited lipid effects. Nor can these elements of the asserted claims be inferred from
9 the quoted statements.

10 (4) WO '118 Does Not Describe the Dependent Claims

11 Defendants fail to address any of the claim elements of the dependent claims.
12 Defendants appear to concede that WO '118 does not expressly teach these elements, as they fail
13 to set forth any meaningful basis for concluding that WO '118 teaches these elements.
14 Defendants further argue that "aspects of the claims relating to effects that are to be achieved by
15 practicing the claimed method represent inherent, natural properties of EPA, and are entitled to
16 no patentable weight." To the extent the recited claim elements relate to the administration step,
17 the dosage form or characteristics of the treated subject and the specific effect produced by the
18 claimed method, Defendants' contentions that the claim limitations are inherent properties of
19 EPA are unavailing. While Defendants assert that the inherent properties are exemplified in WO
20 '118, they fail to identify any basis, explanation, or even supporting argument for that assertion.
21 Defendants have not met the burden to establish anticipation with the naked assertion that the
22 effects are inherent, natural properties of EPA.

23 Further, Defendants entirely fail to prove that inherently discloses the recited claim
24 limitations. A prior art reference that "only 'probably' or 'possibly' meets the claims cannot

1 inherently anticipate as a matter of law.”⁵⁷⁴⁵ “[A]nticipation by inherent disclosure is appropriate
2 only when the reference discloses prior art that must *necessarily* include the unstated
3 limitation.”⁵⁷⁴⁶ “It is not sufficient if a material element or limitation is ‘merely probably or
4 possibly present’ in the prior art.”⁵⁷⁴⁷ Defendants fail to show that WO ‘118 “*necessarily*” meets
5 the recited claim elements relating to the administration step, the dosage form or characteristics
6 of the treated subject and the specific effect produced by the claimed method *every time*. WO
7 ‘118 fails to provide any data related to the TG, LDL-C, VLDL-C, non-HDL-C, Lp-PLA2, total
8 cholesterol, Apo-B, or any other lipid effect of the disclosed invention on patients described in
9 the publication. Further, WO ‘118 is a translated Japanese disclosure that makes no reference to,
10 let alone a disclosure of, a Western diet. Therefore, Defendants fail to prove by clear and
11 convincing evidence that the composition disclosed by WO ‘118 meets any dependent claim
12 elements.

13 3. The Claims of the ‘372 Patent Would Not Have Been Obvious In 14 Light of the Asserted References

15 Defendants identify 77 separate references that it asserts somehow render the claims of
16 the ‘372 patent obvious.⁵⁷⁴⁸ Defendants fail to demonstrate by clear and convincing evidence
17 that any of these references, alone or in combination, would render obvious any claims of the
18 ‘372 patent. Defendants’ arguments rely on hindsight by impermissibly using the blueprint of
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21 ⁵⁷⁴⁵ *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

22 ⁵⁷⁴⁶ *Transclean Corp. v. Bridgewood Servs., Inc.*, 290 F.3d 1364, 1373 (Fed. Cir. 2002) (emphasis in original).

23 ⁵⁷⁴⁷ *In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1378 (Fed. Cir. 2007).

24 ⁵⁷⁴⁸ Defendants’ Joint Invalidity Contentions at 13-25.

1 the '372 patent itself to guide its combination of references.⁵⁷⁴⁹ Defendants chart a laundry list
2 of 77 separate references, without explanation. Defendants' disclosures do not comply with
3 Local Patent Rule 1-8(d) and fail to put Plaintiffs on notice of how these references allegedly
4 establish that the asserted claims are allegedly *prima facie* obviousness. Consequently, Plaintiffs
5 cannot respond to undisclosed combinations and arguments.⁵⁷⁵⁰

6 Despite the general, non-limiting nature of Defendants' Joint Invalidity Contentions,
7 Plaintiffs have discerned and will specifically respond to the following alleged prior art
8 combinations:

- 9 • 1) “. . .the asserted claims of the '372 patent would have been obvious over the
10 Omacor PDR/Lovaza PDR in combination with the known clinical benefits of
11 administering pure EPA as evidenced by Katayama and/or Matsuzawa, further in
12 view of Nozaki and/or Hayashi, and further in view of Leigh-Firbank and/or Mori
13 2000.”
- 14 • 2) “. . .the asserted claims of the '372 patent would have been obvious over the
15 Omacor PDR/Lovaza PDR in combination with the known clinical benefits of
16 administering purified EPA as evidenced by Katayama, Matsuzawa and/or Takaku,
17 further in view of Nozaki and/or Hayashi, and further in view of Grimsgaard, Mori
18 2000 and/or Maki.”
- 19 • 3) “. . .the asserted claims of the '372 patent would have been obvious over the
20 Omacor PDR/Lovaza PDR in combination with the known clinical benefits of
21 administering pure EPA as evidenced by Katayama in view of Satoh and/or in view
22 of Satoh or Shinozaki in further view of Contacos.”
- 23 • 4) “. . . the asserted claims of the '372 patent would have been obvious over WO '118
24 or WO '900 in combination with treatment regimen of Lovaza as evidenced by the
Lovaza PDR, and further in view of Leigh-Firbank and/or Mori 2000.”

20 ⁵⁷⁴⁹ *In re Suong-Hyu Hyon*, 679 F.3d 1363, 1371 (Fed. Cir. 2012) (“It is impermissible to use the claimed invention
21 as an instruction manual or ‘template’ to piece together the teachings of the prior art so that the claimed invention is
obvious.” (citing *In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992))).

22 ⁵⁷⁵⁰ This includes Defendants' improper attempt to incorporate by reference any alleged prior art or argument,
23 including Defendants' attempt to incorporate by reference “the reasons set forth in the opposition proceedings for
24 EP 2 395 991 B1” in the European Patent Office. Such wholesale incorporation by reference does not satisfy the
Defendants' obligations or burden of proof and is contrary to the Nevada Local Patent Rules, which require that
each prior art be identified specifically. *See* Local Pat. R. 1-8. Plaintiffs reserve the right to strike any attempt to
rely on undisclosed or insufficiently disclosed references or argument.

- 1
- 2 • 5) “. . . the asserted claims of the ’372 patent would have been obvious over WO
 - 3 ’118, WO ’900, Grimsgaard, Mori 2000 and/or Maki in combination with treatment
 - 4 regimen of Omacor/Lovaza as evidenced by the Omacor PDR/Lovaza PDR, and
 - 5 further in view of Katayama, Matsuzawa and/or Takaku.”

6 A patent claim is invalid “if the differences between the subject matter sought to be

7 patented and the prior art are such that the subject matter as a whole would have been obvious at

8 the time the invention was made to a person having ordinary skill in the art.”⁵⁷⁵¹ Obviousness is

9 a legal determination, but it turns on factual inquiries into (1) the level of ordinary skill in the art,

10 (2) the scope and content of the prior art, and (3) the differences between the prior art and the

11 claims at issue.⁵⁷⁵²

12 In evaluating obviousness, each prior art reference must be evaluated for all that it

13 teaches, including the portions that would lead away from the claimed invention.⁵⁷⁵³ Indeed, any

14 teaching in the art that points away from the claimed invention must be considered.⁵⁷⁵⁴ A

15 reference teaches away if a person of ordinary skill, upon reading the reference, would be

16 discouraged from following the path set out in the reference, or would be led in a direction

17 divergent from the path that was taken by the applicant.⁵⁷⁵⁵ For instance, a reference teaches

18 away if it suggests that the line of development flowing from the reference’s disclosure is

19 unlikely to be productive of the result sought by the applicant.⁵⁷⁵⁶

20 ⁵⁷⁵¹ 35 U.S.C. § 103(a).

21 ⁵⁷⁵² *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966); *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007).

22 ⁵⁷⁵³ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

23 ⁵⁷⁵⁴ *Tec Air, Inc. v. Denso Mfg. Mich. Inc.*, 192 F.3d 1353, 1359-60 (Fed. Cir. 1999)

24 ⁵⁷⁵⁵ *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994)

⁵⁷⁵⁶ *Id.*

1 In order to find obviousness based on a combination of references, there must be some
2 rationale for combining the references in the way claimed that is separate and apart from the
3 hindsight provided by the patented invention itself.⁵⁷⁵⁷ The law prohibits an obviousness
4 challenge based on a hindsight reconstruction of the claimed invention from isolated prior art
5 references. It is improper for “the claims [to be] used as a frame, and individual, naked parts of
6 separate prior art references [to be] employed as a mosaic to recreate a facsimile of the claimed
7 invention.”⁵⁷⁵⁸ “The invention must be viewed not after the blueprint has been drawn by the
8 inventor, but as it would have been perceived in the state of the art that existed at the time the
9 invention was made.”⁵⁷⁵⁹

10 “The determination of obviousness is made with respect to the subject matter as a whole,
11 not separate pieces of the claim.”⁵⁷⁶⁰ “[A] patent composed of several elements is not proved
12 obvious merely by demonstrating that each of its elements was, independently, known in the
13 prior art.”⁵⁷⁶¹ “This is so because inventions in most, if not all, instances rely upon building
14 blocks long since uncovered, and claimed discoveries almost of necessity will be combinations
15 of what, in some sense, is already known.”⁵⁷⁶²

16 Accordingly, it is improper to pick and choose isolated elements from the prior art and
17 combine them so as to yield the invention⁵⁷⁶³ or to modify a prior art reference in a way that

19 ⁵⁷⁵⁷ *Immogenetics, N.V. v. Abbott Labs*, 512 F.3d 1363, 1373–74 (Fed. Cir. 2008)

20 ⁵⁷⁵⁸ See *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1552 (Fed. Cir. 1983)

21 ⁵⁷⁵⁹ *Sensonics, Inc. v. Aerosonic Corp.*, 81 F.3d 1566, 1570 (Fed. Cir. 1996)

22 ⁵⁷⁶⁰ *Sanofi Syntheolabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008)

23 ⁵⁷⁶¹ *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007))

24 ⁵⁷⁶² *KSR*, 550 U.S. at 418-419.

⁵⁷⁶³ *Abbott Labs v. Sandoz, Inc.*, 544 F.3d 1341, 1348 (Fed. Cir. 2008)

1 “would destroy the fundamental characteristics of that reference.”⁵⁷⁶⁴ Moreover, a combination
2 is not obvious where “it would be impossible to apply these teachings [of the secondary
3 reference] to the [primary reference] without entirely changing the basic mechanism and
4 procedure thereof,”⁵⁷⁶⁵ or where the proposed combination requires “material and radical
5 modification in order to conform to [the patentee’s] claims” or a “total reconstruction” of the
6 prior art device.⁵⁷⁶⁶ Furthermore, it is improper “to modify the secondary reference before it is
7 employed to modify the primary reference” in assessing obviousness.⁵⁷⁶⁷

8 Further, a party asserting obviousness in view of a combination of prior art disclosures
9 must show that a person of ordinary skill in the relevant field had an “apparent reason” to
10 combine the elements in the manner claimed⁵⁷⁶⁸ and “a reasonable expectation of success.”⁵⁷⁶⁹

11 For chemical compounds, there must have been a reason both to select the prior art
12 compound “most promising to modify” and to make the necessary changes to arrive at the
13 claimed compound.⁵⁷⁷⁰ This protects against the use of hindsight to pick through the prior art
14

15 ⁵⁷⁶⁴ *Apple, Inc. v. Samsung Elec. Co., Ltd.*, 678 F.3d 1314, 1331 (Fed. Cir. 2012)

16 ⁵⁷⁶⁵ *In re Irmischer*, 262 F.2d 85, 87 (CCPA 1958)

17 ⁵⁷⁶⁶ *Id.* at 88.

18 ⁵⁷⁶⁷ *In re Hummer*, 241 F.2d 742, 745 (CCPA 1957)

19 ⁵⁷⁶⁸ *KSR*, 550 U.S. at 417–19; *TriMed, Inc. v. Stryker Corp.*, 608 F.3d 1333, 1341 (Fed. Cir. 2010). Hindsight may
20 not be employed to identify relevant prior art and relevant teachings therein: *Heidelberger Druckmaschinen AG v.*
Hantscho Comm. Prods., Inc., 21 F.3d 1068, 1071–72 (Fed. Cir. 1994); *Monarch Knitting Mach. Corp. v. Sulzer*
Morat GmbH, 139 F.3d 877, 881 (Fed. Cir. 1998).

21 ⁵⁷⁶⁹ *Proctor & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (henceforth, “P&G”);
Takeda Chem. Indus. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1361 (Fed. Cir. 2007); *KSR*, 550 U.S. at 416 (a
22 combination of elements “must do more than yield a predictable result;” combining elements that work together “in
an unexpected and fruitful manner” would not have been obvious).

23 ⁵⁷⁷⁰ *Daiichi Sankyo Co. v. Matrix Labs. Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010); *Takeda*, 492 F.3d at 1355, 1359–
24 60; P&G, 566 F.3d at 994–95; *Eisai Co. Ltd. v. Dr. Reddy’s Labs., Ltd.*, 533 F.3d 1533, 1358 (Fed. Cir. 2008); *Eli*
Lilly & Co. v. Zenith Goldline Pharms., Inc., 471 F.3d 1369, 1378–80 (Fed. Cir. 2006).

1 based solely on structural similarity to the claimed compound.⁵⁷⁷¹ Any assertion of an “apparent
2 reason” must find a basis in the factual record.⁵⁷⁷²

3 The “reasonable expectation of success” for a chemical compound must be of all of a
4 claimed compound’s relevant properties,⁵⁷⁷³ including those discovered after the patent was filed
5 or even issued.⁵⁷⁷⁴ “The basic principle behind this rule is straight-forward—that which would
6 have been surprising to a person of ordinary skill in a particular art would not have been
7 obvious.”⁵⁷⁷⁵ Any assertion of a “reasonable expectation of success” must find a basis in the
8 factual record.⁵⁷⁷⁶

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10 ⁵⁷⁷¹ *Daiichi Sankyo*, 619 F.3d at 1354; *Pfizer*, 2010 WL 339042, at *14. *Accord In re Vaidyanathan*, 381. 985, 994
11 (Fed. Cir. 2010) (nonprecedential); *Processing Corp. v. Am. Maize-Products Co.*, 840 F.2d 902, 907 (Fed. Cir.
12 1988); *Power-One*, 599 F.3d at 1351–52; *Crown Ops. Int’l, Ltd. v. Solutia, Inc.*, 289 F.3d 1367, 1376 (Fed. Cir.
13 2002).

14 ⁵⁷⁷² *See, e.g., Vaidyanathan*, 381. at 993–94 (“[W]hile KSR relaxed some of the formalism of earlier decisions
15 requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did not remove the need to
16 anchor the analysis in explanation of how a person of ordinary skill would select and apply the teachings of the
17 references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi Sankyo*, 619 F.3d at
18 1354 (The assertion of a starting point “must avoid hindsight bias; it must look at the state of the art *at the time the*
19 *invention was made* to find a motivation to select and then modify a lead compound to arrive at the claimed
20 invention.” This turns on the known “properties and elements of the prior art compounds.”); *Forest Labs.*, 438
21 F.Supp.2d at 492–93 (rejecting defendants’ contention that claims to (+)-citalopram were “prima facie obvious in
22 light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding that
23 defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been
24 motivated to resolve citalopram in June 1988”).

25 ⁵⁷⁷³ *Yamanouchi Pharm. Co., Ltd. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1345 (Fed. Cir. 2000) (“The success
26 of discovering famotidine . . . was finding a compound that had high activity, few side effects, and lacked toxicity. . .
27 . [T]he ordinary medicinal chemist would not have expected famotidine to have the ‘most desirable combination of
28 pharmacological properties’ that it possesses.”); *Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 364 F.Supp.2d
29 820, 908 (S.D. Ind. 2005) (“[S]uccess was not simply finding a compound as active as clozapine . . . Here, the
30 ordinary medicinal chemist . . . would not have expected olanzapine to have the highly desirable combination of
31 pharmacological properties that it possesses.”).

32 ⁵⁷⁷⁴ *Knoll Pharm. Inc. v. Teva Pharms. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004); *Eli Lilly*, 364 F.Supp.2d at
33 908.

34 ⁵⁷⁷⁵ *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995) (“The principle applies most often to the less predictable fields,
such as chemistry, where minor changes in a product or process may yield substantially different results.”).

⁵⁷⁷⁶ *See, e.g., Sanofi-Synthelabo*, 550 F.3d at 1089 (“Aptex argues that the district court applied an incorrect
inquiry, and that the correct inquiry is not whether the results obtained with the separated enantiomer were

1 In an obviousness determination, any objective indicia of nonobviousness must be taken
2 into account.⁵⁷⁷⁷ An objective indicium is any “event[] proved to have actually happened in the
3 real world” that evidences the nonobvious nature of the invention.⁵⁷⁷⁸ The existence of an
4 enduring, unmet need, difficulties encountered by those skilled in the field, unexpected or
5 surprising results, expressions of skepticism, industry praise, commercial success, and copying
6 are classical indicia of nonobviousness.⁵⁷⁷⁹ These factual inquiries “guard against slipping into
7 use of hindsight,”⁵⁷⁸⁰ and “may often be the most probative and cogent evidence of
8 nonobviousness.”⁵⁷⁸¹

9 Also, as with assertions of anticipation, in order for an invention to be obvious, it must
10 have been fully “in possession” of the public—which requires that the claimed invention have
11 been enabled.⁵⁷⁸²

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13
14 unexpected, but whether it would have been obvious to separate and test the enantiomers, based on the general
15 knowledge that enantiomers can exhibit different properties. Apotex refers to *In re Adamson*, 275 F.2d [952,] 955
16 [(C.C.P.A. 1960)], where the CCPA held that an enantiomer would have been obvious in view of its racemate.
17 However, the scientific facts differed from these herein, for in *Adamson* the court found that it was ‘particularly
18 expected’ that the specific enantiomer would have the observed properties. In contrast, as Sanofi points out, in *In re*
19 *May*, 574 F.2d at 1095, the CCPA held, as to the enantiomer claimed therein, that the appellant ‘established a
20 substantial record of unpredictability vis-à-vis a highly significant combination of properties.’”).

21 ⁵⁷⁷⁷ *Graham*, 383 U.S. at 17–18; KSR, 550 U.S. at 406; *Jones v. Hardy*, 727 F.2d 1524, 1530–31 (Fed. Cir. 1984).

22 ⁵⁷⁷⁸ *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1569 (Fed. Cir. 1987).

23 ⁵⁷⁷⁹ *Graham*, 383 U.S. at 17–18; KSR, 550 U.S. at 406; *U.S. v. Adams*, 383 U.S. 39, 52 (1966); *Merck & Co. v. Teva*
24 *Pharm. USA, Inc.*, 395 F.3d 1364, 1376 (Fed. Cir. 2005); *Panduit*, 810 F.2d at 1569; *In re Soni*, 54 F.3d 746, 750
(Fed. Cir. 1995); *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988); *Janissen*, 456 F.Supp.2d at 669–72.

⁵⁷⁸⁰ *Graham*, 383 U.S. at 36.

⁵⁷⁸¹ *Ortho-McNeil Pharm. Inc. v. Mylan Labs. Inc.*, 520 F.3d 1358, 1365 (Fed. Cir. 2008) (quoting *Catalina Lighting*
Inc. v. Lamps Plus, Inc., 295 F.3d 1277, 1288 (Fed. Cir. 2002)).

⁵⁷⁸² *In re Kumar*, 418 F.3d 1361, 1368 (Fed. Cir. 2005) (“[I]n order to render an invention unpatentable for
obviousness, the prior art must enable a person of ordinary skill to make and use the invention.”); *In re Hoeksema*,
399 F.2d 269, 274 (C.C.P.A. 1968) (“[I]f the prior art of record fails to disclose or render obvious a method for
making a claimed compound, at the time the invention was made, it may not be legally concluded that the compound
itself is in the possession of the public.”).

1 A element-by-element analysis, identifying each limitation of each asserted claim that is
2 absent from the prior art, is provided below, and also provided at Exhibit M. The contentions
3 below are incorporated by reference into Exhibit M, and vice-versa.

4 a) General Overview

5 Defendants fail to provide a single prior art reference that discloses administration of the
6 recited composition of EPA ethyl (in the recited purity) to the very-high TG patient population
7 (≥ 500 mg/dL) and the resulting lipid effects. Instead, they rely on a large number of studies,
8 many of which are not placebo controlled, which administer EPA, DHA, or both, in varying
9 degrees of purity, in a wide range of doses and administration periods, to subjects who have
10 baseline TG levels lower than 500 mg/dL and in many cases significantly lower. The importance
11 of a placebo-controlled study cannot be overstated. Randomized, double-blind placebo
12 controlled studies are considered the “gold standard” of clinical studies. Studies involving the
13 administration of fish oils or omega-3 fatty acids which are not placebo controlled cannot
14 distinguish between the effect of the placebo from that of the active agent. Studies which
15 administer mixtures enriched for either EPA or DHA are not suitable for evaluating the
16 independent effects of EPA and DHA.⁵⁷⁸³ Inconsistency in dosages and administration periods
17 and variations in the administered fatty acid compositions also complicate the interpretation of
18 the results and limit the application of these studies.

19 Defendants also rely on the ANCHOR study to argue that Amarin’s use of “patients with
20 very high TGs together with patients with high and borderline high TGs indicates that there is no
21 medical difference in responsiveness to treatment among the groups of people.”⁵⁷⁸⁴ Defendants
22

23 ⁵⁷⁸³ Mori 2006 at 96.

24 ⁵⁷⁸⁴ Defendants’ Joint Invalidity Contentions at 752-53 (*see* FN 146).

1 mischaracterize the ANCHOR study. The ANCHOR study was a multi-center, placebo-
2 controlled, randomized, double-blind, 12-week pivotal Phase 3 study on the effects of Vascepa in
3 patients with high triglycerides (≥ 200 mg/dL and < 500 mg/dL) who were also on statin therapy.
4 Defendants point to the reported “Min-max” TG levels, 157-782 mg/dL, for the AMR101 4g
5 daily group to argue that Amarin used very-high TG patients with high and borderline-high TG
6 patients. However, the mean TG level for this same group, 281.1 mg/dL, makes it clear that
7 almost all of the 233 patients in this group had baseline TG values well below 500 mg/dL.⁵⁷⁸⁵ In
8 addition, the mean baseline TG values for the Placebo and AMR101 2g daily groups were
9 reported as 270.6 mg/dL and 270.2 mg/dL, respectively. Further, Amarin did *not* attempt to use
10 the results of ANCHOR to predict lipid effects in the very high TG patient population. Neither a
11 person of ordinary skill, nor the FDA, would attempt to draw conclusions or gain insight into the
12 very high TG patient population from the ANCHOR trial. In fact, Amarin simultaneously (to
13 ANCHOR) conducted an independent study with Vascepa in patients with very high TG levels.
14 Contrary to Defendants’ assertion, the ANCHOR study does *not* indicate that there is no medical
15 difference in responsiveness to treatment between the very-high TG patient population and lower
16 TG patient populations merely because there was possibly one patient with baseline TG levels of
17 at least 500 mg/dL.

18 As discussed above in Section III, patients with very-high TG levels were considered
19 fundamentally different from patients with borderline-high or high TGs from a clinical,
20 regulatory, and therapeutic perspective.⁵⁷⁸⁶ Clinically, the authoritative guidance to physicians

22 ⁵⁷⁸⁵ FDA Briefing Document, Oct. 16, 2013 at pg. 26 (The mean baseline TG value for the placebo group was 270.6
23 mg/dL, AMR101 2g group was 270.2 mg/dL, and AMR101 4g group was 281.1 mg/dL. While there may have been
a few patients with TG > 500mg/dL in the AMR101 4g group, it is clear that the overwhelming majority had baseline
TG values < 500 mg/dL).

24 ⁵⁷⁸⁶ See Bays Jan. 8, 2012 Decl., ¶ 20.

1 on the treatment of lipid disorders throughout the last decade, the Adult Treatment Panel III
2 (ATP-III) divided hypertriglyceridemic patients into three groups: normal/borderline high TG;
3 high TG; and very high TG. The primary risk faced by borderline-high and high TG patients
4 was atherosclerosis, while the primary risk faced by very-high TG patients was acute
5 pancreatitis. Therefore, the primary focus of treatment, as described by the ATP III, for
6 borderline-high and high TG patients was to lower LDL-C levels. In contrast, the priority for
7 very-high TG patients was TG reduction. This distinction between patients with borderline-
8 high/high TG levels and patients with very high TG levels is also observed on the regulatory
9 level. The FDA recognized the different clinical status of the very-high TG population by
10 approving some drugs specifically for the very-high TG group without granting treatment
11 indications for the borderline-high or high TG populations (i.e. Lovaza/Omacor).⁵⁷⁸⁷

12 Finally, from a therapeutic standpoint, a person of ordinary skill understood that the
13 effects of lipid-lowering therapies on lipid parameters, such as LDL-C, varied depending on the
14 patient's baseline TG level. Fibrates and prescription omega-3 therapies (two well-known
15 classes of drugs used to treat patient with very-high TGs to lower TG levels at the time of the
16 invention), for example, exhibit different effects on LDL-C levels, depending on the baseline TG
17 level of the patient receiving treatment.

18 Fibrates lower both TGs and LDL-C in normal and borderline-high TG patients, but
19 *increase* LDL-C in very-high TG patients.⁵⁷⁸⁸ The fibrate, Tricor (fenofibrate), for example,
20 decreased LDL-C significantly in both patients with normal baseline TG values (about 31%)⁵⁷⁸⁹

21
22 ⁵⁷⁸⁷ See Bays Jan. 8, 2012 Decl., ¶ 22.

23 ⁵⁷⁸⁸ See Bays 2008 II, at 214-15 (noting that a fibrate caused LDL-C to go down in borderline-high group, remain
roughly the same in high TG group, and increase by around 50% in the very-high TG group).

24 ⁵⁷⁸⁹ Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

1 and high baseline TG values (mean baseline TG value of 231.9 mg/dL) (about 20%).⁵⁷⁹⁰ In
 2 patients approaching very-high TGs levels (mean baseline TG value of 432 mg/dL), a non-
 3 significant increase in LDL-C was observed.⁵⁷⁹¹ In patients with very-high TGs (mean baseline
 4 TG = 726 mg/dL), a significant increase in LDL-C was observed (about 45%).⁵⁷⁹² Similar
 5 results were seen with the administration of Lopid (gemfibrozil).⁵⁷⁹³ The differing effects of
 6 fibrates, such as Tricor, on TG, LDL-C, HDL-C and Total-C based on baseline TG values
 7 demonstrates how a person of ordinary skill at the time of the invention would have understood
 8 that one could not simply assume that an observed effect of a TG-lowering agent on lipid
 9 parameters in patients with normal, borderline-high or high TG levels would be the same in
 10 patients with very-high TG levels (at least 500 mg/dL) compared to a patient with high or
 11 borderline-high TG levels (150-499 mg/dL). As illustrated in the table, below, patients with
 12 normal or high baseline TG levels experience reduced LDL-C levels upon treatment with a TG-
 13 reducing agent such as the fibrate, Tricor. Patients approaching very high TG levels (mean
 14 baseline TG level of 432 mg/dL) and patients with very high TG levels (mean baseline TG level
 15 of 726 mg/dL) experience significantly increased LDL-C levels.

Fibrate	Mean Baseline TG Value	TG	LDL-C	HDL-C	Total-C
Tricor (fenofibrate) ⁵⁷⁹⁴	101.7 mg/dL	-23.5%*	-31.4%*	+9.8%*	-22.4%*
	231.9 mg/dL	-35.9%*	-20.1%*	+14.6%*	-16.8%*
	432 mg/dL	-46.2*	+14.5	+19.6*	-9.1*

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20 ⁵⁷⁹⁰ *Id.*

21 ⁵⁷⁹¹ *Id.* See also, Trilipix Label at 27.

22 ⁵⁷⁹² *Id.* See also, Trilipix Label at 27.

23 ⁵⁷⁹³ See Otvos at 1558 (showing administration of Gemfibrozil to patients with borderline-high baseline TG levels had no impact on LDL-C levels); Manttari at 14 and 16 (stating that the effect of gemfibrozil on LDL-C was dependent on initial TG levels, no change was observed for LDL-C in subjects with high baseline TG levels while subjects with normal or borderline-high baseline TG levels showed significant decreases in LDL-C).

24 ⁵⁷⁹⁴ Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

	726 mg/dL	-54.5*	+45.0*	+22.9*	-13.8*

* = p < 0.05 vs. Placebo

Lovaza/Omacor was (and is) a prescription omega-3 therapy known to have differing lipid effects depending on the patient’s baseline TG level. When administered to patients with borderline-high baseline TG levels, Lovaza/Omacor significantly reduced TGs and raised HDL-C.⁵⁷⁹⁵ It had no significant effect on other lipid-related variable, including LDL-C and Apo-B.⁵⁷⁹⁶ However, when administered to patients with very-high baseline TG levels, TGs were reduced significantly by nearly 50% while LDL-C increased sharply by nearly 50%.⁵⁷⁹⁷ Although the increase in LDL-C was concerning, it was understood that the overall lipid effect of Lovaza/Omacor was beneficial.⁵⁷⁹⁸

Fibrates and prescription Omega-3 therapies demonstrate that one could not simply assume that a lipid lowering agent would have the same effect in a patient with very-high TG

⁵⁷⁹⁵ Chan 2002 I at 2379-81.

⁵⁷⁹⁶ *Id.*; See also, Westphal at 918.

⁵⁷⁹⁷ See Weintraub Sept. 7, 2011 Decl., ¶ 23 (citing Lovaza package insert); Bays May 16, 2011 Decl., ¶ 10; see also, Lovaza PDR and Omacor PDR.

⁵⁷⁹⁸ See Pownall *et al.*, *Correlation of serum triglyceride and its reduction by ω-3 fatty acids with lipid transfer activity and the neutral lipid compositions of high-density and low-density lipoproteins*, 143 *Atherosclerosis* 285, 295 (1999) (“Treatment with ω-3 fatty acids appear to change the lipid profile of individuals with elevated TG to one that may be less atherogenic by changing LDL structure; lowering serum [cholesterol ester transfer activity], serum TG and VLDL-C; and increasing serum HDL-C.”); Stalenhoef at 134 (stating that “Omacor . . . adversely raise LDL cholesterol concentration but the increase in LDL cholesterol concentration reflects a less atherogenic light LDL subfraction profile that may be favorable”); Harris 1997 at 389 (“The increase in LDL, which was substantial on a percentage basis, has been a common finding in past studies in [very-high TG] patients. It may not be as problematic as it appears, however.” And “the use of omega-3 fatty acids for the treatment of severe hypertriglyceridemia may be beneficial not only for the short-term prevention of acute pancreatitis, but also for the long-term prevention of CHD”); Bays III at 248 (“No clinical trial data exist that this rise in LDL-C represents harm or potential “toxicity” to patients. In fact, most evidence supports that omega-3 fatty acids reduce cardiovascular risk as do fibrates. Importantly, clinical trials mostly support that even with increases in LDL-C, omega-3 fatty acids decrease the total cholesterol (TC) carried by atherogenic lipoproteins, as reflected by decreased non-HDL-C levels (TC minus HDL-C.)”)

1 levels (≥ 500 mg/dL) as a patient with borderline-high or high TG levels (150-499 mg/dL). They
2 also demonstrate that one of ordinary skill would not expect to see an increase in LDL-C when
3 the normal, borderline-high or high TG patient populations were administered omega-3 fatty
4 acids. As discussed in Section III, the increase in LDL-C for very-high TG patients was
5 expected as a natural consequence of lowering TGs. A person of ordinary skill would have
6 considered the rise in LDL-C to be a direct consequence of TG lowering through increased
7 VLDL particle conversion.⁵⁷⁹⁹ Because normal to high TG patients did not have the large
8 backlog of VLDL particles that very high TG patients have, a person of ordinary skill did not
9 expect LDL-C to increase in normal to high TG patients. It was also well known that the degree
10 of LDL-C elevation observed with prescription omega-3 fatty acids, such as Lovaza/Omacor,
11 was linked to baseline TG levels; that LDL-C levels increased the most in patients with the
12 highest baseline TG levels⁵⁸⁰⁰ and did not increase for patients with lower TG levels. Therefore,
13 the prior art defendants rely upon to show that EPA did *not* increase LDL-C levels in normal,
14 borderline-high or high TG patients was *expected*.

15 Defendants contend that “a composition and its properties are inseparable, and therefore
16 do not impart any additional patentability,” and that “all of the limitations regarding the
17 properties of the ethyl EPA compound identified in the claims of the ‘372 patent are inherent to
18 the compound when administered to a human subject.”⁵⁸⁰¹ Inherency may not supply a missing

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20 ⁵⁷⁹⁹ Bays May 16, 2011 Decl., ¶ 11 (noting the “general knowledge in the art that omega-3 fatty acids as a class
21 increase LDL-C” in very-high TG patients); McKenney 2007, at 724 (“Because of the increase in LDL levels
22 observed in some patients treated with prescription omega-3, LDL levels also should be periodically assessed during
treatment.”); Bays in Kwiterovich at 247 (noting that increased LPL activity caused by fish oil “helps explain some
of the seemingly paradoxical lipid effects found with their clinical use, for example, the rise in LDL-C with the
decrease in VLDL.”).

23 ⁵⁸⁰⁰ Bays 2008 I at 400-402.

24 ⁵⁸⁰¹ Defendants’ Joint Invalidity Contentions at 753-54.

1 claim limitation in an obviousness analysis unless the inherency would have been obvious to one
2 of ordinary skill in the art.⁵⁸⁰² Obviousness is based on what is *known* in the art at the time of the
3 invention.⁵⁸⁰³ It was not known or reasonably expected at the time of the claimed invention that
4 purified EPA, when administered to patients with very-high TG levels (≥ 500 mg/dL), would not
5 substantially increase LDL-C or would reduce Apo-B. Nor was EPA’s effect on LDL-C and
6 Apo-B necessarily present, or the natural result of the combination of elements explicitly
7 disclosed by the prior art.⁵⁸⁰⁴ Therefore, inherency does not supply the missing claim elements
8 in the prior art cited by Defendants.

9 Defendants argue that the claims of the ‘372 patent which contain “a limiting clause, such
10 as ‘to effect’ or ‘is effective to,’” simply express the intended result of a process step positively
11 recited and therefore are not elements.⁵⁸⁰⁵ This is incorrect. “There is nothing inherently wrong
12 with defining some part of an invention in functional terms.”⁵⁸⁰⁶ When a clause “states a
13 condition that is material to patentability, it cannot be ignored in order to change the substance of
14 the invention.”⁵⁸⁰⁷ The claim term “to effect” acts as a positive limitation if the term represents

17 ⁵⁸⁰² See, e.g., *PAR Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1195–96 (Fed. Cir. 2014) (“A party must . . .
18 meet a high standard in order to rely on inherency to establish the existence of a claim limitation in the prior art in an
obviousness analysis—the limitation at issue necessarily must be present, or the natural result of the combination of
19 elements explicitly disclosed by the prior art.”); *In re Rijckaert*, 9 F.3d 1531, 1533–34 (Fed. Cir. 1993) (“The mere
fact that a certain thing may result from a given set of circumstances is not sufficient [to establish inherency].”) (internal quotation omitted).

20 ⁵⁸⁰³ *In re Spormann*, 363 F.2d 444, 448 (CCPA 1966) (“That which may be inherent is not necessarily known.
Obviousness cannot be predicated on what is unknown.”).

21 ⁵⁸⁰⁴ See discussions below for *Grimsgaard*, *Park*, *Nozaki Kurabayashi* and *Hayashi*.

22 ⁵⁸⁰⁵ Defendants’ Joint Invalidity Contentions at 754.

23 ⁵⁸⁰⁶ See MPEP 2173.05(g) (citing *In re Swinehart*, 439 F.2d 210 (CCPA 1971)).

24 ⁵⁸⁰⁷ *Hoffer v. Microsoft Corp.*, 405 F.3d 1326, 1329 (Fed. Cir. 2005).

1 “unexpected and improved effects of administration of the claimed compound.”⁵⁸⁰⁸ In addition,
2 the elements represent unexpected and improved effects of administration of purified EPA,
3 because a person of ordinary skill would not have expected no substantial increase in LDL-C or
4 reduction in Apo-B when administering EPA to treat severe hypertriglyceridemia. Therefore, the
5 requirements for no substantial increase in LDL-C and reduction in Apo-B must be accorded
6 patentable weight.

7 b) Identification of Claim Elements Absent from Each Item of Prior
8 Art

9 Plaintiffs identify each limitation of each asserted claim that Plaintiffs believe is absent.
10 Where a limitation is absent from any Independent Claim, that limitation is absent from all
11 asserted claims, and that analysis is incorporated by reference into each dependent claim. For
12 any reference, the fact that Plaintiffs do not list a particular limitation as absent from the asserted
13 claims is not a concession that such limitation is present in the reference. By discussing
14 Defendants’ analysis of the “limitations” in the claims, Plaintiffs do not concede that Defendants
15 have appropriately divided the claim language for any purpose.

16 (1) WO ‘118

17 WO ‘118 discloses a composition containing EPA-E for preventing the occurrence of
18 cardiovascular events in multiple risk patients.

19 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of WO
20 ‘118 disclose or suggest elements of the ‘372 Claims. The cited portions of WO ‘118 do not
21 disclose or suggest these elements at least because they do not disclose or suggest identifying a
22 group of subjects with the recited very high TG levels. The cited portions of WO ‘118 further do

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24 ⁵⁸⁰⁸ *AstraZeneca AB v. Dr. Reddy’s Labs., Ltd.*, No. CIV.A.05-5553 JAP, 2010 WL 1981790, at *11–12 (D.N.J.
May 18, 2010).

1 not disclose or suggest administration to at least one subject in the group of subjects, the claimed
2 pharmaceutical composition with the recited fatty acid compositions or dosage. The cited
3 portions of WO '118 further do not disclose or suggest a method to effect the recited TG
4 reduction in the at least one subject with the claimed TG level.

5 With respect to Claims 1, 10 and 17 of the '372 Patent (and therefore all asserted claims),
6 WO '118 does not disclose or suggest identifying a group of subjects with the recited very high
7 TG levels. WO '118 also does not disclose or suggest administration to at least one subject in
8 the group of subjects, the claimed pharmaceutical composition with the recited fatty acid
9 compositions or dosage. WO '118 further does not disclose or suggest a method to effect the
10 recited TG reduction in the at least one subject with the claimed TG level.

11 Further, with respect to Claims 2, 11 and 18, this reference fails to disclose or suggest the
12 group of subjects having the recited baseline LDL-C level. With respect to Claims 4, 13 and 20,
13 this reference fails to disclose or suggest the recited TG and LDL-C effects in the at least one
14 subject with the claimed TG level. With respect to Claims 5, 14 and 21, this reference fails to
15 disclose or suggest the recited reduction in Apolipoprotein B in the at least one subject with the
16 claimed TG level. With respect to Claims 6, 15 and 22, this reference fails to disclose or suggest
17 the recited reduction in VLDL-C in the at least one subject with the claimed TG level. With
18 respect to Claims 7, 16 and 23, this reference fails to disclose or suggest the group of subjects
19 having the recited very high TG level.

20 (2) WO '900

21 WO '900 describes methods for obtaining EPA-rich compositions.

22 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of WO
23 '900 disclose or suggest elements of the '372 Claims. The cited portions of WO '900 do not
24 disclose or suggest these elements at least because they do not disclose or suggest identifying a

1 group of subjects with the recited very high TG levels. The cited portions of WO '900 further do
2 not disclose or suggest administration to at least one subject, the claimed pharmaceutical
3 composition with the recited fatty acid dosage or administration period. The cited portions of
4 WO '900 further do not disclose or suggest a method to effect the recited TG reduction in the at
5 least one subject with the claimed TG level.

6 With respect to Claims 1, 10 and 17 of the '372 Patent (and therefore all asserted claims),
7 WO '900 does not disclose or suggest identifying a group of subjects with the recited very high
8 TG level. WO '900 also does not disclose or suggest administration to at least one subject, the
9 claimed pharmaceutical composition with the recited fatty acid dosage or administration period.
10 WO '900 further does not disclose or suggest a method to effect the recited TG reduction in the
11 at least one subject with the claimed TG level. WO '900 further does not disclose the claimed
12 pharmaceutical composition.

13 Further, with respect to Claims 2, 11 and 18, this reference fails to disclose or suggest the
14 group of subjects having the recited baseline LDL-C level. With respect to Claims 3, 12 and 19,
15 this reference fails to disclose or suggest the group of subjects having the recited baseline lipid
16 levels. With respect to Claims 4, 13 and 20, this reference fails to disclose or suggest the recited
17 TG and LDL-C effects in the at least one subject with the claimed TG level. With respect to
18 Claims 5, 14 and 21, this reference fails to disclose or suggest the recited reduction in
19 Apolipoprotein B in the at least one subject with the claimed TG level. With respect to Claims 6,
20 15 and 22, this reference fails to disclose or suggest the recited reduction in VLDL-C in the at
21 least one subject with the claimed TG level. With respect to Claims 7, 16 and 23, this reference
22 fails to disclose or suggest the group of subjects having the recited very high TG level.

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CONFIDENTIAL

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(3) Contacos

Contacos describes a study designed to determine the safety and efficacy of a statin (pravastatin) combined with fish oil either alone or in combination, for the management of patients with mixed hyperlipidemia. Contacos does not administer EPA of the purity recited in the claims.

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Contacos disclose or suggest elements of the ‘372 Claims. The cited portions of Contacos do not disclose or suggest these elements at least because they do not disclose or suggest identifying a group of subjects with the recited very high TG levels. The cited portions of Contacos further do not disclose or suggest administration to at least one subject, the claimed pharmaceutical composition with the recited fatty acid compositions, dosage, or administration period. The cited portions of Contacos further do not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction in the at least one subject with the claimed TG level.

With respect to Claims 1, 10 and 17 of the ‘372 Patent (and therefore all asserted claims), Contacos does not disclose or suggest identifying a group of subjects with the recited very high TG level. Contacos also does not disclose or suggest administration to at least one subject, the claimed pharmaceutical composition with the recited fatty acid compositions, dosage, or administration period. Contacos further does not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction in the at least one subject with the claimed TG level. With respect to Claim 8, Contacos does not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction based on a comparison to a placebo control.

1 Further, with respect to Claims 4, 13 and 20, this reference fails to disclose or suggest the
2 administration of the claimed pharmaceutical composition to effect the recited TG and LDL-C
3 effects. With respect to Claims 5, 14 and 21, this reference fails to disclose or suggest the
4 administration of the claimed pharmaceutical composition to effect the recited reduction in
5 Apolipoprotein B. With respect to Claims 6, 15 and 22, this reference fails to disclose or suggest
6 the administration of the claimed pharmaceutical composition to effect the recited reduction in
7 VLDL-C. With respect to Claims 7, 16 and 23, this reference fails to disclose or suggest the
8 group of subjects having the recited very high TG level.

9 (4) Grimsgaard

10 Grimsgaard conducted a double-blind, randomized, placebo-controlled, parallel design
11 intervention study to evaluate the dietary supplementation with EPA or DHA on serum lipids,
12 apolipoproteins, and serum phospholipid fatty acid composition in subjects with normal TG
13 levels.

14 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of
15 Grimsgaard disclose or suggest elements of the '372 Claims. The cited portions of Grimsgaard
16 do not disclose or suggest these elements at least because they do not disclose or suggest
17 identifying a group of subjects with the recited very high TG levels. The cited portions of
18 Grimsgaard further do not disclose or suggest administration to at least one subject in the group
19 of subjects, the claimed pharmaceutical composition with the recited administration period. The
20 cited portions of Grimsgaard further do not disclose or suggest a method to effect the recited TG
21 reduction in the at least one subject with the claimed TG level.

22 With respect to Claims 1, 10 and 17 of the '372 Patent (and therefore all asserted claims),
23 Grimsgaard does not disclose or suggest identifying a group of subjects with the recited very
24 high TG levels. Grimsgaard also does not disclose or suggest administration to at least one

1 subject in the group of subjects, the claimed pharmaceutical composition with the recited
2 administration period. Grimsgaard further does not disclose or suggest a method to effect the
3 recited TG reduction in the at least one subject with the claimed TG level.

4 Further, with respect to Claims 4, 13 and 20, this reference fails to disclose or suggest the
5 recited TG and LDL-C effects in the at least one subject with the claimed TG level. With respect
6 to Claims 5, 14 and 21, this reference fails to disclose or suggest the recited reduction in
7 Apolipoprotein B in the at least one subject with the claimed TG level. With respect to Claims 6,
8 15 and 22, this reference fails to disclose or suggest the recited reduction in VLDL-C in the at
9 least one subject with the claimed TG level. With respect to Claims 7, 16 and 23, this reference
10 fails to disclose or suggest the group of subjects having the recited very high TG level.

11 (5) Hayashi

12 Hayashi is directed to administration of ethyl icosapentate 1800mg (6 capsules) daily for
13 8 weeks. The purity of the composition is not reported. The study was not placebo controlled
14 and was conducted in 28 patients with familial combined hyperlipidemia and a serum trygliceride
15 concentration higher than 150 mg/dl or serum total cholestorol concentration higher than 220
16 mg/dl.

17 The portions of Hayashi cited by Defendants do not disclose or suggest elements of the
18 '372 patent claims. For example, the cited portions of Hayashi do not disclose or suggest
19 administration of EPA with the recited purity to a subject with the recited very high TG levels
20 who does not receive concurrent lipid altering therapy. Figure 2 demonstrates that no subject
21 had a TG level above 400 mg/dl. The cited portions of Hayahsi further do not disclose or
22 suggest the claimed pharmaceutical composition with the recited fatty acid compositions or
23 dosage. The cited portions of Hayashi further do not disclose or suggest a method to effect the
24

1 recited TG reduction without substantially increasing LDL-C in a subject with the recited very
2 high TG levels.

3 With respect to Claims 1, 10 and 17 of the '372 Patent (and therefore all asserted claims),
4 Hayashi does not disclose or suggest identifying a group of subjects with the recited very high
5 TG level. Hayashi also does not disclose or suggest administration to at least one subject, the
6 claimed pharmaceutical composition with the recited fatty acid composition or dosage. Hayashi
7 further does not disclose or suggest a method to effect the recited TG reduction in the at least one
8 subject with the claimed TG level.

9 Further, with respect to Claims 2, 11 and 18, this reference fails to disclose or suggest the
10 group of subjects having the recited baseline LDL-C level. With respect to Claims 4, 13 and 20,
11 this reference fails to disclose or suggest the recited TG and LDL-C effects in the at least one
12 subject with the claimed TG level. With respect to Claims 5, 14 and 21, this reference fails to
13 disclose or suggest the recited reduction in Apolipoprotein B in the at least one subject with the
14 claimed TG level. With respect to Claims 6, 15 and 22, this reference fails to disclose or suggest
15 the recited reduction in VLDL-C in the at least one subject with the claimed TG level. With
16 respect to Claims 7, 16 and 23, this reference fails to disclose or suggest the group of subjects
17 having the recited very high TG level.

18 (6) Katayama

19 Katayama was directed to an investigation of the safety and efficacy of Epadel during
20 long term treatment in patients with hyperlipidemia that was not placebo controlled. Notably,
21 Katayama did not disclose or suggest any LDL-C related data or describe any LDL-C effects and
22 was not placebo controlled.

23 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of
24 Katayama disclose or suggest elements of the '372 Claims. The cited portions of Katayama do

1 not disclose or suggest these elements at least because they do not disclose or suggest identifying
2 a group of subjects with the recited very high TG levels. The cited portions of Katayama further
3 do not disclose or suggest administration to at least one subject, the claimed pharmaceutical
4 composition with the recited fatty acid composition or dosage. The cited portions of Katayama
5 further do not disclose or suggest a method to effect the recited TG reduction in the at least one
6 subject with the claimed TG level.

7 With respect to Claims 1, 10 and 17 of the '372 Patent (and therefore all asserted claims),
8 Katayama does not disclose or suggest identifying a group of subjects with the recited very high
9 TG level. Katayama also does not disclose or suggest administration to at least one subject, the
10 claimed pharmaceutical composition with the recited fatty acid composition or dosage.
11 Katayama further does not disclose or suggest a method to effect the recited TG reduction in the
12 at least one subject with the claimed TG level.

13 Further, with respect to Claims 2, 11 and 18, this reference fails to disclose or suggest the
14 group of subjects having the recited baseline LDL-C level. With respect to Claims 4, 13 and 20,
15 this reference fails to disclose or suggest the recited TG and LDL-C effects in the at least one
16 subject with the claimed TG level. With respect to Claims 5, 14 and 21, this reference fails to
17 disclose or suggest the recited reduction in Apolipoprotein B in the at least one subject with the
18 claimed TG level. With respect to Claims 6, 15 and 22, this reference fails to disclose or suggest
19 the recited reduction in VLDL-C in the at least one subject with the claimed TG level. With
20 respect to Claims 7, 16 and 23, this reference fails to disclose or suggest the group of subjects
21 having the recited very high TG level.

1 (7) Leigh-Firbank

2 Leigh-Firbank studied the impact of fish-oil intervention on LDL oxidation, particle
3 density and concentration in subjects with an atherogenic lipoprotein phenotype. Leigh-Firbank
4 does not administer EPA of the purity recited in the claims.

5 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of
6 Leigh-Firbank disclose or suggest elements of the '372 Claims. The cited portions of Leigh-
7 Firbank do not disclose or suggest these elements at least because they do not disclose or suggest
8 identifying a group of subjects with the recited very high TG levels. The cited portions of Leigh-
9 Firbank further do not disclose or suggest administration to at least one subject, the claimed
10 pharmaceutical composition with the recited fatty acid compositions, dosage, or administration
11 period. The cited portions of Leigh-Firbank further do not disclose or suggest a method of
12 administering the claimed pharmaceutical composition to effect the recited TG reduction in the
13 at least one subject with the claimed TG level.

14 With respect to Claims 1, 10 and 17 of the '372 Patent (and therefore all asserted claims),
15 Leigh-Firbank does not disclose or suggest identifying a group of subjects with the recited very
16 high TG level. Leigh-Firbank also does not disclose or suggest administration to at least one
17 subject, the claimed pharmaceutical composition with the recited fatty acid compositions,
18 dosage, or administration period. Leigh-Firbank further does not disclose or suggest a method of
19 administering the claimed pharmaceutical composition to effect the recited TG reduction in the
20 at least one subject with the claimed TG level. With respect to Claim 8, Leigh-Firbank does not
21 disclose or suggest a method of administering the claimed pharmaceutical composition to effect
22 the recited TG reduction based on a comparison to a placebo control.

23 Further, with respect to Claims 4, 13 and 20, this reference fails to disclose or suggest the
24 administration of the claimed pharmaceutical composition to effect the recited TG and LDL-C

1 effects. With respect to Claims 5, 14 and 21, this reference fails to disclose or suggest the
2 administration of the claimed pharmaceutical composition to effect the recited reduction in
3 Apolipoprotein B. With respect to Claims 6, 15 and 22, this reference fails to disclose or suggest
4 the administration of the claimed pharmaceutical composition to effect the recited reduction in
5 VLDL-C. With respect to Claims 7, 16 and 23, this reference fails to disclose or suggest the
6 group of subjects having the recited very high TG level.

7 (8) Lovaza PDR

8 The Lovaza PDR is the Physicians' Desk Reference describing Lovaza.

9 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of the
10 Lovaza PDR disclose or suggest elements of the '372 Claims. The cited portions of the Lovaza
11 PDR do not disclose or suggest these elements at least because they do not disclose or suggest
12 administration to at least one subject, the claimed pharmaceutical composition with the recited
13 fatty acid compositions or administration period. The cited portions of the Lovaza PDR further
14 do not disclose or suggest a method of administering the claimed pharmaceutical composition to
15 effect the recited TG reduction.

16 With respect to Claims 1, 10 and 17 of the '372 Patent (and therefore all asserted claims),
17 the Lovaza PDR does not disclose or suggest administration to at least one subject, the claimed
18 pharmaceutical composition with the recited fatty acid compositions or administration period.
19 The Lovaza PDR further does not disclose or suggest a method of administering the claimed
20 pharmaceutical composition to effect the recited TG reduction. With respect to Claim 8, the
21 Lovaza PDR does not disclose or suggest a method of administering the claimed pharmaceutical
22 composition to effect the recited TG reduction based on a comparison to a placebo control.

23 Further, with respect to Claims 4, 13 and 20, this reference fails to disclose or suggest the
24 administration of the claimed pharmaceutical composition to effect the recited TG and LDL-C

1 effects. With respect to Claims 5, 14 and 21, this reference fails to disclose or suggest the
2 administration of the claimed pharmaceutical composition to effect the recited reduction in
3 Apolipoprotein B. With respect to Claims 6, 15 and 22, this reference fails to disclose or suggest
4 the administration of the claimed pharmaceutical composition to effect the recited reduction in
5 VLDL-C.

6 (9) Maki

7 Maki administered 1.52g/day DHA supplements to patients with below-average levels of
8 HDL-C. Maki does not administer EPA of the purity recited in the claims.

9 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of
10 Leigh-Firbank disclose or suggest elements of the '372 Claims. The cited portions of Leigh-
11 Firbank do not disclose or suggest these elements at least because they do not disclose or suggest
12 identifying a group of subjects with the recited very high TG levels. The cited portions of Leigh-
13 Firbank further do not disclose or suggest administration to at least one subject, the claimed
14 pharmaceutical composition with the recited fatty acid compositions, dosage, or administration
15 period. The cited portions of Leigh-Firbank further do not disclose or suggest a method of
16 administering the claimed pharmaceutical composition to effect the recited TG reduction in the
17 at least one subject with the claimed TG level.

18 With respect to Claims 1, 10 and 17 of the '372 Patent (and therefore all asserted claims),
19 Leigh-Firbank does not disclose or suggest identifying a group of subjects with the recited very
20 high TG level. Leigh-Firbank also does not disclose or suggest administration to at least one
21 subject, the claimed pharmaceutical composition with the recited fatty acid compositions,
22 dosage, or administration period. Leigh-Firbank further does not disclose or suggest a method of
23 administering the claimed pharmaceutical composition to effect the recited TG reduction in the
24 at least one subject with the claimed TG level. With respect to Claim 8, Leigh-Firbank does not

1 disclose or suggest a method of administering the claimed pharmaceutical composition to effect
2 the recited TG reduction based on a comparison to a placebo control.

3 Further, with respect to Claims 4, 13 and 20, this reference fails to disclose or suggest the
4 administration of the claimed pharmaceutical composition to effect the recited TG and LDL-C
5 effects. With respect to Claims 5, 14 and 21, this reference fails to disclose or suggest the
6 administration of the claimed pharmaceutical composition to effect the recited reduction in
7 Apolipoprotein B. With respect to Claims 6, 15 and 22, this reference fails to disclose or suggest
8 the administration of the claimed pharmaceutical composition to effect the recited reduction in
9 VLDL-C. With respect to Claims 7, 16 and 23, this reference fails to disclose or suggest the
10 group of subjects having the recited very high TG level.

11 (10) Matsuzawa

12 Matsuzawa administered Epadel to patients with hyperlipaemia in order to study its long-
13 term use in the treatment of the disease and was not placebo controlled.

14 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of
15 Matsuzawa disclose or suggest elements of the '372 Claims. The cited portions of Matsuzawa
16 do not disclose or suggest these elements at least because they do not disclose or suggest
17 identifying a group of subjects with the recited very high TG levels. The cited portions of
18 Matsuzawa further do not disclose or suggest administration to at least one subject, the claimed
19 pharmaceutical composition with the recited fatty acid composition or dosage. The cited
20 portions of Matsuzawa further do not disclose or suggest a method of administering the claimed
21 pharmaceutical composition to effect the recited TG reduction in the at least one subject with the
22 claimed TG level.

23 With respect to Claims 1, 10 and 17 of the '372 Patent (and therefore all asserted claims),
24 Matsuzawa does not disclose or suggest identifying a group of subjects with the recited very high

1 TG level. Matsuzawa also does not disclose or suggest administration to at least one subject, the
2 claimed pharmaceutical composition with the recited fatty acid composition or dosage.
3 Matsuzawa further does not disclose or suggest a method of administering the claimed
4 pharmaceutical composition to effect the recited TG reduction in the at least one subject with the
5 claimed TG level.

6 Further, with respect to Claims 4, 13 and 20, this reference fails to disclose or suggest the
7 recited TG and LDL-C effects in the at least one subject with the claimed TG level. With respect
8 to Claims 5, 14 and 21, this reference fails to disclose or suggest the administration of the
9 claimed pharmaceutical composition to effect the recited reduction in Apolipoprotein B in the at
10 least one subject with the claimed TG level. With respect to Claims 6, 15 and 22, this reference
11 fails to disclose or suggest the administration of the claimed pharmaceutical composition to
12 effect the recited reduction in VLDL-C in the at least one subject with the claimed TG level.
13 With respect to Claims 7, 16 and 23, this reference fails to disclose or suggest the group of
14 subjects having the recited very high TG level.

15 (11) Mori 2000

16 Mori 2000 aimed to determine whether EPA and DHA have differential effects on serum
17 lipids and lipoproteins, glucose and insulin in humans.

18 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Mori
19 2000 disclose or suggest elements of the '372 Claims. The cited portions of Mori 2000 do not
20 disclose or suggest these elements at least because they do not disclose or suggest identifying a
21 group of subjects with the recited very high TG levels. The cited portions of Mori 2000 further
22 do not disclose or suggest administration to at least one subject in the group of subjects, the
23 claimed pharmaceutical composition with the recited administration period. The cited portions
24

1 of Mori 2000 further do not disclose or suggest a method to effect the recited TG reduction in the
2 at least one subject with the claimed TG level.

3 With respect to Claims 1, 10 and 17 of the '372 Patent (and therefore all asserted claims),
4 Mori 2000 does not disclose or suggest identifying a group of subjects with the recited very high
5 TG levels. Mori 2000 also does not disclose or suggest administration to at least one subject in
6 the group of subjects, the claimed pharmaceutical composition with the recited administration
7 period. Mori 2000 further does not disclose or suggest a method to effect the recited TG
8 reduction in the at least one subject with the claimed TG level.

9 Further, with respect to Claims 4, 13 and 20, this reference fails to disclose or suggest the
10 recited TG and LDL-C effects in the at least one subject with the claimed TG level. With respect
11 to Claims 5, 14 and 21, this reference fails to disclose or suggest the recited reduction in
12 Apolipoprotein B in the at least one subject with the claimed TG level. With respect to Claims 6,
13 15 and 22, this reference fails to disclose or suggest the recited reduction in VLDL-C in the at
14 least one subject with the claimed TG level. With respect to Claims 7, 16 and 23, this reference
15 fails to disclose or suggest the group of subjects having the recited very high TG level.

16 (12) Mori 2006

17 Mori 2006 is a review which reports data from clinical trials which compared the
18 independent effects of EPA and DHA in individuals at increased risk of cardiovascular disease.

19 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Mori
20 2006 disclose or suggest elements of the '372 Claims. The cited portions of Mori 2006 do not
21 disclose or suggest these elements at least because they do not disclose or suggest identifying a
22 group of subjects with the recited very high TG levels. The cited portions of Mori 2006 further
23 do not disclose or suggest administration to at least one subject, the claimed pharmaceutical
24 composition with the recited fatty acid dosage or administration period. The cited portions of

1 Mori 2006 further do not disclose or suggest a method to effect the recited TG reduction in the at
2 least one subject with the claimed TG level.

3 With respect to Claims 1, 10 and 17 of the '372 Patent (and therefore all asserted claims),
4 Mori 2006 does not disclose or suggest identifying a group of subjects with the recited very high
5 TG level. Mori 2006 also does not disclose or suggest administration to at least one subject, the
6 claimed pharmaceutical composition with the recited fatty acid dosage or administration period.
7 Mori 2006 further does not disclose or suggest a method to effect the recited TG reduction in the
8 at least one subject with the claimed TG level.

9 Further, with respect to Claims 2, 11 and 18, this reference fails to disclose or suggest the
10 group of subjects having the recited baseline LDL-C level. With respect to Claims 3, 12 and 19,
11 this reference fails to disclose or suggest the group of subjects having the recited baseline lipid
12 levels. With respect to Claims 4, 13 and 20, this reference fails to disclose or suggest the recited
13 TG and LDL-C effects in the at least one subject with the claimed TG level. With respect to
14 Claims 5, 14 and 21, this reference fails to disclose or suggest the recited reduction in
15 Apolipoprotein B in the at least one subject with the claimed TG level. With respect to Claims 6,
16 15 and 22, this reference fails to disclose or suggest the recited reduction in VLDL-C in the at
17 least one subject with the claimed TG level. With respect to Claims 7, 16 and 23, this reference
18 fails to disclose or suggest the group of subjects having the recited very high TG level.

19 (13) Nozaki

20 Nozaki is directed to administration of 2.7 g ethyl icosapentate per day for 6 months. The
21 purity of the composition is reported as 90%. The study was not placebo controlled and was
22 conducted in 14 hypercholesterolemic subjects. The average baseline TG level was only 165
23 mg/dL, while the baseline LDL-C level was 185 mg/dL, which is unusually high for this TG
24 patient population.

1 The portions of Nozaki cited by Defendants do not disclose or suggest elements of the
2 ‘372 patent claims. For example, the cited portions of Nozaki do not disclose or suggest
3 administration of EPA with the recited purity to a subject with the recited very high TG levels
4 who does not receive concurrent lipid altering therapy. The cited portions of Nozaki further do
5 not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid
6 compositions or dosage. The cited portions of Nozaki further do not disclose or suggest a
7 method to effect the recited TG reduction without substantially increasing LDL-C in a subject
8 with the recited very high TG levels.

9 Defendants assert that certain cited sections of Nozaki disclose or suggest elements of the
10 ‘372 Claims. The cited portions of Nozaki do not disclose or suggest these elements at least
11 because they do not disclose or suggest administration of EPA with the recited purity to a subject
12 with the recited very high TG levels who does not receive concurrent lipid altering therapy. The
13 cited portions of Nozaki further do not disclose or suggest the claimed pharmaceutical
14 composition with the recited fatty acid compositions or dosage. The cited portions of Nozaki
15 further do not disclose or suggest a method to effect the recited TG reduction without
16 substantially increasing LDL-C.

17 With respect to Claims 1, 10 and 17 of the ‘372 Patent (and therefore all asserted claims),
18 Nozaki does not disclose or suggest identifying a group of subjects with the recited very high TG
19 level. Nozaki also does not disclose or suggest administration to at least one subject, the claimed
20 pharmaceutical composition with the recited fatty acid composition or dosage. Nozaki further
21 does not disclose or suggest a method to effect the recited TG reduction in the at least one
22 subject with the claimed TG level.

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1 Further, with respect to Claims 2, 11 and 18, this reference fails to disclose or suggest the
2 group of subjects having the recited baseline LDL-C level. With respect to Claims 4, 13 and 20,
3 this reference fails to disclose or suggest the recited TG and LDL-C effects in the at least one
4 subject with the claimed TG level. With respect to Claims 5, 14 and 21, this reference fails to
5 disclose or suggest the recited reduction in Apolipoprotein B in the at least one subject with the
6 claimed TG level. With respect to Claims 6, 15 and 22, this reference fails to disclose or suggest
7 the recited reduction in VLDL-C in the at least one subject with the claimed TG level. With
8 respect to Claims 7, 16 and 23, this reference fails to disclose or suggest the group of subjects
9 having the recited very high TG level.

10 (14) Omacor PDR

11 The Omacor PDR is the Physicians' Desk Reference describing Omacor.

12 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of the
13 Omacor PDR disclose or suggest elements of the '372 Claims. The cited portions of the Omacor
14 PDR do not disclose or suggest these elements at least because they do not disclose or suggest
15 administration to at least one subject, the claimed pharmaceutical composition with the recited
16 fatty acid compositions or administration period. The cited portions of the Omacor PDR further
17 do not disclose or suggest a method of administering the claimed pharmaceutical composition to
18 effect the recited TG reduction.

19 With respect to Claims 1, 10 and 17 of the '372 Patent (and therefore all asserted claims),
20 the Omacor PDR does not disclose or suggest administration to at least one subject, the claimed
21 pharmaceutical composition with the recited fatty acid compositions or administration period.
22 The Omacor PDR further does not disclose or suggest a method of administering the claimed
23 pharmaceutical composition to effect the recited TG reduction. With respect to Claim 8, the
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1 Omacor PDR does not disclose or suggest a method of administering the claimed pharmaceutical
2 composition to effect the recited TG reduction based on a comparison to a placebo control.

3 Further, with respect to Claims 4, 13 and 20, this reference fails to disclose or suggest the
4 administration of the claimed pharmaceutical composition to effect the recited TG and LDL-C
5 effects. With respect to Claims 5, 14 and 21, this reference fails to disclose or suggest the
6 administration of the claimed pharmaceutical composition to effect the recited reduction in
7 Apolipoprotein B. With respect to Claims 6, 15 and 22, this reference fails to disclose or suggest
8 the administration of the claimed pharmaceutical composition to effect the recited reduction in
9 VLDL-C.

10 (15) Satoh

11 Satoh administered 1.8g/day of >98% EPA to patients in order to measure the effects of
12 PEA on C-reactive protein and examine how alteration of lipoprotein profile by EPA affects
13 systemic inflammation.

14 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of
15 Satoh disclose or suggest elements of the '372 Claims. The cited portions of Satoh do not
16 disclose or suggest these elements at least because they do not disclose or suggest identifying a
17 group of subjects with the recited very high TG levels. The cited portions of Satoh further do not
18 disclose or suggest administration to at least one subject in the group of subjects, the claimed
19 pharmaceutical composition with the recited fatty acid dosage. The cited portions of Satoh
20 further do not disclose or suggest a method to effect the recited TG reduction in the at least one
21 subject with the claimed TG level.

22 With respect to Claims 1, 10 and 17 of the '372 Patent (and therefore all asserted claims),
23 Satoh does not disclose or suggest identifying a group of subjects with the recited very high TG
24 levels. Satoh also does not disclose or suggest administration to at least one subject in the group

1 of subjects, the claimed pharmaceutical composition with the recited fatty acid dosage. Satoh
2 further does not disclose or suggest a method to effect the recited TG reduction in the at least one
3 subject with the claimed TG level.

4 Further, with respect to Claims 4, 13 and 20, this reference fails to disclose or suggest the
5 recited TG and LDL-C effects in the at least one subject with the claimed TG level. With respect
6 to Claims 5, 14 and 21, this reference fails to disclose or suggest the recited reduction in
7 Apolipoprotein B in the at least one subject with the claimed TG level. With respect to Claims 6,
8 15 and 22, this reference fails to disclose or suggest the recited reduction in VLDL-C in the at
9 least one subject with the claimed TG level. With respect to Claims 7, 16 and 23, this reference
10 fails to disclose or suggest the group of subjects having the recited very high TG level.

11 (16) Shinozaki

12 Shinozaki studied the long-term effect of EPA on serum levels of Lipoprotein (a) and
13 lipids such as triglycerides, total cholesterol, and low density lipoprotein particles.

14 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of
15 Shinozaki disclose or suggest elements of the '372 Claims. The cited portions of Shinozaki do
16 not disclose or suggest these elements at least because they do not disclose or suggest identifying
17 a group of subjects with the recited very high TG levels. The cited portions of Shinozaki further
18 do not disclose or suggest administration to at least one subject in the group of subjects, the
19 claimed pharmaceutical composition with the recited fatty acid dosage. The cited portions of
20 Shinozaki further do not disclose or suggest a method to effect the recited TG reduction in the at
21 least one subject with the claimed TG level.

22 With respect to Claims 1, 10 and 17 of the '372 Patent (and therefore all asserted claims),
23 Shinozaki does not disclose or suggest identifying a group of subjects with the recited very high
24 TG levels. Shinozaki also does not disclose or suggest administration to at least one subject in

1 the group of subjects, the claimed pharmaceutical composition with the recited fatty acid dosage.
2 Shinozaki further does not disclose or suggest a method to effect the recited TG reduction in the
3 at least one subject with the claimed TG level.

4 Further, with respect to Claims 2, 11 and 18, this reference fails to disclose or suggest the
5 group of subjects having the recited baseline LDL-C level. With respect to Claims 3, 12 and 19,
6 this reference fails to disclose or suggest the group of subjects having the recited baseline lipid
7 levels. With respect to Claims 4, 13 and 20, this reference fails to disclose or suggest the recited
8 TG and LDL-C effects in the at least one subject with the claimed TG level. With respect to
9 Claims 5, 14 and 21, this reference fails to disclose or suggest the recited reduction in
10 Apolipoprotein B in the at least one subject with the claimed TG level. With respect to Claims 6,
11 15 and 22, this reference fails to disclose or suggest the recited reduction in VLDL-C in the at
12 least one subject with the claimed TG level. With respect to Claims 7, 16 and 23, this reference
13 fails to disclose or suggest the group of subjects having the recited very high TG level.

14 (17) Takaku

15 Takaku administered Epadel to patients with hyperlipaemia in order to study its long-
16 term use and was not placebo controlled.

17 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of
18 Takaku disclose or suggest elements of the '372 Claims. The cited portions of Takaku do not
19 disclose or suggest these elements at least because they do not disclose or suggest identifying a
20 group of subjects with the recited very high TG levels. The cited portions of Takaku further do
21 not disclose or suggest administration to at least one subject, the claimed pharmaceutical
22 composition with the recited fatty acid composition or dosage. The cited portions of Takaku
23 further do not disclose or suggest a method of administering the claimed pharmaceutical
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1 composition to effect the recited TG reduction in the at least one subject with the claimed TG
2 level.

3 With respect to Claims 1, 10 and 17 of the '372 Patent (and therefore all asserted claims),
4 Takaku does not disclose or suggest identifying a group of subjects with the recited very high TG
5 level. Takaku also does not disclose or suggest administration to at least one subject, the claimed
6 pharmaceutical composition with the recited fatty acid composition or dosage. Takaku further
7 does not disclose or suggest a method of administering the claimed pharmaceutical composition
8 to effect the recited TG reduction in the at least one subject with the claimed TG level.

9 Further, with respect to Claims 2, 11 and 18, this reference fails to disclose or suggest the
10 group of subjects having the recited baseline LDL-C level. With respect to Claims 3, 12 and 19,
11 this reference fails to disclose or suggest the group of subjects having the recited baseline lipid
12 levels. With respect to Claims 4, 13 and 20, this reference fails to disclose or suggest the recited
13 TG and LDL-C effects in the at least one subject with the claimed TG level. With respect to
14 Claims 5, 14 and 21, this reference fails to disclose or suggest the recited reduction in
15 Apolipoprotein B in the at least one subject with the claimed TG level. With respect to Claims 6,
16 15 and 22, this reference fails to disclose or suggest the recited reduction in VLDL-C in the at
17 least one subject with the claimed TG level. With respect to Claims 7, 16 and 23, this reference
18 fails to disclose or suggest the group of subjects having the recited very high TG level.

19 c) The Prior Art Does Not Render the Claims Obvious

20 Defendants have not identified by clear and convincing evidence that the asserted claims
21 of the '372 patent would have been *prima facie* obvious in light of the references cited, either
22 alone or in combination. As described above, none of the references discloses all of the elements
23 in any of the asserted claims. Defendants chart a laundry list of 66 separate references, without
24 explanation, and argue they somehow must be combined to render obvious the asserted claims.

1 Where Defendants have failed to make disclosures with the specificity required by Local Patent
2 Rule 1-8(d), it has failed to put Plaintiffs on notice of how these references allegedly disclose the
3 claim elements at issue.

4 Facts supporting the non-obviousness of the claims of the '372 patent are discussed in
5 detail below. The objective indicia discussed in Section V.O further demonstrate that the '372
6 patent is not obvious. In short, Defendants have not met their burden of showing that the claims
7 would have been obvious.

8 (1) Defendants Do Not Demonstrate that the Independent
9 Claims of the '372 Patent Would Have Been Obvious

10 (a) Defendants Do Not Demonstrate that a Person of
11 Ordinary Skill in the Art Would Have Had Any
12 Reason to Replace the Mixed Fish Oil Active
13 Ingredient in Lovaza with Pure EPA

14 (i) The '372 patent is not Obvious Over the
15 Omacor PDR/Lovaza PDR, in Combination
16 with Katayama and/or Matsuzawa, further in
17 view of Nozaki and/or Hayashi, and Further
18 in View of Leigh-Firbank and/or Mori 2000

19 With respect to the '372 patent, Defendants present a combination of seven references:
20 "the Omacor PDR/Lovaza PDR in combination with the known clinical benefits of administering
21 pure EPA as evidenced by Katayama and/or Matsuzawa, further in view of Nozaki and/or
22 Hayashi, and further in view of Leigh-Firbank and/or Mori 2000."⁵⁸⁰⁹ Defendants also present
23 charts purporting to assert that an additional 61 references may be combined in order to render
24 the Claims obvious. Not only do Defendants ignore the improbability that a person of ordinary
skill would combine 61 separate references, they additionally do not identify any motivation for

⁵⁸⁰⁹ Defendants' Joint Invalidity Contentions at 748.

1 combining these references.^{5810, 5811} Although Defendants need not point to an explicit statement
2 in the prior art motivating the combination of these references, any assertion of an “apparent
3 reason” to combine must find a basis in the factual record.⁵⁸¹² Defendants’ unsupported cobbling
4 of selective disclosures represents hindsight reconstruction.⁵⁸¹³ Defendants’ contentions are no
5 more than an assertion that certain claim elements were known in the prior art. Throughout their
6 contentions, Defendants’ selectively cite to data points in a reference without considering other
7 disclosures or even the reference as a whole. Each reference, however, must be evaluated for all

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10 ⁵⁸¹⁰ Defendants’ bare assertion that the asserted claims are obvious “in view of one or more of Omacor or Lovaza (as
11 described in the references cited above in Section V.B.2 in view of, at least, the references cited in V.B.3 and 4,
12 including, the ‘954 publication, WO ‘900, WO ‘118, Ando, Grimsgaard, Hayashi, Katayama, Matsuzawa, Mataka,
13 Mori 2000, Nakamura, Nozaki, Okumura, Park, Saito 1998, Saito 2008 Satoh, Shinozaki, Takaku, Yokoyama 2003,
14 Yokoyama 2007, Calabresi, Chan 2002, Chan 2003, Contacos, Geppert, Kelley, Leigh-Firbank, Maki, Mori 2006,
15 Rambjør, Sanders or Theobald,” similarly fails to meet the disclosure requirements of the Nevada Local Patent
16 Rules, and fails to provide any motivation to combine these references. *See* Defendants’ Joint Invalidity
17 Contentions at 754-755.

18 ⁵⁸¹¹ Defendants’ bare assertion that “the motivation or reason to combine or modify the prior art to create
19 invalidating combinations under 35 U.S.C. §103 can be found in the references identified above in Section III.C,”
20 and that “[c]ommon sense, design incentives. Market forces, and the background knowledge possessed by a person
21 having ordinary skill in the art provide the reasons or rationales for combining the teachings of multiple references
22 or modifying references to render obvious the claimed inventions of the asserted claims,” fails to meet the disclosure
23 requirements of the Nevada Local Patent Rules. *See* Defendants’ Joint Invalidity Contentions at 746.

24 ⁵⁸¹² *See, e.g., In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the
formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did
not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply
the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi
Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must
avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to
select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and
elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp.
2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie*
obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding
that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been
motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

⁵⁸¹³ *See, e.g., Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under
KSR, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention
without any explanation as to how or why the references would be combined to produce the claimed invention”).

1 that it teaches.⁵⁸¹⁴ Accordingly, Defendants fail to meet their burden to establish *prima facie*
2 obviousness.

3 The Lovaza PDR fails to disclose or even suggest the claimed method of reducing
4 triglycerides in a subject with the claimed pharmaceutical composition containing the claimed
5 fatty acid compositions or administration period. The Lovaza PDR further does not disclose a
6 method to effect the specified TG reduction without substantially increasing LDL-C. Indeed, the
7 Lovaza PDR discloses the exact opposite. The EPA/DHA composition of Lovaza causes a
8 significant increase in LDL-C levels in the very high TG patient population, for whom the
9 product is indicated. At most, the Lovaza PDR discloses administration of a prescription fish oil,
10 a combination of approximately 465 mg EPA and 375 mg DHA, as an adjunct to diet to reduce
11 TG levels in adult patients with very-high (≥ 500 mg/dL) TG levels.

12 The proposed combinations do not render the independent claims of the '372 patent
13 obvious and Defendants' burden to prove otherwise is especially difficult because the PTO
14 considered Matsuzawa, Katayama, Mori 2000, and Lovaza (both generally and the Lovaza
15 package insert specifically) during prosecution.⁵⁸¹⁵

16 The analysis of the independent claims of the '372 patent is incorporated into all asserted
17 claims that depend from those Claims.

18 (a) A Person of Ordinary Skill Would
19 Not Have Been Motivated to
20

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22 ⁵⁸¹⁴ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

23 ⁵⁸¹⁵ *See, e.g., Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012)(taking into account that “the
24 examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention.
Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear
and convincing standard came into play”).

3 For an invention to be obvious, there must have been an “apparent reason” to make it.

4 The subject matter of the ‘372 patent claims would not have been obvious in light of these
5 references because a person of ordinary skill would not have been motivated to purify EPA or
6 been able to reasonably expect that the claimed pharmaceutical composition would reduce TG
7 levels without an increase in LDL-C levels.

8 (i) Katayama and/or Matsuzawa
9 Do Not Disclose Purported
Known Clinical Benefits of
Administering Pure EPA

10 Both Katayama and Matsuzawa are long term studies directed to an investigation of the
11 safety and efficacy of Epadel in patients with a wide range of baseline TG levels. These studies
12 were not placebo controlled. A person of ordinary skill in the art understood that a placebo may
13 itself cause an effect. Without accounting for the placebo effect, a person of ordinary skill in the
14 art would not and could not attribute any observed effect (and the magnitude of that effect) to
15 that of the drug. Any observed effect could be placebo dependent.⁵⁸¹⁶ As discussed above in
16 Section III, a person of ordinary skill would not expect the same LDL-C effect in patients with
17 lower baseline TG levels—the subjects of Katayama and Matsuzawa—as in very-high TG
18 patients because patients with higher TG levels had different lipid responses compared to
19 patients with lower TG levels. Patients with very-high TG levels were considered fundamentally
20 different from patients with borderline-high or high TGs from a lipid chemistry, medical, clinical
21 guideline, regulatory, and therapeutic standpoint. As previously discussed, a person of ordinary

22 _____
23 ⁵⁸¹⁶See Grimsgaard at 652 (Although administration of EPA reduced Apo-B compared to baseline, it was not a
24 statistically significant effect when compared to placebo. Grimsgaard’s disclosure highlights the importance of a
placebo-controlled study and why results compared only to baseline may be misleading.)

1 skill in the art would expect to see an increase in LDL-C levels when omega-3 fatty acids were
2 administered to patients with normal, borderline-high or high TG levels. Therefore, the prior art
3 Defendants rely upon to show that EPA did not increase LDL-C levels in normal, borderline-
4 high or high TG patients, was expected. At the priority date of the '372 patent, a person of
5 ordinary skill in the art would have expected an *increase* in LDL-C for very-high TG patients
6 receiving a TG-lowering agent, as a natural consequence of lowering TGs. This pattern had been
7 demonstrated for both fibrates and fish oils and was understood as a direct consequence of TG
8 lowering through increased VLDL particle conversion.

9 Defendants argue that these studies disclose known “clinical benefits” of administering
10 pure EPA, lowering triglycerides without raising LDL-C.⁵⁸¹⁷ This is an incorrect characterization
11 of these two studies. Katayama and Matsuzawa both were only designed to confirm the safety of
12 long term treatment of Epadel and its ability to lower both serum total cholesterol and TG levels.
13 They do just that. They do not discuss any purported “benefits” observed related to LDL-C.
14 Defendants’ selective citation of LDL-C data from these references represents the improper use
15 of hindsight bias. A person of ordinary skill would understand the focus of Katayama and
16 Matsuzawa to be TG and total cholesterol effects and not LDL-C levels, and would not draw
17 conclusions regarding LDL-C from these studies. Indeed, Katayama does not mention LDL-C
18 levels at all. Defendants’ characterization of Katayama and Matsuzawa as disclosing the
19 lowering of TG levels without increasing LDL-C to be a “clinical benefit” is incorrect.⁵⁸¹⁸ The
20 references don’t disclose or suggest that the LDL-C results obtained were a clinical benefit, nor
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23 ⁵⁸¹⁷ Defendants’ Joint Invalidation Contentions at 748 and 749.

24 ⁵⁸¹⁸ Defendants’ Joint Invalidation Contentions at 748.

1 would a person of ordinary skill view these references as teaching such a benefit for very-high
2 TG patients.

3 Further, both Katayama and Matsuzawa administered only EPA and studied its lipid
4 effects. These studies fail to provide a head to head comparison of EPA versus DHA.
5 Therefore, a person of ordinary skill in the art would not rely on Katayama or Matsuzawa to
6 draw any conclusions related to possible differences between the lipid effects of EPA and DHA.

7 In addition, Katayama and Matsuzawa do not disclose the purity of the Epadel used. The
8 purity of Epadel has varied over time and across different formulations of the product, therefore
9 it is difficult to determine the purity of the version of Epadel used unless it is specified by the
10 disclosure. One cannot simply rely on the fact that Epadel was administered and assume that the
11 composition comprised at least about 96%, by weight of all fatty acids present, EPA, and
12 substantially no DHA, as required by the asserted claims. Defendants fail to provide a reference
13 disclosing the purity of the form of Epadel used in the Katayama and Matsuzawa studies.

14 Nishikawa,⁵⁸¹⁹ published in 1997, discloses a form of Epadel that was a 91% E-EPA preparation.
15 Nishikawa reflects that versions of Epadel used in some clinical studies do not have the requisite
16 purity.⁵⁸²⁰

17 Further, Katayama and Matsuzawa were small studies conducted in only Japanese
18 patients. These studies would not have been extrapolated to Western populations because the
19 Japanese diet contains much more fish and has a number of other different attributes. The
20 Japanese consume a higher amount of EPA and DHA in their diets than Western populations. In
21

22 ⁵⁸¹⁹ Nishikawa et al., *Effects of Eicosapentaenoic Acid (EPA) on Prostacyclin Production in Diabetics: GC/MS*
23 *Analysis of PGI₂ and PGI₃ Levels*, 19 METHODS FIND EXP CLIN PHARMACOL. 429 (1997).

24 ⁵⁸²⁰ See also, Ando at 2177 (Epadel with purity greater than 91%), Nakamura at 23 (Epadel with purity > 90%).

1 fact, Yokoyama 2007 (cited in Defendants’ contentions) states that the results from studies where
2 the patient population is exclusively Japanese cannot be generalized to other populations.⁵⁸²¹
3 The Japanese diet comprises between 8 and 15 times more EPA and DHA than the typical
4 Western Diet. The Western diet typically consists of higher amounts of polyunsaturated omega-
5 6 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand
6 that the Japanese respond differently to lipid lowering agents than Westerners.

7 Defendants rely on Katayama to demonstrate the “known clinical benefits of
8 administering pure EPA - lowering triglycerides without raising LDL-C.”⁵⁸²² However,
9 Katayama was directed to an investigation of the safety and efficacy of Epadel during long-term
10 treatment in patients with hyperlipidemia.⁵⁸²³ Katayama does not disclose *any* LDL-C related
11 data or describe *any* LDL-C effects, and a person of ordinary skill would not understand that
12 reference to provide any such disclosure. The only results disclosed by Katayama were a
13 significant reduction in TGs and total cholesterol when Epadel (EPA of undisclosed purity) was
14 administered to patients with borderline-high to high TG levels, and its safety for long term use
15 in this patient population.⁵⁸²⁴ In addition to Katayama’s lack of disclosure regarding LDL-C,
16 Defendants identify no other basis upon which a person of ordinary skill would have sought to
17 combine the composition disclosed in Katayama with the Lovaza PDR.

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21 ⁵⁸²¹ Yokoyama 2007 at 1097 (“Because our population was exclusively Japanese, we cannot generalise our results to other populations.”).

22 ⁵⁸²² Defendants’ Joint Invalidity Contentions at 748 and 749.

23 ⁵⁸²³ Katayama at 2.

24 ⁵⁸²⁴ *Id.* at 16.

1 Defendants similarly rely on Matsuzawa to demonstrate the “known clinical benefits of
2 administering pure EPA - lowering triglycerides without raising LDL-C.”⁵⁸²⁵ However,
3 Matsuzawa included 26 participants, of whom 23 were adopted for the evaluation of overall
4 safety, 22 were adopted for the evaluation of usefulness, 20 were adopted for evaluation of
5 general improvement, 15 were adopted for improvement in serum total cholesterol levels, and 13
6 were evaluated for improvement in serum triglycerides levels.⁵⁸²⁶ It is unclear which of the 26
7 patients were included in each separate evaluation; therefore one cannot determine the baseline
8 lipid characteristics for each subset of patients evaluated. Further, the small sample size and lack
9 of a placebo control makes it less likely that the results of this study can be generalized as an
10 effect on any population as a whole and provides no insight with respect to the very-high TG
11 patient population.

12 Matsuzawa discloses that 3 of the 26 participants had 400 mg/dL < TG < 1000 mg/dL,
13 and one participant with TG levels > 1,000 mg/dL.⁵⁸²⁷ However, when analyzing the lipid
14 impact of Epadel, Matsuzawa excluded the patient with a TG level greater than 1,000 mg/dL
15 because he was a “heavy drinker” and the “effect of alcohol made it impossible to assess
16 triglyceride levels.”⁵⁸²⁸ Fig. 4, which depicts the changes in serum triglycerides, shows that the
17 mean triglycerides of the 12 patients with TG greater than 150 mg/dL was well below 500
18 mg/dL. Furthermore, as shown in Table 4, patients with TG levels above 500 mg/dL (other than
19 the excluded patient who had TG above 1,000 mg/dL) were not treated in the study with EPA (of
20 undisclosed purity). The identification of three patients with TG levels between 400 and less

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22 ⁵⁸²⁵ Defendants’ Joint Invalidation Contentions at 748.

23 ⁵⁸²⁶ Matsuzawa at 7 and 19.

24 ⁵⁸²⁷ *Id.* at 23.

⁵⁸²⁸ *Id.* at 10.

1 than 1,000 mg/dL does not disclose a patient with TG levels above 500 mg/dl, and a person of
2 ordinary skill would not understand that the reference makes any such disclosure. As discussed
3 above, one of ordinary skill in the art would not expect LDL-C to increase in a patient with TG
4 less than 500 mg/dL upon treatment with a TG-lowering agent. Matsuzawa provides no
5 evidence to the contrary.

6 Matsuzawa demonstrated mixed results related to LDL-C over time, at first showing a
7 2% decrease, and then a 1% increase in LDL-C by the end of 52 weeks.⁵⁸²⁹ The disclosure
8 further reflects that the 4 patients with serum triglyceride levels of at least 400 mg/dL were
9 excluded from the LDL-C results because the Friedewald's Equation was used to calculate LDL-
10 C levels. The Friedewald's Equation cannot be used for patients with triglyceride levels of at
11 least 400 mg/dL. Therefore, the LDL-C results only reflect the LDL-C changes in patients with
12 triglyceride levels below 400 mg/dL. Matsuzawa fails to provide any information to a person of
13 ordinary skill regarding the LDL-C effect in the very-high TG population. A person of ordinary
14 skill in the art, however, would have expected the same treatment in patients with very high TG
15 levels to produce a substantial increase in LDL-C. In addition, Matsuzawa acknowledges that
16 there have been conflicting results related to the LDL-C impact of EPA preparations that lowered
17 triglyceride levels.⁵⁸³⁰ At best, Matsuzawa demonstrates the uncertainty and confusion related to
18 the LDL-C effect EPA had on patients with hyperlipidemia. Further, Defendants fail to identify
19 any other basis upon which a person of ordinary skill would have sought to combine the
20 composition disclosed in Matsuzawa with the Lovaza PDR.

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22 ⁵⁸²⁹ *Id.* at 11.

23 ⁵⁸³⁰ *Id.* at 15. Matsuzawa suggests the conflicting results are due to differences in the EPA content of the EPA
24 preparation administered. However, Matsuzawa fails to identify the specific conflicting studies, disclose the specific
compositions used, or identify the patient populations were observed.

1 Further, a person of ordinary skill would understand that the baseline LDL-C level in this small
2 patient population were abnormally high and would not have relied upon these results. Further,
3 the person of skill in the art would not have looked to this patient population to predict the Apo-
4 B or LDL-C effect of EPA therapy on very high TG patients. Nozaki acknowledges that as of
5 1991, “[t]here is still controversy concerning the effects of fish oil” on LDL and HDL cholesterol
6 levels.⁵⁸³² Nozaki does not provide a motivation or reasonable expectation of success for
7 administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA and
8 substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL, to
9 effect a reduction in triglycerides without increasing LDL-C when purified EPA is administered
10 to the very high TG patient population.

11 In Hayashi, 1.8 g/day of EPA was administered to 28 patients for 8 weeks. The purity of
12 the EPA and the DHA content in the composition that was administered is unknown. A person
13 of ordinary skill would not have found the results of Hayashi reliable. The study involved 28
14 patients and it was conducted for only 8 weeks. Hayashi shows that changes in Apo-B and LDL-
15 C were not statistically significant.⁵⁸³³ Further, the person of skill in the art would not have
16 looked to this patient population to predict the Apo-B or LDL-C effect of EPA therapy on very
17 high TG patients. Hayashi does not provide a motivation or reasonable expectation of success
18 for administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA
19 and substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL,
20 to effect a reduction in triglycerides without increasing LDL-C when purified EPA is
21 administered to the very high TG patient population.

23 ⁵⁸³² Nozaki at 256.

24 ⁵⁸³³ Hayashi at 26, Table I.

1 Further, Hayashi was a small study conducted in only Japanese patients and was not
2 placebo controlled. This study would not have been extrapolated to Western populations
3 because the Japanese diet contains much more fish and has a number of other different attributes.
4 The Japanese consume a higher amount of EPA and DHA in their diets than Western
5 populations. In fact, Defendants' own reference states that the results from studies where the
6 patient population is exclusively Japanese cannot be generalized to other populations.⁵⁸³⁴ The
7 Japanese diet comprises between 8 and 15 times more EPA and DHA than typical the typical
8 Western diet. The Western diet typically consists of higher amounts of polyunsaturated omega-6
9 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand that
10 the Japanese respond differently to lipid lowering agents than Westerners.

11 Further, Defendants have failed to offer a purported combination of references as part of
12 their obviousness contentions that include Nozaki and Hayashi. Similarly, they fail to offer any
13 motivation to combine Nozaki and Hayashi with the other references of their purported
14 obviousness combinations. Therefore, Defendants should be precluded from relying on these
15 references.

16 (iii) Leigh-Firbank and/or Mori
17 2000 Do Not Disclose
18 Purported Knowledge that
19 DHA was Responsible for the
20 Increase in LDL-C

19 Defendants assert, incorrectly, that "it was known in the art as of February 2009 that
20 administration of DHA (alone or in a mixture) resulted in the negative effect of increasing LDL-
21 C levels."⁵⁸³⁵ Defendants' caveat of DHA being "alone or in a mixture" is telling that it was *not*

22 _____
23 ⁵⁸³⁴ Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to
other populations.").

24 ⁵⁸³⁵ Defendants' Joint Invalidity Contentions at 751.

1 known that DHA alone resulted in an increase in LDL-C levels. Further, the prior art Defendants
2 rely upon to support this statement does not categorize the increase in LDL-C as a “negative
3 effect” in light of the overall impact of the disclosed composition on all lipid parameters.
4 Further, the patients in Leigh Firbank and Mori 2000 had normal to high baseline TG levels. As
5 discussed above in Section III, a person of ordinary skill would not expect the same LDL-C
6 effect in patients with lower baseline TG levels—the subjects of Leigh-Firbank and Mori 2000—
7 as in very-high TG patients because patients with higher TG levels had different lipid responses
8 compared to patients with lower TG levels. Patients with very-high TG levels were considered
9 fundamentally different from patients with borderline-high or high triglycerides from a lipid
10 chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint. Instead, a person
11 of ordinary skill in the art would have expected that fish oils (and other TG lowering agents)
12 would not increase LDL-C substantially in patients with normal to borderline high TG levels, but
13 would substantially increase LDL-C in patients with very high TG levels.

14 Defendants rely upon Leigh-Firbank to demonstrate that it was known that “DHA was
15 responsible for the increase in LDL-C levels.” Leigh-Firbank, however, administered fish oil,
16 comprising 1.67 g of EPA and 1.34 g of DHA per day, for six weeks, to patients with triglyceride
17 levels between 133 mg/dL and 354 mg/dL. Leigh-Firbank does not evaluate the effect of either
18 EPA or DHA alone because it did not disclose the administration of EPA or DHA alone. A
19 person of ordinary skill would similarly understand that Leigh-Firbank does not offer any
20 disclosure regarding the effect of EPA and DHA separately or gain any understanding of the
21 separate impact of DHA or EPA on any lipid parameter. Mori 2006 (also cited by defendants)
22 acknowledges that EPA- and DHA-enriched oils, which are contaminated with other saturated
23 and polyunsaturated fatty acids, are not suitable for evaluating the independent effects of EPA
24

1 and DHA.⁵⁸³⁶ A person of ordinary skill would understand that studies directed to EPA and
2 DHA-enriched oils are not indicative or predictive of the impact of the EPA or DHA alone on
3 lipid parameters. Defendants’ own prior art refutes the validity of the results disclosed by Leigh-
4 Firbank, because purified EPA and DHA were not administered separately.

5 Leigh-Firbank is a poor quality study. Leigh-Firbank makes conclusion on independent
6 effects of EPA and DHA individually, even though it administered a combination of EPA and
7 DHA, not EPA alone and DHA alone. The error in this approach is evident from the conclusions
8 of Leigh-Firbank itself. For example, Leigh-Firbank concludes that changes in platelet
9 phospholipid EPA were *independently* associated with the decrease in fasting TGs,⁵⁸³⁷ and DHA
10 is *not* associated with decreases in fasting TGs. This is incorrect and inconsistent with the state
11 of the art and numerous publications cited by Defendants.⁵⁸³⁸ It is widely accepted that DHA
12 also has a hypotriglyceridemic effect.

13 Mori 2000 compared the administration of 4g daily of EPA, DHA, or olive oil to patients
14 with borderline-high TG levels for 6 weeks. Although Mori 2000 discloses an increase in LDL-
15 C for patients administered DHA, it also teaches that DHA is preferable to EPA—thus teaching
16 away from the claimed invention. “A reference may be said to teach away when a person of
17 ordinary skill, upon [examining] the reference, would be discouraged from following the path set
18 out in the reference, or would be led in a direction divergent from the path that was taken by the
19 applicant.”⁵⁸³⁹ Although teaching away is fact-dependent, “in general, a reference will teach

21 ⁵⁸³⁶ Mori 2006 at 96.

22 ⁵⁸³⁷ Leigh-Firbank at 440.

23 ⁵⁸³⁸ See, e.g. Grimsgaard at 654.

24 ⁵⁸³⁹ *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994).

1 away if it suggests that the line of development flowing from the reference’s disclosures is
2 unlikely to be productive of the result sought by the applicant.”⁵⁸⁴⁰

3 Mori 2000 concludes that the changes effected by DHA supplementation “may represent
4 a more favorable lipid profile than after EPA supplementation.”⁵⁸⁴¹ For example, it states that
5 “DHA, but not EPA, improved serum lipid status, in particular a small increase in HDL
6 cholesterol and a significant increase in the HDL₂-cholesterol subfraction, without adverse
7 effects on fasting glucose concentrations.”⁵⁸⁴² Mori 2000 also states that “[d]espite an increase
8 in LDL cholesterol after DHA supplementation, LDL particle size increased—a finding that may
9 be favorable.”⁵⁸⁴³ Therefore, based on the “favorable lipid profile” of DHA over EPA in Mori
10 2000, a person of ordinary skill would *not* have been motivated to use EPA to treat patients, the
11 exact opposite of what Defendants argue in their contentions. Therefore, the art taught away
12 from using purified EPA. At a minimum, the teachings of Mori 2000 provide reasons for
13 favoring or selecting DHA over EPA and highlight Defendants’ hindsight-driven focus on EPA,
14 despite disclosed advantages of DHA. A person of ordinary skill would take into consideration
15 the entire disclosure, including lipid effects other than LDL-C. Engaging in hindsight bias,
16 Defendants ignore, without explanation, the other effects of DHA that a person of ordinary skill
17 would consider. Defendants fail to identify any other basis upon which a person of ordinary skill
18 would have sought to combine Mori 2000 with the Lovaza PDR.

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21 ⁵⁸⁴⁰ *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994); *see also Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354
(Fed. Cir. 2012) (quoting *Gurley*); *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1552 (Fed. Cir. 1983)
(“[P]roceed[ing] contrary to the accepted wisdom of the prior art ... is strong evidence of nonobviousness.”).

22 ⁵⁸⁴¹ Mori 2000 at 1092.

23 ⁵⁸⁴² Mori 2000 at 1088.

24 ⁵⁸⁴³ Mori 2000 at 1092.

1 factual record.⁵⁸⁴⁶ Defendants’ unsupported cobbling of selective disclosures represents
2 hindsight reconstruction.⁵⁸⁴⁷ Defendants’ contentions are no more than an assertion that certain
3 claim elements were known in the prior art. Throughout their contentions, Defendants’
4 selectively cite to data points in a reference without considering other disclosures or even the
5 reference as a whole. Each reference, however, must be evaluated for all that it teaches.⁵⁸⁴⁸
6 Accordingly, Defendants fail to meet their burden to establish *prima facie* obviousness.

7 The Omacor PDR and Lovaza PDR fail to disclose or even suggest the claimed method
8 of reducing triglycerides in a subject with the claimed pharmaceutical composition with the
9 recited fatty acid compositions or administration period. The Omacor PDR and Lovaza PDR
10 further do not disclose a method to effect the claimed TG reduction without substantially
11 increasing LDL-C. Indeed, the Omacor PDR and Lovaza PDR disclose the opposite: EPA/DHA
12 causes a significant increase in LDL-C levels in a very high TG patient population, for whom the
13 product (Lovaza/Omacor) is indicated. At most, the Omacor PDR and Lovaza PDR disclose
14 administration of a prescription fish oil, a combination of approximately 465 mg EPA and 375
15

16 ⁵⁸⁴⁶ See, e.g., *In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the
17 formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did
18 not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply
19 the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi*
20 *Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must
21 avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to
22 select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and
23 elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp.
24 2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie*
obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding
that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been
motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

⁵⁸⁴⁷ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under
KSR, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention
without any explanation as to how or why the references would be combined to produce the claimed invention”).

⁵⁸⁴⁸ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

1 mg DHA, as an adjunct to diet to reduce TG levels in adult patients with very-high (at least 500
2 mg/dL) TG levels. The proposed combinations do not render the independent claims of the '372
3 patent obvious and Defendants' burden to prove otherwise is especially difficult because the
4 PTO considered Matsuzawa, Katayama, and Mori 2000, Grimsgaard, Maki, and Lovaza (both
5 generally and the Lovaza package insert specifically) during prosecution.⁵⁸⁴⁹

6 The analysis of the independent claims of the '372 patent is incorporated into all asserted
7 claims that depend from those Claims.

8 (a) A Person of Ordinary Skill Would
9 Not Have Been Motivated to
10 Replace the Mixed Fish Oil Active
11 Ingredient in Omacor/Lovaza with
12 EPA of the Claimed Purity

11 For an invention to be obvious, there must have been an "apparent reason" to make it.
12 The subject matter of the '372 patent claims would not have been obvious in light of these
13 references because a person of ordinary skill would not have been motivated to purify EPA or
14 been able to reasonably expect that the claimed pharmaceutical composition would reduce TG
15 levels without an increase in LDL-C levels.

16 (i) Grimsgaard, Katayama,
17 Matsuzawa and/or Takaku
18 Do Not Disclose Purported
19 Known Clinical Benefits of
20 Administering Pure EPA

19 Defendants rely on Grimsgaard, Katayama, Matsuzawa and/or Takaku to demonstrate the
20 "known clinical benefits of administering pure EPA - lowering triglycerides without raising
21 LDL-C." As discussed in Section V.M.3.c.1.a.i.a.i, incorporated herein by reference, Katayama

22 _____
23 ⁵⁸⁴⁹ See, e.g., *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012)(taking into account that "the
24 examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention.
Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear
and convincing standard came into play").

1 and Matsuzawa merely confirm the safety of long term treatment of Epadel and its ability to
2 lower both serum total cholesterol and triglyceride levels. They do not discuss any purported
3 “benefits” observed related to LDL-C. Katayama and Matsuzawa do not disclose or suggest that
4 the LDL-C results obtained were a clinical benefit.

5 Defendants also rely on Grimsgaard to support their assertion that “administration of
6 purified EPA-E reduced TG levels while minimally impacting the LDL-C levels.”⁵⁸⁵⁰ However,
7 the results of Grimsgaard demonstrate that both EPA and DHA had no measureable impact on
8 LDL-C levels, and in fact were indistinguishable from the control (placebo) group.

9 Grimsgaard examined the effect of 3.8g/day of EPA versus 3.6g/day of DHA
10 administered to people with normal triglyceride levels for 7 weeks.⁵⁸⁵¹ The results from the
11 Grimsgaard study show that both DHA and EPA reduce triglycerides. The authors state that the
12 net decrease in triglycerides was consistently greater for DHA. Grimsgaard also concludes that
13 DHA may be responsible for the beneficial increase in HDL-C observed with some n-3 fatty acid
14 supplements, which is consistent with previous studies which “suggested that serum HDL-C is
15 better maintained with oil rich in DHA than oil rich in EPA.”⁵⁸⁵² Although Grimsgaard states
16 that EPA may produce a small decrease in serum total cholesterol, it does not specifically
17 comment on EPA’s effect on LDL-C.

18 Defendants completely misconstrue the results of Grimsgaard. Defendants attempt to
19 characterize a non-significant increase in LDL-C by DHA and a non-significant decrease in
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21 ⁵⁸⁵⁰ Defendants’ Joint Invalidity Contentions at 751.

22 ⁵⁸⁵¹ Defendants state in their Joint Invalidity Contentions at 211 that Grimsgaard was conducted in patients with TG
23 levels in the borderline-high/high ranges. This is incorrect; Grimsgaard was conducted in patients with normal TG
24 levels. (See Grimsgaard at Abstract (describing participants as “healthy”) and Table 4).

⁵⁸⁵² Grimsgaard at 654.

LDL-C by EPA, as confirmation “that administration of purified DHA results in increased LDL-C levels while administration of purified EPA resulted in a decrease in LDL-C levels.”⁵⁸⁵³ The results of Grimsgaard, reproduced below, show that EPA and DHA’s impact on LDL-C were the same as placebo (corn oil); that is, there was no difference between EPA, DHA, or placebo’s effect on LDL-C levels. Further, although administration of EPA reduced Apo-B compared to baseline, it was not a statistically significant effect when compared to placebo. Grimsgaard’s disclosure highlights the importance of a placebo-controlled study and why results compared only to baseline may be misleading. This type of exaggeration and misinterpretation of the results published in the prior art is seen throughout the Defendants’ Joint Invalidity Contentions.

TABLE 4
Serum lipids and apolipoproteins at baseline and change after 7 wk of supplementation with docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), or corn oil

	DHA (n = 72)		EPA (n = 75)		Corn oil (n = 77)		F test; P ^f	Contrasts between groups: P		
	Baseline	Change	Baseline	Change	Baseline	Change		DHA vs EPA	DHA vs corn oil	EPA vs corn oil
Triacylglycerols (mmol/L)	1.24 ± 0.58 ²	-0.22 ± 0.31 ²	1.23 ± 0.57	-0.15 ± 0.40 ^d	1.22 ± 0.55	0.11 ± 0.34 ^d	0.0001	0.14	0.0001	0.0001
Total cholesterol (mmol/L)	6.00 ± 0.95	0.03 ± 0.49	5.98 ± 0.94	-0.15 ± 0.55 ³	6.02 ± 1.08	0.10 ± 0.55	0.01	0.04	0.4	0.004
LDL cholesterol (mmol/L)	4.06 ± 0.86	0.07 ± 0.46	4.06 ± 0.83	-0.08 ± 0.48	4.04 ± 0.98	0.06 ± 0.48	0.10	—	—	—
HDL cholesterol (mmol/L)	1.36 ± 0.30	0.06 ± 0.13 ³	1.33 ± 0.31	0.01 ± 0.12	1.41 ± 0.28	-0.01 ± 0.11	0.001	0.009	0.0005	0.4
Apolipoprotein A-I (g/L)	1.38 ± 0.21	0.02 ± 0.13	1.38 ± 0.20	-0.04 ± 0.10 ³	1.46 ± 0.23	0.00 ± 0.12	0.003	0.0008	0.3	0.02
Apolipoprotein B (g/L)	1.00 ± 0.21	-0.01 ± 0.11	1.01 ± 0.23	-0.03 ± 0.11 ³	1.02 ± 0.28	0.02 ± 0.11	0.05	—	—	—
HDL:apolipoprotein A-I	0.97 ± 0.14	0.04 ± 0.07 ³	0.96 ± 0.13	0.04 ± 0.08 ³	0.97 ± 0.12	-0.01 ± 0.06	0.0001	0.8	0.0003	0.0001
Total:HDL cholesterol	4.62 ± 1.19	-0.19 ± 0.52 ^d	4.70 ± 1.24	-0.13 ± 0.47 ³	4.43 ± 1.19	0.11 ± 0.62	0.002	0.4	0.0006	0.007

^f ANOVA for between-group comparisons of change.

² $\bar{x} \pm$ SD.

³⁻⁵ One-sample t test of difference between baseline and 7 wk: ³ P < 0.001, ⁴ P < 0.01, ⁵ P < 0.05.

Grimsgaard concludes that both DHA and EPA lower TG levels but have “differential effects on lipoprotein and fatty acid metabolism.”⁵⁸⁵⁴ However, Grimsgaard does not conclude that DHA and EPA have differential effects on LDL-C because Table 4 clearly demonstrates that neither DHA nor EPA had a measurable impact on LDL-C. Table 4 demonstrates that EPA and DHA had the same effect on LDL-C. In fact, one of ordinary skill in the art, when reading Grimsgaard, may have been motivated to use purified DHA instead of EPA for the treatment of

⁵⁸⁵³ Defendants’ Joint Invalidity Contentions at 751 (see FN 143).

⁵⁸⁵⁴ Grimsgaard at 657.

1 patients with very-high triglycerides, because net decrease in triglycerides was consistently
2 greater for DHA and DHA caused a statistically significant increase in HDL-C when compared
3 to placebo. Grimsgaard states that “DHA may be responsible for the increase in HDL
4 cholesterol observed with some n-3 fatty acid supplements.”⁵⁸⁵⁵ Grimsgaard makes no such
5 statement regarding LDL-C.

6 Defendants cherry-pick results, regardless of whether the effect is found to be statistically
7 significant compared to placebo, in an attempt to force the studies to support their argument that
8 it was well known to one of ordinary skill in the art that DHA increases LDL-C while EPA did
9 not. This illustrates the hindsight reasoning driving Defendants’ analysis of the prior art and
10 proposed combinations of prior art. Defendants point to a non-significant increase in DHA and
11 non-significant decrease in EPA in Grimsgaard as confirmation “that administration of purified
12 DHA results in increased LDL-C levels while administration of purified EPA resulted in a
13 decrease in LDL-C levels.” The results from Grimsgaard clearly show that EPA and DHA did
14 not have statistically significantly effects on LDL-C compared to placebo.⁵⁸⁵⁶ A person of
15 ordinary skill would not draw conclusions regarding differences between EPA and DHA based
16 on statistically insignificant results.

17 Defendants also rely on Takaku to support their assertion that “clinical benefits of
18 administering purified EPA—lowering triglycerides without raising LDL-C” was known in the
19

20 ⁵⁸⁵⁵ Grimsgaard at 654.

21 ⁵⁸⁵⁶In Mori 2000, EPA resulted in a non-significant 0.18 mmol/L increase in LDL-C, while DHA caused a
22 statistically significant 0.37 mmol/L increase in LDL-C compared to placebo. Applying the same logic used to
23 interpret Grimsgaard, that non-significant effects are nonetheless confirmation of an effect, Defendants should have
24 argued that Mori 2000 was confirmation that both EPA and DHA increases LDL-C. However, they do not make
such arguments for the obvious reason that it does not support their argument that EPA was known to have little or
no impact on LDL-C levels.

1 art.⁵⁸⁵⁷ Similar to Katayama and Matsuzawa, Takaku was conducted to test the efficacy and
2 safety of Epadel (of undisclosed purity)⁵⁸⁵⁸ based on long-term administration.⁵⁸⁵⁹

3 A person of ordinary skill would not have concluded based on Takaku that EPA lowers
4 triglycerides without raising LDL-C, because of its unreliable study method. Takaku candidly
5 acknowledges that “only a few subjects were examined” and cautions against drawing a
6 conclusion “only from the results of the present study.”⁵⁸⁶⁰ Because the study did not include
7 any placebo control, a person of ordinary skill in the art would understand these reports do not
8 provide the ability to conclude that the observed lipid effects would have occurred independent
9 of the drug that is administered. In addition, the study was conducted exclusively in Japanese
10 patients, and a person of ordinary skill would not have expected the results to be applicable to the
11 general population.⁵⁸⁶¹

12 The mean baseline triglyceride level of the patients in Takaku was 245 mg/dL, and a
13 person of ordinary skill would not have expected the results to be applicable to patients with
14 triglycerides above 500 mg/dL. Takaku also excluded 6 subjects from the LDL-C study because
15 measurement was not feasible due to “insufficient sample.”⁵⁸⁶² It is possible that patients with
16 triglycerides above 500 mg/dL were among those excluded because of the challenges involved in
17

18 _____
⁵⁸⁵⁷ Defendants’ Joint Invalidity Contentions at 748.

19 ⁵⁸⁵⁸ It is possible that the version of Epadel used in the Katayama study fails to meet the purity limitation required by
20 the claims. See Nishikawa (91% E-EPA preparation), Ando at 2177 (Epadel with purity greater than 91%),
Nakamura at 23 (Epadel with purity > 90%).

21 ⁵⁸⁵⁹ Takaku at ICOSAPENT_DFNDT00006834.

22 ⁵⁸⁶⁰ Takaku at ICOSAPENT_DFNDT00006897.

23 ⁵⁸⁶¹ Yokoyama 2007 at 1097 (“[b]ecause our population was exclusively Japanese, we cannot generalise our results
to other populations.”)

24 ⁵⁸⁶² Takaku at ICOSAPENT_DFNDT00006884.

1 calculating LDL-C levels when triglyceride level is above 400 mg/dL.⁵⁸⁶³ Moreover, the study
2 does not provide different LDL-C graphs based on the baseline triglyceride levels.⁵⁸⁶⁴ Therefore,
3 it is impossible to determine whether the patients with triglycerides above 500 mg/dL had
4 increased or decreased LDL-C after taking MND-21. In addition, the graph of the rate of LDL-C
5 change in patients with normal baseline LDL-C shows that the LDL-C change was volatile
6 throughout the study period, decreasing slightly at times but increasing by more than 8% at other
7 times.⁵⁸⁶⁵ Because of this volatility, a person of ordinary skill would not be able to conclude
8 what effect EPA has on LDL-C. Indeed, Takaku did not conclude that there was no increase in
9 LDL-C, stating only that the fluctuation in LDL-C was not significant.⁵⁸⁶⁶

10 A person of ordinary skill would not have concluded, based on Takaku, that purified EPA
11 had any advantage over fish oil in its effect on LDL-C. Takaku states that a previous study has
12 “confirmed a decrease in serum VLDL-cholesterol and serum LDL-cholesterol through the
13 administration of *fish oil* to hypercholesterolemia patients.”⁵⁸⁶⁷ In contrast, Takaku states merely
14 that the fluctuation in LDL-C was not significant in its study. Therefore, a person of ordinary
15 skill would have concluded based on Takaku that any favorable LDL-C effect seen in the study
16 was attributable to fish oil in general, not EPA specifically.

17 Therefore, Grimsgaard, Katayama, Matsuzawa and/or Takaku fail to substantiate
18 Defendants’ assertion that pure EPA lowers triglycerides without raising LDL-C. Further, other
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21 ⁵⁸⁶³ See Matsuzawa at ICOSPENT_DFNDTS00006450.

22 ⁵⁸⁶⁴ Takaku at Fig. 13, ICOSAPENT_DFNDT00006882.

23 ⁵⁸⁶⁵ Takaku at Fig. 14, ICOSAPENT_DFNDT00006883.

24 ⁵⁸⁶⁶ Takaku at ICOSAPENT_DFNDT00006897.

⁵⁸⁶⁷ Takaku at ICOSAPENT_DFNDT00006897.

1 studies cited by Defendants suggest that EPA increases LDL-C.⁵⁸⁶⁸ Defendants identify no other
2 basis upon which a person of ordinary skill would have sought to combine the Omacor
3 PDR/Lovaza PDR with Katayama, Matsuzawa, Takaku, Grimsgaard, Mori 2000 and/or Maki.

4 (ii) Nozaki and/or Hayashi
5 Would Not Have Rendered
6 the Asserted Claims Obvious

7 Defendants contend that the asserted claims of the '372 Patent would have been obvious
8 in view Nozaki and/or Hayashi in combination with other references, but they do not explain
9 why Nozaki and/or Hayashi render the asserted claims obvious or what element of the asserted
10 claims is found in Nozaki or Hayashi. Nozaki and Hayashi do not disclose or suggest a
11 reduction in triglycerides without increasing LDL-C when purified EPA is administered to the
12 very high TG patient population.

13 Nozaki administered 2.7 g/day of 90% EPA (DHA < 1%) to 14 primary
14 hypercholesterolemia subjects. A person of ordinary skill would not have found the results of
15 Nozaki reliable. Nozaki was not placebo-controlled, nor did the study compare lipid effect of
16 EPA to that of DHA. The average baseline TG level was only 165 mg/dL, while the baseline
17 LDL-C level was 185 mg/dL, which is unusually high for this TG patient population. A person
18 of skill in the art would not look to a study consisting of patients with baseline TG levels of 165
19 mg/dL in order to understand the impact of EPA therapy on the very high TG patient population.
20 Further, a person of ordinary skill would understand that the baseline LDL-C level in this small
21 patient population were abnormally high and would not have relied upon these results. Further,
22 the person of skill in the art would not have looked to this patient population to predict the Apo-

23 ⁵⁸⁶⁸ See, e.g., Rambjor.
24

1 B or LDL-C effect of EPA therapy on very high TG patients. Nozaki acknowledges that as of
2 1991, “[t]here is still controversy concerning the effects of fish oil” on LDL and HDL cholesterol
3 levels.⁵⁸⁶⁹ Nozaki does not provide a motivation or reasonable expectation of success for
4 administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA and
5 substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL, to
6 effect a reduction in triglycerides without increasing LDL-C when purified EPA is administered
7 to the very high TG patient population.

8 In Hayashi, 1.8 g/day of EPA was administered to 28 patients for 8 weeks. The purity of
9 the EPA and the DHA content in the composition that was administered is unknown. A person
10 of ordinary skill would not have found the results of Hayashi reliable. The study involved 28
11 patients and it was conducted for only 8 weeks. Hayashi shows that changes in Apo-B and LDL-
12 C were not statistically significant.⁵⁸⁷⁰ Further, the person of skill in the art would not have
13 looked to this patient population to predict the Apo-B or LDL-C effect of EPA therapy on very
14 high TG patients. Hayashi does not provide a motivation or reasonable expectation of success
15 for administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA
16 and substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL,
17 to effect a reduction in triglycerides without increasing LDL-C when purified EPA is
18 administered to the very high TG patient population.

19 Further, Hayashi was a small study conducted in only Japanese patients and was not
20 placebo controlled. This study would not have been extrapolated to Western populations
21 because the Japanese diet contains much more fish and has a number of other different attributes.

23 ⁵⁸⁶⁹ Nozaki at 256.

24 ⁵⁸⁷⁰ Hayashi at 26, Table I.

1 The Japanese consume a higher amount of EPA and DHA in their diets than Western
2 populations. In fact, Defendants' own reference states that the results from studies where the
3 patient population is exclusively Japanese cannot be generalized to other populations.⁵⁸⁷¹ The
4 Japanese diet comprises between 8 and 15 times more EPA and DHA than typical the typical
5 Western diet. The Western diet typically consists of higher amounts of polyunsaturated omega-6
6 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand that
7 the Japanese respond differently to lipid lowering agents than Westerners.

8 Further, Defendants have failed to offer a purported combination of references as part of
9 their obviousness contentions that include Nozaki and Hayashi. Similarly, they fail to offer any
10 motivation to combine Nozaki and Hayashi with the other references of their purported
11 obviousness combinations. Therefore, Defendants should be precluded from relying on these
12 references.

13 (iii) Grimsgaard, Mori 2000
14 and/or Maki Do Not Disclose
15 Purported Knowledge that
16 DHA was Responsible for the
17 Increase in LDL-C

18 Defendants assert, incorrectly, that "it was known in the art as of February 2009 that
19 administration of DHA (alone or in a mixture) resulted in the negative effect of increasing LDL-
20 C levels."⁵⁸⁷² Defendants' caveat of DHA being "alone or in a mixture" is telling that it was *not*
21 known that DHA alone resulted in an increase in LDL-C levels. Further, the prior art Defendants
22 rely on to support this statement does not categorize the increase in LDL-C as a "negative effect"
23 in light of the overall impact of the disclosed composition on all lipid parameters. Further, the

23 ⁵⁸⁷¹ Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to
other populations.").

24 ⁵⁸⁷² Defendants' Joint Invalidity Contentions at 751.

1 patients in Grimsgaard, Mori 2000 and Maki had normal to borderline-high baseline TG levels.
2 As discussed above in Section III, a person of ordinary skill would not expect the same LDL-C
3 effect in patients with lower baseline TG levels—the subjects of Grimsgaard, Mori 2000 and/or
4 Maki—as in very-high TG patients because patients with higher TG levels had different lipid
5 responses compared to patients with lower TG levels. Patients with very-high TG levels were
6 considered fundamentally different from patients with borderline-high or high triglycerides from
7 a lipid chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint. A person of
8 ordinary skill in the art would have expected that fish oils (and other TG lowering agents) would
9 not increase LDL-C substantially in patients with normal to borderline high TG levels, but would
10 substantially increase LDL-C in patients with very high TG levels.

11 Defendants rely on Grimsgaard, Mori 2000 and/or Maki to demonstrate that it was known
12 that “DHA was responsible for the increase in LDL-C levels.”⁵⁸⁷³ The discussion related to
13 Grimsgaard in Section V.M.3.c.1.a.ii.a.i and Mori 2000 in Section V.M.3.c.1.a.i.a.iii is
14 incorporated herein by reference.

15 Defendants argue that Maki discloses the administration of purified DHA resulted in the
16 desired reduction of TGs, but also significantly increased LDL-C levels.⁵⁸⁷⁴ Maki was designed
17 to assess the impact of 1.52g/day DHA supplements on the serum lipid profile of patients with
18 below-average levels of HDL-C levels.⁵⁸⁷⁵ The DHA supplemented group was administered
19 capsules containing 1.52 g/day DHA **and** 0.84 g/day palmitic acid, in addition to other saturated,
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22 ⁵⁸⁷³ Defendants’ Joint Invalidity Contentions at 756.

23 ⁵⁸⁷⁴ Defendants’ Joint Invalidity Contentions at 751.

24 ⁵⁸⁷⁵ Maki at 190.

1 monounsaturated and polyunsaturated fatty acids.⁵⁸⁷⁶ Therefore, Maki demonstrated that when
2 1.52 g/day DHA and 0.84 g/day palmitic acid is administered to patients with below-average
3 levels of HDL-C levels and borderline-high TG levels, a significant increase in LDL-C is
4 observed.⁵⁸⁷⁷ However, one cannot attribute the rise in LDL-C solely to DHA, because the
5 authors admit that “changes in fatty acid intake other than DHA, particularly palmitate, may have
6 also contributed to the elevation in LDL cholesterol.”⁵⁸⁷⁸ Further, Maki admits that the
7 “mechanism(s) responsible for the changes in the lipid profile associated with DHA
8 supplementation are not fully understood.”⁵⁸⁷⁹ Therefore, the results of Maki are inconclusive as
9 to DHA’s effect alone on LDL-C levels.

10 Defendants mischaracterize the rise in LDL-C associated with the administration of
11 omega-3 fatty acids as being a “negative effect” because they incorrectly focus on only the LDL-
12 C effect and fail to look at the lipid effects as a whole. In fact, Maki does not find the increase in
13 LDL-C to be troublesome; Maki states that “the lack of increase in the total/HDL cholesterol
14 ratio, the decline in the triglyceride/HDL cholesterol ratio and the reduction in the proportion of
15 cholesterol carried by small, dense LDL particles render the changes in LDL cholesterol level
16 less worrisome.”⁵⁸⁸⁰ Therefore, when one of ordinary skill in the art reviewed all the lipid effects
17 of the DHA-rich algal triglycerides, they would have understood that the increase in LDL-C was
18 “less worrisome” because of the “potentially favorable effects on triglycerides, the
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20 ⁵⁸⁷⁶ Maki at 191.

21 ⁵⁸⁷⁷ Maki at 195.

22 ⁵⁸⁷⁸ Maki at 197; Yu et al., *Plasma Cholesterol-Predictive Equations Demonstrate that Stearic Acid is Neutral and Monounsaturated Fatty Acids are Hypocholesterlemic*, 61 AM J CLIN NUTR 1129, 1136 (1995).

23 ⁵⁸⁷⁹ Maki at 197.

24 ⁵⁸⁸⁰ Maki at 197.

1 triglyceride/HDL cholesterol ratio and the fraction of LDL cholesterol carried by small, dense
2 particles.”⁵⁸⁸¹

3 Therefore, Grimsgaard, Mori 2000 and/or Maki fail to substantiate Defendants’ assertion
4 that it was known that DHA was responsible for the increase in LDL-C levels. Further,
5 Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or
6 has little effect on LDL-C levels.⁵⁸⁸² Defendants identify no other basis upon which a person of
7 ordinary skill would have sought to combine the Omacor PDR/Lovaza PDR with Katayama,
8 Matsuzawa, Takaku, Grimsgaard, Mori 2000 and/or Maki.

9 (iii) The ‘372 Patent is not Obvious Over the
10 Omacor PDR/Lovaza PDR, in Combination
11 with Katayama in View of Satoh and/or in
view of Satoh or Shinozaki in Further View
of Contacos

12 With respect to the ‘372 patent, Defendants present a combination of five references: “the
13 Omacor PDR/Lovaza PDR, in combination with the known clinical benefits of administering
14 pure EPA as evidenced by Katayama in view of Satoh and/or in view of Satoh or Shinozaki in
15 further view of Contacos.”⁵⁸⁸³ Defendants also present charts purporting to assert that an
16 additional 60 references may be combined in order to render the Claims obvious. Not only do
17 Defendants ignore the improbability that a person of ordinary skill would combine 60 separate
18 references, they additionally do not suggest any identify for combining these references.
19 Although Defendants need not point to an explicit statement in the prior art motivating the
20 combination of these references, any assertion of an “apparent reason” to combine must find a
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22 ⁵⁸⁸¹ Maki at 197.

23 ⁵⁸⁸² See e.g., Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

24 ⁵⁸⁸³ Defendants’ Joint Invalidity Contentions at 749.

1 basis in the factual record.⁵⁸⁸⁴ Defendants’ unsupported cobbling of selective disclosures
2 represents hindsight reconstruction.⁵⁸⁸⁵ Defendants’ contentions are no more than an assertion
3 that certain claim elements were known in the prior art. Throughout their contentions,
4 Defendants’ selectively cite to data points in a reference without considering other disclosures or
5 even the reference as a whole. Each reference, however, must be evaluated for all that it
6 teaches.⁵⁸⁸⁶ Accordingly, Defendants fail to meet their burden to establish *prima facie*
7 obviousness.

8 The Lovaza PDR fails to disclose or even suggest the claimed method of reducing
9 triglycerides in a subject with the claimed pharmaceutical composition with the specified fatty
10 acid compositions or administration period. The Lovaza PDR further does not disclose a method
11 to effect the specified TG reduction without substantially increasing LDL-C. Indeed, the Lovaza
12 PDR discloses the exact opposite, that the EPA/DHA composition contained within the reference
13 would cause a significant increase in LDL-C levels in the very high TG patient population, for
14 whom the product is indicated. At most, the Lovaza PDR discloses administration of a
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16 ⁵⁸⁸⁴ See, e.g., *In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the
17 formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did
18 not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply
19 the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi*
20 *Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must
21 avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to
22 select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and
23 elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp.
24 2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie*
obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding
that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been
motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

⁵⁸⁸⁵ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under
KSR, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention
without any explanation as to how or why the references would be combined to produce the claimed invention”).

⁵⁸⁸⁶ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

1 prescription fish oil, a combination of approximately 465 mg EPA and 375 mg DHA, as an
2 adjunct to diet to reduce TG levels in adult patients with very-high (at least 500 mg/dL) TG
3 levels.

4 Defendants formulate an obviousness argument that relies on Contacos.⁵⁸⁸⁷ However,
5 Defendants fail to provide any factual or legal basis as to why Contacos discloses a claim
6 element or an “apparent reason” or motivation to combine the elements in the manner
7 claimed,⁵⁸⁸⁸.

8 Contacos disclosed administration of fish oil, pravastatin, and combination of fish oil and
9 pravastatin, but it does not disclose administration of EPA of the recited composition. Therefore,
10 Contacos fails to provide motivation to administer purified EPA to a very high TG patient
11 population. Contacos also fails to provide motivation to administer purified EPA to a very high
12 TG patient population.

13 The proposed combinations do not render the independent claims of the ’372 patent
14 obvious and Defendants’ burden to prove otherwise is especially difficult because the PTO
15 considered Katayama, Satoh, Shinozaki, Contacos, Geppert, Kelley and Lovaza (both generally
16 and the Lovaza package insert specifically) during prosecution.⁵⁸⁸⁹

17 The analysis of the independent claims of the ’372 patent is incorporated into all asserted
18 claims that depend from those Claims.

19 ⁵⁸⁸⁷ *Id.*

20 ⁵⁸⁸⁸ *KSR*, 550 U.S. at 417–19; *TriMed, Inc. v. Stryker Corp.*, 608 F.3d 1333, 1341 (Fed. Cir. 2010). Hindsight may
21 not be employed to identify relevant prior art and relevant teachings therein: *Heidelberger Druckmaschinen AG v.*
22 *Hantscho Comm. Prods., Inc.*, 21 F.3d 1068, 1071–72 (Fed. Cir. 1994); *Monarch Knitting Mach. Corp. v. Sulzer*
Morat GmbH, 139 F.3d 877, 881 (Fed. Cir. 1998).

23 ⁵⁸⁸⁹ *See, e.g., Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012)(taking into account that “the
24 examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention.
Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear
and convincing standard came into play”).

1 (a) A Person of Ordinary Skill Would
2 Not Have Been Motivated to
3 Replace the Mixed Fish Oil Active
4 Ingredient in Lovaza with EPA of
5 the Recited Composition

6 For an invention to be obvious, there must have been an “apparent reason” to make it.
7 The subject matter of the ‘372 patent claims would not have been obvious in light of these
8 references because a person of ordinary skill would not have been motivated to purify EPA or
9 been able to reasonably expect that the claimed pharmaceutical composition would reduce TG
10 levels without an increase in LDL-C levels.

11 (i) Katayama, Satoh and/or
12 Shinozaki Do Not Disclose
13 Purported Known Clinical
14 Benefits of Administering
15 Pure EPA

16 Defendants rely on Katayama, Satoh and/or Shinozaki to demonstrate the “known clinical
17 benefits of administering pure EPA - lowering triglycerides without raising LDL-C.” As
18 discussed in Section V.M.3.c.1.a.i.a.i, incorporated herein by reference, Katayama merely
19 confirms the safety of long term treatment of Epadel and its ability to lower both serum total
20 cholesterol and triglyceride levels. Katayama does not mention LDL-C levels at all, let alone
21 discuss any purported “benefits” observed related to LDL-C. Katayama does not disclose or
22 suggest that the LDL-C results obtained were a clinical benefit, nor would a person of ordinary
23 skill view these references as teaching such a benefit for very-high TG patients.

24 Satoh administered 1.8g/day of >98% EPA to patients in order to measure the effects of
EPA on C-reactive protein and examine how alteration of lipoprotein profile by EPA affects
systemic inflammation. Satoh reported a statistically significant reduction in LDL-C only when

1 compared to baseline, there was no significant effect when compared to placebo.⁵⁸⁹⁰
2 Defendants' characterization of Satoh as disclosing the lowering of TG levels without increasing
3 LDL-C to be a "clinical benefit" is incorrect.⁵⁸⁹¹ Satoh does not disclose or suggest that the
4 LDL-C results obtained were a clinical benefit, nor would a person of ordinary skill view these
5 references as teaching such a benefit for very-high TG patients. As discussed above, one of
6 ordinary skill in the art would not expect LDL-C to increase in a patient with TG below 500
7 mg/dL and Satoh provides no evidence to the contrary. A person of ordinary skill in the art,
8 however, would have expected that fish oils (and other TG lowering agents) would substantially
9 increase LDL-C in patients with very high TG levels. Satoh fails to provide motivation to
10 administer purified EPA to a very high TG patient population.

11 Further, Satoh was a small study conducted in only Japanese patients. This study would
12 not have been extrapolated to Western populations because the Japanese diet contains much
13 more fish and has a number of other different attributes. The Japanese consume a higher amount
14 of EPA and DHA in their diets than Western populations. In fact, Defendants' own reference
15 states that the results from studies where the patient population is exclusively Japanese cannot be
16 generalized to other populations.⁵⁸⁹² The Japanese diet comprises between 8 and 15 times more
17 EPA and DHA than typical the typical Western diet. The Western diet typically consists of
18 higher amounts of polyunsaturated omega-6 fatty acids and saturated fatty acids. Therefore, a
19 person of ordinary skill would understand that the Japanese respond differently to lipid lowering
20 agents than Westerners.

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⁵⁸⁹⁰ Satoh at 145.

23 ⁵⁸⁹¹ Defendants' Joint Invalidation Contentions at 748-49.

24 ⁵⁸⁹² Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to other populations.").

1 Shinozaki studied the long-term effect of EPA on serum levels of Lipoprotein (a) (Lp(a))
2 and lipids such as triglycerides, total cholesterol, and low density lipoprotein particles.
3 Defendants' characterization of Shinozaki as disclosing the lowering of TG levels without
4 increasing LDL-C to be a "clinical benefit" is incorrect.⁵⁸⁹³ Shinozaki says nothing about an
5 LDL-C effect because it measured LDL particle number, not LDL-C. The finding disclosed by
6 Shinozaki was that "long term administration of EPA may lower Lp(a) and serum lipids."⁵⁸⁹⁴ In
7 addition to Shinozaki's lack of disclosure regarding LDL-C, Defendants identify no other basis
8 upon which a person of ordinary skill would have sought to combine the composition disclosed
9 in Shinozaki.

10 Therefore, Katayama, Satoh and/or Shinozaki fail to substantiate Defendants' assertion
11 that pure EPA lowers triglycerides without raising LDL-C. Further, other studies cited by
12 Defendants suggest that EPA increases LDL-C.⁵⁸⁹⁵ Defendants identify no other basis upon
13 which a person of ordinary skill would have sought to combine the Lovaza PDR with Katayama,
14 Satoh, Shinozaki and/or Contacos.

15 (ii) Geppert and/or Kelley Do
16 Not Disclose Purported
17 Knowledge that DHA was
Responsible for the Increase
in LDL-C

18 Defendants assert, incorrectly, that "it was known in the art as of February 2009 that
19 administration of DHA (alone or in a mixture) resulted in the negative effect of increasing LDL-
20 C levels."⁵⁸⁹⁶ Defendants' caveat of DHA being "alone or in a mixture" is telling that it was *not*

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22 ⁵⁸⁹³ Defendants' Joint Invalidation Contentions at 748-49.

23 ⁵⁸⁹⁴ Shinozaki at 107-109.

24 ⁵⁸⁹⁵ See, e.g., Rambjor.

⁵⁸⁹⁶ Defendants' Joint Invalidation Contentions at 751.

1 known that DHA alone resulted in an increase in LDL-C levels. Further, the prior art Defendants
2 rely on to support this statement do not categorize the increase in LDL-C as a “negative effect”
3 in light of the overall impact of the disclosed composition on all lipid parameters. Further, the
4 patients in Geppert and Kelley had normal and borderline-high/high baseline TG levels,
5 respectively. As discussed above in Section III, a person of ordinary skill would not expect the
6 same LDL-C effect in patients with lower baseline TG levels—the subjects of Geppert and/or
7 Kelley—as in very-high TG patients because patients with higher TG levels had different lipid
8 responses compared to patients with lower TG levels. Patients with very-high TG levels were
9 considered fundamentally different from patients with borderline-high or high triglycerides from
10 a lipid chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint. Although a
11 person of ordinary skill in the art would have expected that fish oils (and other TG lowering
12 agents) would not increase LDL-C substantially in patients with normal to borderline high TG
13 levels, a person of ordinary skill in the art would expect a substantial increase in LDL-C in
14 patients with very high TG levels.

15 Defendants rely on Geppert and/or Kelley to demonstrate that it was known that “DHA
16 was responsible for the increase in LDL-C levels.”⁵⁸⁹⁷ Both Geppert and Kelley administer
17 DHA-rich oil that is contaminated with other saturated and polyunsaturated fatty acids.
18 Therefore, a person of ordinary skill would have known it is unsuitable for evaluating the
19 independent effects of DHA because it is not clear how much of the supplement’s effects can be
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⁵⁸⁹⁷ Defendants’ Joint Invalidity Contentions at 749.
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1 attributed to DHA.⁵⁸⁹⁸ For example, Defendants’ own prior art teaches that changes in fatty acid
2 intake other than DHA, particularly palmitate, may contribute to elevations in LDL-C.⁵⁸⁹⁹

3 In Geppert, 0.94 g/day of DHA derived from microalgae oil was administered to
4 normolipidaemic vegetarians for 8 weeks. A person of ordinary skill would not have been
5 convinced that DHA increases LDL-C based on Geppert. As Geppert acknowledges, prior
6 studies have shown “[i]nconsistent effects of DHA on LDL cholesterol.”⁵⁹⁰⁰ Rather than reading
7 Geppert in isolation, a person of ordinary skill would have read Geppert together with the prior
8 studies cited in Geppert. As such, a person of ordinary skill would have concluded that there
9 was confusion in the art and it was unclear whether DHA increased LDL-C.

10 A person of ordinary skill would have expected that Geppert’s results would be
11 applicable to other components of fish oil such as EPA. Nothing in Geppert suggests that DHA
12 was the only component of fish oil to increase LDL-C. For example, there is no data comparing
13 DHA to fish oil or EPA. In fact, Geppert discusses DHA and fish oil together when trying
14 explain the mechanism of LDL-C increase.⁵⁹⁰¹ A person of ordinary skill would have not
15 expected that EPA and DHA would have different effects on LDL-C based on Geppert.

16 Defendants contend that Kelley shows that DHA was responsible for the increase in
17 LDL-C.⁵⁹⁰² In Kelley, patients fasting serum TG levels of 150 to 400 mg/dL received 7.5 g/day
18 of DHA oil containing 3 g of DHA for 90 days. Kelley does not show that DHA is responsible
19 for the increase in LDL-C. Kelley suggests that increase in LDL-C is a general phenomenon

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21 ⁵⁸⁹⁸ See Mori 2006 at 96.

22 ⁵⁸⁹⁹ Maki at 197.

23 ⁵⁹⁰⁰ Geppert at 784.

24 ⁵⁹⁰¹ *Id.*

⁵⁹⁰² Defendants’ Joint Invalidation Contentions at 749.

1 associated with triglyceride-lowering drugs, stating that a similar increase was induced by fibrate
2 therapy.⁵⁹⁰³ Further, Kelley teaches that the increase in LDL-C is not harmful when viewed in
3 context with the other lipid effects reported in the study. Kelley states that:

4 DHA supplementation may lower the risk of CVD by reducing
5 plasma triacylglycerols; triacylglycerol:HDL; the number of small,
6 dense LDL particles; and mean diameter of VLDL particles. An
7 increase was observed in fasting LDL cholesterol, but it is unlikely
8 this increase is detrimental because no increase was observed in the
9 overall number of LDL particles; actually, there was an 11%
10 reduction that was statistically not significant. The reason LDL
11 cholesterol increased despite no change in LDL particle number was
12 that the LDL particles were made larger and hence more cholesterol
13 rich by DHA treatment.⁵⁹⁰⁴

14 Kelley specifically teaches that the increase in LDL-C caused by DHA supplementation
15 is unlikely to be “detrimental” because there was not a parallel increase in overall LDL particle
16 number. Kelley’s ultimate conclusion is that “[o]verall, DHA supplementation reduced the
17 concentrations of atherogenic lipids and lipoproteins and increased concentrations of
18 cardioprotective lipoproteins” and that “DHA supplementation may improve cardiovascular
19 health.”⁵⁹⁰⁵ Rather than concluding that DHA was uniquely responsible for a rise in LDL-C
20 levels, a person of ordinary skill would understand Kelley to disclose that DHA had uniquely
21 beneficial cardioprotective effects. Indeed, instead of identifying DHA as composition with
22 negative attributes, a person of ordinary skill would understand that the reference taught towards
23 the use of DHA. In addition, none of the study subjects in Kelley had a TG level above 400
24 mg/dL and, for the reasons previously discussed, a person of ordinary skill would understand the
very high TG patient population to be different in terms of their response to lipid therapy,

22 ⁵⁹⁰³ Kelley at 329.

23 ⁵⁹⁰⁴ Kelley at 329

24 ⁵⁹⁰⁵ Kelley at 324, 332.

1 including administration of DHA. A person of ordinary skill in the art would have expected that
2 fish oils (and other TG lowering agents) would not increase LDL-C substantially in patients with
3 normal to borderline high TG levels, but a person of ordinary skill in the art would expect a
4 substantial increase in LDL-C in patients with very high TG levels.

5 Therefore, Geppert and/or Kelley fail to substantiate Defendants' assertion that it was
6 known that DHA was responsible for the increase in LDL-C levels.

7 Throughout their contentions, Defendants' selectively cite to data points in a reference
8 without considering other disclosures or even the reference as a whole. Each reference,
9 however, must be evaluated for all that it teaches.⁵⁹⁰⁶ As is the case with Kelley, Defendants use
10 hindsight to characterize a reference based on LDL-C levels alone without considering the other
11 lipid effects studied, considered and reported.⁵⁹⁰⁷ The isolated manner in which Defendants
12 select such data points is not the approach that a person of ordinary skill would have taken at the
13 time of the invention. Defendants' approach represents the use of impermissible hindsight bias.
14 A person of ordinary skill would take into consideration the entire disclosure of a reference,
15 including lipid effects other than LDL-C. In pointing only to LDL-C, Defendants ignore,
16 without explanation, the other effects of DHA that a person of ordinary skill would consider.
17 With respect to Kelley, These effects would teach a person of ordinary skill that DHA has a
18 favorable effect in hypertriglyceridemic patients.

19 Therefore, Geppert and/or Kelley fail to substantiate Defendants' assertion that it was
20 known that DHA was responsible for the increase in LDL-C levels. Further, Defendants ignore,

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22 ⁵⁹⁰⁶ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

23 ⁵⁹⁰⁷ Kelley at 324 (providing that the objectives of the study were to determine "the effects of DHA supplementation
24 on the concentrations of apoproteins; large, medium, and small VLDL, LDL, and HDL particles; and the mean
diameters of these particles in fasting and postprandial plasma.").

1 without explanation, other studies that demonstrate that DHA decreases or has little effect on
2 LDL-C levels.⁵⁹⁰⁸ Defendants identify no other basis upon which a person of ordinary skill
3 would have sought to combine the Lovaza PDR with Katayama, Satoh, Shinozaki, Contacos,
4 Geppert and/or Kelley.

5 (iv) A Person of Ordinary Skill Would Not Have
6 been Motivated to Find an Omega-3 Fatty
7 Acid “Therapy that Would Reduce TG
8 Levels in Patients with TG Levels \geq 500
9 mg/dL.”

8 Plaintiffs agree that although there was a *need* to find a therapy that would reduce TG
9 levels in patients with very-high TG levels, without negatively impacting LDL-C levels, there
10 was no motivation to find an *omega-3 fatty acid* therapy, or to modify Lovaza/Omacor, to effect
11 a reduction in TG levels without increasing LDL-C levels for very-high TG patients at the time
12 of the invention. A person of ordinary skill in the art understood that the rise in LDL-C caused
13 by omega-3 fatty acids (or fibrates) and Lovaza/Omacor was a consequence of the TG-lowering
14 mechanism. The therapies that were available at the time of the invention to treat very-high TGs
15 were niacin, fibrates and prescription omega-3 fatty acids (Lovaza/Omacor). However, niacin
16 was associated with a highly undesirable side effects—including “flushing” (or reddening of the
17 face and other areas with a burning sensation) and dyspepsia—that limited their usefulness.⁵⁹⁰⁹
18 Fibrates were effective at reducing TGs, but they also caused an increase in LDL-C levels in
19 patients with very-high TG levels. To combat the rise of LDL-C, doctors often prescribed
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22 ⁵⁹⁰⁸ See e.g., Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

23 ⁵⁹⁰⁹ See *id.* at 991-92; McKenney 2007, at 718; ATP-III at 3315 (noting that patients often could not tolerate higher
24 doses of niacin due to side effects).

1 fibrates in combination with an LDL-C lowering medication such as a statin.⁵⁹¹⁰ However, the
2 risk of rhabdomyolysis increased five-fold if fibrates were administered with a statin.⁵⁹¹¹
3 Therefore, physicians were reluctant to recommend, and patients were hesitant embrace, a
4 combination fibrate/statin course of treatment.⁵⁹¹² Finally, Lovaza/Omacor were also effective at
5 reducing TG levels, but, similar to fibrates, could cause a substantial increase in LDL-C levels
6 for very-high TG patients. However, Lovaza/Omacor could be safely administered with statins
7 in order to mitigate increased LDL-C.

8 In any event, a person of ordinary skill in the art would have understood that omega 3-
9 fatty acids, including DHA and EPA, and fibrates cause an increase in LDL-C among very high
10 TG patients, as reflected in the prior art. Accordingly, a person of ordinary skill in the art would
11 not have been motivated to look to omega 3-fatty acids in order to obtain a reduction in TGs
12 without increasing LDL-C in very high TG patients:

	LDL-C Effect	
	Borderline-High or High TG Patients	Very-High TG Patients
Fibrate ⁵⁹¹³	-20%	+45%
Lovaza/Omacor ⁵⁹¹⁴	-6%	+45%

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17 That Epadel has been approved for decades but not approved for use in the very high TG
18 patient population prior to the invention of the asserted patents is a real-world reflection of the
19 lack of motivation. Research into the pharmaceutical uses of EPA started as early as the 1970s.

20 ⁵⁹¹⁰ Bays May 16, 2011 Decl., ¶ 8; Topol, at 71 (noting that in high TG patients “the addition of a statin to a fibrate
21 is often required to achieve LDL-C and non-HDL-C goals”);

22 ⁵⁹¹¹ See *Id.*; McKenney 2007, at 719 (“[F]ibrates may cause rhabdomyolysis, especially when combined with
23 statins.”).

24 ⁵⁹¹² See *Id.*, ¶ 17

⁵⁹¹³ Tricor®, Physicians’ Desk Reference 502-505 (62d ed. 2008).

⁵⁹¹⁴ Chan 2002 I at 2381 (Table 3).

1 In 1990, Mochida Pharmaceutical, began to market Epadel, a high purity EPA drug. There have
2 been countless studies conducted which administer Epadel and report the effects observed.
3 Although a few studies administer Epadel to a patient population which included a few patients
4 with TG levels > 500 mg/dL, Defendants fail to identify a single reference directed to the
5 administration of Epadel to patients with very-high TG levels, reflecting the lack of motivation.

6 Defendants offer no “apparent reason” to administer EPA as claimed to patients with
7 fasting baseline TG levels of at least 500 mg/dl. Defendants rely on Lovaza/Omacor as the
8 starting point to “find a therapy that would reduce TG levels in patients with TG levels \geq 500
9 mg/dL.”⁵⁹¹⁵ Ironically, Lovaza/Omacor significantly reduces TGs in patients with TG levels of
10 at least 500 mg/dL but significantly increases LDL-C--an effect understood to be a consequence
11 of TG reduction and the increased conversion of VLDL to LDL particles.⁵⁹¹⁶

12 It was well known at the time of the invention that omega-3 fatty acids, including both
13 EPA and DHA, caused significant decrease in the production of VLDL particles and a significant
14 increase in the conversion of VLDL to IDL and LDL, supporting the understanding that omega-3
15 fatty acids worked in part by inhibiting VLDL production and improving the conversion of
16 VLDL particles to LDL.⁵⁹¹⁷ A person of ordinary skill in the art understood that EPA and DHA
17 had the *same* TG-lowering mechanism and did not differentiate between EPA and DHA when
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20 ⁵⁹¹⁵ Defendants’ Joint Invalidation Contentions at 750.

21 ⁵⁹¹⁶ See Bays 2008 Rx Omega-3 p. 402; McKenny 2007 Role of Prescription Omega-3 at 720 (finding that “[t]hese
22 results illustrate that with prescription omega-3, fewer VLDL particles are secreted into the systemic circulation, and
secreted VLDL particles are rapidly converted to LDL particle, thus explaining why LDL levels may increase in
patients with very-high triglyceride levels when given prescription omega-3 therapy”); Chan 2003

23 ⁵⁹¹⁷ Chan 202 at 2378-84; see also Westphal at 917 (stating “our data confirm the well-known and pronounced
24 decrease in VLDLs after n-3 fatty acid treatment”)

1 discussing the TG-lowering mechanism of omega-3 fatty acids.⁵⁹¹⁸ The discussion related to the
2 TG-lowering mechanism of omega-3 fatty acids is discussed above in Section III and
3 incorporated herein by reference.

4 In fact, it was well understood that the degree of LDL-C elevation observed with
5 prescription omega-3 therapy, such as Lovaza/Omacor, generally related to pretreatment TG
6 levels; that is, prescription omega-3 therapy, such as Lovaza/Omacor, increased LDL-C levels
7 the most in patients with the highest pretreatment TG levels.⁵⁹¹⁹ Therefore, a person of ordinary
8 skill in the art would have viewed increased LDL-C levels caused by Lovaza/Omacor as a direct
9 consequence of lowering triglycerides in patients with TG levels ≥ 500 mg/dL. The rise in LDL-
10 C was often offset by concurrent treatment with statins.⁵⁹²⁰ The safety and efficacy of using
11 prescription omega-3 in combination with a statin has been well-established.⁵⁹²¹

12 Although an increase in LDL-C was generally observed when omega-3 fatty acids were
13 administered to patients with very-high TG levels, the increase in LDL-C was not necessarily a
14 cause for concern because LDL-C is often low in patients with severe hypertriglyceridemia.
15 Therefore, the final LDL-C concentration may still be in the normal range.⁵⁹²² Furthermore, it
16 was understood that the overall lipid effect of Lovaza/Omacor was beneficial.⁵⁹²³

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18 ⁵⁹¹⁸ Bays I, at 398; Harold E. Bays, *Fish Oils in the Treatment of Dyslipidemia and Cardiovascular Disease*, in *The Johns Hopkins Textbook of Dyslipidemia* 245, 247 (Peter O. Kwiterovich Jr. ed., 2009 (Bays III))

19 ⁵⁹¹⁹ See Bays 2008 Rx Omega-3 p. 402.

20 ⁵⁹²⁰ See Harris 2008 at 14, McKenney at 722.

21 ⁵⁹²¹ McKenney at 722-23.

22 ⁵⁹²² See Westphal at 918, Harris 1997 at 389.

23 ⁵⁹²³ See Pownall at 295 (stating that “[t]reatment with ω -3 fatty acids appear to change the lipid profile of individuals
24 with elevated TG to one that may be less atherogenic by changing LDL structure; lowering serum [cholesterol] ester transfer activity), serum TG and VLDL-C; and increasing serum HDL-C”); Harris 1997 at 389 (stating that “[t]he increase in LDL, which was substantial on a percentage basis, has been a common finding in past studies in [very-high TG] patients. It may not be as problematic as it appears, however,” and “the use of omega-3 fatty acids for the

1 In two pivotal studies in very-high TG patients, both of which used prospective,
2 randomized, double-blind, placebo-controlled study designs, Lovaza/Omacor increased HDL
3 levels from baseline 13% (p=0.014) and 5.9% (p=0.057).⁵⁹²⁴ Correspondingly, prescription
4 omega-3 fatty acids were known to have favorable effects on non-HDL-C levels.⁵⁹²⁵ Therefore,
5 “[i]n patients with very-high triglyceride levels, prescription omega-3 fatty acids 4 g/day can
6 substantially reduce triglycerides and VLDL levels and may increase LDL levels, but the net
7 effect is a reduction in non-HDL levels. Modest increases in HDL level are also common in
8 patients treated with prescription omega-3 fatty acids.” Prescription omega-3 therapy was also
9 known to alter lipoprotein particle size and composition in a favorable manner by decreasing the
10 number of small, dense LDL particles to larger LDL particles.⁵⁹²⁶ Lovaza/Omacor “adversely
11 raise[d] LDL cholesterol concentration but the increase in LDL cholesterol concentration
12 reflect[ed] a less atherogenic light LDL subfraction profile that may be favorable.”⁵⁹²⁷
13 Therefore, one of ordinary skill in the art believed that the use of Lovaza/Omacor, and omega-3
14 fatty acids generally, “for the treatment of severe hypertriglyceridemia may be beneficial not
15 only for the short-term prevention of acute pancreatitis, but also for the longer-term prevention
16 of [coronary heart disease].”⁵⁹²⁸

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18 treatment of severe hypertriglyceridemia may be beneficial not only for the short-term prevention of acute
19 pancreatitis, but also for the long-term prevention of CHD”); Bays III at 248 (“No clinical trial data exist that this
20 rise in LDL-C represents harm or potential “toxicity” to patients. In fact, most evidence supports that omega-3 fatty
21 acids reduce cardiovascular risk as do fibrates. Importantly, clinical trials mostly support that even with increases in
22 LDL-C, omega-3 fatty acids decrease the total cholesterol (TC) carried by atherogenic lipoproteins, as reflected by
23 decreased non-HDL-C levels (TC minus HDL-C”).

21 ⁵⁹²⁴ McKenney 2007 at 721 (citing Harris 1997 and Pownall).

22 ⁵⁹²⁵ McKenney 2007 at 722 (see Fig. 1).

23 ⁵⁹²⁶ McKenney 2007 at 722 (citing Calabresi and Stalenhoef).

24 ⁵⁹²⁷ Stalenhoef at 134.

⁵⁹²⁸ Harris 1997 at 389.

1 Therefore, contrary to Defendants’ assertion that “a person of ordinary skill in the art at
2 the time of the claimed inventions would have been motivated to find a therapy that would
3 reduce TG levels in patients with TG levels of at least 500 mg/dL without negatively impacting
4 LDL-C levels,” one of ordinary skill in the art at the time of the invention understood that the
5 rise in LDL-C caused by omega-3 fatty acids was a by-product of reducing TGs in patients with
6 very-high TG levels. A person of ordinary skill in the art would have expected LDL-C to
7 increase in very-high TG patients, and in some instances the rise was not concerning because
8 LDL-C is often low in patients with severe hypertriglyceridemia and therefore final
9 concentration would still be in the normal range. When LDL-C levels increased beyond what
10 was recommended by the ATP-III, prescribers often relied on statins to safely and effectively
11 reduce LDL-C levels. Furthermore, it was well known that the overall lipid effect of
12 Lovaza/Omacor was beneficial because non-HDL-C levels often increased. Defendants fail to
13 identify any other basis upon which a person of ordinary skill would have been motivated to find
14 a therapy that would reduce TG levels in patients with very-high TG levels without negatively
15 impacting LDL-C levels. Further, a person of ordinary skill in the art would have understood
16 that EPA therapy would *not* reduce Apo-B⁵⁹²⁹ (which is a reflection of total atherogenic
17 lipoproteins)⁵⁹³⁰ in very high TG patients, and accordingly would not have been motivated to
18 administer the claimed EPA composition to the very high TG patient population.

19 Defendants make the conclusory allegation that “routine optimization” by a person of
20 ordinary skill would yield the claimed invention.⁵⁹³¹ Defendants, however, have offered no
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22 ⁵⁹²⁹ *see* Section V.O.

23 ⁵⁹³⁰ *see* Section III.

24 ⁵⁹³¹ *See, e.g.*, Defendants’ Joint Invalidation Contentions at 746.

1 explanation to support that allegation and they further fail to establish any of the required criteria
2 of “routine optimization” or the prerequisites to this argument. They also fail to provide any
3 factual detail to support their allegation and they fail to link the allegation to any particular claim
4 or claim element. Defendants mere allegation constitute an improper placeholder to later
5 advance arguments not disclosed in their contentions as required by the Local Rules. In addition,
6 for the reasons discussed herein, a person of ordinary skill would not be motivated to make the
7 combinations alleged by Defendants and, for the same reasons, it would not be routine to
8 combine such references. Where, for example, defendants argue that it would be routine to go
9 from the high TG patient population to the very high TG patient population,⁵⁹³² they provide no
10 basis for that conclusory assertion and are incorrect. As discussed, a person of ordinary skill
11 would have understood these patient populations to be distinct with different impacts of lipid
12 therapy on blood-lipid chemistry for each group. Accordingly, a person of ordinary skill would
13 not have considered the dosage modification suggested by defendants to be routine; Defendants’
14 argument to the contrary represents hindsight bias.

15 In addition, a person of ordinary skill would have no motivation to combine these
16 references because EPA would have been expected to have same result as the mixture of EPA
17 and DHA used in Lovaza/Omacor.

- 18 (b) Defendants Have Not Shown It Would Have Been
19 Obvious to Administer Purified EPA in the Dosing
20 Regimen Recited in the Claims
- 21 (i) The ‘372 Patent is not Obvious Over WO
22 ‘118 or WO ‘900, in Combination with the

23 _____
24 ⁵⁹³²Defendants’ Joint Invalidity Contentions at 752-53.

With respect to the '372 patent, Defendants present a combination of five references:

“WO '118 or WO '900, in combination with treatment regimen of Lovaza as evidenced by the Lovaza PDR, and further in view of Leigh-Firbank and/or Mori 2000.”⁵⁹³³ Defendants also present charts arguing that an additional 61 references may be combined in order to render the Claims obvious. Not only do Defendants ignore the improbability that a person of ordinary skill would combine 61 separate references, they additionally do not identify any motivation for combining these references.^{5934, 5935} Although Defendants need not point to an explicit statement in the prior art motivating the combination of these references, any assertion of an “apparent reason” to combine must find a basis in the factual record.⁵⁹³⁶ Defendants’ unsupported cobbling

⁵⁹³³ Defendants’ Joint Invalidity Contentions at 755.

⁵⁹³⁴ Defendants’ bare assertion that the asserted claims are obvious “in view of one or more the references cited in V.B.3 and 4, including, the '954 publication, WO '900, WO '118, Ando, Grimsgaard, Hayashi, Katayama, Matsuzawa, Matakai, Mori 2000, Nakamura, Nozaki, Okumura, Park, Saito 1998, Saito 2008 Satoh, Shinozaki, Takaku, Yokoyama 2003, Yokoyama 2007, Calabresi, Chan 2002, Chan 2003, Contacos, Geppert, Kelley, Leigh-Firbank, Maki, Mori 2006, Rambjør, Sanders or Theobold in combination with the knowledge of a person of ordinary skill in the art in light of the dosing regimen employed with Lovaza/Omacor” similarly fails to meet the disclosure requirements of the Nevada Local Patent Rules, and fails to provide any motivation to combine these references. *See* Defendants’ Joint Invalidity Contentions at 754-755.

⁵⁹³⁵ Defendants’ bare assertion that “the motivation or reason to combine or modify the prior art to create invalidating combinations under 35 U.S.C. §103 can be found in the references identified above in Section III.C,” and that “[c]ommon sense, design incentives. Market forces, and the background knowledge possessed by a person having ordinary skill in the art provide the reasons or rationales for combining the teachings of multiple references or modifying references to render obvious the claimed inventions of the asserted claims,” fails to meet the disclosure requirements of the Nevada Local Patent Rules. *See* Defendants’ Joint Invalidity Contentions at 746.

⁵⁹³⁶ *See, e.g., In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (stating that the assertion of a starting point “must avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to select and then modify a lead compound to arrive at the claimed invention,” which turns on the known “properties and limitations of the prior art compounds”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp. 2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima*

1 of selective disclosures represents hindsight reconstruction.⁵⁹³⁷ Defendants’ contentions are no
2 more than an assertion that certain claim elements were known in the prior art. Throughout their
3 contentions, Defendants’ selectively cite to data points in a reference without considering other
4 disclosures or even the reference as a whole. Each reference, however, must be evaluated for all
5 that it teaches.⁵⁹³⁸ Accordingly, Defendants fail to meet their burden to establish *prima facie*
6 obviousness.

7 WO ‘118 is directed at the composition containing EPA for the purpose of preventing the
8 occurrence of cardiovascular events in multiple risk patients. Further, the invention of WO ‘118
9 is directed, “in particular, [to] preventing occurrence of cardiovascular events in
10 hypercholesterolemia patients who have been treated with HMG-CoA RI but still suffer from the
11 risk of the cardiovascular events.”⁵⁹³⁹ Contrary to Defendants’ assertion that WO ‘118 discloses
12 “the administration of 4 g of pure EPA with no DHA,”⁵⁹⁴⁰ WO ‘118 fails to disclose the claimed
13 subject with the specified very high TG levels who does not receive concurrent lipid altering
14 therapy, the claimed pharmaceutical composition with the specified fatty acid compositions or
15 dosage, or the claimed method to effect the specified TG reduction without substantially
16 increasing LDL-C. WO ‘118 discloses a composition with a wide range of possible EPA

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19 *facie* obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and
20 concluding that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art
would have been motivated to resolve citalopram in June 1988”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

21 ⁵⁹³⁷ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under
KSR, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention
without any explanation as to how or why the references would be combined to produce the claimed invention”).

22 ⁵⁹³⁸ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

23 ⁵⁹³⁹ WO ‘118 at 9.

24 ⁵⁹⁴⁰ Defendants’ Joint Invalidity Contentions at 755.

1 content, dosages, and teaches that DHA is a “preferable fatty acid” to include in the disclosed
2 composition.⁵⁹⁴¹

3 WO ’118 does not disclose administration of highly-purified ethyl-EPA to the target
4 population of the claimed invention. The asserted claims are directed to persons with severe
5 hypertriglyceridemia (i.e. TG level above 500 mg/dL). WO ’118 on the other hand only
6 discloses administration of EPA to persons with triglyceride of at least 150 mg/dL.⁵⁹⁴² WO
7 ’118’s emphasis on reducing cardiovascular events suggests that its disclosure is directed to
8 patients with borderline-high to high TG levels, since the primary goal for patients with very-
9 high TG is to prevent acute pancreatitis by decreasing TG levels.⁵⁹⁴³

10 WO ’118 also does not distinguish EPA from DHA in its disclosures regarding the
11 effectiveness of the substances for treating hypertriglyceridemia.⁵⁹⁴⁴ WO ’118 states that
12 “[a]nother preferable fatty acid . . . is DHA-E,” and that “the compositional ratio of EPA-
13 E/DHA-E, content of EPA-E and DHA-E . . . in the total fatty acid, and dosage of (EPA-E +
14 DHA-E) are not particularly limited as long as intended effects of the present invention are
15 attained.”⁵⁹⁴⁵ It further states that “the composition is preferably the one having a high purity of
16 EPA-E and DHA-E.”⁵⁹⁴⁶ Further, WO ’118 does not disclose EPA’s effect on LDL-C, VLDL-C,
17 Apo-B, or Lp-PLA2.

20 ⁵⁹⁴¹ WO ’118 at 22-23.

21 ⁵⁹⁴² WO ’118 at 8.

22 ⁵⁹⁴³ See Section III.

23 ⁵⁹⁴⁴ WO ’118 at 11, 13, 16-21 (“the composition containing at least EPA-E and/or DHA-E as its effective
component”).

24 ⁵⁹⁴⁵ WO ’118 at 22-23.

⁵⁹⁴⁶ WO ’118 at 23.

1 WO '900 is directed to a process for producing purified EPA from a culture of micro-
2 organisms. WO '900 fails to disclose the claimed subject with the specified very high TG levels
3 who does not receive concurrent lipid altering therapy, the claimed pharmaceutical composition
4 with the specified dosage or administration period, or the claimed method to effect the specified
5 TG reduction without substantially increasing LDL-C. WO '900 only discloses the method of
6 producing purified EPA for therapeutic use, it does not teach *administration* of pure EPA. WO
7 '900 has no discussion, for example, regarding claimed patient population or method of
8 treatment.

9 WO '900 does not teach administration of pure EPA to treat hypertriglyceridemia. It lists
10 more than 30 diseases that can be treated with pure EPA, but hypertriglyceridemia is not one of
11 them.⁵⁹⁴⁷ Moreover, WO '900 does not teach the desired effect of EPA other than commenting
12 generally that it “may promote health and ameliorate or even reverse the effects of a range of
13 common diseases.”⁵⁹⁴⁸ It has no discussion, for example, on any TG-lowering effect of EPA.
14 Although WO '900 identifies DHA as an “undesired molecule”, it does not identify the *specific*
15 undesired effect of DHA or other impurities it is trying to prevent other than commenting
16 generally that “the desired effects of EPA may be limited or reversed” by them.⁵⁹⁴⁹ It has no
17 discussion related to any LDL-C effects caused by DHA.

18 The proposed combination does not render the independent claims of the '372 patent
19 obvious and Defendants' burden to prove otherwise is especially difficult because the PTO
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22 ⁵⁹⁴⁷ See, e.g., '900 Pub. at 16-17.

23 ⁵⁹⁴⁸ '900 Pub. at 5.

24 ⁵⁹⁴⁹ '900 Pub. at 39.

1 considered WO '118, WO '900, Mori 2000, and Lovaza (both generally and the Lovaza package
2 insert specifically) during prosecution.⁵⁹⁵⁰

3 The analysis of the independent claims of the '372 patent is incorporated into all asserted
4 claims that depend from those Claims.

5 (a) Leigh-Firbank and Mori 2000 Do
6 Not Disclose Purported Knowledge
7 that DHA was Responsible for the
8 Increase in LDL-C

9 Defendants contend that a “person of ordinary skill in the art would have been motivated
10 to administer pure EPA to severely hypertriglyceridemic patients according to Lovaza’s known
11 regimen, particularly in light of the knowledge that DHA is responsible for the increase in LDL-
12 C levels as evidenced by Leigh-Firbank or Mori 2000.”⁵⁹⁵¹

13 Defendants fail to identify a specific motivation to combine WO '118 or WO '900 with
14 the treatment regimen of Lovaza, as evidenced by the Lovaza PDR. Although Defendants need
15 not point to an explicit statement in the prior art motivating the combination of these references,
16 any assertion of an “apparent reason” to combine must find a basis in the factual record.⁵⁹⁵²

17 ⁵⁹⁵⁰ See, e.g., *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012)(taking into account that “the
18 examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention.
19 Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear
20 and convincing standard came into play”).

21 ⁵⁹⁵¹ Defendants’ Joint Invalidity Contentions at 755.

22 ⁵⁹⁵² See, e.g., *In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the
23 formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did
24 not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply
the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi
Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must
avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to
select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and
elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp.
2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie*
obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding

1 Defendants' unsupported cobbling of selective disclosures represents hindsight
2 reconstruction.⁵⁹⁵³ Defendants' contentions are no more than an assertion that certain claim
3 elements were known in the prior art. Accordingly, Defendants fail to meet their burden to
4 establish *prima facie* obviousness.

5 Contrary to Defendants' assertion, Leigh-Firbank and Mori 2000 do *not* disclose that
6 DHA is responsible for the increase in LDL-C level. The discussion regarding Leigh-Firbank
7 and Mori 2000 in Section V.M.3.c.1.a.i.a.iii is incorporated herein by reference. Leigh-Firbank
8 cannot comment on the effect of EPA and DHA alone because it did not administer EPA and
9 DHA separately. A person of ordinary skill would similarly understand that Leigh-Firbank does
10 not offer any disclosure regarding the effect of EPA and DHA separately or gain any
11 understanding of the separate impact of DHA or EPA on lipid parameters. Although Mori 2000
12 discloses an increase in LDL-C for patients administered DHA, it also teaches that DHA is
13 preferable to EPA—thus teaching away from the claimed invention and reflecting no motivation
14 to combine with WO '118 or WO '900. Engaging in hindsight bias, Defendants ignore, without
15 explanation, the other effects of DHA that a person of ordinary skill would consider. Defendants
16 fail to identify any other basis upon which a person of ordinary skill would have sought to
17 combine Mori 2000 with the Lovaza PDR.

18 Therefore, Leigh-Firbank and Mori 2000 fail to substantiate Defendants' assertion that it
19 was known that DHA was responsible for the increase in LDL-C levels. Further, Defendants
20

21 that defendants "have not demonstrated by clear and convincing evidence that one skilled in the art would have been
22 motivated to resolve citalopram in June 1988."), *aff'd*, 501 F.3d 1263 (Fed. Cir. 2007).

23 ⁵⁹⁵³ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under
24 *KSR*, "[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention
without any explanation as to how or why the references would be combined to produce the claimed invention").

1 ignore, without explanation, other studies that demonstrate that DHA decreases or has little
2 effect on LDL-C levels.⁵⁹⁵⁴ Defendants identify no other basis upon which a person of ordinary
3 skill would have sought to combine WO '118, WO '900, the Lovaza PDR, Leigh-Firbank and/or
4 Mori.

5 (ii) The '372 Patent is not Obvious Over WO
6 '118, WO '900, Grimsgaard, Mori 2000
7 and/or Maki in Combination with the
8 Omacor PDR/Lovaza PDR, and Further in
9 View of Katayama, Matsuzawa and/or
10 Takaku.

11 With respect to the '372 patent, Defendants present a combination of nine references:
12 "WO '118, WO '900, Grimsgaard, Mori 2000 and/or Maki in combination with treatment
13 regimen of Omacor/Lovaza as evidenced by the Omacor PDR/Lovaza PDR, and further in view
14 of Katayama, Matsuzawa and/or Takaku."⁵⁹⁵⁵ Defendants also present charts arguing that an
15 additional 56 references may be combined in order to render the Claims obvious. Not only do
16 Defendants ignore the improbability that a person of ordinary skill would combine 56 separate
17 references, they additionally do not identify any motivation for combining these references.
18 Although Defendants need not point to an explicit statement in the prior art motivating the
19 combination of these references, any assertion of an "apparent reason" to combine must find a
20 basis in the factual record.⁵⁹⁵⁶ Defendants' unsupported cobbling of selective disclosures

21 ⁵⁹⁵⁴ See e.g., Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

22 ⁵⁹⁵⁵ Defendants' Joint Invalidity Contentions at 756.

23 ⁵⁹⁵⁶ See, e.g., *In re Vaidyanathan*, 381 F. App'x 985, 993–94 (Fed. Cir. 2010) ("[W]hile KSR relaxed some of the
24 formalism of earlier decisions requiring a 'teaching, suggestion, or motivation' to combine prior art references, it did
not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply
the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight."); *Daiichi
Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point "must
avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to
select and then modify a lead compound to arrive at the claimed invention." This turns on the known "properties and

1 represents hindsight reconstruction.⁵⁹⁵⁷ Defendants’ contentions are no more than an assertion
2 that certain claim elements were known in the prior art. Throughout their contentions,
3 Defendants’ selectively cite to data points in a reference without considering other disclosures or
4 even the reference as a whole. Each reference, however, must be evaluated for all that it
5 teaches.⁵⁹⁵⁸ Accordingly, Defendants fail to meet their burden to establish *prima facie*
6 obviousness.

7 The discussion related to WO ‘118 and WO ‘900 in Section V.M.3.c.1.b.i is incorporated
8 herein by reference. The discussion related to Grimsgaard, Mori 2000 and/or Maki in Section
9 V.M.3.c.1.a.ii.a.iii is incorporated herein by reference. Defendants contend that “Grimsgaard
10 and Mori 2000 also disclose the administration of 4 g per day of highly purified EPA with no
11 DHA.” However, neither Grimsgaard nor Mori 2000 discloses the administration of 4g/day EPA
12 to the *very high TG patient population*. Neither Grimsgaard nor Mori 2000 provides motivation
13 to administer 4g/day EPA to the *very high TG patient population*. Defendants identify no other
14 basis upon which a person of ordinary skill would have sought to combine the composition
15 disclosed in Grimsgaard or Mori 2000.

16 Defendants argue that it “would have been obvious to a person of ordinary skill in the art
17 to use EPA as described in WO ‘118, WO ‘900, Grimsgaard or Mori 2000 in the treatment

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20 elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp.
21 2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie*
22 obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding
23 that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been
24 motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

⁵⁹⁵⁷ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under
KSR, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention
without any explanation as to how or why the references would be combined to produce the claimed invention”).

⁵⁹⁵⁸ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

1 regimen used for Omacor/Lovaza as described in the Omacor PDR/Lovaza PDR,” but their
2 assertions fail to provide a motivation for combining the references.⁵⁹⁵⁹ Although Defendants
3 need not point to an explicit statement in the prior art motivating the combination of these
4 references, any assertion of an “apparent reason” to combine must find a basis in the factual
5 record.⁵⁹⁶⁰ Defendants’ assertions related to motivation are insufficient,⁵⁹⁶¹ and accordingly
6 Defendants fail to meet their burden to establish *prima facie* obviousness.

7 Defendants formulate an obviousness argument that relies on Katayama, Matsuzawa, or
8 Takaku. However, they’ve failed to provide any factual or legal basis as to why each reference
9 discloses a claim element, an “apparent reason” or motivation to combine the elements in the
10 manner claimed.⁵⁹⁶² Therefore, Defendants should be precluded from relying on this these
11 references.

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13 ⁵⁹⁵⁹ Defendants’ Joint Invalidity Contentions at 756.

14 ⁵⁹⁶⁰ See, e.g., *In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the
15 formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did
16 not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply
17 the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi*
18 *Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must
19 avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to
20 select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and
21 elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp.
22 2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie*
23 obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding
24 that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been
motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

⁵⁹⁶¹ For example, Defendants’ assertion that “WO ’118 may be combined with other prior art in the field of treating
hypertriglyceridemia” is nothing more than a statement that a reference can be combined but fails to provide any
basis for that statement. While the paragraph associated with that statement makes assertions regarding the
disclosure of certain other references, it does not provide a basis for the assertion of motivation to combine with WO
’118. See Defendants’ Joint Invalidity Contentions at 756.

⁵⁹⁶² *KSR*, 550 U.S. at 417–19; *TriMed, Inc. v. Stryker Corp.*, 608 F.3d 1333, 1341 (Fed. Cir. 2010). Hindsight may
not be employed to identify relevant prior art and relevant teachings therein: *Heidelberger Druckmaschinen AG v.*
Hantscho Comm. Prods., Inc., 21 F.3d 1068, 1071–72 (Fed. Cir. 1994); *Monarch Knitting Mach. Corp. v. Sulzer*
Morat GmbH, 139 F.3d 877, 881 (Fed. Cir. 1998).

1 As discussed above in Section V.M.3.c.1.a.i.a.i, Katayama and Matsuzawa were both
2 only designed to confirm the safety of long term treatment of Epadel and its ability to lower both
3 serum total cholesterol and triglyceride levels. They fail to provide motivation to administer
4 purified EPA to the very high TG patient population. As discussed above in Section
5 V.M.3.c.1.a.ii.a.i, Takaku candidly acknowledges that “only a few subjects were examined” and
6 cautions against drawing a conclusion “only from the results of the present study.”⁵⁹⁶³ Further,
7 the study did not include any placebo control, therefore, a person of ordinary skill in the art
8 would understand these reports do not provide the ability to conclude that the observed lipid
9 effects would have occurred independent of the drug that is administered. In addition, the study
10 was conducted exclusively in Japanese patients, and a person of ordinary skill would not have
11 expected the results to be applicable to the general population.⁵⁹⁶⁴

12 The proposed combination does not render the independent claims of the '372 patent
13 obvious and Defendants' burden to prove otherwise is especially difficult because the PTO
14 considered WO '118, WO '900, Grimsgaard, Mori 2000, Maki, Katayama, Matsuzawa and
15 Lovaza (both generally and the Lovaza package insert specifically) during prosecution.⁵⁹⁶⁵

16 The analysis of the independent claims of the '372 patent is incorporated into all asserted
17 claims that depend from those Claims.

18 (a) Grimsgaard, Mori 2000 and/or Maki
19 Do Not Disclose Purported
20 Knowledge that DHA was

21 ⁵⁹⁶³ Takaku at ICOSAPENT_DFNDT00006897.

22 ⁵⁹⁶⁴ Yokoyama 2007 at 1097 (“[b]ecause our population was exclusively Japanese, we cannot generalise our results
to other populations.”)

23 ⁵⁹⁶⁵ See, e.g., *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012) (taking into account that “the
24 examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention.
Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear
and convincing standard came into play”).

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3 Defendants contend that a “person of ordinary skill in the art would have been motivated
4 to administer pure EPA to hypertriglyceridemic patients according to Omacor/Lovaza’s known
5 regimen, Katayama, Matsuzawa or Takaku, particularly in light of the knowledge that DHA is
6 responsible for the increase in LDL-C levels as evidenced by Grimsgaard, Mori 2000 or
7 Maki.”⁵⁹⁶⁶

8 Contrary to Defendants’ assertion, Grimsgaard, Mori 2000 and/or Maki do *not* disclose
9 that DHA is responsible for the increase in LDL-C level. The discussion related to Grimsgaard,
10 Mori 2000 and/or Maki in Section V.M.3.c.1.a.ii.a.iii is incorporated herein by reference. A
11 person of ordinary skill would understand that the results of Grimsgaard demonstrated that EPA
12 and DHA’s impact on LDL-C were the same as the effect of the placebo corn oil group; that is,
13 there was no difference between EPA, DHA, or placebo’s effect on LDL-C levels. Although
14 Mori 2000 discloses an increase in LDL-C for patients administered DHA, the reference does not
15 disclose administration of DHA to the requisite patient population and teaches that DHA is
16 preferable to EPA—thus teaching away from the claimed invention. Engaging in hindsight bias,
17 Defendants ignore, without explanation, the other effects of DHA that a person of ordinary skill
18 would consider. Most controlled studies in patients with normal to high baseline TG levels
19 indicated that DHA had little or no effect on LDL-C.⁵⁹⁶⁷ Therefore, a person of ordinary skill
20 would not have concluded that DHA increases LDL-C in patients with normal to high baseline
21 TG levels. Maki demonstrated that when 1.52 g/day DHA and 0.84 g/day palmitic acid is

22 ⁵⁹⁶⁶ Defendants’ Joint Invalidity Contentions at 756.

23 ⁵⁹⁶⁷ Mori 2006 at 98. Moreover, Mori 2000, the only study which compared EPA versus DHA, and is placebo
24 controlled, found an increase in LDL-C after DHA administration.

1 administered to patients with below-average levels of HDL-C levels and borderline-high TG
2 levels, a significant increase in LDL-C is observed.⁵⁹⁶⁸ However, one of ordinary skill in the art
3 knew that saturated fatty acids, such as palmitate, may contributed to the elevation in LDL-C.⁵⁹⁶⁹
4 Therefore, the results of Maki are inconclusive as to DHA’s effect alone on LDL-C levels.

5 Therefore, Grimsgaard, Mori 2000 and/or Maki fail to substantiate Defendants’ assertion
6 that it was known that DHA was responsible for the increase in LDL-C levels. Further,
7 Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or
8 has little effect on LDL-C levels.⁵⁹⁷⁰ Defendants identify no other basis upon which a person of
9 ordinary skill would have sought to combine WO ‘118, WO ‘900, Grimsgaard, Mori 2000, Maki,
10 the Omacor PDR/the Lovaza PDR, Katayama, Matsuzawa and/or Takaku.

11 (iii) A Person of Ordinary Skill Would Not Have
12 Been Motivated to Administer Purified EPA
13 in the Treatment Regimen Recited in the
14 Claims

15 For an invention to be obvious, there must have been an “apparent reason” to make it.
16 Defendants assert that a “person of ordinary skill in the art would have been motivated to
17 administer 4 grams of highly-purified EPA to patients with triglycerides greater than or equal to
18 500 mg/dL, with a reasonable expectation of success in lowering triglycerides.”⁵⁹⁷¹ However, as
19 set forth below, Defendants fail to address why a person of ordinary skill in the art would have

20 ⁵⁹⁶⁸ Maki at 195.

21 ⁵⁹⁶⁹ Maki at 197; Yu et al., *Plasma Cholesterol-Predictive Equations Demonstrate that Stearic Acid is Neutral and*
22 *Monounsaturated Fatty Acids are Hypocholesterlemic*, 61 AM J CLIN NUTR 1129, 1136 (1995); Weber 2000 (“A
number of the earlier-formulated (older) omega-3 fatty acid supplements contained significant amounts of saturated
fat and cholesterol, both of which are known to elevate LDL-C.”).

23 ⁵⁹⁷⁰ See e.g., Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

24 ⁵⁹⁷¹ Defendants’ Joint Invalidity Contentions at 757.

1 been motivated to administer 4 grams of highly-purified EPA to patients with triglycerides
2 greater than or equal to 500 mg/dL.

3 A person of ordinary skill in the art would have understood that omega 3-fatty acids,
4 including DHA and EPA, and fibrates cause an increase in LDL-C among very high TG patients,
5 as reflected in the prior art. Accordingly, a person of ordinary skill in the art would not have been
6 motivated to look to omega 3-fatty acids in order to obtain a reduction in TGs without increasing
7 LDL-C in very high TG patients:

	LDL-C Effect	
	Borderline-High or High TG Patients	Very-High TG Patients
Fibrate ⁵⁹⁷²	-20%	+45%
Lovaza/Omacor ⁵⁹⁷³	-6%	+45%

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12 That Epadel has been approved for decades but not approved for use in the very high TG
13 patient population prior to the invention of the asserted patents is a real-world reflection of the
14 lack of motivation. Research into the pharmaceutical uses of EPA started as early as the 1970s.
15 In 1990, Mochida Pharmaceutical, began to market Epadel, a high purity EPA drug. There have
16 been countless studies conducted which administer Epadel and report the effects observed.
17 Although a few studies administer Epadel to a patient population which included a few patients
18 with TG levels > 500 mg/dL, Defendants fail to identify a single reference directed to the
19 administration of Epadel to patients with very-high TG levels, reflecting a lack of motivation.

20 Defendants further argue that the disclosure in WO '118 would combine with the prior art
21 concerning Lovaza for at least two reasons; first, "products containing DHA were reported to

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23 ⁵⁹⁷² Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

24 ⁵⁹⁷³ Chan 2002 I at 2381 (Table 3).

1 increase LDL-C levels while products containing only EPA did not,” and second, “WO ‘118
2 reports a reduction in cardiovascular events in hypertriglyceridemic patients administered highly-
3 purified ethyl-EPA.”⁵⁹⁷⁴ Both of the “reasons” identified by Defendants are false.

4 Regarding Defendants’ first reason, that “products containing DHA were reported to
5 increase LDL-C levels while products containing only EPA did not,” most controlled studies in
6 patients with normal to high baseline TG levels indicated that DHA had little or no effect on
7 LDL-C.⁵⁹⁷⁵ Therefore, a person of ordinary skill would not have concluded that DHA increases
8 LDL-C in patients with normal to high baseline TG levels. Specifically, Leigh-Firbank, Kelley,
9 and Theobald does *not* disclose that “DHA raises LDL-C, an effect associated with heart disease,
10 while EPA does not.”⁵⁹⁷⁶ First, Leigh-Firbank cannot comment on the effect of EPA and DHA
11 alone because it did not administer EPA and DHA separately.⁵⁹⁷⁷ A person of ordinary skill
12 would similarly understand that Leigh-Firbank does not offer any disclosure regarding the effect
13 of EPA and DHA separately or gain any understanding of the separate impact of DHA or EPA
14 on lipid parameters. Second, Kelley administered DHA-rich oil that was contaminated with
15 other saturated and polyunsaturated fatty acids.⁵⁹⁷⁸ Therefore, a person of ordinary skill would
16 have known it is unsuitable for evaluating the independent effects of DHA because it is not clear
17 how much of the supplement’s effects can be attributed to DHA.⁵⁹⁷⁹ Kelley does not show that

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⁵⁹⁷⁴ Defendants’ Joint Invalidation Contentions at 757.

20 ⁵⁹⁷⁵ Mori 2006 at 98. Moreover, Mori 2000, the only study which compared EPA versus DHA, and is placebo
21 controlled, found an increase in LDL-C after DHA administration.

22 ⁵⁹⁷⁶ Defendants’ Joint Invalidation Contentions at 761.

23 ⁵⁹⁷⁷ The discussion related to Leigh-Firbank in Section V.M.3.c.1.a.i.a.iii is incorporated herein by reference.

24 ⁵⁹⁷⁸ The discussion related to Kelley in Section V.M.3.c.1.a.iii.a.ii is incorporated herein by reference.

⁵⁹⁷⁹ See Mori 2006 at 96.

1 DHA is responsible for the increase in LDL-C. Kelley suggests that increase in LDL-C is a
2 general phenomenon associated with triglyceride-lowering drugs, stating that a similar increase
3 was induced by fibrate therapy.⁵⁹⁸⁰ Kelley specifically teaches that the increase in LDL-C
4 caused by DHA supplementation is unlikely to be “detrimental” because there was not a parallel
5 increase in overall LDL particle number. Rather than concluding that DHA was uniquely
6 responsible for a rise in LDL-C levels, a person of ordinary skill would understand Kelley to
7 disclose that DHA had uniquely beneficial cardioprotective effects.⁵⁹⁸¹ Finally, Theobald also
8 does not teach that DHA increases LDL-C. In Theobald, 0.7 g/day of DHA was administered for
9 3 months in patients with normal baseline TG levels. Theobald found that LDL-C increased by
10 7% when compared to placebo. However, the DHA composition that was administered in
11 Theobald contained significant amounts of other fatty acids, such as myristic acid, palmitic acid,
12 and oleic acid. Therefore, a person of ordinary skill would have known that the DHA
13 administered by Theobald is unsuitable for evaluating the independent effects of DHA because it
14 impossible to determine whether or how much of the supplement’s effects can be attributed to
15 DHA.⁵⁹⁸² Contrary to Defendants’ assertion that there was “a reported advantage to using EPA
16 vs. DHA in hypertriglyceridemic subjects,”⁵⁹⁸³ there was no known advantage to using EPA vs.
17 DHA. In fact, a number of the references Defendants cite in their contentions ultimately
18 conclude that DHA supplementation “may represent a more favorable lipid profile than after
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20 ⁵⁹⁸⁰ Kelley at 329.

21 ⁵⁹⁸¹ Kelley at 324, 332 (Kelley’s ultimate conclusion is that “[o]verall, DHA supplementation reduced the
22 concentrations of atherogenic lipids and lipoproteins and increased concentrations of cardioprotective lipoproteins”
and that “DHA supplementation may improve cardiovascular health.”)

23 ⁵⁹⁸² See Mori 2006 at 96.

24 ⁵⁹⁸³ Defendants’ Joint Invalidation Contentions at 757.

1 EPA supplementation.”⁵⁹⁸⁴ In addition, a person of ordinary skill would have recognized any
2 impact of DHA reported by the study to be applicable to EPA because they would have
3 understood these substances to function by the same mechanism. Furthermore, as discussed
4 above in Section III, a person of ordinary skill would not expect the same LDL-C effect in
5 patients with lower baseline TG levels, including healthy patients, as in very-high TG patients
6 because patients with higher TG levels had different lipid responses compared to patients with
7 lower TG levels.

8 Regarding Defendants’ second reason, that “WO ‘118 reports a reduction in
9 cardiovascular events in hypertriglyceridemic patients administered highly-purified ethyl-EPA,”
10 the cardioprotective effects of omega-3 fatty acids, including both EPA and DHA, have been
11 well documented.⁵⁹⁸⁵ Lovaza/Omacor has been shown to reduce the risk for cardiovascular
12 death plus nonfatal myocardial infarction and nonfatal stroke.⁵⁹⁸⁶ Omega-3 fatty acids have been
13 shown to exert cardioprotective effects in both primary and secondary coronary heart disease
14 prevention trials.⁵⁹⁸⁷ Omega-3 fatty acids were known to reduce TG concentration, have
15 antiarrhythmic effects, decrease platelet aggregation, stabilize plaque, reduce blood pressure
16 and/or reduce heart rate.⁵⁹⁸⁸

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19 ⁵⁹⁸⁴ Mori 2000 at 1092.

20 ⁵⁹⁸⁵ Harris et al., *Tissue n-3 and n-6 Fatty Acids and Risk for Coronary Heart Disease Events*, 193
ATHEROSCLEROSIS, 1, 8 (2007) (“Overall, these findings confirm the well-known relationship between the n-3 FA
and CHD risk.”) (“Harris 2007”); Bays 2008 II at 229-230.

21 ⁵⁹⁸⁶ See Bays, *Clinical Overview of Omacor: A Concentrated Formulation of Omega-3 Polyunsaturated Fatty Acids*,
98 AM. J. CARDIOL 71i (2006) (“Bays 2006”).

22 ⁵⁹⁸⁷ Harris et al., *Omega-3 Fatty Acids and Coronary Heart Disease Risk: Clinical and Mechanistic Perspectives*,
197 ATHEROSCLEROSIS 12, 13 (2008) (“Harris 2008”).

23 ⁵⁹⁸⁸ Harris 2008 at 13.
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1 Defendants argue that a “person of ordinary skill in the art would have appreciated the
2 fact that highly-purified ethyl-EPA, and not Lovaza, had been demonstrated to reduce
3 cardiovascular events in high-risk hypertriglyceridemic patients, and understood the benefits of
4 replacing the EPA+DHA of Lovaza with the highly purified ethyl-EPA of WO ‘118.”⁵⁹⁸⁹ As
5 discussed above, the cardioprotective effects of omega-3 fatty acids, including both EPA, DHA
6 and Lovaza/Omacor have been well documented.⁵⁹⁹⁰

7 In fact, a meta-analysis of twenty-five studies which examined the risk of coronary heart
8 disease endpoints as a function of tissue FA composition found that the evidence suggested that
9 DHA is *more* cardioprotective than EPA.⁵⁹⁹¹ This study found that “depressed levels of long-
10 chain *n*-3 FA (especially DHA) in tissues is a consistent marker of increased risk for coronary
11 heart disease events.”⁵⁹⁹² Further, the study found that DHA levels, with or without EPA, were
12 significantly lower in fatal endpoints.⁵⁹⁹³ This study suggests that DHA is preferable to EPA—
13 thus teaching away from the claimed invention.⁵⁹⁹⁴ Defendants rely on hindsight bias to argue
14 that a person of ordinary skill would have been motivated to use purified EPA, when both EPA
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16 ⁵⁹⁸⁹ Defendants’ Joint Invalidity Contentions at 758.

17 ⁵⁹⁹⁰ Harris et al., *Tissue n-3 and n-6 Fatty Acids and Risk for Coronary Heart Disease Events*, 193
ATHEROSCLEROSIS, 1, 8 (2007) (“Overall, these findings confirm the well-known relationship between the *n*-3 FA
18 and CHD risk.”) (“Harris 2007”).

19 ⁵⁹⁹¹ Harris 2007 at 8.

20 ⁵⁹⁹² *Id.*

21 ⁵⁹⁹³ Harris 2007 at 7, Table 5; *see also* Harris 2007 at 8 (“Low DHA was the most common finding across all
22 studies, suggesting that this FA was perhaps more cardioprotective than EPA as others have suggested.”).

23 ⁵⁹⁹⁴ *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994) (A reference may be said to teach away when a person of
24 ordinary skill, upon [examining] the reference, would be discouraged from following the path set out in the
reference, or would be led in a direction divergent from the path that was taken by the applicant.”); *W.L. Gore & Assocs.,
Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1552 (Fed. Cir. 1983) (“[P]roceed[ing] contrary to the accepted wisdom of the
prior art ... is strong evidence of nonobviousness.”).

1 and DHA were known to have cardioprotective effects, and there were studies suggesting DHA
2 was *more* cardioprotective than EPA.

3 Defendants argue that the following claim elements were known: the administration of
4 highly-purified EPA-E to reduce TG levels in patients with normal to high TG levels, the
5 administration of purified EPA to patients with TG levels > 500 mg/dL, to administer EPA-E to
6 patients with high and very high TG levels who were not receiving concurrent lipid altering
7 therapy, and the dose of 4g/day and 12-week regimen.⁵⁹⁹⁵ Defendants then argue that the “only
8 question is whether one skilled in the art would have been motivated to use the DHA-free,
9 highly-purified EPA-E of the prior art for the treatment of patients with triglyceride levels of at
10 least 500 mg/dL as part of the claimed dosage regimen.”⁵⁹⁹⁶

11 Defendants’ contentions are no more than a recitation that certain claim elements were
12 known in the prior art. Defendants’ assertions to the contrary represent hindsight
13 reconstruction.⁵⁹⁹⁷ Notably, Defendants *do not* assert that a person of ordinary skill would have
14 known that purified EPA, when administered to patients with very-high TG levels (≥ 500 mg/dL),
15 *would not substantially increase LDL-C*. Further, Defendants point to three Japanese studies,⁵⁹⁹⁸
16 which included a small minority of patients with baseline TG levels > 500 mg/dL to argue that “a
17 number of prior art references disclosed the administration of purified EPA to patients with TG
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⁵⁹⁹⁵ Defendants’ Joint Invalidity Contentions at 759.

21 ⁵⁹⁹⁶ Defendants’ Joint Invalidity Contentions at 759.

22 ⁵⁹⁹⁷ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that even under
23 KSR, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention
without any explanation as to how or why the references would be combined to produce the claimed invention.”).

24 ⁵⁹⁹⁸ Nakamura, Matsuzawa, and Takaku.

1 levels > 500 mg/dL.”^{5999, 6000} The disclosures of Nakamura (one patient), Matsuzawa (disclosure
2 of three patients with TG between 400 and 1000 mg/dL, with no evidence or support for the
3 assertion that the patients had very high TGs), and Takaku (three patients) reflect that a person of
4 ordinary skill in the art would *not* understand these references to relate to the use of EPA in
5 patients with very high TGs, nor would a person of ordinary skill in the art draw any conclusions
6 regarding these references in terms of the very high TG patient population. In Nakamura, one
7 patient had a baseline TG level > 500 mg/dL.⁶⁰⁰¹ However, the mean baseline TG for all patients
8 was 2.07 mmol/l (183 mg/dL), indicating that the baseline TG values for the other patients was
9 well below 500 mg/dL.⁶⁰⁰² In Matsuzawa, three patients had TG levels between 400 and 1000
10 mg/dL and one patient had TG levels > 1,000 mg/dL.⁶⁰⁰³ Based on this disclosure, only one
11 patient definitively had a baseline TG level \geq 500 mg/dL. Further, this one patient was excluded
12 when analyzing the lipid impact because he was a “heavy drinker” and the “effect of alcohol
13 made it impossible to assess triglyceride levels.”⁶⁰⁰⁴ In Takaku, three patients had baseline TG
14 levels above 500 mg/dL.⁶⁰⁰⁵ However, the mean baseline TG level for all patients was 245
15 mg/dL.⁶⁰⁰⁶ Indeed, the mean baseline TG level of the patients in all three studies was well below
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17 ⁵⁹⁹⁹ Defendants’ Joint Invalidation Contentions at 759.

18 ⁶⁰⁰⁰ Okumura and Hayashi also fail to disclose administration of purified EPA to patients with TG levels > 500
19 mg/dL. Hayashi states that the baseline TG level was 300 +/- 233 mg/dL. However, the standard error is unusually
20 high and there is no specific disclosure of a single subject with TG levels > 500 mg/dL. Okumura specifically
21 states that its hypertriglyceridemia patients had baseline TG levels between 150 and 500 mg/dL.

22 ⁶⁰⁰¹ Nakamura at 23, Table 1.

23 ⁶⁰⁰² Nakamura at 23, Tables 1 and 2.

24 ⁶⁰⁰³ *Id.* at 23.

⁶⁰⁰⁴ *Id.* at 10.

⁶⁰⁰⁵ Takaku at ICOSAPENT_DFNDTS00006895.

⁶⁰⁰⁶ Takaku at ICOSAPENT_DFNDTS00006875.

1 500 mg/dL; therefore, a person of ordinary skill would not have expected the results to be
2 applicable to patients with triglycerides above 500 mg/dL. Further, in each of these studies,
3 patients with >500 mg/dL were most likely excluded from the LDL-C calculations because the
4 Friedewald's Equation cannot be used for patients with triglyceride levels \geq 400 mg/dL.⁶⁰⁰⁷
5 Defendants have failed to identify all of the claimed elements and fail to provide motivation to
6 use the DHA-free, highly-purified EPA-E of the prior art for the treatment of patients with
7 triglyceride levels of at least 500 mg/dL as part of the claimed dosage regimen.

8 Defendants contend that a "person of ordinary skill in the art would have been motivated
9 to administer highly-purified EPA-E capsules, for at least 12 weeks . . . in order to achieve the
10 known TG-lowering effects of highly-purified EPA-E."⁶⁰⁰⁸ This argument is flawed. The prior
11 art demonstrates a wide range of administration periods utilized in different clinical studies. For
12 example, EPA was administered for 4 weeks in Park, for 7 weeks in Grimsgaard, for 8 weeks in
13 Hayashi, for 1 year in Takaku, for 2 years in Katayama, and for 5 years in Yokoyama 2007.
14 Given the large number of choices of administration periods disclosed in prior art, Defendants
15 have not shown that a person of ordinary skill would not have been motivated to administer
16 highly-purified EPA-E capsules for 12 weeks and offer no basis for their assertions.

17 Moreover, a person of ordinary skill would not have been motivated to administer highly-
18 purified *EPA-E* capsules, as opposed to DHA or a combination of EPA and DHA (such as
19 Lovaza), for 12 weeks. It was well known that both EPA and DHA reduced blood
20 triglycerides.⁶⁰⁰⁹ In fact, Defendants acknowledge in their Joint Invalidity Contentions that

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22 ⁶⁰⁰⁷ See Matsuzawa at ICOSAPENT_DFNDTS00006450.

23 ⁶⁰⁰⁸ Defendants' Joint Invalidity Contentions at 759.

24 ⁶⁰⁰⁹ Mori 2006 at 98.

1 “DHA and EPA were both known to comparably reduce triglycerides, independently of one
2 another.”⁶⁰¹⁰ Data from some studies even suggested that DHA or fish oil may reduce
3 triglyceride more effectively than EPA.⁶⁰¹¹ Therefore, a person of ordinary skill would not have
4 been motivated to administer highly-purified *EPA-E* capsules instead of DHA or a combination
5 of EPA and DHA (such as Lovaza) for 12 weeks.

6 Defendants argue that a “person of ordinary skill in the art also would have been
7 motivated to administer 4 g/day highly-pure ethyl EPA . . . because of the observed significant
8 reduction in TG that was achieved in six weeks of treatment,” citing Mori 2000.⁶⁰¹² This
9 argument is incorrect. The administration of 4 g/day of highly-pure ethyl EPA to patients with
10 *mild* hypertriglyceridemia for *six* weeks does not provide a person of ordinary skill motivation to
11 administer the same dose to patients with *severe* hypertriglyceridemia for *twelve* weeks.

12 Defendants also, once again, fail to demonstrate that a person of ordinary skill would have
13 chosen to administer 4g/day EPA as opposed to DHA or a combination of EPA and DHA (such
14 as Lovaza).

15 Defendants further argue that “because Katayama and Saito 1998 teach that higher doses
16 of highly-purified EPA-E reduce TG level to a greater extent than lower doses . . . a person of
17 ordinary skill in the art would have been motivated to administer highly-purified EPA-E at a
18 dose of 4 g/day rather than a lower dose.”⁶⁰¹³ A person of ordinary skill would not have relied
19 on either reference to determine the EPA dosage required to treat severe hypertriglyceridemia,
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21 ⁶⁰¹⁰ Defendants’ Joint Invalidation Contentions at 763.

22 ⁶⁰¹¹ Mori 2000 (showing that EPA reduced triglyceride by 18% while DHA reduced triglyceride by 20%); Rambjor
(showing that fish oil reduced triglyceride more than EPA); Grimsgaard (showing that decrease in triglyceride was
23 grater with DHA supplementation than EPA supplementation).

24 ⁶⁰¹² Defendants’ Joint Invalidation Contentions at 760.

⁶⁰¹³ Defendants’ Joint Invalidation Contentions at 760.

1 because these studies were not designed to determine the effect of dose on the degree of TG
2 reduction. Second, Katayama and Saito do not suggest that 4 g/day of EPA, rather than a lower
3 dose or a higher dose, would be the right dosage to treat severe hypertriglyceridemia.

4 Moreover, as discussed above, it was well known that both EPA and DHA reduced blood
5 triglycerides.⁶⁰¹⁴ Therefore, a person of ordinary skill would not have been motivated to
6 administer 4 g/day of highly-purified *EPA-E* capsules, as opposed to DHA or a combination of
7 EPA and DHA (such as Lovaza).

8 Defendants further argue that a “person of ordinary skill in the art would have also been
9 motivated to treat subjects having baseline TG levels of at least 500 mg/dl with highly-purified
10 EPA-E, as suggested by Yokoyama’s teaching that TG was reduced to a much greater extent in
11 subjects having higher baseline TG levels . . . and because Katayama and Saito 1998 treated
12 subjects having baseline triglyceride levels greater than 500 mg/dl.”⁶⁰¹⁵ This argument is
13 incorrect. It was well known that any TG-reducing therapy will reduce TG to a greater extent in a
14 patient having higher baseline TG levels. Therefore, a person of ordinary skill would not have
15 been motivated to administer highly-purified *EPA-E* capsules as opposed to any other omega-3
16 fatty acid composition, fibrate, or other TG-lowering therapy, to treat subjects having baseline
17 TG levels above 500mg/dL. Further, a person of ordinary skill would have expected that a
18 greater decrease in TG levels, in the very high TG patient population, would lead to a greater
19 increase in LDL-C levels.

20 Defendants contend that a “person of ordinary skill in the art would have been motivated
21 to administer highly-purified EPA-E—either on its own or with statin therapy—to effect a
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23 ⁶⁰¹⁴ See Section III.

24 ⁶⁰¹⁵ Defendants’ Joint Invalidity Contentions at 774.

1 reduction in TG levels without affecting LDL-C if treatment was without statin therapy, or to
2 effect a reduction in TG and LDL-C, if treatment was with statin therapy.” Defendants first
3 support this argument by asserting that a person of ordinary skill in the art would have known
4 that EPA could lower TG levels without increasing LDL-C in very high TG patients. That is
5 incorrect. As discussed above, a person of ordinary skill in the art would not have expected EPA
6 to raise LDL-C levels in very high TG patients. Defendants’ broadly cite to “Yokoyama 2003,
7 Yokoyama 2007, Mori 2000, Mori 2006, Saito 1998, and the other references discussed in
8 V.B.4. and 5” to support this proposition, however these references do not disclose or suggest to
9 a person of ordinary skill that EPA could lower TG levels without increasing LDL-C in very
10 high TG patients.⁶⁰¹⁶

11 Defendants next argue again that DHA was known to be responsible for the increase in
12 LDL-C levels in very high TG patients, but as discussed above, *see* Section III, a person of
13 ordinary skill would understand that both EPA and DHA function similarly, and that both would
14 have little to no impact on borderline-high TG patients in terms of LDL-C levels and would
15 increase LDL-C levels in patients with very high TGs.

16 Defendants argue that a person of ordinary skill in the art “would have known that an
17 increase in LDL-C was an adverse health effect to be avoided.” While an increase in LDL-C
18 was seen as a *possible* adverse health effect, a person of ordinary skill in the art understood that
19 the increase in LDL-C seen in the very-high TG patient population with Lovaza, and omega-3
20 fatty acids generally, was related to increased conversion of VLDL to LDL particles.⁶⁰¹⁷

21
22 ⁶⁰¹⁶ See Section IV.

23 ⁶⁰¹⁷ See Bays 2008 I at 402; McKenny 2007 at 720 (finding that “[t]hese results illustrate that with prescription
24 omega-3, fewer VLDL particles are secreted into the systemic circulation, and secreted VLDL particles are rapidly
converted to LDL particle, thus explaining why LDL levels may increase in patients with very-high triglyceride
levels when given prescription omega-3 therapy”); Chan 2003.

1 Defendants rely on Kelley and the Lovaza label to argue that one of ordinary skill in the
2 art would have been motivated, with a reasonable expectation of success, to administer a highly-
3 purified EPA-E dosage form, with little to no DHA, “in order to avoid the expected increase in
4 LDL-C with DHA.”⁶⁰¹⁸ However, a person of ordinary skill in the art expected an increase in
5 LDL-C in the very high TG population, with both EPA and DHA. It was well known at the time
6 of the invention that omega-3 fatty acids, including both EPA and DHA, caused significant
7 decrease in the production of VLDL particles and a significant increase in the conversion of
8 VLDL to IDL and LDL, supporting the theory that omega-3 fatty acids worked in part by
9 inhibiting VLDL production and improving the conversion of VLDL particles to LDL.⁶⁰¹⁹ A
10 person of ordinary skill in the art understood that EPA and DHA had the *same* TG-lowering
11 mechanism and did not differentiate between EPA and DHA when discussing the TG-lowering
12 mechanism of omega-3 fatty acids.⁶⁰²⁰ The discussion related to the TG-lowering mechanism of
13 omega-3 fatty acids is discussed above in Section III and incorporated herein by reference.
14 Further, a person of ordinary skill in the art would have understood that EPA therapy would *not*
15 reduce Apo-B⁶⁰²¹ (which is a reflection of total atherogenic lipoproteins)⁶⁰²² in very high TG
16 patients, and accordingly would not have been motivated to administer the claimed EPA
17 composition to the very high TG patient population.

18 Accordingly, a person of ordinary skill would not have been motivated to combine WO
19 '118, WO '900, Grimsgaard, Mori 2000 and/or Maki in with the Omacor PDR/Lovaza PDR, and

20 ⁶⁰¹⁸ Defendants' Joint Invalidity Contentions at 763.

21 ⁶⁰¹⁹ Chan 202 at 2378-84; *see also* Westphal at 917 (stating “our data confirm the well-known and pronounced
22 decrease in VLDLs after n-3 fatty acid treatment”).

23 ⁶⁰²⁰ Bays 2008 I, at 398; Bay *in* Kwiterovich at 247.

24 ⁶⁰²¹ *see* Section V.O.

⁶⁰²² *see* Section III.

1 Katayama, Matsuzawa and/or Takaku. A person of ordinary skill in the art further would not
2 have been motivated to combine WO '118 or WO '900, with the Lovaza PDR, or with Leigh-
3 Firbank and/or Mori 2000.

4 (2) Dependent Claims

5 (a) Defendants Have Not Shown that Claims 2, 11 and
6 18 of the '372 Patent Would Have Been Obvious

7 Plaintiffs incorporate by reference the discussion related to the Independent Claims in
8 Section V.M.3. Because Defendants have not shown the obviousness of the Independent Claims
9 by clear and convincing evidence, they also have not adequately proven the obviousness of
10 Claims 2, 11 and 18.

11 Defendants contend that it would be obvious that a person receiving the claimed EPA
12 compositions would have a fasting baseline LDL-C from 50 mg/dL to about 300 mg/dL because
13 hypertriglyceridemic patients in the Lovaza label had a mean LDL-C level of 100 mg/dL. These
14 contentions: 1) fail to address whether the specific combination of claim elements were all
15 present in the prior art references that would have been combined by a person of ordinary skill in
16 the art to produce the claimed invention with a reasonable expectation of success; and 2) fail to
17 establish *prima facie* obviousness. Defendants do not offer an obvious analysis, but trivialize the
18 claim element to the point of reading the element out of the claim. Although convenient and
19 expedient, Defendants' approach does not conform with the Local Patent Rules of this District,
20 the law of claim construction, or the law of obviousness.

21 Defendants do not identify any combination of references. Because Defendants do not
22 identify any combination of references, they necessarily fail to offer any evidence that a person
23 of skill in the art would be motivated to combine those references in order to achieve the
24 invention of the claim as a whole. Further, Defendants do not discuss at all whether a person of

1 ordinary skill would have been motivated to combine the elements, other than stating that a
2 patient with LDL-C levels of 50 mg/dL to about 300 mg/dL would benefit from receiving the
3 claimed fish oil treatment. Defendants also state erroneously that a patient with LDL-C levels of
4 50 mg/dL to about 300 mg/dL would be considered hypertriglyceridemic. Defendants do not
5 establish that a person of ordinary skill would have been motivated to combine the elements to
6 achieve the claimed invention.⁶⁰²³

7 Similarly, without the disclosure of a combination of references and a motivation/reason
8 to combine or modify the references, Defendants necessarily fail to offer any evidence that a
9 person of ordinary skill in the art would have had a reasonable expectation of success in
10 achieving the claimed invention. Defendants do not even discuss whether a person of ordinary
11 skill would have expected that the combination to work for its intended purpose for treating the
12 recited patient population.⁶⁰²⁴ As such, Defendants fail to demonstrate reasonable expectation of
13 success of the claimed invention.

14 (b) Defendants Have Not Shown that Claims 3, 12, and
15 19 of the '372 Patent Would Have Been Obvious

16 Plaintiffs incorporate by reference the discussion related to the Independent Claims in
17 Section V.M.3. Because Defendants have not shown the obviousness of the Independent Claims
18 by clear and convincing evidence, they also have not adequately proven the obviousness of
19 Claims 3, 12 and 19.

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21 ⁶⁰²³ *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the *KSR*
22 Court rejected a rigid application of the teaching, suggestion, or motivation (‘TSM’) test in an obviousness inquiry,
the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill
in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness
determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

23 ⁶⁰²⁴ *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable
24 result’ discussed in *KSR* refers not only to the expectation that prior art elements are capable of being physically
combined, but also that the combination would have worked for its intended purpose.”)

1 Defendants do not identify any combination of references and simply provide a laundry
2 list of references without explaining how each reference relates to the claimed invention.
3 Defendants further contend, without any support, that a person of ordinary skill would have been
4 able to determine the patient population in need of the claimed methods of treatment, would seek
5 to measure the HDL-C, VLDL-C and cholesterol baselines of a patient, and would seek to treat
6 those patients having very high triglycerides regardless of the baseline values of these lipids.⁶⁰²⁵
7 These contentions: 1) do not assert what the prior art discloses to a person of ordinary skill in
8 the art; 2) are irrelevant to an obvious analysis; 3) fail to address whether the specific
9 combination of claim elements were all present in the prior art references that would have been
10 combined by a person of ordinary skill in the art to produce the claimed invention with a
11 reasonable expectation of success; and 4) fail to establish *prima facie* obviousness. Defendants
12 do not offer an obvious analysis, but trivialize the claim element to the point of reading the
13 element out of the claim. Although convenient and expedient, Defendants' approach does not
14 conform with the Local Patent Rules of this District, the law of claim construction, or the law of
15 obviousness.

16 Defendants fail to show a specific combination of references that discloses each element
17 of the claimed invention. Defendants merely list references, without reference to a specific page
18 or section, that purportedly disclose disparate elements without explaining how they can be
19 combined.⁶⁰²⁶ As such, Defendants discuss the claim elements in isolation, and fail to address
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22 ⁶⁰²⁵ *Id.*

23 ⁶⁰²⁶ *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)) (“[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”).
24

1 the claimed invention as a whole.⁶⁰²⁷ Moreover, by simply identifying prior art references
2 without discussing the specific teachings of each reference, Defendants fail to consider each
3 prior art reference as a whole.⁶⁰²⁸ Each reference must be evaluated for all that it teaches.
4 Defendants' unsupported cobbling of selective disclosures represents hindsight
5 reconstruction.⁶⁰²⁹

6 Because Defendants do not identify any combination of references, they necessarily fail
7 to offer any evidence that a person of skill in the art would be motivated to combine those
8 references in order to achieve the invention of the claim as a whole. Defendants make a
9 conclusory statement that a person of ordinary skill "would indeed seek" to perform the claimed
10 methods of treatment, without providing a reason that would have prompted a person of ordinary
11 skill to combine the elements.⁶⁰³⁰ Such a naked assertion does not show why a person of
12 ordinary skill would have been motivated to treat the recited patient population using the claimed
13 methods of treatment.⁶⁰³¹

15 ⁶⁰²⁷ *Sanofi Syntheolabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008) ("The determination of obviousness is
made with respect to the subject matter as a whole, not separate pieces of the claim").

16 ⁶⁰²⁸ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011) ("A prior
17 patent must be considered in its entirety, i.e., as a whole, including portions that would lead away from the invention
in suit.") (internal citation and quotation marks omitted).

18 ⁶⁰²⁹ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under
19 *KSR*, "[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention
without any explanation as to how or why the references would be combined to produce the claimed invention").

20 ⁶⁰³⁰ *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) ("Rejections on obviousness grounds cannot be
21 sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational
underpinning to support the legal conclusion of obviousness.") (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir.
2006)) (internal quotation marks omitted)

22 ⁶⁰³¹ *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) ("While the *KSR*
23 Court rejected a rigid application of the teaching, suggestion, or motivation ('TSM') test in an obviousness inquiry,
the Court acknowledged the importance of identifying 'a reason that would have prompted a person of ordinary skill
24 in the relevant field to combine the elements in the way the claimed new invention does' in an obviousness
determination.") (quoting *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

1 Similarly, without the disclosure of a combination of references and a motivation/reason
2 to combine or modify the references, Defendants necessarily fail to offer any evidence that a
3 person of ordinary skill in the art would have had a reasonable expectation of success in
4 achieving the claimed invention. In fact, other than simply identifying prior art references that
5 purportedly disclose disparate elements, Defendants do not even discuss whether a person of
6 ordinary skill would have expected that the combination to work for its intended purpose for
7 treating the recited patient population.⁶⁰³² As such, Defendants fail to demonstrate reasonable
8 expectation of success of the claimed invention.

9 (c) Defendants Have Not Shown that Claims 4, 13 and
10 20 of the '372 Patent Would Have Been Obvious

11 Plaintiffs incorporate by reference the discussion related to the Independent Claims in
12 Section V.M.3. Because Defendants have not shown the obviousness of the Independent Claims
13 by clear and convincing evidence, they also have not adequately proven the obviousness of
14 Claims 4, 13 and 20.

15 Defendants contend, without support, that the recited reduction in TG represents
16 therapeutic efficacy, and that a person of ordinary skill would naturally seek to reduce TG to
17 therapeutic efficacy. Defendants further contend that it would have been obvious to a person of
18 ordinary skill to seek to reduce TG by the recited amount because there is no significance
19 attached to the amount. Defendants conclude, without support, that there was a reasonable
20 expectation of success without identifying any combination of references and without explaining

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23 ⁶⁰³² *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable
24 result’ discussed in KSR refers not only to the expectation that prior art elements are capable of being physically
combined, but also that the combination would have worked for its intended purpose.”)

1 | how each reference relates to the claimed invention.⁶⁰³³ These contentions: 1) do not assert
2 | what the prior art discloses to a person of ordinary skill in the art; 2) are irrelevant to an obvious
3 | analysis; 3) fail to address whether the specific combination of claim elements were all present in
4 | the prior art references that would have been combined by a person of ordinary skill in the art to
5 | produce the claimed invention with a reasonable expectation of success; and 4) fail to establish
6 | *prima facie* obviousness. Defendants do not offer an obvious analysis, but trivialize the claim
7 | element to the point of reading the element out of the claim. Although convenient and expedient,
8 | Defendants’ approach does not conform with the Local Patent Rules of this District, the law of
9 | claim construction, or the law of obviousness.

10 | Defendants further contend, without support, that a person of ordinary skill would
11 | “reasonably expect to see the same hypotriglyceridemic effect from a pure EPA formulation
12 | containing no DHA,” as a formulation containing both EPA and DHA. Defendants conclude,
13 | without support, that it would have been obvious to administer a composition containing EPA,
14 | but containing no DHA, with a reasonable expectation of success in reducing triglycerides while
15 | avoiding an increase in LDL. These contentions: 1) do not assert what the prior art discloses to
16 | a person of ordinary skill in the art; 2) fail to address whether the specific combination of claim
17 | elements were all present in the prior art references that would have been combined by a person
18 | of ordinary skill in the art to produce the claimed invention with a reasonable expectation of
19 | success; and 3) fail to establish *prima facie* obviousness. Defendants do not offer an obvious
20 | analysis, but trivialize the claim element to the point of reading the element out of the claim.

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23 | ⁶⁰³³ Ando, Calabresi, Contacos, Grimsgaard, Harris, Hayashi, Katayama, Kris_Etherton 2002, Kurabayashi, Leigh-
24 | Firbank, Lovaza 2007 Label, Lovaza PDR, Omacor 2004 Label, Omacor PDR, Lovegrove, Matsuzawa, McKenney
2003, McKenney 2007, Mori 2000, Mori 2006, Nakamura, Nestel, Nozaki, Pownall, Sanders, Shinozaki, Takaku,
von Schacky, Wojenski, Yokoyama 2003, and/or Yokoyama 2007.

1 Although convenient and expedient, Defendants’ approach does not conform with the Local
2 Patent Rules of this District, the law of claim construction, or the law of obviousness.

3 Defendants do not identify any combination of references and simply provide a laundry
4 list of references that purportedly disclose disparate elements without explaining how they can
5 be combined.⁶⁰³⁴ Defendants fail to provide any references directed toward the LDL-C claim
6 element. As such, Defendants discuss the claim elements in isolation, and fail to address the
7 claimed invention as a whole.⁶⁰³⁵ Defendants selectively cite to an unspecified isolated
8 disclosure within a reference without considering other disclosures or even the reference as a
9 whole. Each reference, however, must be evaluated for all that it teaches.⁶⁰³⁶ Defendants’
10 unsupported cobbling of selective disclosures represents hindsight reconstruction.⁶⁰³⁷

11 Because Defendants do not identify any combination of references, they necessarily fail
12 to offer any evidence that a person of skill in the art would be motivated to combine those
13 references in order to achieve the invention of the claim as a whole. Defendants make a
14 conclusory statement that “it would have been obvious to the ordinarily skilled artisan to seek to
15 reduce triglycerides by 5% to 25%,” without providing a reason that would have prompted a
16 person of ordinary skill to reduce triglycerides by the recited amount.⁶⁰³⁸ Defendants fail to
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18 ⁶⁰³⁴ *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int’l Co. v.*
19 *Teleflex Inc.*, 550 U.S. 398, 418 (2007)) (“[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”).

20 ⁶⁰³⁵ *Sanofi Syntheolabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008) (“The determination of obviousness is
made with respect to the subject matter as a whole, not separate pieces of the claim”).

21 ⁶⁰³⁶ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

22 ⁶⁰³⁷ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under
KSR, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention
without any explanation as to how or why the references would be combined to produce the claimed invention”).

23 ⁶⁰³⁸ *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (“Rejections on obviousness grounds cannot be
24 sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational

1 make any motivations arguments for the LDL-C claim element. Defendants’ burden to establish
2 *prima facie* obviousness is not discharged because there is allegedly “no significance” attached
3 to the recited TG reduction amount.⁶⁰³⁹ Defendants have not met the burden with the naked
4 assertion that it would have been obvious to seek the claim elements.

5 Similarly, without the disclosure of a combination of references and a motivation/reason
6 to combine or modify the references, Defendants necessarily fail to offer any evidence that a
7 person of ordinary skill in the art would have had a reasonable expectation of success in
8 achieving the claimed invention. Defendants make a conclusory statement that there was a
9 reasonable expectation of success, without providing a support other than merely identifying
10 prior art references that purportedly disclose disparate elements.⁶⁰⁴⁰ The mere fact that elements
11 are capable of being physically combined does not establish reasonable expectation of
12 success.⁶⁰⁴¹

13 (i) A Person of Ordinary Skill Would Not Have
14 Had a Reasonable Expectation of Success in

15 _____
16 underpinning to support the legal conclusion of obviousness.”) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir.
17 2006)) (internal quotation marks omitted); *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350,
18 1356-57 (Fed. Cir. 2007) (“While the *KSR* Court rejected a rigid application of the teaching, suggestion, or
motivation (‘TSM’) test in an obviousness inquiry, the Court acknowledged the importance of identifying ‘a reason
that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the
claimed new invention does’ in an obviousness determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S.
398, 418 (2007)).

19 ⁶⁰³⁹ Plaintiffs do not have to show that a claimed range is critical unless a *prima facie* case of obviousness has been
established. See *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003) (“An applicant may overcome a *prima facie*
case of obviousness by establishing that the claimed range is critical”) (internal quotation marks omitted).

20 ⁶⁰⁴⁰ *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (“Rejections on obviousness grounds cannot be
21 sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational
underpinning to support the legal conclusion of obviousness.”) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir.
2006)) (internal quotation marks omitted).

22 ⁶⁰⁴¹ *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable
23 result’ discussed in *KSR* refers not only to the expectation that prior art elements are capable of being physically
combined, but also that the combination would have worked for its intended purpose.”).

Defendants provide no evidence that a person of ordinary skill would have had a reasonable expectation of successfully obtaining the claimed invention—a method of reducing triglycerides in a subject having very-high triglyceride levels by administering EPA of the recited purity to effect a reduction in triglycerides *with the claimed LDL-C effect*—by combining the references cited by defendants. For a particular combination of references, there must be a reasonable expectation that the combination will produce the claimed invention. In this case, the art taught that DHA and EPA have similar effects on LDL-C levels in patients with very-high TG levels.⁶⁰⁴² A person of ordinary skill would have expected EPA, like Lovaza/Omacor, to raise LDL-C levels when administered to patients in the very-high TG patient population. As discussed in Section III and above, it was well known that TG-lowering agents, specifically fibrates and Lovaza/Omacor, and little or no effect on LDL-C levels for normal to high TG patients, but caused significant increases in LDL-C levels for patients with very-high triglycerides. The art cited by Defendants provides no basis for a person of ordinary skill to expect anything to the contrary. A person of ordinary skill would have understood that omega 3-fatty acids, including DHA and EPA, and fibrates cause an increase in LDL-C among very high TG patients, as reflected in the prior art:

	LDL-C Effect	
	Borderline-High or High TG Patients	Very-High TG Patients

⁶⁰⁴² As discussed above, see *supra* section III, a person of ordinary skill would have understood EPA and DHA to have the same TG lowering mechanism and would have further understood that the increase in LDL-C accompanying the TG-lowering effects of Lovaza was a product of that same mechanism. Accordingly, a person of ordinary skill would have expected EPA to increase LDL-C levels in patients with very-high TG levels in similar fashion to Lovaza or DHA alone.

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Fibrate ⁶⁰⁴³	-20%	+45%
Lovaza/Omacor ⁶⁰⁴⁴	-6%	+45%

Accordingly, a person of ordinary skill would *not* have a reasonable expectation of success in achieving a reduction in TG levels *with the claimed LDL-C effect* in patients with very-high TG levels.⁶⁰⁴⁵

Defendants’ position that a person of ordinary skill would have had a reasonable expectation of success in administering purified EPA to patients with very high triglyceride levels to achieve TG lowering *with the claimed LDL-C effect* is belied by the fact that Defendants’ provide no evidence that anyone thought to administer Epadel.⁶⁰⁴⁶ Epadel was available for many years prior to the invention of the ’372 patent, to patients with very-high TGs as a treatment. A person of ordinary skill did not expect Epadel, which consisted of mostly EPA, to have superior qualities over a drug such as Lovaza/Omacor, which comprised a mixture of EPA and DHA, in patients with very-high triglycerides. Indeed, none of clinical studies cited by Defendants are directed to the use of purified EPA in the very-high TG population.

Research into the pharmaceutical uses of EPA started as early as the 1970s. In 1990, Mochida Pharmaceutical, began to market Epadel, a high purity EPA drug. There have been countless studies conducted which administer Epadel and report the effects observed. Although a few studies administer Epadel to a patient population which included a few patients with TG levels > 500 mg/dL, Defendants fail to identify a single reference directed to the administration

⁶⁰⁴³ Tricor®, Physicians’ Desk Reference 502-505 (62d ed. 2008).

⁶⁰⁴⁴ Chan 2002 I at 2381 (Table 3).

⁶⁰⁴⁵ Indeed, as discussed above, a person of ordinary skill would have understood that DHA had a better overall effect on lipid parameters, teaching away from this combination.

⁶⁰⁴⁶ Although Epadel was available at different levels of purity, the fact that Epadel—at any level of purity—was not examined in any study directed to the very-high TG patient population supports Amarin’s position.

1 of Epadel to patients with very-high TG levels. The fact is, a person of ordinary skill did not
2 expect Epadel, which consisted of mostly EPA, to have superior qualities over a drug such as
3 Lovaza/Omacor, which comprised a mixture of EPA and DHA, in patients with very-high
4 triglycerides.

5 Defendants argue that because Grimsgaard administered purified ethyl EPA to patients
6 with borderline-high/high TG, it would have been obvious to try administering purified ethyl
7 EPA to patients with very-high TG levels with a reasonable expectation of success. Defendants
8 base this unsupported conclusion on Grimsgaard, Lovaza/Omacor, the known administration of
9 2.7 grams of purified EPA to patients with greater than 500 mg/dL TG by Matsuzawa.

10 Defendants' contentions are no more than a demonstration that certain claim elements was
11 known in the prior art and demonstrates impermissible hindsight reconstruction.⁶⁰⁴⁷ As is
12 reflected in Table 4 of Grimsgaard, the study authors found no difference between the DHA,
13 EPA, and control in terms of LDL-C levels. Defendants use hindsight to argue that, despite EPA
14 and DHA showing the same effect on LDL-C, one would have chosen EPA and expected that
15 administration to very-high TG would have resulted in little or no impact on LDL-C. Notably,
16 none of these references would provide a person of ordinary skill in the art with a reasonable
17 expectation of successfully obtaining the claimed invention even if there were reasons to
18 combine disparate, independent elements found in the prior art, which there were not.

23 ⁶⁰⁴⁷ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that even under
24 KSR, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention
without any explanation as to how or why the references would be combined to produce the claimed invention.”).

TABLE 4
Serum lipids and apolipoproteins at baseline and change after 7 wk of supplementation with docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), or corn oil

	DHA (n = 72)		EPA (n = 75)		Corn oil (n = 77)		F test: <i>P</i> ¹	Contrasts between groups: <i>P</i>		
	Baseline	Change	Baseline	Change	Baseline	Change		DHA vs EPA	DHA vs corn oil	EPA vs corn oil
Triacylglycerols (mmol/L)	1.24 ± 0.58 ²	-0.22 ± 0.31 ³	1.23 ± 0.57	-0.15 ± 0.40 ⁴	1.22 ± 0.55	0.11 ± 0.34 ⁴	0.0001	0.14	0.0001	0.0001
Total cholesterol (mmol/L)	6.00 ± 0.95	0.03 ± 0.49	5.98 ± 0.94	-0.15 ± 0.55 ⁵	6.02 ± 1.08	0.10 ± 0.55	0.01	0.04	0.4	0.004
LDL cholesterol (mmol/L)	4.06 ± 0.86	0.07 ± 0.46	4.06 ± 0.83	-0.08 ± 0.48	4.04 ± 0.98	0.06 ± 0.48	0.10	—	—	—
HDL cholesterol (mmol/L)	1.36 ± 0.30	0.06 ± 0.13 ³	1.33 ± 0.31	0.01 ± 0.12	1.41 ± 0.28	-0.01 ± 0.11	0.001	0.009	0.0005	0.4
Apolipoprotein A-I (g/L)	1.38 ± 0.21	0.02 ± 0.13	1.38 ± 0.20	-0.04 ± 0.10 ³	1.46 ± 0.23	0.00 ± 0.12	0.003	0.0008	0.3	0.02
Apolipoprotein B (g/L)	1.00 ± 0.21	-0.01 ± 0.11	1.01 ± 0.23	-0.03 ± 0.11 ³	1.02 ± 0.28	0.02 ± 0.11	0.05	—	—	—
HDL:apolipoprotein A-I	0.97 ± 0.14	0.04 ± 0.07 ³	0.96 ± 0.13	0.04 ± 0.08 ³	0.97 ± 0.12	-0.01 ± 0.06	0.0001	0.8	0.0003	0.0001
Total:HDL cholesterol	4.62 ± 1.19	-0.19 ± 0.52 ⁴	4.70 ± 1.24	-0.13 ± 0.47 ³	4.43 ± 1.19	0.11 ± 0.62	0.002	0.4	0.0006	0.007

¹ ANOVA for between-group comparisons of change.

²⁻⁵ $\bar{x} \pm$ SD.

³⁻⁵ One-sample *t* test of difference between baseline and 7 wk: ³ *P* < 0.001, ⁴ *P* < 0.01, ⁵ *P* < 0.05.

In addition, Grimsgaard was conducted in patients with normal TG levels, so a person of ordinary skill would have expected no difference between EPA and DHA in terms of LDL-C level change and would have expected no significant increase (or decrease) in LDL-C, as reported by that publication. A person of ordinary skill would further have understood that the data reported by Grimsgaard to be consistent with the understanding that while LDL-C levels are not significantly impacted in normal to high TG patient populations, LDL-C levels would increase significantly in very-high TG patients.

Matsuzawa similarly provides no basis for a reasonable expectation of success in achieving the claimed invention. The subjects of Matsuzawa had a wide range of baseline TG levels and the study was not directed to the very-high TG patient population. Accordingly, just as with Grimsgaard, Matsuzawa would not provide a reasonable expectation of success as a person of ordinary skill would understand patients with very-high TG levels to be different in terms of LDL-C effect than patients with lower TG levels.

To the extent that Defendants' arguments are based on results that are not statistically significant and not reported by Grimsgaard as significant, a person of ordinary skill would not draw conclusions from these statistically insignificant differences. Indeed, the standard deviation for the changes reported is greater than the value of the change itself.

Defendants argue that it would have been obvious to try administering purified ethyl EPA to patients with very-high TG levels with a reasonable expectation of success. However, the

1 Federal Circuit has often rejected the notion that showing something may have been “obvious-to-
2 try” proves that the claimed invention was obvious where the prior art did not suggest what to
3 try.⁶⁰⁴⁸ Rather than there being a limited number of options, the state of the art provided a
4 plethora of compositions and administration protocols associated with multiple kinds of TG-
5 lowering therapies.⁶⁰⁴⁹ There were not a finite number of options for a person of ordinary skill
6 seeking to reduce TG levels without increasing LDL-C among the very-high TG patient
7 population.

8 Defendants argue that a person of ordinary skill at the time of the invention, based on
9 studies in normal, borderline-high and high TG patients, knew that administration of DHA alone
10 resulted in undesirable increased LDL-C levels while administration of EPA alone had little to
11 no impact on LDL-C levels. However, that statement does not conform with what was known
12 regarding the effect of Epadel and Lovaza/Omacor in normal, borderline-high and high TG
13 patients. Instead as Defendants’ own prior art demonstrates, Epadel and Lovaza/Omacor were
14 both known to have little or no effect on LDL-C in patients with borderline-high/high TG levels.

15 With the lack of any reasonable expectation of success, Defendants argue that their
16 proposed combination amounts to a simple substitution of one known element for another, and
17 that that these changes yield predictable results. Such an argument, however, represents pure
18 and impermissible hindsight bias and further does not consider that reasons for which a person of
19 ordinary skill would not be motivated to combine these references and affirmatives ways in
20 which the art taught away from these combinations.

21 (ii) A Person of Ordinary Skill Would Not Have
22 Had a Reasonable Expectation of Success in

23 ⁶⁰⁴⁸ See *Sanofi*, 748 F.3d at 1360–61.

24 ⁶⁰⁴⁹ See *supra* Section III.

Administering the Purified EPA in the
Dosing Regimen Recited in the Claims

1
2
3 Defendants contend that a “person of ordinary skill in the art would have been motivated
4 to administer 4 grams of highly-purified EPA to patients with triglycerides greater than or equal
5 to 500 mg/dL, with a reasonable expectation of success in lowering triglycerides.” Defendants
6 also argue that “[a]t least Katayama, Saito 1998, Yokoyama 2007, and Mori 2000 . . . would
7 have given a person of ordinary skill in the art a reasonable expectation of successfully
8 administering 4 g/day of highly-purified EPA-E for at least 12 weeks to lower triglycerides in
9 these subjects relative to baseline or placebo.” However, Defendants provide no evidence that a
10 person or ordinary skill would have had a reasonable expectation of success in a method of
11 reducing triglycerides in a subject having very-high triglyceride levels by administering purified
12 EPA to effect a reduction in triglycerides *with the claimed LDL-C effect*. Therefore, Defendants
13 fail to provide a reasonable expectation of success for the claimed invention.

14 Defendants further argue, that “because it was known that DHA and EPA were
15 comparably efficacious in reducing triglycerides . . . one of ordinary skill in the art would have
16 reasonably expected to see the same hypotriglyceridemic effect from a 4 g/day dose of purified
17 EPA-E as seen with 4 g/day of a combination of both EPA and DHA. Thus, it would have been
18 obvious to one of ordinary skill in the art to administer a highly-purified EPA-E composition
19 with a reasonable expectation of success that such administration would result in reducing
20 triglycerides while avoiding an increase in LDL.” Defendants argument is without any basis. To
21 the contrary, because a person of ordinary skill in the art would have understood DHA and EPA
22 to lower TGs via the same mechanism, the person of ordinary skill in the art would have
23 expected DHA and EPA to have the same impact on LDL-C levels. Defendants provide no
24 explanation and cite to no article to support their argument that the similar effects on TG levels is

1 a basis to differentiate the efficacy of DHA and EPA with respect to LDL-C impact. Based on
2 the hypotriglyceridemic effect alone, a person of ordinary skill would have reasonably expected
3 both EPA and DHA, whether administered alone or in combination, would cause an increase in
4 LDL-C when administered to the very high TG patient population.

5 The prior art taught that DHA and EPA have similar effects on LDL-C levels in patients
6 with very-high TG. A person of ordinary skill would have thus expected EPA, like
7 Lovaza/Omacor, to raise LDL-C levels when administered to the very-high TG patient
8 population. It was well known that TG-lowering agents, specifically fibrates and
9 Lovaza/Omacor, and little or no effect on LDL-C levels for normal to high TG patients, but
10 caused significant increases in LDL-C levels for patients with very-high triglycerides. The art
11 cited by Defendants provides no basis for a person of ordinary skill to expect anything to the
12 contrary. A person of ordinary skill would have understood that omega 3-fatty acids, including
13 DHA and EPA, and fibrates cause an increase in LDL-C among very high TG patients, as
14 reflected in the prior art:

	LDL-C Effect	
	Borderline-High or High TG Patients	Very-High TG Patients
Fibrate ⁶⁰⁵⁰	-20%	+45%
Lovaza/Omacor ⁶⁰⁵¹	-6%	+45%

19 Accordingly, a person of ordinary skill would not have a reasonable expectation of
20 success in achieving a reduction in TG levels *with the claimed LDL-C effect* in patients with
21 very-high TG levels using EPA.

23 ⁶⁰⁵⁰ Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

24 ⁶⁰⁵¹ Chan 2002 I at 2381 (Table 3).

1 Defendants' position that a person of ordinary skill would have had a reasonable
2 expectation of success in administrating purified EPA to the requisite patient population to
3 achieve a lowering in TG levels *with the claimed LDL-C effect* is belied by the fact that
4 Defendants' provide no evidence that anyone thought to administer Epadel, which was available
5 for many years prior to the invention of the '372 patent, to patients with very-high TGs as a
6 treatment. Indeed, none of clinical studies cited by Defendants are directed to the use of purified
7 EPA in the very-high TG population.

8 Research into the pharmaceutical uses of EPA started as early as the 1970s. In 1990,
9 Mochida Pharmaceutical, began to market Epadel, a high purity EPA drug. There have been
10 countless studies conducted which administer Epadel and report the effects observed. Although
11 a few studies administer Epadel to a patient population which included a few patients with TG
12 levels > 500 mg/dL, Defendants fail to identify a single reference directed to the administration
13 of Epadel to patients with very-high TG levels. The fact is, a person of ordinary skill did not
14 expect Epadel, which consisted of mostly EPA, to have superior qualities over a drug such as
15 Lovaza/Omacor, which comprised a mixture of EPA and DHA, in patients with very-high
16 triglycerides.

17 Accordingly, a person of ordinary skill would not have a reasonable expectation of
18 success in achieving the claimed invention.

19 (d) Defendants Have Not Shown that Claims 5, 14 and
20 21 of the '372 Patent Would Have Been Obvious

21 Plaintiffs incorporate by reference the discussion related to the Independent Claims in
22 Section V.M.3. Because Defendants have not shown the obviousness of the Independent Claims
23 by clear and convincing evidence, they also have not adequately proven the obviousness of
24 Claims 5, 14 and 21.

1 Defendants contend, without providing any support, that it would be obvious to one of
2 skill in the art to administer a composition containing EPA, but containing no DHA, or not more
3 than 4% DHA, with a reasonable expectation of success in reducing Apo-B levels while avoiding
4 an increase in LDL-C associated with DHA. These contentions: 1) do not assert what the prior
5 art discloses to a person of ordinary skill in the art; 2) are irrelevant to an obvious analysis; 3)
6 fail to address whether the specific combination of claim elements were all present in the prior
7 art references that would have been combined by a person of ordinary skill in the art to produce
8 the claimed invention with a reasonable expectation of success; and 4) fail to establish *prima*
9 *facie* obviousness. Defendants do not offer an obvious analysis, but trivialize the claim element
10 to the point of reading the element out of the claim. Although convenient and expedient,
11 Defendants' approach does not conform with the Local Patent Rules of this District, the law of
12 claim construction, or the law of obviousness.

13 Defendants fail to show a specific combination of references that discloses each element
14 of the claimed invention. None of the cited references discloses administration of the claimed
15 EPA to very high TG patients. Defendants further fail to explain how the cited references can be
16 combined to teach the administration of the claimed EPA to very high TG patients.⁶⁰⁵²

17 Defendants selectively cite to an unspecified, isolated disclosure within a reference without
18 considering other disclosures or even the reference as a whole. Each reference, however, must
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22 ⁶⁰⁵² *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int'l Co. v.*
23 *Teleflex Inc.*, 550 U.S. 398, 418 (2007)) (“[A] patent composed of several elements is not proved obvious merely by
24 demonstrating that each of its elements was, independently, known in the prior art”).

1 be evaluated for all that it teaches.⁶⁰⁵³ Defendants’ unsupported cobbling of selective disclosures
2 represents hindsight reconstruction.⁶⁰⁵⁴

3 Defendants fail to show a motivation or reason to combine or modify the references
4 recited above. Defendants make a conclusory statement that the claimed methods of treatment
5 would have been obvious but such a naked assertion does not show why a person of ordinary
6 skill would have been motivated to combine the references to achieve the claimed invention.⁶⁰⁵⁵

7 Defendants fail to show a reasonable expectation that a person of ordinary skill would
8 have successfully achieved the claimed invention. In fact, Defendants do not even discuss
9 whether a person of ordinary skill would have expected that the combination to work for its
10 intended purpose.⁶⁰⁵⁶ As such, Defendants fail to demonstrate reasonable expectation of success
11 of the claimed invention.

12 Defendants cite to Kelley for the proposition that it was known that DHA
13 supplementation decreases VLDL diameter and increases the concentrations of small VLDL
14 particles.⁶⁰⁵⁷ Subsequently, they argue that because of the increase in small VLDL particles, a
15 person of skill in the art would expect that DHA therapy would increase Apo-B. That is

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17 ⁶⁰⁵³ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

18 ⁶⁰⁵⁴ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under
19 *KSR*, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention
20 without any explanation as to how or why the references would be combined to produce the claimed invention”).

21 ⁶⁰⁵⁵ *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the *KSR*
22 Court rejected a rigid application of the teaching, suggestion, or motivation (“TSM”) test in an obviousness inquiry,
23 the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill
24 in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness
determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

⁶⁰⁵⁶ *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable
result’ discussed in *KSR* refers not only to the expectation that prior art elements are capable of being physically
combined, but also that the combination would have worked for its intended purpose.”)

⁶⁰⁵⁷ Similarly, citing Olofsson and Bays, they assert that Apo-B is a component of VLDL, ignoring the relationship
of Apo-B to all atherogenic lipoproteins. See Section III.

1 incorrect. As discussed above, *see* Section III, Apo-B is associated with all atherogenic
2 lipoproteins, not simply small VLDL particles. Citing Leigh-Firbank, Defendants also assert that
3 DHA was known to increase LDL-C levels, which is incorrect for the reasons discussed above
4 and in Sections III and IV. Further, as discussed below, the Lovaza clinical trials showed that
5 DHA supplementation in very high TG patients *did not* increase Apo-B levels. A person of skill
6 in the art would have been aware of these data and accordingly would not have expected DHA
7 therapy to increase Apo-B levels in very high TG patients.

8 Defendants rely on Theobald, but *not* for the proposition that the asserted claim is
9 obvious. Instead, Defendants cite Theobald for the proposition that it was known that Apo-B is a
10 component of LDL-C. Defendants cite to no passage or page of Theobald in connection with
11 that argument and no support for their argument that Theobald makes such a disclosure.
12 Defendants appear to suggest a correlation between Apo-B and LDL-C but ignore that Apo-B is
13 present on all atherogenic lipoproteins.⁶⁰⁵⁸

14 Defendants then make the unsupported assertion that “one of ordinary skill in the art
15 would reasonably expect that a pure EPA composition would reduce Apo-B, as it is known to
16 reduce VLDL syntheses.” They are incorrect. Neither Defendants’ characterization of the
17 references identified with respect to these claims, nor the disclosures of those references teach
18 that EPA compositions would reduce Apo-B or render these claims obvious. Defendants’
19 assertion that EPA was known to reduce VLDL synthesis ignores that, as discussed above, *see*
20 Section III, DHA was also understood to reduce VLDL synthesis. Nor do defendants explain the
21 relevance of VLDL synthesis to their arguments with respect to these claims or Apo-B levels.
22
23

24 ⁶⁰⁵⁸ June 26, 2012 Bays Declaration; *see also* Section III.

As discussed above, *see* Section IV, Theobald discloses the administration of a triacylglycerol composition derived from *Cryptocodinium cohnii* to healthy subjects. While Defendants make an unexplained citation to Theobald regarding the proposition that Apo-B is a component of LDL-C, they fail to discuss the reference’s disclosures regarding the impact of administration of the triacylglycerol composition on Apo-B levels. In doing so, they fail to consider the reference for all that it teaches. Theobald discloses an *increase* in Apo-B following administration of the triacylglycerol composition of that reference.⁶⁰⁵⁹

TABLE 3
Serum lipoproteins before treatment and after 3 mo of docosahexaenoic acid (DHA) and placebo treatment in all subjects

	DHA		Placebo		Treatment effect ¹
	Before treatment	After treatment	Before treatment	After treatment	
Total cholesterol (mmol/L)	5.15 ± 0.145 ²	5.44 ± 0.174	5.08 ± 0.168	5.22 ± 0.155	0.22 (0.01, 0.42) ³
LDL cholesterol (mmol/L)	3.16 ± 0.129	3.48 ± 0.152	3.16 ± 0.146	3.25 ± 0.131	0.23 (0.08, 0.38) ⁴
HDL cholesterol (mmol/L) ⁵	1.47 ± 0.052	1.55 ± 0.064	1.46 ± 0.062	1.48 ± 0.056	0.07 (0.005, 0.14)
Triacylglycerol (mmol/L) ⁶	1.03 ± 0.094	1.01 ± 0.089	1.06 ± 0.106	1.19 ± 0.103	-0.18 (-0.37, 0.05)
Apolipoprotein B (g/L)	0.84 ± 0.027	0.87 ± 0.026	0.83 ± 0.028	0.84 ± 0.028	0.03 (0.002, 0.055)⁷
LDL cholesterol:apo B (mmol/g)	3.75 ± 0.376	3.96 ± 0.462	3.74 ± 0.521	3.84 ± 0.409	0.12 (0.004, 0.24) ³
Weight (kg) ⁸	70.1 ± 2.04	70.6 ± 2.06	70.5 ± 2.01	70.6 ± 2.01	0 (-0.85, 0.24)

¹ Mean difference between active treatment and placebo; 95% CI in parentheses.

² $\bar{x} \pm \text{SEM}$ (all such values); $n = 38$.

^{3,4,7} Paired t test: ³ $P = 0.04$, ⁴ $P = 0.004$, ⁷ $P = 0.03$.

⁵ HDL increased in subjects receiving DHA first. Significant treatment × order effect, $P = 0.005$.

⁶ $n = 37$; data were log transformed before analysis by paired t test.

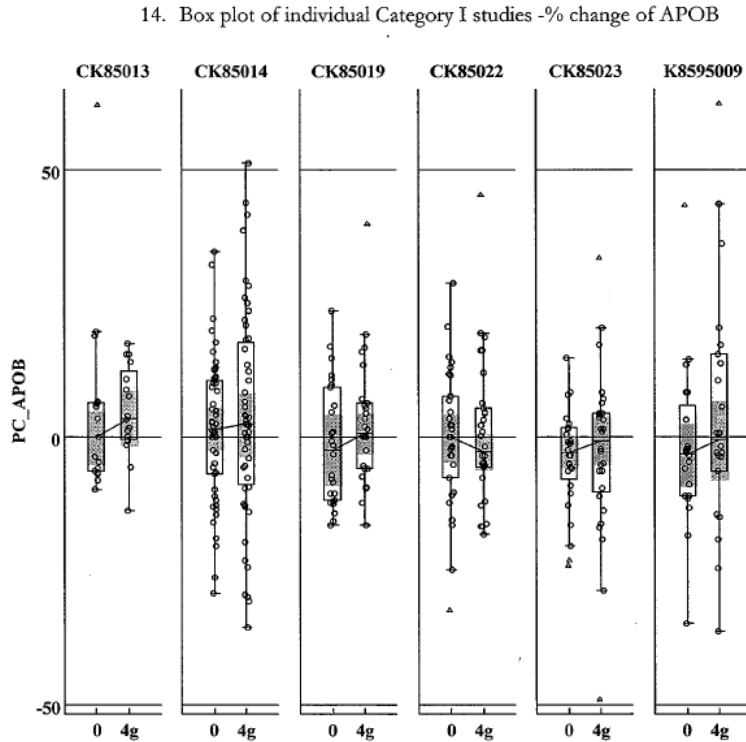
⁸ Weight increased over the entire study period. Significant order × time effect, $P = 0.001$.

As discussed above, *see* Section III, a person of skill in the art would not have distinguished between the lipid effects of EPA and DHA therapy. To the extent, then that a person of ordinary skill would have considered Theobald, they would not conclude from the reference that EPA therapy decreases Apo-B levels in very high TG patients.

A person of skill in the art would *not* have understood that EPA therapy in very high TG patients would yield a reduction in Apo-B levels. A person of ordinary skill would have looked to the Lovaza clinical trials—the only clinical trial to study the effects of omega-3 fatty acids on

⁶⁰⁵⁹ Theobald at 561, table 3.

1 Apo-B levels in patients with very high TG levels.⁶⁰⁶⁰ The Lovaza clinical trial, which was a
2 large study conducted on patients with very high TG levels, shows no difference between a
3 placebo-control group and the treatment group with respect to Apo-B levels.⁶⁰⁶¹



16 In each of these studies, including K8595009, where subjects had a median baseline TG
17 level of 818 mg/dL,⁶⁰⁶² there was no change in Apo-B between the control and treatment groups.
18 Likewise, pooling the data from the different studies of Lovaza in the EU and US also reflected
19 that treatment with Lovaza did not impact Apo-B compared to placebo.⁶⁰⁶³

20

21

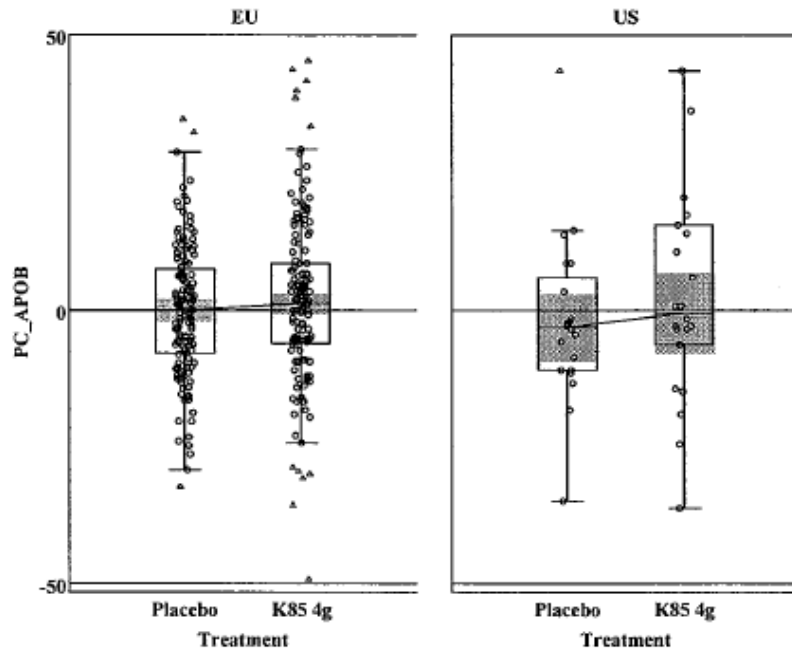
22 ⁶⁰⁶⁰ May 8, 2012 Bays Declaration.

23 ⁶⁰⁶¹ Lovaza Approval Package at Table 14.

24 ⁶⁰⁶² The parameters for each study reports can be located at page 4 of the Lovaza Approval Package.

⁶⁰⁶³ Lovaza Approval Package at Table 7.

7. Box plot of pooled Category I studies -% change of APOB



Indeed, none of the data reported in the Lovaza clinical trials reflects a decrease in Apo-B. In addition to the Lovaza studies, a person of ordinary skill would have understood that the literature reported, in a variety of clinical studies, that omega-3s do not impact Apo-B levels.⁶⁰⁶⁴ While Theobald does not even support Defendants' obviousness arguments, their selective citation of that reference represents impermissible hindsight bias. The examiner had before him a large number of prior art references reporting Apo-B effects and, even as defendants concede, agreed that the Apo-B effects reported by the claimed inventions were unexpected in light of

⁶⁰⁶⁴ See Grimsgaard, Okumura, Hayashi, Hayasaka 1995, and Aoki 1993.

1 those references, also reflecting a lack of motivation and no reasonable expectation of
2 success.⁶⁰⁶⁵

3 Further, a person of skill in the art would have understood Apo-B to be a surrogate for the
4 number of atherogenic lipoproteins (VLDL, IDL, LDL) present in the body.⁶⁰⁶⁶ The person of
5 skill in the art would also have recognized that, as TG levels in patients with very high TG levels
6 rose, an increasing amount of TGs in those patients were contained within chylomicrons. As
7 discussed above, *see* Section III, the processing of chylomicrons would not yield atherogenic
8 lipoproteins, but instead smaller, denser particles referred to as remnant.⁶⁰⁶⁷ Accordingly,
9 because very high TG patients had increasing levels of TGs stored in chylomicrons and because
10 chylomicron processing would not have been understood to yield changes in Apo-B, a person of
11 skill in the art would have believed that TG-lowering therapies directed to very high TG patients
12 would not significantly impact Apo-B.

13 Accordingly, a person of ordinary skill in the art would not have been motivated to
14 replace EPA with the composition of Lovaza, nor would the person of ordinary skill in the art
15 have been motivated to administer the EPA composition of the claimed invention to very high
16 TG patients. For the same reasons, a person of ordinary skill in the art would not have a
17 reasonable expectation of success in achieving the claimed invention.

18 (e) Defendants Have Not Shown that Claims 6, 15 and
19 22 of the '372 Patent Would Have Been Obvious

20 Plaintiffs incorporate by reference the discussion related to the Independent Claims in
21 Section V.M.3. Because Defendants have not shown the obviousness of the Independent Claims

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⁶⁰⁶⁵ Defendants' Contentions at 236.

23 ⁶⁰⁶⁶ ATP-III at 3170; Bays 2008 I at 395.

24 ⁶⁰⁶⁷ Kwiterovich in Kwiterovich at 4.

1 by clear and convincing evidence, they also have not adequately proven the obviousness of
2 Claims 6, 15 and 22.

3 Defendants contend that it would have been obvious to use the claimed composition to
4 reduce VLDL-C levels, and that the recited VLDL-C reduction represents therapeutic efficacy.
5 These contentions: 1) do not assert what the prior art discloses to a person of ordinary skill in
6 the art; 2) are irrelevant to an obvious analysis; 3) fail to address whether the specific
7 combination of claim elements were all present in the prior art references that would have been
8 combined by a person of ordinary skill in the art to produce the claimed invention with a
9 reasonable expectation of success; and 4) fail to establish *prima facie* obviousness. Defendants
10 do not offer an obvious analysis, but trivialize the claim element to the point of reading the
11 element out of the claim. Although convenient and expedient, Defendants' approach does not
12 conform with the Local Patent Rules of this District, the law of claim construction, or the law of
13 obviousness.

14 Defendants do not identify any combination of references. Because Defendants do not
15 identify any combination of references, they necessarily fail to offer any evidence that a person
16 of skill in the art would be motivated to combine those references in order to achieve the
17 invention of the claim as a whole. In fact, Defendants do not discuss at all whether a person of
18 ordinary skill would have been motivated to combine the elements.⁶⁰⁶⁸ As such, Defendants fail
19 to demonstrate that there was no motivation to combine the references to achieve the claimed
20 invention.

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22 ⁶⁰⁶⁸ *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the *KSR*
23 Court rejected a rigid application of the teaching, suggestion, or motivation (‘TSM’) test in an obviousness inquiry,
24 the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill
in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness
determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

1 Similarly, without the disclosure of a combination of references and a motivation/reason
2 to combine or modify the references, Defendants necessarily fail to offer any evidence that a
3 person of ordinary skill in the art would have had a reasonable expectation of success in
4 achieving the claimed invention. Defendants make conclusory statements without providing any
5 support. What is more, Defendants do not even discuss the reasonable expectation of reducing
6 VLDL-C levels. As such, Defendants fail to demonstrate reasonable expectation of success of
7 reducing VLDL-C levels using the claimed methods.

8 (f) Defendants Have Not Shown that Claims 7, 16 and
9 23 of the '372 Patent Would Have Been Obvious

10 Plaintiffs incorporate by reference the discussion related to the Independent Claims in
11 Section V.M.3. Because Defendants have not shown the obviousness of the Independent Claims
12 by clear and convincing evidence, they also have not adequately proven the obviousness of
13 Claims 7, 16 and 23.

14 Defendants do not identify any combination of references. Defendants contend, without
15 meaningful support, that a person of ordinary skill would have been able to determine the patient
16 population in need of the claimed methods of treatment, would seek to measure the fasting
17 baseline TG level of a patient, and would seek to treat those patients having very high
18 triglycerides. Defendants point to Lovaza and argue that it would have been obvious to one of
19 skill in the art to administer fish oil treatment to subjects with TG levels in the range of 500 to
20 1500 mg/dL. These contentions: 1) do not assert what the prior art discloses to a person of
21 ordinary skill in the art; 2) are irrelevant to an obvious analysis; 3) fail to address whether the
22 specific combination of claim elements were all present in the prior art references that would
23 have been combined by a person of ordinary skill in the art to produce the claimed invention
24 with a reasonable expectation of success; and 4) fail to establish *prima facie* obviousness.

1 Defendants do not offer an obvious analysis, but trivialize the claim element to the point of
2 reading the element out of the claim. Although convenient and expedient, Defendants' approach
3 does not conform with the Local Patent Rules of this District, the law of claim construction, or
4 the law of obviousness.

5 Defendants fail to show a specific combination of references that discloses each element
6 of the claimed invention. Because Defendants do not identify any combination of references,
7 they necessarily fail to offer any evidence that a person of skill in the art would be motivated to
8 combine those references in order to achieve the invention of the claim as a whole. Defendants
9 make conclusory statements without providing a reason that would have prompted a person of
10 ordinary skill to combine the elements.⁶⁰⁶⁹ Such a naked assertion does not show why a person
11 of ordinary skill would have been motivated to treat the recited patient population using the
12 claimed methods of treatment.⁶⁰⁷⁰

13 Similarly, without the disclosure of a combination of references and a motivation/reason
14 to combine or modify the references, Defendants necessarily fail to offer any evidence that a
15 person of ordinary skill in the art would have had a reasonable expectation of success in
16 achieving the claimed invention. Defendants do not even discuss whether a person of ordinary
17 skill would have expected that the combination to work for its intended purpose for treating the
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19 ⁶⁰⁶⁹ *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (“Rejections on obviousness grounds cannot be
20 sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational
21 underpinning to support the legal conclusion of obviousness.”) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir.
2006)) (internal quotation marks omitted)

22 ⁶⁰⁷⁰ *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the *KSR*
23 Court rejected a rigid application of the teaching, suggestion, or motivation (‘TSM’) test in an obviousness inquiry,
24 the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill
in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness
determination.”) (quoting *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

1 recited patient population.⁶⁰⁷¹ As such, Defendants fail to demonstrate reasonable expectation of
2 success of the claimed invention.

3 (g) Defendants Have Not Shown that Claims 8, 9, 24
4 and 25 of the '372 Patent Would Have Been
Obvious

5 Plaintiffs incorporate by reference the discussion related to the Independent Claims in
6 Section V.M.3. Because Defendants have not shown the obviousness of the Independent Claims
7 by clear and convincing evidence, they also have not adequately proven the obviousness of
8 Claims 8, 9, 24 and 25.

9 Defendants contend, without providing meaningful support, that the claim element was
10 well known in the art. These contentions: 1) do not assert what the prior art discloses to a
11 person of ordinary skill in the art; 2) are irrelevant to an obvious analysis; 3) fail to address
12 whether the specific combination of claim elements were all present in the prior art references
13 that would have been combined by a person of ordinary skill in the art to produce the claimed
14 invention with a reasonable expectation of success; and 4) fail to establish *prima facie*
15 obviousness. Defendants do not offer an obvious analysis, but trivialize the claim element to the
16 point of reading the element out of the claim. Although convenient and expedient, Defendants'
17 approach does not conform with the Local Patent Rules of this District, the law of claim
18 construction, or the law of obviousness.

19 Defendants fail to show a specific combination of references that discloses each element
20 of the claimed invention. Defendants make a conclusory statement that the claimed method of

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23 ⁶⁰⁷¹ *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable
24 result’ discussed in KSR refers not only to the expectation that prior art elements are capable of being physically
combined, but also that the combination would have worked for its intended purpose.”)

1 treatment was well known in the art, but such a naked assertion does not show why a person of
2 ordinary skill would have been motivated to combine the references to achieve the claimed
3 invention.⁶⁰⁷² Further Defendants cite to the “Lovaza product” without identifying the prior art
4 reference to which they refer. Such a reference is inadequate.

5 Defendants fail to show a reasonable expectation that a person of ordinary skill would
6 have successfully achieved the claimed invention. Defendants do not even discuss whether a
7 person of ordinary skill would have expected that the combination to work for its intended
8 purpose.⁶⁰⁷³ As such, Defendants fail to demonstrate reasonable expectation of success of the
9 claimed invention.

10 4. The '372 Patent is Not Invalid Under § 112

11 a) Defendants Have Not Demonstrated that the Claims of the '372 12 Patent Are Invalid for Indefiniteness

13 35 U.S.C. ¶ 112(b) requires that a patentee “particularly point[] out and distinctly claim[]
14 the subject matter which the applicant regards as his invention.”⁶⁰⁷⁴ Patent claims are valid in
15 light of an indefiniteness challenge if they “inform, with reasonable certainty, those skilled in the
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17 ⁶⁰⁷²*Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the *KSR*
18 Court rejected a rigid application of the teaching, suggestion, or motivation (‘TSM’) test in an obviousness inquiry,
19 the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill
20 in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness
21 determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

20 ⁶⁰⁷³ *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable
21 result’ discussed in *KSR* refers not only to the expectation that prior art elements are capable of being physically
22 combined, but also that the combination would have worked for its intended purpose.”)

22 ⁶⁰⁷⁴ Defendants were required to disclose the basis for their assertion of indefiniteness with respect to each term, and
23 they have not met that requirement. They simply make conclusory assertions regarding indefiniteness despite
24 bearing the burden of proof. Moreover, Defendants’ failure prevents Plaintiffs from responding to their assertions
other than by making conclusory assertions in return. Therefore, Defendants should be precluded from
supplementing their naked assertions with new basis in the course of the litigation.

1 art about the scope of the invention” in light of the specification and the prosecution history.⁶⁰⁷⁵

2 The Supreme Court has recognized that “absolute precision is unattainable” in claim language
3 and “the certainty which the law requires in patents is not greater than is reasonable.”⁶⁰⁷⁶

4 Defendants allege that a number of terms containing the phrases “about” and
5 “substantially” are indefinite. Defendants do not provide any reason why these terms are
6 indefinite other than that they contain the phrases “about” and “substantially.” But, of course,
7 these terms are routinely used in patent claims, and are not *per se* indefinite.⁶⁰⁷⁷ In particular,
8 courts have held repeatedly that claims that contain the words “about” and “substantially” are not
9 indefinite.⁶⁰⁷⁸ Here, a person of ordinary skill would understand with reasonable certainty what
10 is claimed when the claims are read in light of the specification and prosecution history.⁶⁰⁷⁹

11 Therefore, the terms that contain the words “about” and “substantially” are not invalid for being
12 indefinite.

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14 ⁶⁰⁷⁵ *Nautilus, Inc. v. Biosig Instruments, Inc.*, 134 S. Ct. 2120, 2124 (2014).

15 ⁶⁰⁷⁶ *Id.* at 2129.

16 ⁶⁰⁷⁷ *Interval Licensing LLC v. AOL, Inc.*, 766 F.3d 1364, 1370 (Fed. Cir. 2014) (“Claim language employing terms
17 of degree has long been found definite where it provided enough certainty to one of skill in the art when read in the
18 context of the invention.”); *see also BJ Servs. Co. v. Halliburton Energy Servs., Inc.*, 338 F.3d 1368, 1372 (Fed. Cir.
19 2003) (“The question becomes whether one of ordinary skill in the art would understand what is claimed when the
20 claim is read in light of the specification.”) (discussing the term “about”); *Verve, LLC v. Crane Cams, Inc.*, 311 F.3d
21 1116, 1120 (Fed. Cir. 2002) (“It is well established that when the term ‘substantially’ serves reasonably to describe
22 the subject matter so that its scope would be understood by persons in the field of the invention, and to distinguish
23 the claimed subject matter from the prior art, it is not indefinite.”).

20 ⁶⁰⁷⁸ *See, e.g., Deere & Co. v. Bush Hog, LLC*, 703 F.3d 1349, 1359 (Fed. Cir. 2012) (rejecting contention that claim
21 term “substantially planar” is indefinite); *Enzo Biochem, Inc. v. Applera Corp.*, 599 F.3d 1325, 1335 (Fed. Cir.
22 2010) (holding that the claim phrase “not interfering substantially” was not indefinite even though the construction
23 “define[d] the term without reference to a precise numerical measurement”); *BJ Services Co. v. Halliburton Energy
24 Services, Inc.*, 338 F.3d 1368, 1372–73 (Fed. Cir. 2003) (affirming jury’s verdict that claims reciting a concentration
as “about 0.06” were not invalid for being indefinite); *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540,
1557 (Fed. Cir. 1983) (ruling that the claim term “stretching ... at a rate exceeding about 10% per second” is not
indefinite).

23 ⁶⁰⁷⁹ *See generally* the ’372 patent and its prosecution history.

1 Defendants further allege that the terms “a pharmaceutical composition comprising ...
2 not more than about 4% docosahexaenoic acid, by weight of all fatty acid” and “about 90% ethyl
3 eicosapentaenoate and not more than about 4% docosahexaenoic acid or its esters, by weight of
4 all fatty acids” are indefinite. They contend that, because there is no indication of how much of
5 the pharmaceutical composition is composed of fatty acids, by extension it is indefinite how
6 much of each fatty acid is present in the composition. This is incorrect. A claim can use a ratio
7 to define amounts of components in a product, using terms such as “percent by weight.”⁶⁰⁸⁰ In
8 light of the specification and prosecution history, a person of ordinary skill would understand
9 with reasonable certainty the range of relative quantities of EPA, DHA and/or other fatty acids in
10 the recited pharmaceutical composition in relation to all fatty acids present.⁶⁰⁸¹ Therefore, these
11 terms are not indefinite and do not render the claims indefinite.

12 Defendants also allege that it is impossible to ascertain the metes and bounds of
13 “identifying a group of subjects having a median triglyceride level of at least 500 mg/dl and
14 orally administering daily to at least one subject in the group.” A person of ordinary skill,
15 however, would understand the metes and bounds of the term in light of the specification and the
16 prosecution history.⁶⁰⁸² Moreover, the method of identifying the recited group and orally
17 administering daily to at least one subject in the group would have been known to a person of
18 ordinary skill at the time of the invention. Therefore, the term does not render the claims
19 indefinite.

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21 ⁶⁰⁸⁰ *T.F.H. Publications, Inc. v. Doskocil Mfg. Co.*, No. CIV.A. 08-4805 FLW, 2012 WL 715628, at *5–6 (D.N.J.
22 Mar. 5, 2012) (construing “by weight” to mean the weight of a first component was in a ratio to the weight of a
23 second component); *Allergan, Inc. v. Sandoz Inc.*, No. 2:09-CV-182, 2011 WL 1599049, at *10 (E.D. Tex. Apr. 27,
24 2011) (construing percent by weight to mean “ratio of the weight of the ingredient in question divided by the total
volume of the solution, with this ratio expressed as a percentage”).

⁶⁰⁸¹ See generally the '372 patent and its prosecution history.

⁶⁰⁸² See generally the '372 patent and its prosecution history.

1 Finally, Defendants contend that the asserted claims improperly mix methods and
2 formulations because Plaintiffs' assertion of contributory infringement apparently suggests that
3 the scope of the claims includes formulations. This is a mistaken interpretation. Indefiniteness
4 analysis is based on what the claim language informs a person of ordinary skill in the art in light
5 of the specification and the prosecution history. Defendants do not identify any actual claim
6 language that mixes methods and formulations. Moreover, contributory infringement may be
7 asserted and proven when a party sells "a material or apparatus for use in *practicing a patented*
8 *process . . . knowing the same to be especially made or especially adapted for use in an*
9 *infringement of such patent.*"⁶⁰⁸³ Plaintiffs assert that Defendants' ANDA products will be used
10 in practicing the claimed methods. Plaintiffs do not assert that the pharmaceutical compound
11 itself directly infringes. Therefore, Defendants' interpretations of Plaintiffs' assertions are
12 mistaken and the '372 patent claims are not indefinite for improperly mixing methods and
13 formulations.

14 b) Defendants Have Not Demonstrated that the Claims of the '372
15 Patent Are Invalid for Insufficient Written Description

16 The first paragraph of 35 U.S.C. § 112 requires that a patent specification "contain a
17 written description of the invention." This requires that the specification "reasonably convey"
18 that the applicant "invented" or "had possession" of the claimed subject matter when the
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24 ⁶⁰⁸³ 35 U.S.C. § 271(c) (emphasis added).

1 application was filed.⁶⁰⁸⁴ Support need not be literal⁶⁰⁸⁵—it may be implicit⁶⁰⁸⁶ or inherent⁶⁰⁸⁷ in
2 the disclosure. In addition, it is unnecessary to include information that is already known or
3 available to persons of ordinary skill.⁶⁰⁸⁸

4 Defendants make three arguments regarding the written description requirement. First,
5 Defendants contend that elements reciting the baseline TG levels of the asserted claims lack
6 written description. This is incorrect. The specification of asserted patents literally discloses the
7 claimed invention.⁶⁰⁸⁹ Defendants do not contend that the patient population of the asserted
8 claims is not literally described by the specification. In fact, the specification at the time of filing
9 described these limitations. Therefore, Defendants have failed to explain whether and how an
10 aspect of the claimed invention has not been described with sufficient particularity such that one
11 skilled in the art would recognize that the applicant had possession of the claimed invention.

12 Second, Defendants contend that “a person of skill in the art would not understand that
13 the inventor was in possession of a method incorporating [] specific dosages and quantities.”
14 Defendants’ assertion is incorrect. The specification of the asserted patents literally discloses the
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17 ⁶⁰⁸⁴ *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010).

18 ⁶⁰⁸⁵ *Id.* at 1352; *Cordis Corp. v. Medtronic AVE, Inc.*, 339 F.3d 1352, 1365 (Fed. Cir. 2003); *In re Wright*, 866 F.2d
422, 425 (Fed. Cir. 1989); *In re Smith*, 481 F.2d 910, 914 (C.C.P.A. 1973).

19 ⁶⁰⁸⁶ *All Dental Prodx, LLC v. Advantage Dental Prods. Inc.*, 309 F.3d 774, 779 (Fed. Cir. 2002); *In re Wright*, 866
F.2d at 424–25.

20 ⁶⁰⁸⁷ *In re Gay*, 309 F.2d 769, 771 (C.C.P.A. 1962).

21 ⁶⁰⁸⁸ *Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1367–68 (Fed. Cir. 2006); *Capon v. Eshhar*, 418 F.3d 1349,
1357 (Fed. Cir. 2005); *In re Gay*, 309 F.2d at 774.

22 ⁶⁰⁸⁹ *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (“[T]he test requires an objective
23 inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art.”);
Snitzer v. Etzel, 465 F.2d 899, 902 (C.C.P.A. 1972) (“[T]he literal description of a species provides the requisite
24 legal foundation for claiming that species.”).

1 dosages and quantities of the claimed methods.⁶⁰⁹⁰ Moreover, the dosages and quantities of the
2 method appear in the claims, as originally filed. Thus, there is a strong presumption that the
3 claimed invention is adequately described.⁶⁰⁹¹ Defendants do not and cannot rebut this
4 presumption. For example, the dosage of the composition was originally claimed as “about 1 g
5 to about 4g.”⁶⁰⁹² The asserted claims recite “4 g.” Defendants do not contend that dosages and
6 quantities of the asserted claims are not literally described by the specification and in the original
7 claims. In fact, the specification and the provisional patent application claims, at the time of
8 filing, described these limitations. Therefore, Defendants have failed to explain whether and
9 how an aspect of the claimed invention has not been described with sufficient particularity such
10 that one skilled in the art would recognize that the applicant had possession of the claimed
11 invention.

12 Third, Defendants contend that “a person of skill in the art would not understand that the
13 inventor was in possession of a method comprising a method of identifying a group.” Although
14 this allegation does not appear to implicate written description, the specification describes the
15 recited group. Moreover, a person of ordinary skill would have known the method identifying
16 such a patient group and administering a composition to a member. Therefore, a person of
17 ordinary skill would have understood that the inventor was in possession of a method comprising
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20 ⁶⁰⁹⁰ *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (“[T]he test requires an objective
21 inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art.”);
Snitzer v. Etzel, 465 F.2d 899, 902 (C.C.P.A. 1972) (“[T]he literal description of a species provides the requisite
22 legal foundation for claiming that species.”).

23 ⁶⁰⁹¹ *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976) (“we are of the opinion that the PTO has the
24 initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure
a description of the invention defined by the claims”).

⁶⁰⁹² See U.S. Provisional Application No. 61/151,291.

1 administration of a composition with the recited properties, based on a specific identification of
2 the recited group.

3 In its 2010 *en banc* decision in *Ariad Pharmaceuticals, Inc. v. Eli Lilly Co.*,⁶⁰⁹³ the court
4 elaborated that “possession” means possession as evidenced by disclosure. In this case, the
5 specification of asserted patents literally disclose the claimed invention in the specification and
6 the claims as originally filed. Thus, an examination of the four corners of the specification from
7 the perspective of a person of ordinary skill in the art demonstrates that the inventors of the
8 asserted patents were in possession of the claimed invention.

9 Defendants conclude by alleging that the specification does not describe anything more
10 than what is obvious, and thus does not provide adequate support for any nonobvious claim.
11 That is incorrect and irrelevant. Nonobviousness does not have to be supported solely by the
12 specification; nonobviousness can be supported by post-filing date evidence for example.⁶⁰⁹⁴
13 Written description requires only that the specification reasonably conveys that the applicant had
14 possession of the claimed subject matter when the application was filed. Therefore, whether the
15 claims are obvious has no bearing on the adequacy of written description.

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⁶⁰⁹³ *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1343-48 (Fed. Cir. 2010).

20 ⁶⁰⁹⁴ *See Sanofi–Aventis Deutschland GmbH v. Glenmark Pharm., Inc.*, 748 F.3d 1354, 1360 (Fed. Cir. 2014)
21 (“Glenmark also argues that later-discovered benefits cannot be considered in an obviousness analysis.... That is
22 incorrect; patentability may consider all of the characteristics possessed by the claimed invention, whenever those
23 characteristics become manifest.”); *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291,
24 1307 (Fed. Cir. 2011) (“[E]vidence of unexpected results may be [considered] ... even if that evidence was obtained
after the patent's filing or issue date.”); *Knoll Pharm. Co. v. Teva Pharm. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir.
2004) (“Evidence developed after the patent grant is not excluded from consideration, for understanding of the full
range of an invention is not always achieved at the time of filing the patent application.”).

1 c) Defendants Have Not Demonstrated that the Claims of the ‘372
2 Patent Are Invalid for Lack of Enablement

3 The first paragraph of 35 U.S.C. § 112 requires that the specification “enable any person
4 skilled in the art . . . to make and use [the claimed invention].” A claim is not enabled if it would
5 require undue experimentation for a person of ordinary skill to make or use the invention.
6 Factors that may be considered include the quantity of experimentation necessary, the amount of
7 direction or guidance presented, the presence or absence of working examples, the nature of the
8 invention, the state of the prior art, the relative skill of those in the art, the predictability or
9 unpredictability of the art, and the breadth of the claims.⁶⁰⁹⁵ The enablement requirement is
10 separate and distinct from the written description requirement,⁶⁰⁹⁶ and as such a claim does not
11 require descriptive support in the disclosure as originally filed for it to be enabled.⁶⁰⁹⁷

12 Defendants make two specific arguments regarding the enablement requirement. First,
13 Defendants contend that “[i]t would take undue experimentation to obtain the actual amounts of
14 the composition found in the ultimate claims.” This is incorrect. As Defendants admit, the
15 claims disclose amounts of the composition to be administered. Therefore, a person of ordinary
16 skill would be able to determine the amounts of the components in the pharmaceutical
17 composition without any experimentation, much less undue experimentation.

18 Second, Defendants contend that it would take undue experimentation to obtain the
19 claimed required results listed in the full scope of the patent claims, including the claimed lipid
20 effects. This is incorrect. The asserted claims require no experimentation to practice the claimed
21 method and certainly not undue experimentation. Administration of a recited amount of a recited

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⁶⁰⁹⁵ See, e.g., *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

23 ⁶⁰⁹⁶ *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991)

24 ⁶⁰⁹⁷ MPEP § 2164.

1 composition, for a recited duration, to a specific, recited patient population produces the recited
2 results. No additional experimentation is required, and Defendants do not explain their
3 allegation that undue experimentation would be required. Defendants also do not contend that
4 following the claimed method (each recited element) does not produce the recited results. The
5 clinical studies included in the VASCEPA® label and submitted to the USPTO clearly
6 demonstrate that administration of EPA of the recited composition, when administered to
7 patients with very high TG levels for at least 12 weeks, as specified, produces the recited
8 results.⁶⁰⁹⁸ Therefore, the claims are not invalid for lack of enablement.

9 Defendants conclude by alleging that the specification does not enable anything more
10 than what is obvious over the prior art or was known to a person of skill in the art. First,
11 Defendants do not cite any case or present a legal theory to support this assertion. As such, they
12 do not allow Plaintiffs to adequately respond to the assertion. Therefore, Defendants should be
13 precluded in the future from raising any new legal theory to support this assertion. Moreover,
14 while the '372 patent's specification enables a person of ordinary skill to obtain the claimed
15 limitations without undue experiment, the claimed limitations would not have been obvious to a
16 person of ordinary skill, as discussed in Section V.M.3. Furthermore, Plaintiffs have initiated
17 human clinical trials and submitted the trial results to the USPTO to substantiate the utility of its
18 claimed methods.^{6099, 6100} Therefore, a person of ordinary skill would have concluded that the
19 claims possessed credible therapeutic utility, and the full scope of the claims was enabled.

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⁶⁰⁹⁸ See VASCEPA Prescribing Information at Table 2.

22 ⁶⁰⁹⁹ *In re Brana*, 51 F.3d 1560, 1567 n.19 (Fed. Cir. 1995) (Post-filing evidence “can be used to substantiate any
23 doubts as to the asserted utility.”); MPEP § 2107.03 (“[A]s a general rule, if an applicant has initiated human clinical
24 trials for a therapeutic product or process, Office personnel should presume that the applicant has established that
the subject matter of that trial is reasonably predictive of having the asserted therapeutic utility.”).

⁶¹⁰⁰ See May 16, 2011 Bays Declaration at Appendix B.

1 N. The '594 Patent

2 1. The '594 Patent Claims Eligible Subject Matter Under § 101

3 Defendants' allegation that the asserted claims of the '594 patent relate to ineligible
4 subject matter under Section 101 is without merit. Defendants do not establish a *prima facie*
5 case under Section 101 or provide a legal or factual basis to support their allegations.

6 As an initial matter, Defendants' disclosure is also insufficient under the Nevada Local
7 Patent Rules as the grounds for any allegation of invalidity under Section 101 must be
8 provided.⁶¹⁰¹ The bare assertion of invalidity under Section 101 without providing the grounds
9 for such an allegation and examining the elements of the asserted claims of the '594 patent does
10 not meet this requirement and thwarts the purpose of the Rules.⁶¹⁰²

11 The inquiry under Section 101 involves a two-step test: first, a court must determine
12 whether the claim at issue is directed to a patent-ineligible concept: a law of nature, physical
13 phenomenon, or abstract idea.⁶¹⁰³ Second, even if the claim is directed to one of these concepts,
14 it still may be patent eligible and the court must determine what else is part of the claim.⁶¹⁰⁴

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17 ⁶¹⁰¹ See Nevada Local Patent Rule 1.8(e) (“[E]ach party opposing a claim of patent infringement, shall serve on all
18 other parties Non-Infringement, Invalidity, and Unenforceability Contentions that must include . . . A detailed
statement of any grounds of invalidity based on 35 U.S.C. § 101.”).

19 ⁶¹⁰² Nor does the preceding paragraph, which provides only a purported summary of the claims of the '594 patent, or
20 subsequent paragraph, which makes what appears to be an argument entirely unrelated to Section 101, provide the
21 grounds for Defendants' allegation of invalidity under 35 U.S.C. § 101. See, e.g., *Silver State Intellectual Techs.,
Inc. v. Garmin Int'l, Inc.*, 32 F. Supp. 3d 1155, 1161–62 (D. Nev. 2014) (“The District of Nevada’s Local Patent
Rules, like the local patent rules for the Northern District of California, are designed to require the parties to provide
early notice of their infringement and invalidity contentions, and to proceed with diligence in amending those
contentions when new information comes to light in the course of discovery”) (internal quotation marks omitted).

22 ⁶¹⁰³ *Alice Corp. Pty. v. CLS Bank Int'l*, 134 S. Ct. 2347, 2355 (2014) (“First, we determine whether the claims at
23 issue are directed to one of those patent-ineligible concepts.”).

24 ⁶¹⁰⁴ *Id.* (quoting *Mayo*, 132 S. Ct. at 1294) (“If so, we then ask, ‘[w]hat else is there in the claims before us?’”).

1 The sole Section 101 case identified by Defendants, *Mayo Collaborative Services v.*
2 *Prometheus Laboratories, Inc.*, 132 S. Ct. 1289 (2012), is inapplicable to the asserted claims of
3 the '594 patent. In *Mayo*, the claims were directed to “well-understood, routine, [and]
4 conventional” steps, and the only novel element related to administering the proper dosage based
5 on a natural law observation.⁶¹⁰⁵ However, the claims merely recited this natural law without
6 reciting any novel application of it.⁶¹⁰⁶ The Court found that providing protection to such
7 claims would result in pre-empting “a broad range of potential uses” and excluding others from
8 using “the basic tools of scientific and technical work.”⁶¹⁰⁷ A method of treatment claim,
9 specifying the subjects, dosage levels, composition, and time course does not raise the concerns
10 of *Mayo* and instead is akin to the typical claims which *Mayo* acknowledges are entitled to patent
11 protection.⁶¹⁰⁸

12 Defendants suggest that the recited EPA composition of each asserted claim is a naturally
13 occurring substance. It is not. Even references contained within Defendants’ own contentions
14 make clear that EPA of the requisite purity and characteristics is not found in nature.⁶¹⁰⁹ As
15 expressed by the patents cited in Defendants’ contentions and well-established precedent, for
16 decades it has been accepted that compositions isolated from nature or purified beyond their

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18 ⁶¹⁰⁵ *Mayo*, 132 S. Ct. at 1294.

19 ⁶¹⁰⁶ *Id.* at 1301.

20 ⁶¹⁰⁷ *Id.*

21 ⁶¹⁰⁸ *Id.* at 1302 (contrasting the patent-ineligible claims of that case to “a typical patent on a new drug or a new way
22 of using an existing drug); *see also Diamond v. Diehr*, 450 U.S. 175, 177, 191-193 (1981) (upholding patentability
23 for “a process for curing synthetic rubber which includes in several of its steps the use of a mathematical formula
24 and a programmed digital computer” under Section 101); *Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc.*, 827 F.3d
1042, 1048-49 (Fed. Cir. 2016) (finding claims patent eligible because by holding otherwise, a host of other patent
eligible claims, such as method of treatment claims, would also be necessarily ineligible).

⁶¹⁰⁹ *See, e.g.*, U.S. Patent No. 5,215,630, “Method of Purifying Eicosapentaenoic Acid or the Ester Derivative
Thereof by Fractional Distillation” (cited in Defendants’ Joint Invalidity Contentions, *e.g.*, at 26–27).

1 natural state are patent-eligible.⁶¹¹⁰ Moreover, Defendants’ assertions are immaterial to a Section
2 101 defense because method of treatment claims like the ones asserted in this case are patent
3 eligible even if they are directed to administration of a naturally occurring substance.⁶¹¹¹

4 To the extent Defendants are arguing that a law of nature both underlies the claims and
5 renders them ineligible, that argument is unsupported and incorrect. Defendants allege that “the
6 claimed effects are the natural result of ingesting a naturally-occurring substance.”⁶¹¹² Since the
7 composition that is the subject of the claims is not naturally occurring, Defendants appear to
8 suggest that all method of treatment claims involve a law of nature. That is not what *Mayo* states
9 or even suggests, and indeed the Federal Circuit has refused to adopt Defendants’ overbroad
10 characterization of laws of nature.⁶¹¹³ To say that the claims of the ’594 patent claim a law of
11 nature is to suggest that all patents claim such laws and engage in an infinitely regressive mode
12 of analysis that the Supreme Court did not adopt in which “all inventions can be reduced to
13 underlying principles of nature” that would “make all inventions unpatentable.”⁶¹¹⁴ Indeed, even
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18 ⁶¹¹⁰ See, e.g., *In re Bergy*, 596 F.2d 952; *In re Kratz*, 592 F.2d 1169 (CCPA 1979); *In re Bergstrom*, 427 F.2d 1394
(CCPA 1970); *Parke-Davis & Co. v. H.K. Mulford Co.*, 189 F.95 (S.D.N.Y. 1911).

19 ⁶¹¹¹ *Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc.*, 827 F.3d 1042, 1048-49 (Fed. Cir. 2016).

20 ⁶¹¹² See Defendants’ Joint Invalidity Contentions at 786.

21 ⁶¹¹³ See *CellzDirect*, 827 F.3d at 1048-49 (“The [asserted] claims are like thousands of others that recite processes
22 to achieve a desired outcome That one way of describing the process is to describe the natural ability of the
subject matter to *undergo* the process does not make the claim ‘directed to’ that natural ability. If that were so, we
would find patent-ineligible methods of . . . treating cancer with chemotherapy (as directed to cancer cells’ inability
to survive chemotherapy), or treating headaches with aspirin (as directed to the human body’s natural response to
aspirin).”).

23 ⁶¹¹⁴ See *Mayo*, 132 S. Ct. at 1034 (quoting *Diamond v. Diehr*, 450 U.S. 175, 188 (1981)).
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1 those concerned about the implications of *Mayo* on future patents were focused on diagnostic
2 claims not treatment claims of the type that *Mayo* stated were typical and patentable.⁶¹¹⁵

3 Even if there is some underlying law of nature in the asserted claims, the subject matter
4 of the '594 patent remains eligible for protection under Section 101. As articulated by *Mayo* and
5 *Diehr*, patents claiming a law of nature, such as a mathematical equation, are entitled to
6 protection where claims “did not ‘seek to pre-empt the use of [the] equation,’ but sought ‘only to
7 foreclose from others the use of that equation in conjunction with all of the other steps in their
8 claimed process.’”⁶¹¹⁶ As discussed above, the asserted claims of the '594 patent contain a
9 novel, unconventional, and specific method of treatment comprising a particularized application
10 of a nonnaturally occurring substance and does not preempt the use of a law of nature.⁶¹¹⁷

11 Defendants also argue that any argument by Amarin in response to Defendants’ § 112
12 arguments are further evidence of invalidity under § 101. This argument is without merit. The
13 claims are enabled and written description is satisfied for the reasons discussed below. In
14 addition, as discussed above, the asserted claims are not merely a naturally-occurring
15 phenomena, and thus satisfy the requirements of § 101.

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20 ⁶¹¹⁵ See *Mayo*, 132 S. Ct. at 1034 (“Prometheus, supported by several *amici*, argues that a principle of law denying
21 patent coverage here will interfere significantly with the ability of medical researchers to make valuable discoveries,
particularly in the area of diagnostic research.”).

22 ⁶¹¹⁶ See *Mayo*, 132 S. Ct. at 1299 (quoting *Diehr*, 450 U.S. at 187).

23 ⁶¹¹⁷ See, e.g., *Tannas Electronics v. Luxell Technologies, Inc.*, 2012 WL 3800822, at *4 (C.D. Cal. July 24, 2012)
24 (rejecting a challenge to the patentability of a claim under Section 101 where the alleged natural phenomenon was
“just one step in the whole process” claimed by the invention).

1 **2. The Asserted Claims of the ‘594 Patent Are Not Anticipated by WO**
2 **‘118**

3 To anticipate, a single prior art reference must sufficiently describe a claimed
4 invention so that the public is in “possession” of that invention.⁶¹¹⁸ Therefore, to anticipate, a
5 reference must set forth every element of the claim, either expressly or inherently, in as complete
6 detail as is contained in the claim.⁶¹¹⁹ The claim elements must also be “arranged” in the prior
7 art reference, just as they are in the claim,⁶¹²⁰ rather than as “multiple, distinct teachings that the
8 artisan might somehow combine to achieve the claimed invention.”⁶¹²¹ In addition, public
9 “possession” requires that the prior art enable a person of ordinary skill to make and use the
10 invention without undue experimentation.⁶¹²² Factors that may be included in this analysis
11 include the quantity of experimentation necessary, the amount of direction or guidance
12 presented, the presence or absence of working examples, the nature of the invention, the state of
13 the prior art, the relative skill of those in the art, the predictability or unpredictability of the art,
14 and the breadth of the claims.⁶¹²³ This inquiry is objective, and thus evidence of undue
15 experimentation need not be prior art.⁶¹²⁴

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⁶¹¹⁸ *Akzo N.V. v. U.S. Int’l Trade Com’n*, 808 F.2d 1471, 1479 (Fed. Cir. 1986).

17 ⁶¹¹⁹ *Id.*; *In re Bond*, 910 F.2d 831, 832 (Fed. Cir. 1990); *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed.
18 Cir. 1989).

⁶¹²⁰ *Bond*, 910 F.2d at 833; *Akzo*, 808 F.2d at 1479.

19 ⁶¹²¹ *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369–71 (Fed. Cir. 2008); *In re Arkley*, 455 F.2d 586, 587
(C.C.P.A. 1972); *In re Ruschig*, 343 F.2d 965, 974 (C.C.P.A. 1965).

20 ⁶¹²² *Akzo*, 808 F.2d at 1479; *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1085 (Fed. Cir. 2008); *Forest Labs.,*
21 *Inc. v. Ivax Pharms., Inc.*, 501 F.3d 1263, 1268–69 (Fed. Cir. 2007).

⁶¹²³ *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

22 ⁶¹²⁴ *Plant Genetic Sys., N.V. v. DeKalb Genetics Corp.*, 315 F.3d 1335, 1344 (Fed. Cir. 2003); *In re Wright*, 999
23 F.2d 1557, 1562 (Fed. Cir. 1993); *Liquid Dynamics Corp. v. Vaughan Co., Inc.*, 449 F.3d 1209, 1224–25 (Fed. Cir.
24 2006); *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1336 (Fed. Cir. 2003); *Gould v. Quigg*, 822
F.2d 1074, 1078 (Fed. Cir. 1987).

1 Defendants assert that Claims 1-7 and 10-26 of the '594 Patent are anticipated by the WO
2 '118 reference.⁶¹²⁵

3 A element-by-element analysis, identifying each element of each asserted claim that is
4 absent from WO '118, is provided below. The contentions below are incorporated by reference
5 into Exhibit P, and vice-versa. WO '118 does not anticipate the claims of the '594 patent
6 because it does not describe, properly arrange, or enable the '594 patent claims.

7 a) WO '118 Does Not Teach Every Element of the Claims of the
8 '594 Patent

9 (1) WO '118 Does Not Describe the Claimed Lipid Effects

10 It is well established that, for a prior art reference to anticipate, “every element of the
11 claimed invention must be identically shown in a single reference.”⁶¹²⁶ Moreover, the elements
12 of the claimed invention must have “strict identity” with the elements of the reference; “minimal
13 and obvious” differences are sufficient to prevent anticipation.⁶¹²⁷ Here, WO '118 entirely fails
14 to disclose the following elements of Claims 1, 10 and 17 of the '594 Patent: *the at least one*
15 *subject exhibits a reduction in triglycerides of at least about 15% without an increase of LDL-C*
16 *of more than 5%.* Defendants appear to concede that WO '118 does not expressly teach these
17 elements, as they fail to set forth any basis for concluding that WO '118 teaches this element.⁶¹²⁸
18 Indeed, Defendants could not set forth any basis for concluding that WO '118 teaches this
19 element because WO '118 does not.

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21 ⁶¹²⁵ References to “WO '118” are to the English translation that was filed with the European application. Plaintiffs
reserve their right to obtain a certified translation of WO '118.

22 ⁶¹²⁶ *Diversitech Corp. v. Century Steps, Inc.*, 850 F.2d 675, 677 (Fed. Cir. 1988); *see also Hybritech Inc. v.*
Monoclonal Antibodies, Inc., 802 F.2d 1367 (Fed. Cir. 1986).

23 ⁶¹²⁷ *Trintech Industries, Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1296 (Fed. Cir. 2002).

24 ⁶¹²⁸ Defendants' Invalidation Contentions at 202-204.

1 Instead, Defendants argue that these elements express the intended result of a method that
2 is positively recited, and therefore is inherently anticipated. However, for the reasons set forth
3 below, WO ‘118 fails to disclose each element of the independent claims of the ‘594 Patent,
4 either expressly or inherently. Therefore, WO ‘118 cannot anticipate the claimed method.
5 Defendants also argue that these elements represent inherent, natural properties of EPA, and are
6 entitled to no patentable weight. This conclusion is incorrect and inconsistent with the law of
7 anticipation and claim construction. Further, while Defendants argue that the inherent properties
8 are exemplified in the prior art, they fail to identify even a single prior art reference that makes
9 such a disclosure. Defendants cannot point to a single, specific prior art reference because the
10 claimed pharmaceutical composition has never been administered in the manner claimed to the
11 claimed patient population. Also, these elements are positively recited in the body of the claim
12 and therefore cannot be construed as a non-limiting preamble and must be given patentable
13 weight.

14 Further, Defendants entirely fail to prove that inherently discloses the claimed lipid
15 effects. A prior art reference that “only ‘probably’ or ‘possibly’ meets the claims cannot
16 inherently anticipate as a matter of law.”⁶¹²⁹ “[A]nticipation by inherent disclosure is appropriate
17 only when the reference discloses prior art that must *necessarily* include the unstated
18 limitation.”⁶¹³⁰ “It is not sufficient if a material element or limitation is ‘merely probably or
19 possibly present’ in the prior art.”⁶¹³¹ WO ‘118 fails to provide any data related to the lipid
20 effects of the disclosed invention on patients described in the publication. Therefore, Defendants
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⁶¹²⁹ *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

23 ⁶¹³⁰ *Transclean Corp. v. Bridgewood Servs., Inc.*, 290 F.3d 1364, 1373 (Fed. Cir. 2002) (emphasis in original).

24 ⁶¹³¹ *In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1378 (Fed. Cir. 2007).

1 fail to prove by clear and convincing evidence that the composition disclosed by WO '118 meets
2 the elements of the independent claims every time it is administered.

3 Defendants fail to demonstrate that administration of the claimed EPA compositions
4 “necessarily” yields the claimed lipid effects. For example, one study cited by Defendants
5 suggests that EPA administration may increase LDL-C.⁶¹³² Rambjor is a clinical study which
6 administered EPA, DHA, fish oil or placebo to human subjects. Rambjor showed that both EPA
7 and fish oil caused a significant increase in LDL-C. On the other hand, DHA effected only a
8 non-significant increase in LDL-C. As reflected by the disclosure of Rambjor, EPA does *not*
9 decrease TG without increasing LDL-C *every time it is administered*.

10 Therefore, WO '118 cannot anticipate the independent claims of the '594 patent.
11 Because the dependent claims include all of the claim elements of the independent claims, WO'
12 118 cannot anticipate any of the dependent claims as well.

13 (2) WO '118 Does Not Disclose Methods of Treating The
14 Claimed Patient Population

15 In addition, WO '118 fails to disclose or suggest the claimed pharmaceutical composition
16 be administered in the manner claimed to the claimed patient population. Defendants attempt to
17 eliminate these important elements by arguing that the preamble is non-limiting. A preamble is
18 the introductory clause of a patent claim and includes everything from the beginning of the claim
19 until a transitional phrase, such as “comprising.” Defendants improperly attempt to truncate the
20 preamble.

21 A claim preamble has patentable weight if, “when read in the context of the entire claim,
22 [it] recites limitations of the claim, or, if the claim preamble is ‘necessary to give life, meaning,

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24 ⁶¹³² See, e.g., Rambjor.

1 and vitality’ to the claim.”⁶¹³³ Additionally, the preamble constitutes a claim element when the
2 claim depends on it for antecedent basis because “it indicates reliance on both the preamble and
3 claim body to define the claimed limitation.”⁶¹³⁴

4 The preamble of the asserted claims is limiting for several reasons. The term “subject” in
5 the preamble of the independent claims defines and provides antecedent basis for the “subject”
6 recited in the body of the claims. When reading the claim, one must rely on both the preamble
7 and the claim body to define the claimed invention.

8 If the preamble states “a fundamental characteristic of the claimed invention,” then it “is
9 properly construed as a limitation of the claim itself.”⁶¹³⁵ The recitation of a “method of
10 reducing triglycerides” in the preamble provides antecedent basis for the effect of reducing
11 triglycerides in the body of the claim and emphasizes the intentional purpose for which the
12 method must be performed - to reduce triglycerides.

13 It is clear that “the claim drafter chose to use both the preamble and the body of the claim
14 to define the subject matter of the claimed invention.”⁶¹³⁶ Thus, the entire preamble in the
15 independent claims of the ‘594 must contain patentable weight.

16 WO ‘118 fails to disclose the patentable elements of the preamble of the asserted claims.
17 WO ‘118 does not describe or suggest that the claimed pharmaceutical composition be
18 administered in the manner claimed to the claimed patient population.

20 ⁶¹³³ *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305 (Fed. Cir. 1999) (citation omitted).

21 ⁶¹³⁴ *Catalina Marketing Int’l v. Coolsavings.com, Inc.*, 289 F.3d 801, 808 (Fed. Cir. 2002) (citation omitted).

22 ⁶¹³⁵ *Poly-Am. L.P. v. GSE Lining Tech., Inc.*, 383 F.3d 1303, 1309 (Fed. Cor. 2004); *see also e.g., Computer*
Docking Station Corp. v. Dell, Inc., 519 F.3d 1366, 1375 (Fed. Cir. 2008) (concluding the preamble phrases
23 “portable computer” and “portable computer microprocessing system” limit the claims because they “clearly recite a
necessary and defining aspect of the invention, specifically its portability,” and because the specification and
prosecution history “emphasize this feature of the invention”).

24 ⁶¹³⁶ *Bicon, Inc. v. Straumann Co.*, 441 F.3d 945, 953 (Fed. Cir. 2006).

1 First, WO '118 fails to expressly disclose “a method of reducing triglycerides.” In fact,
2 the invention disclosed by WO '118 relates to a composition for preventing occurrence of
3 cardiovascular events, as evidenced by the title which reads “Composition for Preventing the
4 Occurrence of Cardiovascular Event in Multiple Risk Patient.” The prevention of the occurrence
5 of cardiovascular events is defined in WO '118 as “all cases of primary prevention, and
6 exemplary cases include prevention of cardiovascular death, fatal myocardial infarction, sudden
7 cardiac death, nonfatal myocardial infarction, cardiovascular angioplasty, new occurrence of rest
8 angina and exercise-induced angina, and destabilization of the angina.”⁶¹³⁷ The invention of WO
9 '118 is intended to be administered to any person in need of prevention of the occurrence of
10 cardiovascular events, who are typically hypercholesterolemia patients.⁶¹³⁸ WO '118 does not
11 expressly describe its invention as a “method of reducing triglycerides,” therefore it cannot
12 anticipate the independent claims.

13 Second, WO '118 fails to disclose the subject as described in the claims. Defendants fail
14 to prove that these elements of the claimed invention have “strict identity” with the elements of
15 the reference.⁶¹³⁹ WO '118 fails to anticipate this claim element because the broad disclosure
16 fails to anticipate the narrow claimed range, and the specific patient population defined in the
17 claims is an essential part of the claimed invention.

18 There is no evidence in that subject as described in the claims were ever treated. In fact,
19 WO '118 fails to disclose baseline lipid levels of a single subject. Defendants rely on the
20 definition of “hypertriglyceridemia” in WO '118 to argue that WO '118 discloses treatment of
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22 ⁶¹³⁷ WO '118 at 12.

23 ⁶¹³⁸ *Id.*

24 ⁶¹³⁹ *Trintech Industries, Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1296 (Fed. Cir. 2002).

1 the subject as described in the claims. It does not. Defendants’ argument rests on the definition
2 in WO ‘118 of “hypertriglyceridemia” as “fasting serum triglyceride levels of at least 150
3 mg/dL.” WO ‘118’s definition is not tied to a specific subject and there are no working
4 examples, data or other reference in WO ‘118 indicating that any subject with fasting TG levels
5 of at least 500 mg/dL received an EPA composition as claimed in the asserted patents, or any
6 EPA at all. In addition, Defendants rely on a reference to “Omacor” in WO ‘118 (at 32) as
7 evidence that a “person of ordinary skill in the art would have understood that the term
8 ‘hypertriglyceridemia’ when used in the WO ‘118 includes patients with triglyceride levels of
9 500 mg/dL to about 1500 mg/dL.” The cited section states that “soft capsules” are preferable
10 and then merely provides examples of commercially available “soft capsules,” such as Omacor.
11 The passage does not define “hypertriglyceridemia” as used in WO ‘118 as referring to patients
12 with triglyceride levels over 500 mg/dL. Nor does it suggest that the claimed EPA should be
13 used in the over 500 mg/dL TG patient population. A prior art reference that “only ‘probably’
14 or ‘possibly’ meets the claims cannot inherently anticipate as a matter of law.”⁶¹⁴⁰ Therefore,
15 Defendants fail to prove by clear and convincing evidence that the composition disclosed by WO
16 ‘118 meets the claim elements of the independent claims every time it is administered.

17 Further, the broad range disclosed by WO ‘118 is insufficient to anticipate the ranges
18 claimed by the ‘594 patent. In *Atofina*, the prior art disclosed a temperature range of 100 to 500
19 degrees and a preferred range of 150 to 350 degrees; the patent at issue claimed a range between
20 330 and 450 degrees. The court found that the broader prior art range could not anticipate the
21 claimed temperature range, “[g]iven the considerable difference between the claimed range and
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23 ⁶¹⁴⁰ *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).
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1 the range in the prior art, no reasonable fact finder could conclude that the prior art describes the
2 claimed range with sufficient specificity to anticipate this element of the claim.”⁶¹⁴¹ A prior art’s
3 teaching of a broad genus does not necessarily disclose every species within that genus. The
4 court explained the slightly overlapping range between the preferred range and claimed range “is
5 not disclosed as . . . a species of the claimed generic range of 330 to 450 °C,”⁶¹⁴² and therefore
6 failed to anticipate the claimed range. Likewise, WO ‘118’s broad disclosure of
7 hypertriglyceridemia as a “fasting serum triglyceride levels of at least 150 mg/dL” does not
8 anticipate the subject as described in the claims because it fails to described the claimed TG
9 range with sufficient specificity.

10 The court in *Atofina* ruled on an additional question of anticipation that also involved a
11 range of numbers. A prior art reference had disclosed a range of 0.001 to 1.0 percent, as
12 compared to the patent’s claimed range of 0.1 to 5.0 percent.⁶¹⁴³ The court explained that
13 “although there is a slight overlap, no reasonable fact finder could determine that this overlap
14 describes the entire claimed range with sufficient specificity to anticipate this limitation of the
15 claim. The ranges are different, not the same. . . . Thus, there is no anticipation.”⁶¹⁴⁴ Similarly,
16 although there may be overlap between the definition of hypertriglyceridemia taught by WO
17 ‘118 and the TG range recited by the claims of the asserted patents, WO ‘118 does not
18 specifically discuss, highlight or otherwise suggest treating patients with TG values above 500
19 mg/dL. In fact, WO ‘118 is directed to compositions and methods for preventing occurrence of
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21 ⁶¹⁴¹ *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006).

22 ⁶¹⁴² *Atofina*, 441 F.3d at 1000.

23 ⁶¹⁴³ *Id.*

24 ⁶¹⁴⁴ *Id.*

1 cardiovascular events, suggesting that the treatment was envisioned for patients with TG levels
2 below 500 mg/dL (the patient population the ATP III identifies the prevention of atherogenic
3 events as the primary clinical objective),⁶¹⁴⁵ WO '118, therefore, does not expressly disclose the
4 specific patient population that is an essential element of the claims of the asserted patents.
5 Therefore, WO '118 cannot anticipate the claims of the asserted patents.

6 The treatment of a patient with elevated TG levels varies depending on their serum
7 triglyceride levels. Identification of the patient population with very high TG levels (at least 500
8 mg/dL) is central to the claimed invention. In the 2000s, physicians treating lipid disorders,
9 including hypertriglyceridemia, relied on the ATP-III for authoritative guidance on the treatment
10 of lipid disorders.⁶¹⁴⁶ The ATP-III divided hypertriglyceridemia patients into three classes based
11 on the levels of TG in their blood—borderline-high (150-199 mg/dL), high (200-499 mg/dL),
12 and very-high TGs (≥ 500 mg/dL)—and recommended substantially different treatment
13 strategies for patients depending on classification.⁶¹⁴⁷ For the borderline-high and high TG
14 groups (150-499 mg/dL), the primary goal was to reduce risk of coronary heart disease.⁶¹⁴⁸
15 Accordingly, in these populations, physicians focused on lowering LDL-C.⁶¹⁴⁹ In this patient
16 population, lowering of TG and non-HDL-C levels were considered secondary treatment goals.
17 In contrast, the primary goal for very-high TG patients (≥ 500 mg/dL) was to reduce the risk of
18 pancreatitis—a potentially life threatening condition expected to be precipitated by elevated
19 TGs— by lowering TG levels. In very high TG patients, lowering LDL-C is a secondary

20 ⁶¹⁴⁵ See Section III.

21 ⁶¹⁴⁶ *Id.*

22 ⁶¹⁴⁷ ATP III at 3335; *See also* Section III.

23 ⁶¹⁴⁸ *Id.*

24 ⁶¹⁴⁹ *Id.*

1 treatment goal.⁶¹⁵⁰ Therefore, as evidenced by the ATP-III, patients with very-high TG levels
2 were considered fundamentally different from patients with borderline-high or high TGs from a
3 lipid chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint.

4 Therefore, WO '118's definition of "hypertriglyceridemia" as "fasting serum triglyceride
5 levels of at least 150 mg/dL" fails to anticipate the claimed subject with very high TG levels. In
6 fact, as described above, WO '118 is not directed toward patients with the claimed TG levels at
7 all. WO 118's disclosure is clearly directed towards preventing the occurrence of cardiovascular
8 risk, which is the primary aim for treatment of patients with high triglycerides (200-499 mg/dL).
9 Thus, WO '118's disclosure is *not* directed towards patients with very high triglyceride levels
10 (where the primary goal is to prevent acute pancreatitis and damage to the pancreas by
11 decreasing triglycerides), as required by the independent claims of the asserted patents, and
12 therefore cannot anticipate the independent claims of the '594 Patent.

13 (3) WO '118 Does Not Describe the Claimed Pharmaceutical
14 Composition or its Specific Administration

15 WO '118 further does not anticipate the claims of the '594 patent because it does not
16 disclose "administering orally to the subject." As WO '118 fails to disclose the subject as
17 claimed, it cannot anticipate oral administration to the claimed "subject."

18 WO '118 additionally cannot anticipate the claims of the '594 patent because it does not
19 disclose administering the pharmaceutical composition at a dose of about 4g per day.
20 Defendants argue that this element is disclosed by WO '118's teaching that the daily dose is
21 "typically 0.3 to 6 g/day." Defendants fail to provide the entire disclosure of WO '118, which
22 states that the daily dose is "typically 0.3 to 6 g/day, preferably 0.9 to 3.6 g/day, and still more

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⁶¹⁵⁰ *Id.*

1 preferably 1.8 to 2.7 g/day. Another preferable daily dose is 0.3 to 2.7 g/day, and 0.3 to 1.8
2 g.day. Another preferable fatty acid included is DHA-E.” WO ‘118 teaches that the dosage is
3 not particularly limited as long as the intended effect, preventing the occurrence of
4 cardiovascular events, is attained. However, Defendants fail to provide any evidence that a dose
5 that is effective to prevent the occurrence of cardiovascular event, is also a dose that would be
6 effective to reduce triglycerides in the claimed patient population. Furthermore, there are no
7 working examples, data or other reference in WO ‘118 indicating that any subject (much less
8 one with fasting TG levels of at least 500 mg/dL) received an EPA composition as claimed in the
9 asserted patents or any EPA at all, much less at the claimed dose of 4 grams/day.

10 As discussed above, in *Atofina*, the prior art disclosed a preferred temperature range of
11 150 to 350 degrees, and the patent at issue claimed a range between 330 and 450 degrees. The
12 court explained that this slight overlap “is not disclosed as . . . a species of the claimed generic
13 range of 330 to 450 °C,”⁶¹⁵¹ and therefore failed to anticipate the claimed range. The court in
14 *Atofina* also found that a prior art disclosure of a range of 0.001 to 1.0 percent failed to anticipate
15 the patent’s claimed range of 0.1 to 5.0 percent.⁶¹⁵² The court explained that “although there is a
16 slight overlap, no reasonable fact finder could determine that this overlap describes the entire
17 claimed range with sufficient specificity to anticipate this limitation of the claim. The ranges are
18 different, not the same. . . . Thus, there is no anticipation.”⁶¹⁵³ Similarly, although there may be
19 some overlap between the daily dose disclosed by WO ‘118 and the dose claimed by the ‘594
20 patent, WO ‘118 does not specifically highlight the overlapping area and, moreover, the range
21

22 _____
⁶¹⁵¹ *Atofina*, 441 F.3d at 1000.

23 ⁶¹⁵² *Id.*

24 ⁶¹⁵³ *Id.*

1 claimed by the '594 patent does not fall within WO '118's preferred range. Defendants
2 conveniently omit the preferred range and mischaracterize the teaching of WO '118. Notably,
3 the example indicates that up to 900 mg of the EPA composition could be used three times per
4 day (2.7 g). Thus, WO '118 does not expressly disclose the 4 g per day dose claimed by the '594
5 patent and cannot anticipate the independent claims of the '594 Patent.

6 WO '118 further does not anticipate the claims of the '594 patent because it does not
7 disclose the claimed EPA pharmaceutical composition. Defendants once again cite only a
8 portion of the disclosure and exclude sections that show the breadth of WO '118's teachings.
9 WO '118's full disclosure recites that "the EPA-E used is preferably the one having a high
10 purity, for example, the one having the proportion of the EPA-E in the total fatty acid and
11 derivatives thereof of preferably 40% by weight or higher, more preferably 90% by weight or
12 higher, and still more preferably 96.5% by weight or higher."⁶¹⁵⁴ Therefore, WO '118 discloses
13 EPA-E with "high purity" is a composition which contains EPA-E of 40% by weight, of total
14 fatty acid and derivatives, or higher. This non-specific disclosure is not a species of the claimed
15 generic range for the EPA composition in the claimed pharmaceutical composition.

16 The Federal Circuit has explained that "a preferred . . . range . . . that slightly overlaps the
17 . . . range claimed in the" patent is insufficient for anticipation.⁶¹⁵⁵ In *Atofina*, the prior art
18 disclosed a preferred temperature range of 150 to 350 degrees, and the patent at issue claimed a
19 range between 330 and 450 degrees. The court explained that this slight overlap "is not
20 disclosed as . . . a species of the claimed generic range of 330 to 450 °C,"⁶¹⁵⁶ and therefore failed

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22 ⁶¹⁵⁴ WO '118 at 22.

23 ⁶¹⁵⁵ *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 1000 (Fed. Cir. 2006).

24 ⁶¹⁵⁶ *Atofina*, 441 F.3d at 1000.

1 to anticipate the claimed range.⁶¹⁵⁷ The court in *Atofina* also found that a prior art disclosure of a
2 range of 0.001 to 1.0 percent failed to anticipate the patent’s claimed range of 0.1 to 5.0
3 percent.⁶¹⁵⁸ The court explained that “although there is a slight overlap, no reasonable fact finder
4 could determine that this overlap describes the entire claimed range with sufficient specificity to
5 anticipate this element of the claim. The ranges are different, not the same. . . . Thus, there is no
6 anticipation.”⁶¹⁵⁹

7 Similarly, although there may be some overlap between the E-EPA content disclosed by
8 WO ‘118 and the ranges claimed by the ‘594 patent, WO ‘118 does not specifically highlight the
9 overlapping area. The high content of E-EPA in the claimed pharmaceutical composition is a
10 critical factor of the invention disclosed in the ‘594 patent. Therefore, WO ‘118’s broad
11 disclosure of the E-EPA content in its invention does not describe the claimed range with
12 sufficient specificity and cannot anticipate the independent claims of the ‘594 patent.

13 WO ‘118 is additionally insufficient for anticipation because it does not expressly
14 disclose the recited DHA content of the claimed pharmaceutical composition. In fact, WO ‘118
15 makes no distinction between EPA and DHA, stating that “[a]nother preferable fatty acid is
16 DHA-E.”⁶¹⁶⁰ The disclosure goes on to state that the composition of the invention is preferably
17 one having high purity of EPA-E and DHA-E. The recited DHA content of the claimed
18 pharmaceutical composition is a critical factor of the invention disclosed in the ‘594 patent.

19 The disclosure of WO ‘118 treats DHA and EPA interchangeably. The disclosed
20 concentrations of EPA and DHA may range from 0 to 100% and every concentration in between.

21 _____
22 ⁶¹⁵⁷ *Atofina*, 441 F.3d at 1000.

23 ⁶¹⁵⁸ *Id.*

24 ⁶¹⁵⁹ *Id.*

⁶¹⁶⁰ WO ‘118 at 22.

1 There is no express teaching or guidance directing the person of ordinary skill in the art to the
2 claimed EPA compositions, Therefore, WO '118's broad disclosure, which indicates no
3 difference between the use of EPA or DHA in its invention, cannot anticipate the independent
4 claims of the '594 patent.

5 Defendants contend that Plaintiffs are estopped from arguing there is any material
6 difference between "not more than about 4% DHA" and "substantially no DHA." Defendants
7 provide no legal basis for their argument of estoppel. Defendants appear to suggest that testing
8 data obtained by Plaintiffs constitutes the basis for their assertion of estoppel. That argument is
9 without merit. Plaintiffs' clinical data cannot form the basis for an estoppel argument and
10 Defendants have cited no authority to support their position suggesting the contrary. The
11 language of "not more than about 4% DHA" and "substantially no DHA" are different phrases
12 and are not co-extensive. Accordingly, plaintiffs are not estopped.

13 In the same paragraph containing their allegation of estoppel, Defendants also quote from
14 Amarin's 2011 10-K. It is unclear whether these quotations are associated with their
15 unexplained estoppel arguments. To the extent that they are, Plaintiffs disagree that these
16 statements form the basis for any theory of estoppel. To the extent that Defendants quote
17 Amarin's post-invention 10-K to make any invalidity argument, that is also unavailing. The
18 quoted statements do not identify any recited claim element, including the specific
19 pharmaceutical composition, the recited patient population, administration in the manner
20 claimed, and recited lipid effects. Nor can these elements of the asserted claims be inferred from
21 the quoted statements.

22 (4) WO '118 Does Not Describe the Dependent Claims

23 Defendants fail to address any of the claim elements of the dependent claims.
24 Defendants appear to concede that WO '118 does not expressly teach these elements, as they fail

1 to set forth any meaningful basis for concluding that WO '118 teaches these elements.
2 Defendants further argue that “aspects of the claims relating to effects that are to be achieved by
3 practicing the claimed method represent inherent, natural properties of EPA, and are entitled to
4 no patentable weight.” To the extent the recited claim elements relate to the administration step,
5 the dosage form or characteristics of the treated subject and the specific effect produced by the
6 claimed method, Defendants’ contentions that the claim limitations are inherent properties of
7 EPA are unavailing. While Defendants assert that the inherent properties are exemplified in WO
8 '118, they fail to identify any basis, explanation, or even supporting argument for that assertion.
9 Defendants have not met the burden to establish anticipation with the naked assertion that the
10 effects are inherent, natural properties of EPA.

11 Further, Defendants entirely fail to prove that inherently discloses the recited claim
12 limitations. A prior art reference that “only ‘probably’ or ‘possibly’ meets the claims cannot
13 inherently anticipate as a matter of law.”⁶¹⁶¹ “[A]nticipation by inherent disclosure is appropriate
14 only when the reference discloses prior art that must *necessarily* include the unstated
15 limitation.”⁶¹⁶² “It is not sufficient if a material element or limitation is ‘merely probably or
16 possibly present’ in the prior art.”⁶¹⁶³ Defendants fail to show that WO '118 “*necessarily*” meets
17 the recited claim elements relating to the administration step, the dosage form or characteristics
18 of the treated subject and the specific effect produced by the claimed method *every time*. WO
19 '118 fails to provide any data related to the TG, LDL-C, VLDL-C, non-HDL-C, Lp-PLA2, total
20 cholesterol, Apo-B, or any other lipid effect of the disclosed invention on patients described in
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22 _____
⁶¹⁶¹ *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

23 ⁶¹⁶² *Transclean Corp. v. Bridgewood Servs., Inc.*, 290 F.3d 1364, 1373 (Fed. Cir. 2002) (emphasis in original).

24 ⁶¹⁶³ *In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1378 (Fed. Cir. 2007).

1 the publication. Further, WO '118 is a translated Japanese disclosure that makes no reference to,
2 let alone a disclosure of, a Western diet. Therefore, Defendants fail to prove by clear and
3 convincing evidence that the composition disclosed by WO '118 meets any dependent claim
4 elements.

5 **3. The Claims of the '594 Patent Would Not Have Been Obvious In**
6 **Light of the Asserted References**

7 Defendants identify 77 separate references that it asserts somehow render the claims of
8 the '594 Patent obvious.⁶¹⁶⁴ Defendants fail to demonstrate by clear and convincing evidence
9 that any of these references, alone or in combination, would render obvious any claims of the
10 '594 Patent. Defendants' arguments rely on hindsight by impermissibly using the blueprint of
11 the '594 Patent itself to guide its combination of references.⁶¹⁶⁵ Defendants chart a laundry list
12 of 77 separate references, without explanation. Defendants' disclosures do not comply with
13 Local Patent Rule 1-8(d) and fail to put Plaintiffs on notice of how these references allegedly
14 establish that the asserted claims are allegedly *prima facie* obviousness. Consequently, Plaintiffs
15 cannot respond to undisclosed combinations and arguments.⁶¹⁶⁶

16 Despite the general, non-limiting nature of Defendants' Joint Invalidation Contentions,
17 Plaintiffs have discerned and will specifically respond to the following alleged prior art
18 combinations:

19 ⁶¹⁶⁴ Defendants' Joint Invalidation Contentions at 13-25.

20 ⁶¹⁶⁵ *In re Suong-Hyu Hyon*, 679 F.3d 1363, 1371 (Fed. Cir. 2012) ("It is impermissible to use the claimed invention
21 as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is
22 obvious." (citing *In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992))).

23 ⁶¹⁶⁶ This includes Defendants' improper attempt to incorporate by reference any alleged prior art or argument,
24 including Defendants' attempt to incorporate by reference "the reasons set forth in the opposition proceedings for
EP 2 395 991 B1" in the European Patent Office. Such wholesale incorporation by reference does not satisfy the
Defendants' obligations or burden of proof and is contrary to the Nevada Local Patent Rules, which require that
each prior art be identified specifically. *See* Local Pat. R. 1-8. Plaintiffs reserve the right to strike any attempt to
rely on undisclosed or insufficiently disclosed references or argument.

- 1 • 1) “. . .the asserted claims of the ’594 patent would have been obvious over the
2 Omacor PDR/Lovaza PDR in combination with the known clinical benefits of
3 administering pure EPA as evidenced by Katayama and/or Matsuzawa, further in
4 view of Nozaki and/or Hayashi, and further in view of Leigh-Firbank and/or Mori
5 2000.”
- 6 • 2) “. . .the asserted claims of the ’594 patent would have been obvious over the
7 Omacor PDR/Lovaza PDR in combination with the known clinical benefits of
8 administering purified EPA as evidenced by Katayama, Matsuzawa and/or Takaku,
9 further in view of Nozaki and/or Hayashi, and further in view of Grimsgaard, Mori
10 2000 and/or Maki.”
- 11 • 3) “. . .the asserted claims of the ’594 patent would have been obvious over the
12 Omacor PDR/Lovaza PDR in combination with the known clinical benefits of
13 administering pure EPA as evidenced by Katayama in view of Satoh and/or in view
14 of Satoh or Shinozaki in further view of Contacos.”
- 15 • 4) “. . . the asserted claims of the ’594 patent would have been obvious over WO ’118
16 or WO ’900 in combination with treatment regimen of Lovaza as evidenced by the
17 Lovaza PDR, and further in view of Leigh-Firbank and/or Mori 2000.”
- 18 • 5) “. . . the asserted claims of the ’594 patent would have been obvious over WO
19 ’118, WO ’900, Grimsgaard, Mori 2000 and/or Maki in combination with treatment
20 regimen of Omacor/Lovaza as evidenced by the Omacor PDR/Lovaza PDR, and
21 further in view of Katayama, Matsuzawa and/or Takaku.”

22 A patent claim is invalid “if the differences between the subject matter sought to be
23 patented and the prior art are such that the subject matter as a whole would have been obvious at
24 the time the invention was made to a person having ordinary skill in the art.”⁶¹⁶⁷ Obviousness is
a legal determination, but it turns on factual inquiries into (1) the level of ordinary skill in the art,
(2) the scope and content of the prior art, and (3) the differences between the prior art and the
claims at issue.⁶¹⁶⁸

In evaluating obviousness, each prior art reference must be evaluated for all that it

⁶¹⁶⁷ 35 U.S.C. § 103(a).

⁶¹⁶⁸ *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966); *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007).

1 teaches, including the portions that would lead away from the claimed invention.⁶¹⁶⁹ Indeed, any
2 teaching in the art that points away from the claimed invention must be considered.⁶¹⁷⁰ A
3 reference teaches away if a person of ordinary skill, upon reading the reference, would be
4 discouraged from following the path set out in the reference, or would be led in a direction
5 divergent from the path that was taken by the applicant.⁶¹⁷¹ For instance, a reference teaches
6 away if it suggests that the line of development flowing from the reference’s disclosure is
7 unlikely to be productive of the result sought by the applicant.⁶¹⁷²

8 In order to find obviousness based on a combination of references, there must be some
9 rationale for combining the references in the way claimed that is separate and apart from the
10 hindsight provided by the patented invention itself.⁶¹⁷³ The law prohibits an obviousness
11 challenge based on a hindsight reconstruction of the claimed invention from isolated prior art
12 references. It is improper for “the claims [to be] used as a frame, and individual, naked parts of
13 separate prior art references [to be] employed as a mosaic to recreate a facsimile of the claimed
14 invention.”⁶¹⁷⁴ “The invention must be viewed not after the blueprint has been drawn by the
15 inventor, but as it would have been perceived in the state of the art that existed at the time the
16 invention was made.”⁶¹⁷⁵

17 “The determination of obviousness is made with respect to the subject matter as a whole,
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19 ⁶¹⁶⁹ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

20 ⁶¹⁷⁰ *Tec Air, Inc. v. Denso Mfg. Mich. Inc.*, 192 F.3d 1353, 1359-60 (Fed. Cir. 1999)

21 ⁶¹⁷¹ *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994)

22 ⁶¹⁷² *Id.*

23 ⁶¹⁷³ *Immogenetics, N.V. v. Abbott Labs*, 512 F.3d 1363, 1373–74 (Fed. Cir. 2008)

24 ⁶¹⁷⁴ *See W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1552 (Fed. Cir. 1983)

⁶¹⁷⁵ *Sensonics, Inc. v. Aerosonic Corp.*, 81 F.3d 1566, 1570 (Fed. Cir. 1996)

1 not separate pieces of the claim.”⁶¹⁷⁶ “[A] patent composed of several elements is not proved
2 obvious merely by demonstrating that each of its elements was, independently, known in the
3 prior art.”⁶¹⁷⁷ “This is so because inventions in most, if not all, instances rely upon building
4 blocks long since uncovered, and claimed discoveries almost of necessity will be combinations
5 of what, in some sense, is already known.”⁶¹⁷⁸

6 Accordingly, it is improper to pick and choose isolated elements from the prior art and
7 combine them so as to yield the invention⁶¹⁷⁹ or to modify a prior art reference in a way that
8 “would destroy the fundamental characteristics of that reference.”⁶¹⁸⁰ Moreover, a combination
9 is not obvious where “it would be impossible to apply these teachings [of the secondary
10 reference] to the [primary reference] without entirely changing the basic mechanism and
11 procedure thereof,”⁶¹⁸¹ or where the proposed combination requires “material and radical
12 modification in order to conform to [the patentee’s] claims” or a “total reconstruction” of the
13 prior art device.⁶¹⁸² Furthermore, it is improper “to modify the secondary reference before it is
14 employed to modify the primary reference” in assessing obviousness.⁶¹⁸³

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18 ⁶¹⁷⁶ *Sanofi Syntheolabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008)

19 ⁶¹⁷⁷ *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007))

20 ⁶¹⁷⁸ *KSR*, 550 U.S. at 418-419.

21 ⁶¹⁷⁹ *Abbott Labs v. Sandoz, Inc.*, 544 F.3d 1341, 1348 (Fed. Cir. 2008)

22 ⁶¹⁸⁰ *Apple, Inc. v. Samsung Elec. Co., Ltd.*, 678 F.3d 1314, 1331 (Fed. Cir. 2012)

23 ⁶¹⁸¹ *In re Irmischer*, 262 F.2d 85, 87 (CCPA 1958)

24 ⁶¹⁸² *Id.* at 88.

⁶¹⁸³ *In re Hummer*, 241 F.2d 742, 745 (CCPA 1957)

1 Further, a party asserting obviousness in view of a combination of prior art disclosures
2 must show that a person of ordinary skill in the relevant field had an “apparent reason” to
3 combine the elements in the manner claimed⁶¹⁸⁴ and “a reasonable expectation of success.”⁶¹⁸⁵

4 For chemical compounds, there must have been a reason both to select the prior art
5 compound “most promising to modify” and to make the necessary changes to arrive at the
6 claimed compound.⁶¹⁸⁶ This protects against the use of hindsight to pick through the prior art
7 based solely on structural similarity to the claimed compound.⁶¹⁸⁷ Any assertion of an “apparent
8 reason” must find a basis in the factual record.⁶¹⁸⁸

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11 ⁶¹⁸⁴ *KSR*, 550 U.S. at 417–19; *TriMed, Inc. v. Stryker Corp.*, 608 F.3d 1333, 1341 (Fed. Cir. 2010). Hindsight may
12 not be employed to identify relevant prior art and relevant teachings therein: *Heidelberger Druckmaschinen AG v.*
13 *Hantscho Comm. Prods., Inc.*, 21 F.3d 1068, 1071–72 (Fed. Cir. 1994); *Monarch Knitting Mach. Corp. v. Sulzer*
14 *Morat GmbH*, 139 F.3d 877, 881 (Fed. Cir. 1998).

13 ⁶¹⁸⁵ *Proctor & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (henceforth, “P&G”);
14 *Takeda Chem. Indus. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1361 (Fed. Cir. 2007); *KSR*, 550 U.S. at 416 (a
combination of elements “must do more than yield a predictable result;” combining elements that work together “in
an unexpected and fruitful manner” would not have been obvious).

15 ⁶¹⁸⁶ *Daiichi Sankyo Co. v. Matrix Labs. Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010); *Takeda*, 492 F.3d at 1355, 1359–
16 60; P&G, 566 F.3d at 994–95; *Eisai Co. Ltd. v. Dr. Reddy’s Labs., Ltd.*, 533 F.3d 1533, 1358 (Fed. Cir. 2008); *Eli*
Lilly & Co. v. Zenith Goldline Pharms., Inc., 471 F.3d 1369, 1378–80 (Fed. Cir. 2006).

17 ⁶¹⁸⁷ *Daiichi Sankyo*, 619 F.3d at 1354; *Pfizer*, 2010 WL 339042, at *14. *Accord In re Vaidyanathan*, 381. 985, 994
18 (Fed. Cir. 2010) (nonprecedential); *Processing Corp. v. Am. Maize-Products Co.*, 840 F.2d 902, 907 (Fed. Cir.
1988); *Power-One*, 599 F.3d at 1351–52; *Crown Ops. Int’l, Ltd. v. Solutia, Inc.*, 289 F.3d 1367, 1376 (Fed. Cir.
2002).

19 ⁶¹⁸⁸ *See, e.g., Vaidyanathan*, 381. at 993–94 (“[W]hile *KSR* relaxed some of the formalism of earlier decisions
20 requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did not remove the need to
21 anchor the analysis in explanation of how a person of ordinary skill would select and apply the teachings of the
22 references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi Sankyo*, 619 F.3d at
23 1354 (The assertion of a starting point “must avoid hindsight bias; it must look at the state of the art *at the time the*
invention was made to find a motivation to select and then modify a lead compound to arrive at the claimed
invention.” This turns on the known “properties and elements of the prior art compounds.”); *Forest Labs.*, 438
24 F.Supp.2d at 492–93 (rejecting defendants’ contention that claims to (+)-citalopram were “prima facie obvious in
light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding that
defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been
motivated to resolve citalopram in June 1988”).

1 The “reasonable expectation of success” for a chemical compound must be of all of a
2 claimed compound’s relevant properties,⁶¹⁸⁹ including those discovered after the patent was filed
3 or even issued.⁶¹⁹⁰ “The basic principle behind this rule is straight-forward—that which would
4 have been surprising to a person of ordinary skill in a particular art would not have been
5 obvious.”⁶¹⁹¹ Any assertion of a “reasonable expectation of success” must find a basis in the
6 factual record.⁶¹⁹²

7 In an obviousness determination, any objective indicia of nonobviousness must be taken
8 into account.⁶¹⁹³ An objective indicium is any “event[] proved to have actually happened in the
9 real world” that evidences the nonobvious nature of the invention.⁶¹⁹⁴ The existence of an
10 enduring, unmet need, difficulties encountered by those skilled in the field, unexpected or
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12 ⁶¹⁸⁹ *Yamanouchi Pharm. Co., Ltd. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1345 (Fed. Cir. 2000) (“The success
13 of discovering famotidine . . . was finding a compound that had high activity, few side effects, and lacked toxicity. . .
14 . [T]he ordinary medicinal chemist would not have expected famotidine to have the ‘most desirable combination of
15 pharmacological properties’ that it possesses.”); *Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 364 F.Supp.2d
820, 908 (S.D. Ind. 2005) (“[S]uccess was not simply finding a compound as active as clozapine Here, the
ordinary medicinal chemist . . . would not have expected olanzapine to have the highly desirable combination of
pharmacological properties that it possesses.”).

16 ⁶¹⁹⁰ *Knoll Pharm. Inc. v. Teva Pharms. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004); *Eli Lilly*, 364 F.Supp.2d at
908.

17 ⁶¹⁹¹ *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995) (“The principle applies most often to the less predictable fields,
18 such as chemistry, where minor changes in a product or process may yield substantially different results.”).

19 ⁶¹⁹² *See, e.g., Sanofi-Synthelabo*, 550 F.3d at 1089 (“Apotex argues that the district court applied an incorrect
20 inquiry, and that the correct inquiry is not whether the results obtained with the separated enantiomer were
21 unexpected, but whether it would have been obvious to separate and test the enantiomers, based on the general
22 knowledge that enantiomers can exhibit different properties. Apotex refers to *In re Adamson*, 275 F.2d [952,] 955
[(C.C.P.A. 1960)], where the CCPA held that an enantiomer would have been obvious in view of its racemate.
However, the scientific facts differed from these herein, for in *Adamson* the court found that it was ‘particularly
expected’ that the specific enantiomer would have the observed properties. In contrast, as Sanofi points out, in *In re*
May, 574 F.2d at 1095, the CCPA held, as to the enantiomer claimed therein, that the appellant ‘established a
substantial record of unpredictability vis-à-vis a highly significant combination of properties.’”).

23 ⁶¹⁹³ *Graham*, 383 U.S. at 17–18; *KSR*, 550 U.S. at 406; *Jones v. Hardy*, 727 F.2d 1524, 1530–31 (Fed. Cir. 1984).

24 ⁶¹⁹⁴ *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1569 (Fed. Cir. 1987).

1 surprising results, expressions of skepticism, industry praise, commercial success, and copying
2 are classical indicia of nonobviousness.⁶¹⁹⁵ These factual inquiries “guard against slipping into
3 use of hindsight,”⁶¹⁹⁶ and “may often be the most probative and cogent evidence of
4 nonobviousness.”⁶¹⁹⁷

5 Also, as with assertions of anticipation, in order for an invention to be obvious, it must
6 have been fully “in possession” of the public—which requires that the claimed invention have
7 been enabled.⁶¹⁹⁸

8 A element-by-element analysis, identifying each limitation of each asserted claim that is
9 absent from the prior art, is provided below, and also provided at Exhibit P. The contentions
10 below are incorporated by reference into Exhibit P, and vice-versa.

11 a) General Overview

12 Defendants fail to provide a single prior art reference that discloses administration of the
13 recited composition of EPA ethyl (in the recited purity) to the very-high TG patient population
14 (≥ 500 mg/dL) and the resulting lipid effects. Instead, they rely on a large number of studies,
15 many of which are not placebo controlled, which administer EPA, DHA, or both, in varying
16 degrees of purity, in a wide range of doses and administration periods, to subjects who have

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18 ⁶¹⁹⁵ *Graham*, 383 U.S. at 17–18; *KSR*, 550 U.S. at 406; *U.S. v. Adams*, 383 U.S. 39, 52 (1966); *Merck & Co. v. Teva*
19 *Pharm. USA, Inc.*, 395 F.3d 1364, 1376 (Fed. Cir. 2005); *Panduit*, 810 F.2d at 1569; *In re Soni*, 54 F.3d 746, 750
(Fed. Cir. 1995); *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988); *Janissen*, 456 F.Supp.2d at 669–72.

20 ⁶¹⁹⁶ *Graham*, 383 U.S. at 36.

21 ⁶¹⁹⁷ *Ortho-McNeil Pharm. Inc. v. Mylan Labs. Inc.*, 520 F.3d 1358, 1365 (Fed. Cir. 2008) (quoting *Catalina Lighting*
Inc. v. Lamps Plus, Inc., 295 F.3d 1277, 1288 (Fed. Cir. 2002)).

22 ⁶¹⁹⁸ *In re Kumar*, 418 F.3d 1361, 1368 (Fed. Cir. 2005) (“[I]n order to render an invention unpatentable for
23 obviousness, the prior art must enable a person of ordinary skill to make and use the invention.”); *In re Hoeksema*,
24 399 F.2d 269, 274 (C.C.P.A. 1968) (“[I]f the prior art of record fails to disclose or render obvious a method for
making a claimed compound, at the time the invention was made, it may not be legally concluded that the compound
itself is in the possession of the public.”).

1 baseline TG levels lower than 500 mg/dL and in many cases significantly lower. The importance
2 of a placebo-controlled study cannot be overstated. Randomized, double-blind placebo
3 controlled studies are considered the “gold standard” of clinical studies. Studies involving the
4 administration of fish oils or omega-3 fatty acids which are not placebo controlled cannot
5 distinguish between the effect of the placebo from that of the active agent. Studies which
6 administer mixtures enriched for either EPA or DHA are not suitable for evaluating the
7 independent effects of EPA and DHA.⁶¹⁹⁹ Inconsistency in dosages and administration periods
8 and variations in the administered fatty acid compositions also complicate the interpretation of
9 the results and limit the application of these studies.

10 Defendants also rely on the ANCHOR study to argue that Amarin’s use of “patients with
11 very high TGs together with patients with high and borderline high TGs indicates that there is no
12 medical difference in responsiveness to treatment among the groups of people.”⁶²⁰⁰ Defendants
13 mischaracterize the ANCHOR study. The ANCHOR study was a multi-center, placebo-
14 controlled, randomized, double-blind, 12-week pivotal Phase 3 study on the effects of Vascepa in
15 patients with high triglycerides (≥ 200 mg/dL and < 500 mg/dL) who were also on statin therapy.
16 Defendants point to the reported “Min-max” TG levels, 157-782 mg/dL, for the AMR101 4g
17 daily group to argue that Amarin used very-high TG patients with high and borderline-high TG
18 patients. However, the mean TG level for this same group, 281.1 mg/dL, makes it clear that
19 almost all of the 233 patients in this group had baseline TG values well below 500 mg/dL.⁶²⁰¹ In
20

21 ⁶¹⁹⁹ Mori 2006 at 96.

22 ⁶²⁰⁰ Defendants’ Joint Invalidity Contentions at 797 (*see* FN 156).

23 ⁶²⁰¹ FDA Briefing Document, Oct. 16, 2013 at pg. 26 (The mean baseline TG value for the placebo group was 270.6
24 mg/dL, AMR101 2g group was 270.2 mg/dL, and AMR101 4g group was 281.1 mg/dL. While there may have been
a few patients with TG > 500mg/dL in the AMR101 4g group, it is clear that the overwhelming majority had baseline
TG values < 500 mg/dL).

1 addition, the mean baseline TG values for the Placebo and AMR101 2g daily groups were
2 reported as 270.6 mg/dL and 270.2 mg/dL, respectively. Further, Amarin did *not* attempt to use
3 the results of ANCHOR to predict lipid effects in the very high TG patient population. Neither a
4 person of ordinary skill, nor the FDA, would attempt to draw conclusions or gain insight into the
5 very high TG patient population from the ANCHOR trial. In fact, Amarin simultaneously (to
6 ANCHOR) conducted an independent study with Vascepa in patients with very high TG levels.
7 Contrary to Defendants' assertion, the ANCHOR study does *not* indicate that there is no medical
8 difference in responsiveness to treatment between the very-high TG patient population and lower
9 TG patient populations merely because there was possibly one patient with baseline TG levels of
10 at least 500 mg/dL.

11 As discussed above in Section III, patients with very-high TG levels were considered
12 fundamentally different from patients with borderline-high or high TGs from a clinical,
13 regulatory, and therapeutic perspective.⁶²⁰² Clinically, the authoritative guidance to physicians
14 on the treatment of lipid disorders throughout the last decade, the Adult Treatment Panel III
15 (ATP-III) divided hypertriglyceridemic patients into three groups: normal/borderline high TG;
16 high TG; and very high TG. The primary risk faced by borderline-high and high TG patients
17 was atherosclerosis, while the primary risk faced by very-high TG patients was acute
18 pancreatitis. Therefore, the primary focus of treatment, as described by the ATP III, for
19 borderline-high and high TG patients was to lower LDL-C levels. In contrast, the priority for
20 very-high TG patients was TG reduction. This distinction between patients with borderline-
21 high/high TG levels and patients with very high TG levels is also observed on the regulatory
22 level. The FDA recognized the different clinical status of the very-high TG population by

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24 ⁶²⁰² See Bays Jan. 8, 2012 Decl., ¶ 20.

1 approving some drugs specifically for the very-high TG group without granting treatment
2 indications for the borderline-high or high TG populations (i.e. Lovaza/Omacor).⁶²⁰³

3 Finally, from a therapeutic standpoint, a person of ordinary skill understood that the
4 effects of lipid-lowering therapies on lipid parameters, such as LDL-C, varied depending on the
5 patient's baseline TG level. Fibrates and prescription omega-3 therapies (two well-known
6 classes of drugs used to treat patient with very-high TGs to lower TG levels at the time of the
7 invention), for example, exhibit different effects on LDL-C levels, depending on the baseline TG
8 level of the patient receiving treatment.

9 Fibrates lower both TGs and LDL-C in normal and borderline-high TG patients, but
10 increase LDL-C in very-high TG patients.⁶²⁰⁴ The fibrate, Tricor (fenofibrate), for example,
11 decreased LDL-C significantly in both patients with normal baseline TG values (about 31%)⁶²⁰⁵
12 and high baseline TG values (mean baseline TG value of 231.9 mg/dL) (about 20%).⁶²⁰⁶ In
13 patients approaching very-high TGs levels (mean baseline TG value of 432 mg/dL), a non-
14 significant increase in LDL-C was observed.⁶²⁰⁷ In patients with very-high TGs (mean baseline
15 TG = 726 mg/dL), a significant increase in LDL-C was observed (about 45%).⁶²⁰⁸ Similar
16 results were seen with the administration of Lopid (gemfibrozil).⁶²⁰⁹ The differing effects of

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18 ⁶²⁰³ See Bays Jan. 8, 2012 Decl., ¶ 22.

19 ⁶²⁰⁴ See Bays 2008 II, at 214-15 (noting that a fibrate caused LDL-C to go down in borderline-high group, remain roughly the same in high TG group, and increase by around 50% in the very-high TG group).

20 ⁶²⁰⁵ Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

21 ⁶²⁰⁶ *Id.*

22 ⁶²⁰⁷ *Id.* See also, Trilipix Label at 27.

23 ⁶²⁰⁸ *Id.* See also, Trilipix Label at 27.

24 ⁶²⁰⁹ See Otvos at 1558 (showing administration of Gemfibrozil to patients with borderline-high baseline TG levels had no impact on LDL-C levels); Manttari at 14 and 16 (stating that the effect of gemfibrozil on LDL-C was dependent on initial TG levels, no change was observed for LDL-C in subjects with high baseline TG levels while subjects with normal or borderline-high baseline TG levels showed significant decreases in LDL-C).

1 fibrates, such as Tricor, on TG, LDL-C , HDL-C and Total-C based on baseline TG values
 2 demonstrates how a person of ordinary skill at the time of the invention would have understood
 3 that one could not simply assume that an observed effect of a TG-lowering agent on lipid
 4 parameters in patients with normal, borderline-high or high TG levels would be the same in
 5 patients with very-high TG levels (at least 500 mg/dL) compared to a patient with high or
 6 borderline-high TG levels (150-499 mg/dL). As illustrated in the table, below, patients with
 7 normal or high baseline TG levels experience reduced LDL-C levels upon treatment with a TG-
 8 reducing agent such as the fibrate, Tricor. Patients approaching very high TG levels (mean
 9 baseline TG level of 432 mg/dL) and patients with very high TG levels (mean baseline TG level
 10 of 726 mg/dL) experience significantly increased LDL-C levels.

Fibrate	Mean Baseline TG Value	TG	LDL-C	HDL-C	Total-C
Tricor (fenofibrate) ⁶²¹⁰	101.7 mg/dL	-23.5%*	-31.4%*	+9.8%*	-22.4%*
	231.9 mg/dL	-35.9%*	-20.1%*	+14.6%*	-16.8%*
	432 mg/dL	-46.2*	+14.5	+19.6*	-9.1*
	726 mg/dL	-54.5*	+45.0*	+22.9*	-13.8*

* = p < 0.05 vs. Placebo

17 Lovaza/Omacor was (and is) a prescription omega-3 therapy known to have differing
 18 lipid effects depending on the patient’s baseline TG level. When administered to patients with
 19 borderline-high baseline TG levels, Lovaza/Omacor significantly reduced TGs and raised HDL-
 20 C.⁶²¹¹ It had no significant effect on other lipid-related variable, including LDL-C and Apo-

6210 Tricor®, Physicians’ Desk Reference 502-505 (62d ed. 2008).

6211 Chan 2002 I at 2379-81.

1 B.⁶²¹² However, when administered to patients with very-high baseline TG levels, TGs were
2 reduced significantly by nearly 50% while LDL-C increased sharply by nearly 50%.⁶²¹³
3 Although the increase in LDL-C was concerning, it was understood that the overall lipid effect of
4 Lovaza/Omacor was beneficial.⁶²¹⁴

5 Fibrates and prescription Omega-3 therapies demonstrate that one could not simply
6 assume that a lipid lowering agent would have the same effect in a patient with very-high TG
7 levels (≥ 500 mg/dL) as a patient with borderline-high or high TG levels (150-499 mg/dL). They
8 also demonstrate that one of ordinary skill would not expect to see an increase in LDL-C when
9 the normal, borderline-high or high TG patient populations were administered omega-3 fatty
10 acids. As discussed in Section III, the increase in LDL-C for very-high TG patients was
11 expected as a natural consequence of lowering TGs. A person of ordinary skill would have
12 considered the rise in LDL-C to be a direct consequence of TG lowering through increased
13
14

15 ⁶²¹² *Id.*; See also, Westphal at 918.

16 ⁶²¹³ See Weintraub Sept. 7, 2011 Decl., ¶ 23 (citing Lovaza package insert); Bays May 16, 2011 Decl., ¶ 10; see also, Lovaza PDR and Omacor PDR.

17 ⁶²¹⁴ See Pownall *et al.*, *Correlation of serum triglyceride and its reduction by ω -3 fatty acids with lipid transfer activity and the neutral lipid compositions of high-density and low-density lipoproteins*, 143 *Atherosclerosis* 285, 295 (1999) (“Treatment with ω -3 fatty acids appear to change the lipid profile of individuals with elevated TG to one that may be less atherogenic by changing LDL structure; lowering serum [cholesterol ester transfer activity], serum TG and VLDL-C; and increasing serum HDL-C.”); Stalenhoef at 134 (stating that “Omacor . . . adversely raise LDL cholesterol concentration but the increase in LDL cholesterol concentration reflects a less atherogenic light LDL subfraction profile that may be favorable”); Harris 1997 at 389 (“The increase in LDL, which was substantial on a percentage basis, has been a common finding in past studies in [very-high TG] patients. It may not be as problematic as it appears, however.” And “the use of omega-3 fatty acids for the treatment of severe hypertriglyceridemia may be beneficial not only for the short-term prevention of acute pancreatitis, but also for the long-term prevention of CHD”); Bays III at 248 (“No clinical trial data exist that this rise in LDL-C represents harm or potential “toxicity” to patients. In fact, most evidence supports that omega-3 fatty acids reduce cardiovascular risk as do fibrates. Importantly, clinical trials mostly support that even with increases in LDL-C, omega-3 fatty acids decrease the total cholesterol (TC) carried by atherogenic lipoproteins, as reflected by decreased non-HDL-C levels (TC minus HDL-C.)”

1 VLDL particle conversion.⁶²¹⁵ Because normal to high TG patients did not have the large
2 backlog of VLDL particles that very high TG patients have, a person of ordinary skill did not
3 expect LDL-C to increase in normal to high TG patients. It was also well known that the degree
4 of LDL-C elevation observed with prescription omega-3 fatty acids, such as Lovaza/Omacor,
5 was linked to baseline TG levels; that LDL-C levels increased the most in patients with the
6 highest baseline TG levels⁶²¹⁶ and did not increase for patients with lower TG levels. Therefore,
7 the prior art defendants rely upon to show that EPA did *not* increase LDL-C levels in normal,
8 borderline-high or high TG patients was *expected*.

9 Defendants contend that “a composition and its properties are inseparable, and therefore
10 do not impart any additional patentability,” and that “all of the limitations regarding the
11 properties of the ethyl EPA compound identified in the claims of the ‘594 patent are inherent to
12 the compound when administered to a human subject.”⁶²¹⁷ Inherency may not supply a missing
13 claim limitation in an obviousness analysis unless the inherency would have been obvious to one
14 of ordinary skill in the art.⁶²¹⁸ Obviousness is based on what is *known* in the art at the time of the
15

16 _____
17 ⁶²¹⁵ Bays May 16, 2011 Decl., ¶ 11 (noting the “general knowledge in the art that omega-3 fatty acids as a class
18 increase LDL-C” in very-high TG patients); McKenney 2007, at 724 (“Because of the increase in LDL levels
19 observed in some patients treated with prescription omega-3, LDL levels also should be periodically assessed during
20 treatment.”); Bays in Kwiterovich at 247 (noting that increased LPL activity caused by fish oil “helps explain some
of the seemingly paradoxical lipid effects found with their clinical use, for example, the rise in LDL-C with the
decrease in VLDL.”).

21 ⁶²¹⁶ Bays 2008 I at 400-402.

22 ⁶²¹⁷ Defendants’ Joint Invalidity Contentions at 852.

23 ⁶²¹⁸ See, e.g., *PAR Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1195–96 (Fed. Cir. 2014) (“A party must . . .
24 meet a high standard in order to rely on inherency to establish the existence of a claim limitation in the prior art in an
obviousness analysis—the limitation at issue necessarily must be present, or the natural result of the combination of
elements explicitly disclosed by the prior art.”); *In re Rijckaert*, 9 F.3d 1531, 1533–34 (Fed. Cir. 1993) (“The mere
fact that a certain thing may result from a given set of circumstances is not sufficient [to establish inherency].”) (internal quotation omitted).

1 invention.⁶²¹⁹ It was not known or reasonably expected at the time of the claimed invention that
2 purified EPA, when administered to patients with very-high TG levels (≥ 500 mg/dL), would not
3 substantially increase LDL-C or would reduce Apo-B. Nor was EPA’s effect on LDL-C and
4 Apo-B necessarily present, or the natural result of the combination of elements explicitly
5 disclosed by the prior art.⁶²²⁰ Therefore, inherency does not supply the missing claim elements
6 in the prior art cited by Defendants.

7 Defendants argue that the claims of the ‘594 patent which contain “a limiting clause, such
8 as ‘to effect’ or ‘is effective to,’” simply express the intended result of a process step positively
9 recited and therefore are not elements.⁶²²¹ This is incorrect. “There is nothing inherently wrong
10 with defining some part of an invention in functional terms.”⁶²²² When a clause “states a
11 condition that is material to patentability, it cannot be ignored in order to change the substance of
12 the invention.”⁶²²³ The claim term “to effect” acts as a positive limitation if the term represents
13 “unexpected and improved effects of administration of the claimed compound.”⁶²²⁴ In addition,
14 the elements represent unexpected and improved effects of administration of purified EPA,
15 because a person of ordinary skill would not have expected no substantial increase in LDL-C or
16 reduction in Apo-B when administering EPA to treat severe hypertriglyceridemia. Therefore, the

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18
19 _____
20 ⁶²¹⁹ *In re Spormann*, 363 F.2d 444, 448 (CCPA 1966) (“That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown.”).

21 ⁶²²⁰ See discussions below for Grimsgaard, Park, Nozaki Kurabayashi and Hayashi.

22 ⁶²²¹ Defendants’ Joint Invalidity Contentions at 799.

23 ⁶²²² See MPEP 2173.05(g) (citing *In re Swinehart*, 439 F.2d 210 (CCPA 1971)).

24 ⁶²²³ *Hoffer v. Microsoft Corp.*, 405 F.3d 1326, 1329 (Fed. Cir. 2005).

⁶²²⁴ *AstraZeneca AB v. Dr. Reddy’s Labs., Ltd.*, No. CIV.A.05-5553 JAP, 2010 WL 1981790, at *11–12 (D.N.J. May 18, 2010).

1 requirements for no substantial increase in LDL-C and reduction in Apo-B must be accorded
2 patentable weight.

3 b) Identification of Claim Elements Absent from Each Item of Prior
4 Art

5 Plaintiffs identify each limitation of each asserted claim that Plaintiffs believe is absent.
6 Where a limitation is absent from any Independent Claim, that limitation is absent from all
7 asserted claims, and that analysis is incorporated by reference into each dependent claim. For
8 any reference, the fact that Plaintiffs do not list a particular limitation as absent from the asserted
9 claims is not a concession that such limitation is present in the reference. By discussing
10 Defendants' analysis of the "limitations" in the claims, Plaintiffs do not concede that Defendants
11 have appropriately divided the claim language for any purpose.

12 (1) WO '118

13 WO '118 discloses a composition containing EPA-E for preventing the occurrence of
14 cardiovascular events in multiple risk patients.

15 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of WO
16 '118 disclose or suggest elements of the '594 Claims. The cited portions of WO '118 do not
17 disclose or suggest these elements at least because they do not disclose or suggest identifying a
18 group of subjects with the recited very high TG levels. The cited portions of WO '118 further do
19 not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid
20 compositions or dosage. The cited portions of WO '118 further do not disclose or suggest the
21 recited TG and LDL-C effects.

22 With respect to Claims 1, 10 and 17 of the '594 Patent (and therefore all asserted claims),
23 WO '118 does not disclose or suggest identifying a group of subjects with the recited very high
24 TG level. WO '118 also does not disclose or suggest the claimed pharmaceutical composition

1 with the recited fatty acid compositions or dosage. WO '118 further does not disclose or suggest
2 the recited TG and LDL-C effects.

3 Further, with respect to Claims 2, 11 and 18, this reference fails to disclose or suggest the
4 group of subjects having the recited baseline LDL-C levels. With respect to Claims 4, 13 and 20,
5 this reference fails to disclose or suggest the recited TG and LDL-C effects in the at least one
6 subject with the claimed TG level. With respect to Claims 5, 14 and 21, this reference fails to
7 disclose or suggest the recited reduction in Apolipoprotein B in the at least one subject with the
8 claimed TG level. With respect to Claims 6, 15, and 22, this reference fails to disclose or
9 suggest the recited reduction in VLDL-C in the at least one subject with the claimed TG level.
10 With respect to Claims 7, 16, and 23, this reference fails to disclose or suggest a group of
11 subjects with the recited very high TG levels. With respect to Claim 24, this reference fails to
12 disclose or suggest the recited fatty acids other than ethyl eicosapentaenoate.

13 (2) WO '900

14 WO '900 describes methods for obtaining EPA-rich compositions.

15 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of WO
16 '900 disclose or suggest elements of the '594 Claims. The cited portions of WO '900 do not
17 disclose or suggest these elements at least because they do not disclose or suggest identifying a
18 group of subjects with the recited very high TG levels. The cited portions of WO '900 further do
19 not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid
20 compositions or dosage. The cited portions of WO '900 further do not disclose or suggest the
21 recited TG and LDL-C effects.

22 With respect to Claims 1, 10 and 17 of the '594 Patent (and therefore all asserted claims),
23 WO '900 does not disclose or suggest identifying a group of subjects with the recited very high
24 TG level. WO '900 also does not disclose or suggest the claimed pharmaceutical composition

1 with the recited fatty acid compositions or dosage. WO '900 further does not disclose or suggest
2 the recited TG and LDL-C effects.

3 Further, with respect to Claims 2, 11 and 18, this reference fails to disclose or suggest the
4 group of subjects having the recited baseline LDL-C levels. With respect to Claims 3, 12 and 19,
5 this reference fails to disclose or suggest the subject having the recited baseline lipid levels.

6 With respect to Claims 4, 13 and 20, this reference fails to disclose or suggest the recited TG and
7 LDL-C effects in the at least one subject with the claimed TG level. With respect to Claims 5,
8 14 and 21, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in
9 the at least one subject with the claimed TG level. With respect to Claims 6, 15, and 22, this
10 reference fails to disclose or suggest the recited reduction in VLDL-C in the at least one subject
11 with the claimed TG level. With respect to Claims 7, 16, and 23, this reference fails to disclose
12 or suggest the group of subjects with the recited very high TG levels. With respect to Claim 24,
13 this reference fails to disclose or suggest the recited fatty acids other than ethyl
14 eicosapentaenoate.

15 (3) Contacos

16 Contacos describes a study designed to determine the safety and efficacy of a statin
17 (pravastatin) combined with fish oil either alone or in combination, for the management of
18 patients with mixed hyperlipidemia.

19 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of
20 Contacos disclose or suggest elements of the '594 Claims. The cited portions of Contacos do not
21 disclose or suggest these elements at least because they do not disclose or suggest identifying a
22 group of subjects with the recited very high TG levels. The cited portions of Contacos further do
23 not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid
24 compositions, dosage, or administration period. The cited portions of Contacos further do not

1 disclose or suggest a method of administering the claimed pharmaceutical composition to effect
2 the recited TG and LDL-C effects.

3 With respect to Claims 1, 10 and 17 of the '594 Patent (and therefore all asserted claims),
4 Contacos does not disclose or suggest identifying a group of subjects with the recited very high
5 TG level. Contacos also does not disclose or suggest the claimed pharmaceutical composition
6 with the recited fatty acid compositions, dosage, or administration period. Contacos further does
7 not disclose or suggest a method of administering the claimed pharmaceutical composition to
8 effect the recited TG and LDL-C effects.

9 Further, with respect to Claims 4, 13 and 20, this reference fails to disclose or suggest the
10 administration of the claimed pharmaceutical composition to effect the recited TG and LDL-C
11 effects. With respect to Claims 5, 14 and 21, this reference fails to disclose or suggest the
12 administration of the claimed pharmaceutical composition to effect the recited reduction in
13 Apolipoprotein B. With respect to Claims 6, 15, and 22, this reference fails to disclose or
14 suggest the administration of the claimed pharmaceutical composition to effect the recited
15 reduction in VLDL-C. With respect to Claims 7, 16, and 23, this reference fails to disclose or
16 suggest the group of subjects with the recited very high TG levels. With respect to Claim 24,
17 this reference fails to disclose or suggest the recited fatty acids other than ethyl
18 eicosapentaenoate.

19 (4) Grimsgaard

20 Grimsgaard conducted a double-blind, randomized, placebo-controlled, parallel design
21 intervention study to evaluate the dietary supplementation with EPA or DHA on serum lipids,
22 apolipoproteins, and serum phospholipid fatty acid composition in subjects with normal TG
23 levels.

24
CONFIDENTIAL

1 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of
2 Grimsgaard disclose or suggest elements of the '594 Claims. The cited portions of Grimsgaard
3 do not disclose or suggest these elements at least because they do not disclose or suggest
4 identifying a group of subjects with the recited very high TG levels. The cited portions of
5 Grimsgaard further do not disclose or suggest the claimed pharmaceutical composition with the
6 recited administration period. The cited portions of Grimsgaard further do not disclose or
7 suggest the recited TG and LDL-C effects in the at least one subject with the claimed TG level.

8 With respect to Claims 1, 10 and 17 of the '594 Patent (and therefore all asserted claims),
9 Grimsgaard does not disclose or suggest identifying a group of subjects with the recited very
10 high TG level. Grimsgaard also does not disclose or suggest the claimed pharmaceutical
11 composition with the recited administration period. Grimsgaard further does not disclose or
12 suggest the recited TG and LDL-C effects in the at least one subject with the claimed TG level.

13 Further, with respect to Claims 4, 13 and 20, this reference fails to disclose or suggest the
14 recited TG and LDL-C effects in the at least one subject with the claimed TG level. With respect
15 to Claims 5, 14 and 21, this reference fails to disclose or suggest the recited reduction in
16 Apolipoprotein B in the at least one subject with the claimed TG level. With respect to Claims 6,
17 15, and 22, this reference fails to disclose or suggest the recited reduction in VLDL-C in the at
18 least one subject with the claimed TG level. With respect to Claims 7, 16, and 23, this reference
19 fails to disclose or suggest a group of subjects with the recited very high TG levels. With respect
20 to Claim 24, this reference fails to disclose or suggest the recited fatty acids other than ethyl
21 eicosapentaenoate.

22 (5) Hayashi

23 Hayashi is directed to administration of ethyl icosapentate 1800mg (6 capsules) daily for
24 8 weeks. The purity of the composition is not reported. The study was not placebo controlled

1 and was conducted in 28 patients with familial combined hyperlipidemia and a serum trygliceride
2 concentration higher than 150 mg/dl or serum total cholestorol concentration higher than 220
3 mg/dl.

4 The portions of Hayashi cited by Defendants do not disclose or suggest elements of the
5 ‘594 patent claims. For example, the cited portions of Hayashi do not disclose or suggest
6 administration of EPA with the recited purity to a subject with the recited very high TG levels
7 who does not receive concurrent lipid altering therapy. Figure 2 demonstrates that no subject
8 had a TG level above 400 mg/dl. The cited portions of Hayahsi further do not disclose or
9 suggest the claimed pharmaceutical composition with the recited fatty acid compositions or
10 dosage. The cited portions of Hayashi further do not disclose or suggest a method to effect the
11 recited TG reduction without substantially increasing LDL-C in a subject with the recited very
12 high TG levels.

13 With respect to Claims 1, 10 and 17 of the ‘594 Patent (and therefore all asserted claims),
14 Hayashi does not disclose or suggest identifying a group of subjects with the recited very high
15 TG level. Hayashi also does not disclose or suggest the claimed pharmaceutical composition
16 with the recited fatty acid compositions or dosage. Hayashi further does not disclose or suggest
17 the recited TG and LDL-C effects.

18 Further, with respect to Claims 2, 11 and 18, this reference fails to disclose or suggest the
19 group of subjects having the recited baseline LDL-C levels. With respect to Claims 4, 13 and 20,
20 this reference fails to disclose or suggest the recited TG and LDL-C effects. With respect to
21 Claims 5, 14 and 21, this reference fails to disclose or suggest the recited reduction in
22 Apolipoprotein B. With respect to Claims 6, 15, and 22, this reference fails to disclose or
23 suggest the recited reduction in VLDL-C. With respect to Claims 7, 16, and 23, this reference
24

1 fails to disclose or suggest the group of subjects with the recited very high TG levels. With
2 respect to Claim 24, this reference fails to disclose or suggest the recited fatty acids other than
3 ethyl eicosapentaenoate.

4 (6) Katayama

5 Katayama was directed to an investigation of the safety and efficacy of Epadel during
6 long term treatment in patients with hyperlipidemia that was not placebo controlled. Notably,
7 Katayama did not disclose or suggest any LDL-C related data or describe any LDL-C effects and
8 was not placebo controlled.

9 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of
10 Katayama disclose or suggest elements of the '594 Claims. The cited portions of Katayama do
11 not disclose or suggest these elements at least because they do not disclose or suggest identifying
12 a group of subjects with the recited very high TG levels. The cited portions of Katayama further
13 do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid
14 compositions or dosage. The cited portions of Katayama further do not disclose or suggest the
15 recited TG and LDL-C effects.

16 With respect to Claims 1, 10 and 17 of the '594 Patent (and therefore all asserted claims),
17 Katayama does not disclose or suggest identifying a group of subjects with the recited very high
18 TG level. Katayama also does not disclose or suggest the claimed pharmaceutical composition
19 with the recited fatty acid compositions or dosage. Katayama further does not disclose or
20 suggest the recited TG and LDL-C effects.

21 Further, with respect to Claims 2, 11 and 18, this reference fails to disclose or suggest the
22 group of subjects having the recited baseline LDL-C levels. With respect to Claims 4, 13 and 20,
23 this reference fails to disclose or suggest the recited TG and LDL-C effects. With respect to
24 Claims 5, 14 and 21, this reference fails to disclose or suggest the recited reduction in

1 Apolipoprotein B. With respect to Claims 6, 15, and 22, this reference fails to disclose or
2 suggest the recited reduction in VLDL-C. With respect to Claims 7, 16, and 23, this reference
3 fails to disclose or suggest the group of subjects with the recited very high TG levels. With
4 respect to Claim 24, this reference fails to disclose or suggest the recited fatty acids other than
5 ethyl eicosapentaenoate.

6 (7) Leigh-Firbank

7 Leigh-Firbank studied the impact of fish-oil intervention on LDL oxidation, particle
8 density and concentration in subjects with an atherogenic lipoprotein phenotype. Leigh-Firbank
9 does not administer EPA of the purity recited in the claims.

10 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of
11 Leigh-Firbank disclose or suggest elements of the '594 Claims. The cited portions of Leigh-
12 Firbank do not disclose or suggest these elements at least because they do not disclose or suggest
13 identifying a group of subjects with the recited very high TG levels. The cited portions of Leigh-
14 Firbank further do not disclose or suggest the claimed pharmaceutical composition with the
15 recited fatty acid compositions, dosage, or administration period. The cited portions of Leigh-
16 Firbank further do not disclose or suggest a method of administering the claimed pharmaceutical
17 composition to effect the recited TG and LDL-C effects.

18 With respect to Claims 1, 10 and 17 of the '594 Patent (and therefore all asserted claims),
19 Leigh-Firbank does not disclose or suggest identifying a group of subjects with the recited very
20 high TG level. Leigh-Firbank also does not disclose or suggest the claimed pharmaceutical
21 composition with the recited fatty acid compositions, dosage, or administration period. Leigh-
22 Firbank further does not disclose or suggest a method of administering the claimed
23 pharmaceutical composition to effect the recited TG and LDL-C effects.

1 Further, with respect to Claims 4, 13 and 20, this reference fails to disclose or suggest the
2 administration of the claimed pharmaceutical composition to effect the recited TG and LDL-C
3 effects. With respect to Claims 5, 14 and 21, this reference fails to disclose or suggest the
4 administration of the claimed pharmaceutical composition to effect the recited reduction in
5 Apolipoprotein B. With respect to Claims 6, 15, and 22, this reference fails to disclose or
6 suggest the administration of the claimed pharmaceutical composition to effect the recited
7 reduction in VLDL-C. With respect to Claims 7, 16, and 23, this reference fails to disclose or
8 suggest the group of subjects with the recited very high TG levels. With respect to Claim 24,
9 this reference fails to disclose or suggest the recited fatty acids other than ethyl
10 eicosapentaenoate.

11 (8) Lovaza PDR

12 The Lovaza PDR is the Physicians' Desk Reference describing Lovaza.

13 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of the
14 Lovaza PDR disclose or suggest elements of the '594 Claims. The cited portions of the Lovaza
15 PDR do not disclose or suggest these elements at least because they do not disclose or suggest
16 the claimed pharmaceutical composition with the recited fatty acid compositions or
17 administration period. The cited portions of the Lovaza PDR further do not disclose or suggest a
18 method of administering the claimed pharmaceutical composition to effect the recited TG and
19 LDL-C effects.

20 With respect to Claims 1, 10 and 17 of the '594 Patent (and therefore all asserted claims),
21 the Lovaza PDR does not the claimed pharmaceutical composition with the recited fatty acid
22 compositions or administration period. The Lovaza PDR further does not disclose or suggest a
23 method of administering the claimed pharmaceutical composition to effect the recited TG and
24 LDL-C effects.

1 Further, with respect to Claims 4, 13 and 20, this reference fails to disclose or suggest the
2 administration of the claimed pharmaceutical composition to effect the recited TG and LDL-C
3 effects. With respect to Claims 5, 14 and 21, this reference fails to disclose or suggest the
4 administration of the claimed pharmaceutical composition to effect the recited reduction in
5 Apolipoprotein B. With respect to Claims 6, 15, and 22, this reference fails to disclose or
6 suggest the administration of the claimed pharmaceutical composition to effect the recited
7 reduction in VLDL-C. With respect to Claim 24, this reference fails to disclose or suggest the
8 recited fatty acids other than ethyl eicosapentaenoate.

9 (9) Maki

10 Maki administered 1.52g/day DHA supplements to patients with below-average levels of
11 HDL-C. Maki does not administer EPA of the purity recited in the claims.

12 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Maki
13 disclose or suggest elements of the '594 Claims. The cited portions of Maki do not disclose or
14 suggest these elements at least because they do not disclose or suggest identifying a group of
15 subjects with the recited very high TG levels. The cited portions of Maki further do not disclose
16 or suggest the claimed pharmaceutical composition with the recited fatty acid compositions,
17 dosage, or administration period. The cited portions of Maki further do not disclose or suggest a
18 method of administering the claimed pharmaceutical composition to effect the recited TG and
19 LDL-C effects.

20 With respect to Claims 1, 10 and 17 of the '594 Patent (and therefore all asserted claims),
21 Maki does not disclose or suggest identifying a group of subjects with the recited very high TG
22 level. Maki also does not disclose or suggest the claimed pharmaceutical composition with the
23 recited fatty acid compositions, dosage, or administration period. Maki further does not disclose
24

1 or suggest a method of administering the claimed pharmaceutical composition to effect the
2 recited TG and LDL-C effects.

3 Further, with respect to Claims 4, 13 and 20, this reference fails to disclose or suggest the
4 administration of the claimed pharmaceutical composition to effect the recited TG and LDL-C
5 effects. With respect to Claims 5, 14 and 21, this reference fails to disclose or suggest the
6 administration of the claimed pharmaceutical composition to effect the recited reduction in
7 Apolipoprotein B. With respect to Claims 6, 15, and 22, this reference fails to disclose or
8 suggest the administration of the claimed pharmaceutical composition to effect the recited
9 reduction in VLDL-C. With respect to Claims 7, 16, and 23, this reference fails to disclose or
10 suggest the group of subjects with the recited very high TG levels. With respect to Claim 24,
11 this reference fails to disclose or suggest the recited fatty acids other than ethyl
12 eicosapentaenoate.

13 (10) Matsuzawa

14 Matsuzawa administered Epadel to patients with hyperlipaemia in order to study its long-
15 term use in the treatment of the disease and was not placebo controlled.

16 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of
17 Matsuzawa disclose or suggest elements of the '594 Claims. The cited portions of Matsuzawa
18 do not disclose or suggest these elements at least because they do not disclose or suggest
19 identifying a group of subjects with the recited very high TG levels. The cited portions of
20 Matsuzawa further do not disclose or suggest a method of administering the claimed
21 pharmaceutical composition to effect the recited TG and LDL-C effects.

22 With respect to Claims 1, 10 and 17 of the '594 Patent (and therefore all asserted claims),
23 Matsuzawa does not disclose or suggest identifying a group of subjects with the recited very high
24

1 TG level. Matsuzawa further does not disclose or suggest a method of administering the claimed
2 pharmaceutical composition to effect the recited TG and LDL-C effects.

3 Further, with respect to Claims 4, 13 and 20, this reference fails to disclose or suggest the
4 administration of the claimed pharmaceutical composition to effect the recited TG and LDL-C
5 effects. With respect to Claims 5, 14 and 21, this reference fails to disclose or suggest the
6 administration of the claimed pharmaceutical composition to effect the recited reduction in
7 Apolipoprotein B. With respect to Claims 6, 15, and 22, this reference fails to disclose or
8 suggest the administration of the claimed pharmaceutical composition to effect the recited
9 reduction in VLDL-C. With respect to Claims 7, 16, and 23, this reference fails to disclose or
10 suggest the group of subjects with the recited very high TG levels. With respect to Claim 24,
11 this reference fails to disclose or suggest the recited fatty acids other than ethyl
12 eicosapentaenoate.

13 (11) Mori 2000

14 Mori 2000 aimed to determine whether EPA and DHA have differential effects on serum
15 lipids and lipoproteins, glucose and insulin in humans.

16 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Mori
17 2000 disclose or suggest elements of the '594 Claims. The cited portions of Mori 2000 do not
18 disclose or suggest these elements at least because they do not disclose or suggest identifying a
19 group of subjects with the recited very high TG levels. The cited portions of Mori 2000 further
20 do not disclose or suggest the claimed pharmaceutical composition with the recited
21 administration period. The cited portions of Mori 2000 further do not disclose or suggest the
22 recited TG and LDL-C effects in the at least one subject with the claimed TG level.

23 With respect to Claims 1, 10 and 17 of the '594 Patent (and therefore all asserted claims),
24 Mori 2000 does not disclose or suggest identifying a group of subjects with the recited very high

1 TG level. Mori 2000 also does not disclose or suggest the claimed pharmaceutical composition
2 with the recited administration period. Mori 2000 further does not disclose or suggest the recited
3 TG and LDL-C effects in the at least one subject with the claimed TG level.

4 Further, with respect to Claims 4, 13 and 20, this reference fails to disclose or suggest the
5 recited TG and LDL-C effects in the at least one subject with the claimed TG level. With respect
6 to Claims 5, 14 and 21, this reference fails to disclose or suggest the recited reduction in
7 Apolipoprotein B in the at least one subject with the claimed TG level. With respect to Claims 6,
8 15, and 22, this reference fails to disclose or suggest the recited reduction in VLDL-C in the at
9 least one subject with the claimed TG level. With respect to Claims 7, 16, and 23, this reference
10 fails to disclose or suggest a group of subjects with the recited very high TG levels. With respect
11 to Claim 24, this reference fails to disclose or suggest the recited fatty acids other than ethyl
12 eicosapentaenoate.

13 (12) Mori 2006

14 Mori 2006 is a review which reports data from clinical trials which compared the
15 independent effects of EPA and DHA in individuals at increased risk of cardiovascular disease.

16 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Mori
17 2006 disclose or suggest elements of the '594 Claims. The cited portions of Mori 2006 do not
18 disclose or suggest these elements at least because they do not disclose or suggest identifying a
19 group of subjects with the recited very high TG levels. The cited portions of Mori 2006 further
20 do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid
21 compositions or dosage. The cited portions of Mori 2006 further do not disclose or suggest the
22 recited TG and LDL-C effects.

23 With respect to Claims 1, 10 and 17 of the '594 Patent (and therefore all asserted claims),
24 Mori 2006 does not disclose or suggest identifying a group of subjects with the recited very high

1 TG level. Mori 2006 also does not disclose or suggest the claimed pharmaceutical composition
2 with the recited fatty acid compositions or dosage. Mori 2006 further does not disclose or
3 suggest the recited TG and LDL-C effects.

4 Further, with respect to Claims 2, 11 and 18, this reference fails to disclose or suggest the
5 group of subjects having the recited baseline LDL-C levels. With respect to Claims 3, 12 and 19,
6 this reference fails to disclose or suggest the subject having the recited baseline lipid levels.
7 With respect to Claims 4, 13 and 20, this reference fails to disclose or suggest the recited TG and
8 LDL-C effects in the at least one subject with the claimed TG level. With respect to Claims 5,
9 14 and 21, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in
10 the at least one subject with the claimed TG level. With respect to Claims 6, 15, and 22, this
11 reference fails to disclose or suggest the recited reduction in VLDL-C in the at least one subject
12 with the claimed TG level. With respect to Claims 7, 16, and 23, this reference fails to disclose
13 or suggest the group of subjects with the recited very high TG levels. With respect to Claim 24,
14 this reference fails to disclose or suggest the recited fatty acids other than ethyl
15 eicosapentaenoate.

16 (13) Nozaki

17 Nozaki is directed to administration of 2.7 g ethyl icosapentate per day for 6 months. The
18 purity of the composition is reported as 90%. The study was not placebo controlled and was
19 conducted in 14 hypercholesterolemic subjects. The average baseline TG level was only 165
20 mg/dL, while the baseline LDL-C level was 185 mg/dL, which is unusually high for this TG
21 patient population.

22 The portions of Nozaki cited by Defendants do not disclose or suggest elements of the
23 '594 patent claims. For example, the cited portions of Nozaki do not disclose or suggest
24 administration of EPA with the recited purity to a subject with the recited very high TG levels

1 who does not receive concurrent lipid altering therapy. The cited portions of Nozaki further do
2 not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid
3 compositions or dosage. The cited portions of Nozaki further do not disclose or suggest a
4 method to effect the recited TG reduction without substantially increasing LDL-C in a subject
5 with the recited very high TG levels.

6 Defendants assert that certain cited sections of Nozaki disclose or suggest elements of the
7 '594 Claims. The cited portions of Nozaki do not disclose or suggest these elements at least
8 because they do not disclose or suggest administration of EPA with the recited purity to a subject
9 with the recited very high TG levels who does not receive concurrent lipid altering therapy. The
10 cited portions of Nozaki further do not disclose or suggest the claimed pharmaceutical
11 composition with the recited fatty acid compositions or dosage. The cited portions of Nozaki
12 further do not disclose or suggest a method to effect the recited TG reduction without
13 substantially increasing LDL-C.

14 With respect to Claims 1, 10 and 17 of the '594 Patent (and therefore all asserted claims),
15 Nozaki does not disclose or suggest identifying a group of subjects with the recited very high TG
16 level. Nozaki also does not disclose or suggest the claimed pharmaceutical composition with the
17 recited fatty acid compositions or dosage. Nozaki further does not disclose or suggest the recited
18 TG and LDL-C effects.

19 Further, with respect to Claims 2, 11 and 18, this reference fails to disclose or suggest the
20 group of subjects having the recited baseline LDL-C levels. With respect to Claims 4, 13 and 20,
21 this reference fails to disclose or suggest the recited TG and LDL-C effects. With respect to
22 Claims 5, 14 and 21, this reference fails to disclose or suggest the recited reduction in
23 Apolipoprotein B. With respect to Claims 6, 15, and 22, this reference fails to disclose or
24

1 suggest the recited reduction in VLDL-C. With respect to Claims 7, 16, and 23, this reference
2 fails to disclose or suggest the group of subjects with the recited very high TG levels. With
3 respect to Claim 24, this reference fails to disclose or suggest the recited fatty acids other than
4 ethyl eicosapentaenoate.

5 (14) Omacor PDR

6 The Omacor PDR is the Physicians' Desk Reference describing Omacor.

7 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of the
8 Omacor PDR disclose or suggest elements of the '594 Claims. The cited portions of the Omacor
9 PDR do not disclose or suggest these elements at least because they do not disclose or suggest
10 the claimed pharmaceutical composition with the recited fatty acid compositions or
11 administration period. The cited portions of the Omacor PDR further do not disclose or suggest
12 a method of administering the claimed pharmaceutical composition to effect the recited TG and
13 LDL-C effects.

14 With respect to Claims 1, 10 and 17 of the '594 Patent (and therefore all asserted claims),
15 the Omacor PDR does not the claimed pharmaceutical composition with the recited fatty acid
16 compositions or administration period. The Omacor PDR further does not disclose or suggest a
17 method of administering the claimed pharmaceutical composition to effect the recited TG and
18 LDL-C effects.

19 Further, with respect to Claims 4, 13 and 20, this reference fails to disclose or suggest the
20 administration of the claimed pharmaceutical composition to effect the recited TG and LDL-C
21 effects. With respect to Claims 5, 14 and 21, this reference fails to disclose or suggest the
22 administration of the claimed pharmaceutical composition to effect the recited reduction in
23 Apolipoprotein B. With respect to Claims 6, 15, and 22, this reference fails to disclose or
24 suggest the administration of the claimed pharmaceutical composition to effect the recited

1 reduction in VLDL-C. With respect to Claim 24, this reference fails to disclose or suggest the
2 recited fatty acids other than ethyl eicosapentaenoate.

3 (15) Satoh

4 Satoh administered 1.8g/day of >98% EPA to patients in order to measure the effects of
5 PEA on C-reactive protein and examine how alteration of lipoprotein profile by EPA affects
6 systemic inflammation.

7 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of
8 Satoh disclose or suggest elements of the '594 Claims. The cited portions of Satoh do not
9 disclose or suggest these elements at least because they do not disclose or suggest identifying a
10 group of subjects with the recited very high TG levels. The cited portions of Satoh further do not
11 disclose or suggest the claimed pharmaceutical composition with the recited dosage. The cited
12 portions of Satoh further do not disclose or suggest the recited TG and LDL-C effects in the at
13 least one subject with the claimed TG level.

14 With respect to Claims 1, 10 and 17 of the '594 Patent (and therefore all asserted claims),
15 Satoh does not disclose or suggest identifying a group of subjects with the recited very high TG
16 level. Satoh also does not disclose or suggest the claimed pharmaceutical composition with the
17 recited dosage. Satoh further does not disclose or suggest the recited TG and LDL-C effects in
18 the at least one subject with the claimed TG level.

19 Further, with respect to Claims 4, 13 and 20, this reference fails to disclose or suggest the
20 recited TG and LDL-C effects in the at least one subject with the claimed TG level. With respect
21 to Claims 5, 14 and 21, this reference fails to disclose or suggest the recited reduction in
22 Apolipoprotein B in the at least one subject with the claimed TG level. With respect to Claims 6,
23 15, and 22, this reference fails to disclose or suggest the recited reduction in VLDL-C in the at
24 least one subject with the claimed TG level. With respect to Claims 7, 16, and 23, this reference

1 fails to disclose or suggest a group of subjects with the recited very high TG levels. With respect
2 to Claim 24, this reference fails to disclose or suggest the recited fatty acids other than ethyl
3 eicosapentaenoate.

4 (16) Shinozaki

5 Shinozaki studied the long-term effect of EPA on serum levels of Lipoprotein (a) and
6 lipids such as triglycerides, total cholesterol, and low density lipoprotein particles.

7 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of
8 Shinozaki disclose or suggest elements of the '594 Claims. The cited portions of Shinozaki do
9 not disclose or suggest these elements at least because they do not disclose or suggest identifying
10 a group of subjects with the recited very high TG levels. The cited portions of Shinozaki further
11 do not disclose or suggest the claimed pharmaceutical composition with the recited dosage. The
12 cited portions of Shinozaki further do not disclose or suggest the recited TG and LDL-C effects
13 in the at least one subject with the claimed TG level.

14 With respect to Claims 1, 10 and 17 of the '594 Patent (and therefore all asserted claims),
15 Shinozaki does not disclose or suggest identifying a group of subjects with the recited very high
16 TG level. Shinozaki also does not disclose or suggest the claimed pharmaceutical composition
17 with the recited dosage. Shinozaki further does not disclose or suggest the recited TG and LDL-
18 C effects in the at least one subject with the claimed TG level.

19 Further, with respect to Claims 2, 11 and 18, this reference fails to disclose or suggest the
20 group of subjects having the recited baseline LDL-C levels. With respect to Claims 3, 12 and 19,
21 this reference fails to disclose or suggest the subject having the recited baseline lipid levels.

22 With respect to Claims 4, 13 and 20, this reference fails to disclose or suggest the recited TG and
23 LDL-C effects in the at least one subject with the claimed TG level. With respect to Claims 5,
24 14 and 21, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in

1 the at least one subject with the claimed TG level. With respect to Claims 6, 15, and 22, this
2 reference fails to disclose or suggest the recited reduction in VLDL-C in the at least one subject
3 with the claimed TG level. With respect to Claims 7, 16, and 23, this reference fails to disclose
4 or suggest a group of subjects with the recited very high TG levels. With respect to Claim 24,
5 this reference fails to disclose or suggest the recited fatty acids other than ethyl
6 eicosapentaenoate.

7 (17) Takaku

8 Takaku administered Epadel to patients with hyperlipaemia in order to study its long-
9 term use and was not placebo controlled.

10 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of
11 Takaku disclose or suggest elements of the '594 Claims. The cited portions of Takaku do not
12 disclose or suggest these elements at least because they do not disclose or suggest identifying a
13 group of subjects with the recited very high TG levels. The cited portions of Takaku further do
14 not disclose or suggest a method of administering the claimed pharmaceutical composition to
15 effect the recited TG and LDL-C effects.

16 With respect to Claims 1, 10 and 17 of the '594 Patent (and therefore all asserted claims),
17 Takaku does not disclose or suggest identifying a group of subjects with the recited very high TG
18 level. Takaku further does not disclose or suggest a method of administering the claimed
19 pharmaceutical composition to effect the recited TG and LDL-C effects.

20 Further, with respect to Claims 2, 11 and 18, this reference fails to disclose or suggest the
21 group of subjects having the recited baseline LDL-C levels. With respect to Claims 3, 12 and 19,
22 this reference fails to disclose or suggest the subject having the recited baseline lipid levels.

23 With respect to Claims 4, 13 and 20, this reference fails to disclose or suggest the recited TG and
24 LDL-C effects in the at least one subject with the claimed TG level. With respect to Claims 5,

1 14 and 21, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in
2 the at least one subject with the claimed TG level. With respect to Claims 6, 15, and 22, this
3 reference fails to disclose or suggest the recited reduction in VLDL-C in the at least one subject
4 with the claimed TG level. With respect to Claims 7, 16, and 23, this reference fails to disclose
5 or suggest a group of subjects with the recited very high TG levels. With respect to Claim 24,
6 this reference fails to disclose or suggest the recited fatty acids other than ethyl
7 eicosapentaenoate.

8 c) The Prior Art Does Not Render the Claims Obvious

9 Defendants have not identified by clear and convincing evidence that the asserted claims
10 of the '594 Patent would have been *prima facie* obvious in light of the references cited, either
11 alone or in combination. As described above, none of the references discloses all of the elements
12 in any of the asserted claims. Defendants chart a laundry list of 66 separate references, without
13 explanation, and argue they somehow must be combined to render obvious the asserted claims.
14 Where Defendants have failed to make disclosures with the specificity required by Local Patent
15 Rule 1-8(d), it has failed to put Plaintiffs on notice of how these references allegedly disclose the
16 claim elements at issue.

17 Defendants' contentions fail to disclose each and every element of the claims of the '594
18 patent. Specifically, Defendants do not contend that the relied upon references disclose the
19 following elements of Claim 1 (and therefore Claims 2-7): (1) identifying a group of subjects
20 having a median triglyceride level of at least 500 mg/dl; or (2) administering the claimed
21 pharmaceutical composition to the at least one subject results in a reduction in triglycerides of at
22 least about 15% without an increase of LDL-C of more than 5%.

23 In addition, Defendants do not contend that the relied upon references disclose the
24 following elements of Claim 10 (and therefore Claims 11-16): (1) identifying a group of subjects

1 having a median triglyceride level of at least 500 mg/dl; or (2) administering the claimed
2 pharmaceutical composition to the at least one subject results in a reduction in triglycerides of at
3 least about 15% without an increase of LDL-C of more than 5%.

4 Further, Defendants do not contend that the relied upon references disclose the following
5 elements of Claim 17 (and therefore Claims 18-26): (1) identifying a group of subjects having a
6 median triglyceride level of at least 500 mg/dl; or (2) administering the claimed pharmaceutical
7 composition to the at least one subject results in a reduction in triglycerides of at least about 15%
8 without an increase of LDL-C of more than 5%.

9 Therefore, Defendants' prior art combinations cannot render the claims *prima facie*
10 obvious.

11 Facts supporting the non-obviousness of the claims of the '594 patent are discussed in
12 detail below. The objective indicia discussed in Section V.O further demonstrate that the '594
13 Patent is not obvious. In short, Defendants have not met their burden of showing that the claims
14 would have been obvious.

15 (1) Defendants Do Not Demonstrate that the Independent
16 Claims of the '594 Patent Would Have Been Obvious

17 (a) Defendants Do Not Demonstrate that a Person of
18 Ordinary Skill in the Art Would Have Had Any
Reason to Replace the Mixed Fish Oil Active
Ingredient in Lovaza with Pure EPA

19 (i) The '594 Patent is not Obvious Over the
20 Omacor PDR/Lovaza PDR, in Combination
with Katayama and/or Matsuzawa, further in
21 view of Nozaki and/or Hayashi, and Further
in View of Leigh-Firbank and/or Mori 2000

22 With respect to the '594 Patent, Defendants present a combination of seven references:
23 "the Omacor PDR/Lovaza PDR in combination with the known clinical benefits of administering
24 pure EPA as evidenced by Katayama and/or Matsuzawa, further in view of Nozaki and/or

1 Hayashi, and further in view of Leigh-Firbank and/or Mori 2000.”⁶²²⁵ Defendants also present
2 charts purporting to assert that an additional 61 references may be combined in order to render
3 the Claims obvious. Not only do Defendants ignore the improbability that a person of ordinary
4 skill would combine 61 separate references, they additionally do not identify any motivation for
5 combining these references.^{6226, 6227} Although Defendants need not point to an explicit statement
6 in the prior art motivating the combination of these references, any assertion of an “apparent
7 reason” to combine must find a basis in the factual record.⁶²²⁸ Defendants’ unsupported cobbling
8
9

10 ⁶²²⁵ Defendants’ Joint Invalidity Contentions at 800.

11 ⁶²²⁶ Defendants’ bare assertion that the asserted claims are obvious “in view of one or more of Omacor or Lovaza (as
12 described in the references cited above in section V.B.2 in view of, at least, the references cited in V.B.3 and 4,
13 including, the ’954 publication, WO ’900, WO ’118, Ando, Grimsgaard, Hayashi, Katayama, Matsuzawa, Matakai,
14 Mori 2000, Nakamura, Nozaki, Okumura, Park, Saito 1998, Saito 2008 Satoh, Shinozaki, Takaku, Yokoyama 2003,
15 Yokoyama 2007, Calabresi, Chan 2002, Chan 2003, Contacos, Geppert, Kelley, Leigh-Firbank, Maki, Mori 2006,
16 Rambjør, Sanders or Theobald,” similarly fails to meet the disclosure requirements of the Nevada Local Patent
17 Rules, and fails to provide any motivation to combine these references. *See* Defendants’ Joint Invalidity
18 Contentions at 792.

15 ⁶²²⁷ Defendants’ bare assertion that “the motivation or reason to combine or modify the prior art to create
16 invalidating combinations under 35 U.S.C. §103 can be found in the references identified above in Section III.C,”
17 and that “[c]ommon sense, design incentives. Market forces, and the background knowledge possessed by a person
18 having ordinary skill in the art provide the reasons or rationales for combining the teachings of multiple references
19 or modifying references to render obvious the claimed inventions of the asserted claims,” fails to meet the disclosure
20 requirements of the Nevada Local Patent Rules. *See* Defendants’ Joint Invalidity Contentions at 790-91.

18 ⁶²²⁸ *See, e.g., In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the
19 formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did
20 not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply
21 the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi*
22 *Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must
23 avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to
24 select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and
elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp.
2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie*
obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding
that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been
motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

1 of selective disclosures represents hindsight reconstruction.⁶²²⁹ Defendants’ contentions are no
2 more than an assertion that certain claim elements were known in the prior art. Throughout their
3 contentions, Defendants’ selectively cite to data points in a reference without considering other
4 disclosures or even the reference as a whole. Each reference, however, must be evaluated for all
5 that it teaches.⁶²³⁰ Accordingly, Defendants fail to meet their burden to establish *prima facie*
6 obviousness.

7 The Lovaza PDR fails to disclose or even suggest the claimed method of reducing
8 triglycerides in a subject with the claimed pharmaceutical composition containing the claimed
9 fatty acid compositions or administration period. The Lovaza PDR further does not disclose a
10 method to effect the specified TG reduction without substantially increasing LDL-C. Indeed, the
11 Lovaza PDR discloses the exact opposite. The EPA/DHA composition of Lovaza causes a
12 significant increase in LDL-C levels in the very high TG patient population, for whom the
13 product is indicated. At most, the Lovaza PDR discloses administration of a prescription fish oil,
14 a combination of approximately 465 mg EPA and 375 mg DHA, as an adjunct to diet to reduce
15 TG levels in adult patients with very-high (≥ 500 mg/dL) TG levels.

16 The proposed combinations do not render the independent claims of the ’594 Patent
17 obvious and Defendants’ burden to prove otherwise is especially difficult because the PTO
18 considered Matsuzawa, Katayama, Mori 2000, and Lovaza (both generally and the Lovaza
19 package insert specifically) during prosecution.⁶²³¹

21 ⁶²²⁹ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under
22 *KSR*, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention
without any explanation as to how or why the references would be combined to produce the claimed invention”).

23 ⁶²³⁰ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

24 ⁶²³¹ See, e.g., *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012)(taking into account that “the
examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention.

1 The analysis of the independent claims of the '594 Patent is incorporated into all asserted
2 claims that depend from those Claims.

3 (a) A Person of Ordinary Skill Would
4 Not Have Been Motivated to
5 Replace the Mixed Fish Oil Active
6 Ingredient in Lovaza with Pure EPA

7 For an invention to be obvious, there must have been an “apparent reason” to make it.
8 The subject matter of the '594 patent claims would not have been obvious in light of these
9 references because a person of ordinary skill would not have been motivated to purify EPA or
10 been able to reasonably expect that the claimed pharmaceutical composition would reduce TG
11 levels without an increase in LDL-C levels.

12 (i) Katayama and/or Matsuzawa
13 Do Not Disclose Purported
14 Known Clinical Benefits of
15 Administering Pure EPA

16 Both Katayama and Matsuzawa are long term studies directed to an investigation of the
17 safety and efficacy of Epedel in patients with a wide range of baseline TG levels. These studies
18 were not placebo controlled. A person of ordinary skill in the art understood that a placebo may
19 itself cause an effect. Without accounting for the placebo effect, a person of ordinary skill in the
20 art would not and could not attribute any observed effect (and the magnitude of that effect) to
21 that of the drug. Any observed effect could be placebo dependent.⁶²³² As discussed above in
22 Section III, a person of ordinary skill would not expect the same LDL-C effect in patients with
23 lower baseline TG levels—the subjects of Katayama and Matsuzawa—as in very-high TG

24 _____
Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear and convincing standard came into play”).

⁶²³²See Grimsgaard at 652 (Although administration of EPA reduced Apo-B compared to baseline, it was not a statistically significant effect when compared to placebo. Grimsgaard’s disclosure highlights the importance of a placebo-controlled study and why results compared only to baseline may be misleading.)

1 patients because patients with higher TG levels had different lipid responses compared to
2 patients with lower TG levels. Patients with very-high TG levels were considered fundamentally
3 different from patients with borderline-high or high TGs from a lipid chemistry, medical, clinical
4 guideline, regulatory, and therapeutic standpoint. As previously discussed, a person of ordinary
5 skill in the art would expect to see an increase in LDL-C levels when omega-3 fatty acids were
6 administered to patients with normal, borderline-high or high TG levels. Therefore, the prior art
7 Defendants rely upon to show that EPA did not increase LDL-C levels in normal, borderline-
8 high or high TG patients, was expected. At the priority date of the '594 patent, a person of
9 ordinary skill in the art would have expected an *increase* in LDL-C for very-high TG patients
10 receiving a TG-lowering agent, as a natural consequence of lowering TGs. This pattern had been
11 demonstrated for both fibrates and fish oils and was understood as a direct consequence of TG
12 lowering through increased VLDL particle conversion.

13 Defendants argue that these studies disclose known “clinical benefits” of administering
14 pure EPA, lowering triglycerides without raising LDL-C.⁶²³³ This is an incorrect characterization
15 of these two studies. Katayama and Matsuzawa both were only designed to confirm the safety of
16 long term treatment of Epadel and its ability to lower both serum total cholesterol and TG levels.
17 They do just that. They do not discuss any purported “benefits” observed related to LDL-C.
18 Defendants’ selective citation of LDL-C data from these references represents the improper use
19 of hindsight bias. A person of ordinary skill would understand the focus of Katayama and
20 Matsuzawa to be TG and total cholesterol effects and not LDL-C levels, and would not draw
21 conclusions regarding LDL-C from these studies. Indeed, Katayama does not mention LDL-C
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23 ⁶²³³ Defendants’ Joint Invalidity Contentions at 792-93.
24

1 levels at all. Defendants' characterization of Katayama and Matsuzawa as disclosing the
2 lowering of TG levels without increasing LDL-C to be a "clinical benefit" is incorrect.⁶²³⁴ The
3 references don't disclose or suggest that the LDL-C results obtained were a clinical benefit, nor
4 would a person of ordinary skill view these references as teaching such a benefit for very-high
5 TG patients.

6 Further, both Katayama and Matsuzawa administered only EPA and studied its lipid
7 effects. These studies fail to provide a head to head comparison of EPA versus DHA.
8 Therefore, a person of ordinary skill in the art would not rely on Katayama or Matsuzawa to
9 draw any conclusions related to possible differences between the lipid effects of EPA and DHA.

10 In addition, Katayama and Matsuzawa do not disclose the purity of the Epadel used. The
11 purity of Epadel has varied over time and across different formulations of the product, therefore
12 it is difficult to determine the purity of the version of Epadel used unless it is specified by the
13 disclosure. One cannot simply rely on the fact that Epadel was administered and assume that the
14 composition comprised at least about 96%, by weight of all fatty acids present, EPA, and
15 substantially no DHA, as required by the asserted claims. Defendants fail to provide a reference
16 disclosing the purity of the form of Epadel used in the Katayama and Matsuzawa studies.

17 Nishikawa,⁶²³⁵ published in 1997, discloses a form of Epadel that was a 91% E-EPA preparation.
18 Nishikawa reflects that versions of Epadel used in some clinical studies do not have the requisite
19 purity.⁶²³⁶

22 ⁶²³⁴ Defendants' Joint Invalidity Contentions at 792-93.

23 ⁶²³⁵ Nishikawa et al., *Effects of Eicosapentaenoic Acid (EPA) on Prostacyclin Production in Diabetics: GC/MS
Analysis of PGI₂ and PGI₃ Levels*, 19 METHODS FIND EXP CLIN PHARMACOL. 429 (1997).

24 ⁶²³⁶ See also, Ando at 2177 (Epadel with purity greater than 91%), Nakamura at 23 (Epadel with purity > 90%).

1 Further, Katayama and Matsuzawa were small studies conducted in only Japanese
2 patients. These studies would not have been extrapolated to Western populations because the
3 Japanese diet contains much more fish and has a number of other different attributes. The
4 Japanese consume a higher amount of EPA and DHA in their diets than Western populations. In
5 fact, Yokoyama 2007 (cited in Defendants' contentions) states that the results from studies where
6 the patient population is exclusively Japanese cannot be generalized to other populations.⁶²³⁷
7 The Japanese diet comprises between 8 and 15 times more EPA and DHA than the typical
8 Western Diet. The Western diet typically consists of higher amounts of polyunsaturated omega-
9 6 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand
10 that the Japanese respond differently to lipid lowering agents than Westerners.

11 Defendants rely on Katayama to demonstrate the "known clinical benefits of
12 administering pure EPA - lowering triglycerides without raising LDL-C."⁶²³⁸ However,
13 Katayama was directed to an investigation of the safety and efficacy of Epadel during long-term
14 treatment in patients with hyperlipidemia.⁶²³⁹ Katayama does not disclose *any* LDL-C related
15 data or describe *any* LDL-C effects, and a person of ordinary skill would not understand that
16 reference to provide any such disclosure. The only results disclosed by Katayama were a
17 significant reduction in TGs and total cholesterol when Epadel (EPA of undisclosed purity) was
18 administered to patients with borderline-high to high TG levels, and its safety for long term use
19 in this patient population.⁶²⁴⁰ In addition to Katayama's lack of disclosure regarding LDL-C,
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21 ⁶²³⁷ Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to
other populations.").

22 ⁶²³⁸ Defendants' Joint Invalidity Contentions at 792-93.

23 ⁶²³⁹ Katayama at 2.

24 ⁶²⁴⁰ *Id.* at 16.

1 Defendants identify no other basis upon which a person of ordinary skill would have sought to
2 combine the composition disclosed in Katayama with the Lovaza PDR.

3 Defendants similarly rely on Matsuzawa to demonstrate the “known clinical benefits of
4 administering pure EPA - lowering triglycerides without raising LDL-C.”⁶²⁴¹ However,
5 Matsuzawa included 26 participants, of whom 23 were adopted for the evaluation of overall
6 safety, 22 were adopted for the evaluation of usefulness, 20 were adopted for evaluation of
7 general improvement, 15 were adopted for improvement in serum total cholesterol levels, and 13
8 were evaluated for improvement in serum triglycerides levels.⁶²⁴² It is unclear which of the 26
9 patients were included in each separate evaluation; therefore one cannot determine the baseline
10 lipid characteristics for each subset of patients evaluated. Further, the small sample size and lack
11 of a placebo control makes it less likely that the results of this study can be generalized as an
12 effect on any population as a whole and provides no insight with respect to the very-high TG
13 patient population.

14 Matsuzawa discloses that 3 of the 26 participants had 400 mg/dL < TG < 1000 mg/dL,
15 and one participant with TG levels > 1,000 mg/dL.⁶²⁴³ However, when analyzing the lipid
16 impact of Epadel, Matsuzawa excluded the patient with a TG level greater than 1,000 mg/dL
17 because he was a “heavy drinker” and the “effect of alcohol made it impossible to assess
18 triglyceride levels.”⁶²⁴⁴ Fig. 4, which depicts the changes in serum triglycerides, shows that the
19 mean triglycerides of the 12 patients with TG greater than 150 mg/dL was well below 500
20 mg/dL. Furthermore, as shown in Table 4, patients with TG levels above 500 mg/dL (other than
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22 ⁶²⁴¹ Defendants’ Joint Invalidity Contentions at 792-93.

23 ⁶²⁴² Matsuzawa at 7 and 19.

24 ⁶²⁴³ *Id.* at 23.

⁶²⁴⁴ *Id.* at 10.

1 the excluded patient who had TG above 1,000 mg/dL) were not treated in the study with EPA (of
2 undisclosed purity). The identification of three patients with TG levels between 400 and less
3 than 1,000 mg/dL does not disclose a patient with TG levels above 500 mg/dl, and a person of
4 ordinary skill would not understand that the reference makes any such disclosure. As discussed
5 above, one of ordinary skill in the art would not expect LDL-C to increase in a patient with TG
6 less than 500 mg/dL upon treatment with a TG-lowering agent. Matsuzawa provides no
7 evidence to the contrary.

8 Matsuzawa demonstrated mixed results related to LDL-C over time, at first showing a
9 2% decrease, and then a 1% increase in LDL-C by the end of 52 weeks.⁶²⁴⁵ The disclosure
10 further reflects that the 4 patients with serum triglyceride levels of at least 400 mg/dL were
11 excluded from the LDL-C results because the Friedewald's Equation was used to calculate LDL-
12 C levels. The Friedewald's Equation cannot be used for patients with triglyceride levels of at
13 least 400 mg/dL. Therefore, the LDL-C results only reflect the LDL-C changes in patients with
14 triglyceride levels below 400 mg/dL. Matsuzawa fails to provide any information to a person of
15 ordinary skill regarding the LDL-C effect in the very-high TG population. A person of ordinary
16 skill in the art, however, would have expected the same treatment in patients with very high TG
17 levels to produce a substantial increase in LDL-C. In addition, Matsuzawa acknowledges that
18 there have been conflicting results related to the LDL-C impact of EPA preparations that lowered
19 triglyceride levels.⁶²⁴⁶ At best, Matsuzawa demonstrates the uncertainty and confusion related to
20 the LDL-C effect EPA had on patients with hyperlipidemia. Further, Defendants fail to identify
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22 ⁶²⁴⁵ *Id.* at 11.

23 ⁶²⁴⁶ *Id.* at 15. Matsuzawa suggests the conflicting results are due to differences in the EPA content of the EPA
24 preparation administered. However, Matsuzawa fails to identify the specific conflicting studies, disclose the specific
compositions used, or identify the patient populations were observed.

1 any other basis upon which a person of ordinary skill would have sought to combine the
2 composition disclosed in Matsuzawa with the Lovaza PDR.

3 Therefore, Katayama and Matsuzawa fail to substantiate Defendants' assertion that
4 compositions comprising EPA as recited in the asserted claims lowers triglycerides without
5 substantially increasing LDL-C. Further, other studies cited by Defendants suggest that EPA
6 increases LDL-C.⁶²⁴⁷ Defendants identify no other basis upon which a person of ordinary skill
7 would have sought to combine the Lovaza PDR with Katayama, Matsuzawa, Leigh-Firbank
8 and/or Mori 2000 or reasonably expected that such a combination would successfully yield the
9 asserted claims of the '594 patent.

10 (ii) Nozaki and/or Hayashi
11 Would Not Have Rendered
12 the Asserted Claims Obvious

12 Defendants contend that the asserted claims of the '594 patent would have been obvious
13 in view Nozaki and/or Hayashi in combination with other references, but they do not explain
14 why Nozaki and/or Hayashi render the asserted claims obvious or what element of the asserted
15 claims is found in Nozaki or Hayashi. Nozaki and Hayashi do not disclose or suggest a
16 reduction in triglycerides without increasing LDL-C when purified EPA is administered to the
17 very high TG patient population.

18 Nozaki administered 2.7 g/day of 90% EPA (DHA < 1%) to 14 primary
19 hypercholesterolemia subjects. A person of ordinary skill would not have found the results of
20 Nozaki reliable. Nozaki was not placebo-controlled, nor did the study compare lipid effect of
21 EPA to that of DHA. The average baseline TG level was only 165 mg/dL, while the baseline
22 LDL-C level was 185 mg/dL, which is unusually high for this TG patient population. A person

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24 ⁶²⁴⁷ See, e.g., Rambjor.

1 of skill in the art would not look to a study consisting of patients with baseline TG levels of 165
2 mg/dL in order to understand the impact of EPA therapy on the very high TG patient population.
3 Further, a person of ordinary skill would understand that the baseline LDL-C level in this small
4 patient population were abnormally high and would not have relied upon these results. Further,
5 the person of skill in the art would not have looked to this patient population to predict the Apo-
6 B or LDL-C effect of EPA therapy on very high TG patients. Nozaki acknowledges that as of
7 1991, “[t]here is still controversy concerning the effects of fish oil” on LDL and HDL cholesterol
8 levels.⁶²⁴⁸ Nozaki does not provide a motivation or reasonable expectation of success for
9 administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA and
10 substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL, to
11 effect a reduction in triglycerides without increasing LDL-C when purified EPA is administered
12 to the very high TG patient population.

13 In Hayashi, 1.8 g/day of EPA was administered to 28 patients for 8 weeks. The purity of
14 the EPA and the DHA content in the composition that was administered is unknown. A person
15 of ordinary skill would not have found the results of Hayashi reliable. The study involved 28
16 patients and it was conducted for only 8 weeks. Hayashi shows that changes in Apo-B and LDL-
17 C were not statistically significant.⁶²⁴⁹ Further, the person of skill in the art would not have
18 looked to this patient population to predict the Apo-B or LDL-C effect of EPA therapy on very
19 high TG patients. Hayashi does not provide a motivation or reasonable expectation of success
20 for administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA
21 and substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL,
22

23 ⁶²⁴⁸ Nozaki at 256.

24 ⁶²⁴⁹ Hayashi at 26, Table I.

1 to effect a reduction in triglycerides without increasing LDL-C when purified EPA is
2 administered to the very high TG patient population.

3 Further, Hayashi was a small study conducted in only Japanese patients and was not
4 placebo controlled. This study would not have been extrapolated to Western populations
5 because the Japanese diet contains much more fish and has a number of other different attributes.
6 The Japanese consume a higher amount of EPA and DHA in their diets than Western
7 populations. In fact, Defendants' own reference states that the results from studies where the
8 patient population is exclusively Japanese cannot be generalized to other populations.⁶²⁵⁰ The
9 Japanese diet comprises between 8 and 15 times more EPA and DHA than typical the typical
10 Western diet. The Western diet typically consists of higher amounts of polyunsaturated omega-6
11 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand that
12 the Japanese respond differently to lipid lowering agents than Westerners.

13 Further, Defendants have failed to offer a purported combination of references as part of
14 their obviousness contentions that include Nozaki and Hayashi. Similarly, they fail to offer any
15 motivation to combine Nozaki and Hayashi with the other references of their purported
16 obviousness combinations. Therefore, Defendants should be precluded from relying on these
17 references.

18 (iii) Leigh-Firbank and/or Mori
19 2000 Do Not Disclose
20 Purported Knowledge that
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22

23 ⁶²⁵⁰ Yokoyama 2007 at 1097 (“Because our population was exclusively Japanese, we cannot generalise our results to
24 other populations.”).

1
2
3 Defendants assert, incorrectly, that “it was known in the art as of February 2009 that
4 administration of DHA (alone or in a mixture) resulted in the negative effect of increasing LDL-
5 C levels.”⁶²⁵¹ Defendants’ caveat of DHA being “alone or in a mixture” is telling that it was *not*
6 known that DHA alone resulted in an increase in LDL-C levels. Further, the prior art Defendants
7 rely upon to support this statement does not categorize the increase in LDL-C as a “negative
8 effect” in light of the overall impact of the disclosed composition on all lipid parameters.
9 Further, the patients in Leigh Firbank and Mori 2000 had normal to high baseline TG levels. As
10 discussed above in Section III, a person of ordinary skill would not expect the same LDL-C
11 effect in patients with lower baseline TG levels—the subjects of Leigh-Firbank and Mori 2000—
12 as in very-high TG patients because patients with higher TG levels had different lipid responses
13 compared to patients with lower TG levels. Patients with very-high TG levels were considered
14 fundamentally different from patients with borderline-high or high triglycerides from a lipid
15 chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint. Instead, a person
16 of ordinary skill in the art would have expected that fish oils (and other TG lowering agents)
17 would not increase LDL-C substantially in patients with normal to borderline high TG levels, but
18 would substantially increase LDL-C in patients with very high TG levels.

19 Defendants rely upon Leigh-Firbank to demonstrate that it was known that “DHA was
20 responsible for the increase in LDL-C levels.” Leigh-Firbank, however, administered fish oil,
21 comprising 1.67 g of EPA and 1.34 g of DHA per day, for six weeks, to patients with triglyceride
22 levels between 133 mg/dL and 354 mg/dL. Leigh-Firbank does not evaluate the effect of either

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24 ⁶²⁵¹ Defendants’ Joint Invalidity Contentions at 796.

1 EPA or DHA alone because it did not disclose the administration of EPA or DHA alone. A
2 person of ordinary skill would similarly understand that Leigh-Firbank does not offer any
3 disclosure regarding the effect of EPA and DHA separately or gain any understanding of the
4 separate impact of DHA or EPA on any lipid parameter. Mori 2006 (also cited by defendants)
5 acknowledges that EPA- and DHA-enriched oils, which are contaminated with other saturated
6 and polyunsaturated fatty acids, are not suitable for evaluating the independent effects of EPA
7 and DHA.⁶²⁵² A person of ordinary skill would understand that studies directed to EPA and
8 DHA-enriched oils are not indicative or predictive of the impact of the EPA or DHA alone on
9 lipid parameters. Defendants' own prior art refutes the validity of the results disclosed by Leigh-
10 Firbank, because purified EPA and DHA were not administered separately.

11 Leigh-Firbank is a poor quality study. Leigh-Firbank makes conclusion on independent
12 effects of EPA and DHA individually, even though it administered a combination of EPA and
13 DHA, not EPA alone and DHA alone. The error in this approach is evident from the conclusions
14 of Leigh-Firbank itself. For example, Leigh-Firbank concludes that changes in platelet
15 phospholipid EPA were *independently* associated with the decrease in fasting TGs,⁶²⁵³ and DHA
16 is *not* associated with decreases in fasting TGs. This is incorrect and inconsistent with the state
17 of the art and numerous publications cited by Defendants.⁶²⁵⁴ It is widely accepted that DHA
18 also has a hypotriglyceridemic effect.

19 Mori 2000 compared the administration of 4g daily of EPA, DHA, or olive oil to patients
20 with borderline-high TG levels for 6 weeks. Although Mori 2000 discloses an increase in LDL-
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22 ⁶²⁵² Mori 2006 at 96.

23 ⁶²⁵³ Leigh-Firbank at 440.

24 ⁶²⁵⁴ See, e.g. Grimsgaard at 654.

1 C for patients administered DHA, it also teaches that DHA is preferable to EPA—thus teaching
2 away from the claimed invention. “A reference may be said to teach away when a person of
3 ordinary skill, upon [examining] the reference, would be discouraged from following the path set
4 out in the reference, or would be led in a direction divergent from the path that was taken by the
5 applicant.”⁶²⁵⁵ Although teaching away is fact-dependent, “in general, a reference will teach
6 away if it suggests that the line of development flowing from the reference’s disclosures is
7 unlikely to be productive of the result sought by the applicant.”⁶²⁵⁶

8 Mori 2000 concludes that the changes effected by DHA supplementation “may represent
9 a more favorable lipid profile than after EPA supplementation.”⁶²⁵⁷ For example, it states that
10 “DHA, but not EPA, improved serum lipid status, in particular a small increase in HDL
11 cholesterol and a significant increase in the HDL₂-cholesterol subfraction, without adverse
12 effects on fasting glucose concentrations.”⁶²⁵⁸ Mori 2000 also states that “[d]espite an increase
13 in LDL cholesterol after DHA supplementation, LDL particle size increased—a finding that may
14 be favorable.”⁶²⁵⁹ Therefore, based on the “favorable lipid profile” of DHA over EPA in Mori
15 2000, a person of ordinary skill would *not* have been motivated to use EPA to treat patients, the
16 exact opposite of what Defendants argue in their contentions. Therefore, the art taught away
17 from using purified EPA. At a minimum, the teachings of Mori 2000 provide reasons for
18 favoring or selecting DHA over EPA and highlight Defendants’ hindsight-driven focus on EPA,
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20 ⁶²⁵⁵ *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994).

21 ⁶²⁵⁶ *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994); *see also Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354
22 (Fed. Cir. 2012) (quoting *Gurley*); *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1552 (Fed. Cir. 1983)
23 (“[P]roceed[ing] contrary to the accepted wisdom of the prior art ... is strong evidence of nonobviousness.”).

24 ⁶²⁵⁷ Mori 2000 at 1092.

⁶²⁵⁸ Mori 2000 at 1088.

⁶²⁵⁹ Mori 2000 at 1092.

1 despite disclosed advantages of DHA. A person of ordinary skill would take into consideration
2 the entire disclosure, including lipid effects other than LDL-C. Engaging in hindsight bias,
3 Defendants ignore, without explanation, the other effects of DHA that a person of ordinary skill
4 would consider. Defendants fail to identify any other basis upon which a person of ordinary skill
5 would have sought to combine Mori 2000 with the Lovaza PDR.

6 Therefore, Leigh-Firbank and Mori 2000 fail to substantiate Defendants' assertion that it
7 was known that DHA alone was responsible for the increase in LDL-C levels. Further,
8 Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or
9 has little effect on LDL-C levels.⁶²⁶⁰ Defendants identify no other basis upon which a person of
10 ordinary skill would have sought to combine the Lovaza PDR with Katayama, Matsuzawa,
11 Leigh-Firbank and/or Mori 2000.

12 (ii) The '594 Patent is not Obvious Over the
13 Omacor PDR/Lovaza PDR, in Combination
14 with Katayama and/or Matsuzawa, and/or
15 Takaku, further in view of Nozaki and/or
Hayashi, and Further in View of
Grimsgaard, Mori 2000 and/or Maki

16 With respect to the '594 Patent, Defendants present a combination of nine references:
17 "the Omacor PDR/Lovaza PDR, in combination with the known clinical benefits of
18 administering pure EPA as evidenced by Katayama, Matsuzawa, and/or Takaku, further in view
19 of Nozaki and/or Hayashi, and further in view of Grimsgaard, Mori 2000 and/or Maki."⁶²⁶¹
20 Defendants also present charts purporting to assert that an additional 58 references may be
21 combined in order to render the Claims obvious. Not only do Defendants ignore the
22 improbability that a person of ordinary skill would combine 58 separate references, they

23 ⁶²⁶⁰ See e.g., Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

24 ⁶²⁶¹ Defendants' Joint Invalidity Contentions at 793.

1 additionally do not identify any motivation for combining these references. Although
2 Defendants need not point to an explicit statement in the prior art motivating the combination of
3 these references, any assertion of an “apparent reason” to combine must find a basis in the
4 factual record.⁶²⁶² Defendants’ unsupported cobbling of selective disclosures represents
5 hindsight reconstruction.⁶²⁶³ Defendants’ contentions are no more than an assertion that certain
6 claim elements were known in the prior art. Throughout their contentions, Defendants’
7 selectively cite to data points in a reference without considering other disclosures or even the
8 reference as a whole. Each reference, however, must be evaluated for all that it teaches.⁶²⁶⁴
9 Accordingly, Defendants fail to meet their burden to establish *prima facie* obviousness.

10 The Omacor PDR and Lovaza PDR fail to disclose or even suggest the claimed method
11 of reducing triglycerides in a subject with the claimed pharmaceutical composition with the
12 recited fatty acid compositions or administration period. The Omacor PDR and Lovaza PDR
13 further do not disclose a method to effect the claimed TG reduction without substantially
14 increasing LDL-C. Indeed, the Omacor PDR and Lovaza PDR disclose the opposite: EPA/DHA
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16 ⁶²⁶² See, e.g., *In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the
17 formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did
18 not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply
19 the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi*
20 *Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must
21 avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to
22 select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and
23 elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp.
24 2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie*
obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding
that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been
motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

⁶²⁶³ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under
KSR, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention
without any explanation as to how or why the references would be combined to produce the claimed invention”).

⁶²⁶⁴ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

1 causes a significant increase in LDL-C levels in a very high TG patient population, for whom the
2 product (Lovaza/Omacor) is indicated. At most, the Omacor PDR and Lovaza PDR disclose
3 administration of a prescription fish oil, a combination of approximately 465 mg EPA and 375
4 mg DHA, as an adjunct to diet to reduce TG levels in adult patients with very-high (at least 500
5 mg/dL) TG levels. The proposed combinations do not render the independent claims of the '594
6 Patent obvious and Defendants' burden to prove otherwise is especially difficult because the
7 PTO considered Matsuzawa, Katayama, and Mori 2000, Grimsgaard, Maki, and Lovaza (both
8 generally and the Lovaza package insert specifically) during prosecution.⁶²⁶⁵

9 The analysis of the independent claims of the '594 Patent is incorporated into all asserted
10 claims that depend from those Claims.

11 (a) A Person of Ordinary Skill Would
12 Not Have Been Motivated to
13 Replace the Mixed Fish Oil Active
Ingredient in Omacor/Lovaza with
EPA of the Claimed Purity

14 For an invention to be obvious, there must have been an "apparent reason" to make it.
15 The subject matter of the '594 patent claims would not have been obvious in light of these
16 references because a person of ordinary skill would not have been motivated to purify EPA or
17 been able to reasonably expect that the claimed pharmaceutical composition would reduce TG
18 levels without an increase in LDL-C levels.

19 (i) Grimsgaard, Katayama,
20 Matsuzawa and/or Takaku
Do Not Disclose Purported

21
22 _____
23 ⁶²⁶⁵ See, e.g., *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012)(taking into account that "the
24 examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention.
Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear
and convincing standard came into play").

1
2
3 Defendants rely on Grimsgaard, Katayama, Matsuzawa and/or Takaku to demonstrate the
4 “known clinical benefits of administering pure EPA - lowering triglycerides without raising
5 LDL-C.” As discussed in Section V.N.3.c.1.a.i.a.i, incorporated herein by reference, Katayama
6 and Matsuzawa merely confirm the safety of long term treatment of Epadel and its ability to
7 lower both serum total cholesterol and triglyceride levels. They do not discuss any purported
8 “benefits” observed related to LDL-C. Katayama and Matsuzawa do not disclose or suggest that
9 the LDL-C results obtained were a clinical benefit.

10 Defendants also rely on Grimsgaard to support their assertion that “administration of
11 purified EPA-E reduced TG levels while minimally impacting the LDL-C levels.”⁶²⁶⁶ However,
12 the results of Grimsgaard demonstrate that both EPA and DHA had no measureable impact on
13 LDL-C levels, and in fact were indistinguishable from the control (placebo) group.

14 Grimsgaard examined the effect of 3.8g/day of EPA versus 3.6g/day of DHA
15 administered to people with normal triglyceride levels for 7 weeks.⁶²⁶⁷ The results from the
16 Grimsgaard study show that both DHA and EPA reduce triglycerides. The authors state that the
17 net decrease in triglycerides was consistently greater for DHA. Grimsgaard also concludes that
18 DHA may be responsible for the beneficial increase in HDL-C observed with some n-3 fatty acid
19 supplements, which is consistent with previous studies which “suggested that serum HDL-C is
20 better maintained with oil rich in DHA than oil rich in EPA.”⁶²⁶⁸ Although Grimsgaard states

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22 ⁶²⁶⁶ Defendants’ Joint Invalidity Contentions at 796.

23 ⁶²⁶⁷ Defendants state in their Joint Invalidity Contentions at 211 that Grimsgaard was conducted in patients with TG
24 levels in the borderline-high/high ranges. This is incorrect; Grimsgaard was conducted in patients with normal TG
levels. (See Grimsgaard at Abstract (describing participants as “healthy”) and Table 4).

⁶²⁶⁸ Grimsgaard at 654.

1 that EPA may produce a small decrease in serum total cholesterol, it does not specifically
 2 comment on EPA's effect on LDL-C.

3 Defendants completely misconstrue the results of Grimsgaard. Defendants attempt to
 4 characterize a non-significant increase in LDL-C by DHA and a non-significant decrease in
 5 LDL-C by EPA, as confirmation "that administration of purified DHA results in increased LDL-
 6 C levels while administration of purified EPA resulted in a decrease in LDL-C levels."⁶²⁶⁹ The
 7 results of Grimsgaard, reproduced below, show that EPA and DHA's impact on LDL-C were the
 8 same as placebo (corn oil); that is, there was no difference between EPA, DHA, or placebo's
 9 effect on LDL-C levels. Further, although administration of EPA reduced Apo-B compared to
 10 baseline, it was not a statistically significant effect when compared to placebo. Grimsgaard's
 11 disclosure highlights the importance of a placebo-controlled study and why results compared
 12 only to baseline may be misleading. This type of exaggeration and misinterpretation of the
 13 results published in the prior art is seen throughout the Defendants' Joint Invalidity Contentions.

14 **TABLE 4**
 Serum lipids and apolipoproteins at baseline and change after 7 wk of supplementation with docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), or corn oil

	DHA (n = 72)		EPA (n = 75)		Corn oil (n = 77)		F test: P ¹	Contrasts between groups: P		
	Baseline	Change	Baseline	Change	Baseline	Change		DHA vs EPA	DHA vs corn oil	EPA vs corn oil
Triacylglycerols (mmol/L)	1.24 ± 0.58 ²	-0.22 ± 0.31 ²	1.23 ± 0.57	-0.15 ± 0.40 ⁴	1.22 ± 0.55	0.11 ± 0.34 ⁴	0.0001	0.14	0.0001	0.0001
Total cholesterol (mmol/L)	6.00 ± 0.95	0.03 ± 0.49	5.98 ± 0.94	-0.15 ± 0.55 ⁵	6.02 ± 1.08	0.10 ± 0.55	0.01	0.04	0.4	0.004
LDL cholesterol (mmol/L)	4.06 ± 0.86	0.07 ± 0.46	4.06 ± 0.83	-0.08 ± 0.48	4.04 ± 0.98	0.06 ± 0.48	0.10	—	—	—
HDL cholesterol (mmol/L)	1.36 ± 0.30	0.06 ± 0.13 ³	1.33 ± 0.31	0.01 ± 0.12	1.41 ± 0.28	-0.01 ± 0.11	0.001	0.009	0.0005	0.4
Apolipoprotein A-I (g/L)	1.38 ± 0.21	0.02 ± 0.13	1.38 ± 0.20	-0.04 ± 0.10 ⁵	1.46 ± 0.23	0.00 ± 0.12	0.003	0.0008	0.3	0.02
Apolipoprotein B (g/L)	1.00 ± 0.21	-0.01 ± 0.11	1.01 ± 0.23	-0.03 ± 0.11 ⁵	1.02 ± 0.28	0.02 ± 0.11	0.05	—	—	—
HDL:apolipoprotein A-I	0.97 ± 0.14	0.04 ± 0.07 ³	0.96 ± 0.13	0.04 ± 0.08 ³	0.97 ± 0.12	-0.01 ± 0.06	0.0001	0.8	0.0003	0.0001
Total:HDL cholesterol	4.62 ± 1.19	-0.19 ± 0.52 ⁴	4.70 ± 1.24	-0.13 ± 0.47 ⁵	4.43 ± 1.19	0.11 ± 0.62	0.002	0.4	0.0006	0.007

¹ ANOVA for between-group comparisons of change.

² $\bar{x} \pm$ SD.

³⁻⁵ One-sample t test of difference between baseline and 7 wk: ³ P < 0.001, ⁴ P < 0.01, ⁵ P < 0.05.

20 Grimsgaard concludes that both DHA and EPA lower TG levels but have "differential
 21 effects on lipoprotein and fatty acid metabolism."⁶²⁷⁰ However, Grimsgaard does not conclude

23 ⁶²⁶⁹ Defendants' Joint Invalidity Contentions at 796 n.153.

24 ⁶²⁷⁰ Grimsgaard at 657.

1 that DHA and EPA have differential effects on LDL-C because Table 4 clearly demonstrates that
2 neither DHA nor EPA had a measurable impact on LDL-C. Table 4 demonstrates that EPA and
3 DHA had the same effect on LDL-C. In fact, one of ordinary skill in the art, when reading
4 Grimsgaard, may have been motivated to use purified DHA instead of EPA for the treatment of
5 patients with very-high triglycerides, because net decrease in triglycerides was consistently
6 greater for DHA and DHA caused a statistically significant increase in HDL-C when compared
7 to placebo. Grimsgaard states that “DHA may be responsible for the increase in HDL
8 cholesterol observed with some n-3 fatty acid supplements.”⁶²⁷¹ Grimsgaard makes no such
9 statement regarding LDL-C.

10 Defendants cherry-pick results, regardless of whether the effect is found to be statistically
11 significant compared to placebo, in an attempt to force the studies to support their argument that
12 it was well known to one of ordinary skill in the art that DHA increases LDL-C while EPA did
13 not. This illustrates the hindsight reasoning driving Defendants’ analysis of the prior art and
14 proposed combinations of prior art. Defendants point to a non-significant increase in DHA and
15 non-significant decrease in EPA in Grimsgaard as confirmation “that administration of purified
16 DHA results in increased LDL-C levels while administration of purified EPA resulted in a
17 decrease in LDL-C levels.” The results from Grimsgaard clearly show that EPA and DHA did
18 not have statistically significantly effects on LDL-C compared to placebo.⁶²⁷² A person of
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21 ⁶²⁷¹ Grimsgaard at 654.

22 ⁶²⁷²In Mori 2000, EPA resulted in a non-significant 0.18 mmol/L increase in LDL-C, while DHA caused a
23 statistically significant 0.37 mmol/L increase in LDL-C compared to placebo. Applying the same logic used to
24 interpret Grimsgaard, that non-significant effects are nonetheless confirmation of an effect, Defendants should have
argued that Mori 2000 was confirmation that both EPA and DHA increases LDL-C. However, they do not make
such arguments for the obvious reason that it does not support their argument that EPA was known to have little or
no impact on LDL-C levels.

1 ordinary skill would not draw conclusions regarding differences between EPA and DHA based
2 on statistically insignificant results.

3 Defendants also rely on Takaku to support their assertion that “clinical benefits of
4 administering purified EPA—lowering triglycerides without raising LDL-C” was known in the
5 art.⁶²⁷³ Similar to Katayama and Matsuzawa, Takaku was conducted to test the efficacy and
6 safety of Epadel (of undisclosed purity)⁶²⁷⁴ based on long-term administration.⁶²⁷⁵

7 A person of ordinary skill would not have concluded based on Takaku that EPA lowers
8 triglycerides without raising LDL-C, because of its unreliable study method. Takaku candidly
9 acknowledges that “only a few subjects were examined” and cautions against drawing a
10 conclusion “only from the results of the present study.”⁶²⁷⁶ Because the study did not include
11 any placebo control, a person of ordinary skill in the art would understand these reports do not
12 provide the ability to conclude that the observed lipid effects would have occurred independent
13 of the drug that is administered. In addition, the study was conducted exclusively in Japanese
14 patients, and a person of ordinary skill would not have expected the results to be applicable to the
15 general population.⁶²⁷⁷

16 The mean baseline triglyceride level of the patients in Takaku was 245 mg/dL, and a
17 person of ordinary skill would not have expected the results to be applicable to patients with
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19 ⁶²⁷³ Defendants’ Joint Invalidation Contentions at 793.

20 ⁶²⁷⁴ It is possible that the version of Epadel used in the Katayama study fails to meet the purity limitation required by
21 the claims. See Nishikawa (91% E-EPA preparation), Ando at 2177 (Epadel with purity greater than 91%),
Nakamura at 23 (Epadel with purity > 90%).

22 ⁶²⁷⁵ Takaku at ICOSAPENT_DFNDT00006834.

23 ⁶²⁷⁶ Takaku at ICOSAPENT_DFNDT00006897.

24 ⁶²⁷⁷ Yokoyama 2007 at 1097 (“[b]ecause our population was exclusively Japanese, we cannot generalise our results
to other populations.”)

1 triglycerides above 500 mg/dL. Takaku also excluded 6 subjects from the LDL-C study because
2 measurement was not feasible due to “insufficient sample.”⁶²⁷⁸ It is possible that patients with
3 triglycerides above 500 mg/dL were among those excluded because of the challenges involved in
4 calculating LDL-C levels when triglyceride level is above 400 mg/dL.⁶²⁷⁹ Moreover, the study
5 does not provide different LDL-C graphs based on the baseline triglyceride levels.⁶²⁸⁰ Therefore,
6 it is impossible to determine whether the patients with triglycerides above 500 mg/dL had
7 increased or decreased LDL-C after taking MND-21. In addition, the graph of the rate of LDL-C
8 change in patients with normal baseline LDL-C shows that the LDL-C change was volatile
9 throughout the study period, decreasing slightly at times but increasing by more than 8% at other
10 times.⁶²⁸¹ Because of this volatility, a person of ordinary skill would not be able to conclude
11 what effect EPA has on LDL-C. Indeed, Takaku did not conclude that there was no increase in
12 LDL-C, stating only that the fluctuation in LDL-C was not significant.⁶²⁸²

13 A person of ordinary skill would not have concluded, based on Takaku, that purified EPA
14 had any advantage over fish oil in its effect on LDL-C. Takaku states that a previous study has
15 “confirmed a decrease in serum VLDL-cholesterol and serum LDL-cholesterol through the
16 administration of *fish oil* to hypercholesterolemia patients.”⁶²⁸³ In contrast, Takaku states merely
17 that the fluctuation in LDL-C was not significant in its study. Therefore, a person of ordinary
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20 ⁶²⁷⁸ Takaku at ICOSAPENT_DFNDT00006884.

21 ⁶²⁷⁹ See Matsuzawa at ICOSPENT_DFNDTS00006450.

22 ⁶²⁸⁰ Takaku at Fig. 13, ICOSAPENT_DFNDT00006882.

23 ⁶²⁸¹ Takaku at Fig. 14, ICOSAPENT_DFNDT00006883.

24 ⁶²⁸² Takaku at ICOSAPENT_DFNDT00006897.

⁶²⁸³ Takaku at ICOSAPENT_DFNDT00006897.

1 skill would have concluded based on Takaku that any favorable LDL-C effect seen in the study
2 was attributable to fish oil in general, not EPA specifically.

3 Therefore, Grimsgaard, Katayama, Matsuzawa and/or Takaku fail to substantiate
4 Defendants' assertion that pure EPA lowers triglycerides without raising LDL-C. Further, other
5 studies cited by Defendants suggest that EPA increases LDL-C.⁶²⁸⁴ Defendants identify no other
6 basis upon which a person of ordinary skill would have sought to combine the Omacor
7 PDR/Lovaza PDR with Katayama, Matsuzawa, Takaku, Grimsgaard, Mori 2000 and/or Maki.

8 (ii) Nozaki and/or Hayashi
9 Would Not Have Rendered
10 the Asserted Claims Obvious

11 Defendants contend that the asserted claims of the '594 patent would have been obvious
12 in view Nozaki and/or Hayashi in combination with other references, but they do not explain
13 why Nozaki and/or Hayashi render the asserted claims obvious or what element of the asserted
14 claims is found in Nozaki or Hayashi. Nozaki and Hayashi do not disclose or suggest a
15 reduction in triglycerides without increasing LDL-C when purified EPA is administered to the
16 very high TG patient population.

17 Nozaki administered 2.7 g/day of 90% EPA (DHA < 1%) to 14 primary
18 hypercholesterolemia subjects. A person of ordinary skill would not have found the results of
19 Nozaki reliable. Nozaki was not placebo-controlled, nor did the study compare lipid effect of
20 EPA to that of DHA. The average baseline TG level was only 165 mg/dL, while the baseline
21 LDL-C level was 185 mg/dL, which is unusually high for this TG patient population. A person
22 of skill in the art would not look to a study consisting of patients with baseline TG levels of 165
23 mg/dL in order to understand the impact of EPA therapy on the very high TG patient population.

24 ⁶²⁸⁴ See, e.g., Rambjor.

1 Further, a person of ordinary skill would understand that the baseline LDL-C level in this small
2 patient population were abnormally high and would not have relied upon these results. Further,
3 the person of skill in the art would not have looked to this patient population to predict the Apo-
4 B or LDL-C effect of EPA therapy on very high TG patients. Nozaki acknowledges that as of
5 1991, “[t]here is still controversy concerning the effects of fish oil” on LDL and HDL cholesterol
6 levels.⁶²⁸⁵ Nozaki does not provide a motivation or reasonable expectation of success for
7 administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA and
8 substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL, to
9 effect a reduction in triglycerides without increasing LDL-C when purified EPA is administered
10 to the very high TG patient population.

11 In Hayashi, 1.8 g/day of EPA was administered to 28 patients for 8 weeks. The purity of
12 the EPA and the DHA content in the composition that was administered is unknown. A person
13 of ordinary skill would not have found the results of Hayashi reliable. The study involved 28
14 patients and it was conducted for only 8 weeks. Hayashi shows that changes in Apo-B and LDL-
15 C were not statistically significant.⁶²⁸⁶ Further, the person of skill in the art would not have
16 looked to this patient population to predict the Apo-B or LDL-C effect of EPA therapy on very
17 high TG patients. Hayashi does not provide a motivation or reasonable expectation of success
18 for administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA
19 and substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL,
20 to effect a reduction in triglycerides without increasing LDL-C when purified EPA is
21 administered to the very high TG patient population.

23 ⁶²⁸⁵ Nozaki at 256.

24 ⁶²⁸⁶ Hayashi at 26, Table I.

1 Further, Hayashi was a small study conducted in only Japanese patients and was not
2 placebo controlled. This study would not have been extrapolated to Western populations
3 because the Japanese diet contains much more fish and has a number of other different attributes.
4 The Japanese consume a higher amount of EPA and DHA in their diets than Western
5 populations. In fact, Defendants' own reference states that the results from studies where the
6 patient population is exclusively Japanese cannot be generalized to other populations.⁶²⁸⁷ The
7 Japanese diet comprises between 8 and 15 times more EPA and DHA than typical the typical
8 Western diet. The Western diet typically consists of higher amounts of polyunsaturated omega-6
9 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand that
10 the Japanese respond differently to lipid lowering agents than Westerners.

11 Further, Defendants have failed to offer a purported combination of references as part of
12 their obviousness contentions that include Nozaki and Hayashi. Similarly, they fail to offer any
13 motivation to combine Nozaki and Hayashi with the other references of their purported
14 obviousness combinations. Therefore, Defendants should be precluded from relying on these
15 references.

16 (iii) Grimsgaard, Mori 2000
17 and/or Maki Do Not Disclose
18 Purported Knowledge that
19 DHA was Responsible for the
20 Increase in LDL-C

19 Defendants assert, incorrectly, that "it was known in the art as of February 2009 that
20 administration of DHA (alone or in a mixture) resulted in the negative effect of increasing LDL-
21 C levels."⁶²⁸⁸ Defendants' caveat of DHA being "alone or in a mixture" is telling that it was *not*

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23 ⁶²⁸⁷ Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to
other populations.").

24 ⁶²⁸⁸ Defendants' Joint Invalidity Contentions at 796.

1 known that DHA alone resulted in an increase in LDL-C levels. Further, the prior art Defendants
2 rely on to support this statement does not categorize the increase in LDL-C as a “negative effect”
3 in light of the overall impact of the disclosed composition on all lipid parameters. Further, the
4 patients in Grimsgaard, Mori 2000 and Maki had normal to borderline-high baseline TG levels.
5 As discussed above in Section III, a person of ordinary skill would not expect the same LDL-C
6 effect in patients with lower baseline TG levels—the subjects of Grimsgaard, Mori 2000 and/or
7 Maki—as in very-high TG patients because patients with higher TG levels had different lipid
8 responses compared to patients with lower TG levels. Patients with very-high TG levels were
9 considered fundamentally different from patients with borderline-high or high triglycerides from
10 a lipid chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint. A person of
11 ordinary skill in the art would have expected that fish oils (and other TG lowering agents) would
12 not increase LDL-C substantially in patients with normal to borderline high TG levels, but would
13 substantially increase LDL-C in patients with very high TG levels.

14 Defendants rely on Grimsgaard, Mori 2000 and/or Maki to demonstrate that it was known
15 that “DHA was responsible for the increase in LDL-C levels.”⁶²⁸⁹ The discussion related to
16 Grimsgaard in Section V.N.3.c.1.a.ii.a.i and Mori 2000 in Section V.N.3.c.1.a.i.a.iii is
17 incorporated herein by reference.

18 Defendants argue that Maki discloses the administration of purified DHA resulted in the
19 desired reduction of TGs, but also significantly increased LDL-C levels.⁶²⁹⁰ Maki was designed
20 to assess the impact of 1.52g/day DHA supplements on the serum lipid profile of patients with
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23 ⁶²⁸⁹ Defendants’ Joint Invalidation Contentions at 793.

24 ⁶²⁹⁰ Defendants’ Joint Invalidation Contentions at 796.

1 below-average levels of HDL-C levels.⁶²⁹¹ The DHA supplemented group was administered
2 capsules containing 1.52 g/day DHA **and** 0.84 g/day palmitic acid, in addition to other saturated,
3 monounsaturated and polyunsaturated fatty acids.⁶²⁹² Therefore, Maki demonstrated that when
4 1.52 g/day DHA **and** 0.84 g/day palmitic acid is administered to patients with below-average
5 levels of HDL-C levels and borderline-high TG levels, a significant increase in LDL-C is
6 observed.⁶²⁹³ However, one cannot attribute the rise in LDL-C solely to DHA, because the
7 authors admit that “changes in fatty acid intake other than DHA, particularly palmitate, may have
8 also contributed to the elevation in LDL cholesterol.”⁶²⁹⁴ Further, Maki admits that the
9 “mechanism(s) responsible for the changes in the lipid profile associated with DHA
10 supplementation are not fully understood.”⁶²⁹⁵ Therefore, the results of Maki are inconclusive as
11 to DHA’s effect alone on LDL-C levels.

12 Defendants mischaracterize the rise in LDL-C associated with the administration of
13 omega-3 fatty acids as being a “negative effect” because they incorrectly focus on only the LDL-
14 C effect and fail to look at the lipid effects as a whole. In fact, Maki does not find the increase in
15 LDL-C to be troublesome; Maki states that “the lack of increase in the total/HDL cholesterol
16 ratio, the decline in the triglyceride/HDL cholesterol ratio and the reduction in the proportion of
17 cholesterol carried by small, dense LDL particles render the changes in LDL cholesterol level
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19

20 ⁶²⁹¹ Maki at 190.

21 ⁶²⁹² Maki at 191.

22 ⁶²⁹³ Maki at 195.

23 ⁶²⁹⁴ Maki at 197; Yu et al., *Plasma Cholesterol-Predictive Equations Demonstrate that Stearic Acid is Neutral and Monounsaturated Fatty Acids are Hypocholesterlemic*, 61 AM J CLIN NUTR 1129, 1136 (1995).

24 ⁶²⁹⁵ Maki at 197.

1 less worrisome.”⁶²⁹⁶ Therefore, when one of ordinary skill in the art reviewed all the lipid effects
2 of the DHA-rich algal triglycerides, they would have understood that the increase in LDL-C was
3 “less worrisome” because of the “potentially favorable effects on triglycerides, the
4 triglyceride/HDL cholesterol ratio and the fraction of LDL cholesterol carried by small, dense
5 particles.”⁶²⁹⁷

6 Therefore, Grimsgaard, Mori 2000 and/or Maki fail to substantiate Defendants’ assertion
7 that it was known that DHA was responsible for the increase in LDL-C levels. Further,
8 Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or
9 has little effect on LDL-C levels.⁶²⁹⁸ Defendants identify no other basis upon which a person of
10 ordinary skill would have sought to combine the Omacor PDR/Lovaza PDR with Katayama,
11 Matsuzawa, Takaku, Grimsgaard, Mori 2000 and/or Maki.

12 (iii) The ‘594 Patent is not Obvious Over the
13 Omacor PDR/Lovaza PDR, in Combination
14 with Katayama in View of Satoh and/or in
View of Satoh or Shinozaki in Further View
of Contacos

15 With respect to the ‘594 Patent, Defendants present a combination of five references: “the
16 Omacor PDR/Lovaza PDR, in combination with the known clinical benefits of administering
17 pure EPA as evidenced by Katayama in view of Satoh and/or in view of Satoh or Shinozaki in
18 further view of Contacos.”⁶²⁹⁹ Defendants also present charts purporting to assert that an
19 additional 60 references may be combined in order to render the Claims obvious. Not only do
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21 ⁶²⁹⁶ Maki at 197.

22 ⁶²⁹⁷ Maki at 197.

23 ⁶²⁹⁸ See e.g., Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

24 ⁶²⁹⁹ Defendants’ Joint Invalidity Contentions at 793.

1 Defendants ignore the improbability that a person of ordinary skill would combine 60 separate
2 references, they additionally do not suggest any identify for combining these references.
3 Although Defendants need not point to an explicit statement in the prior art motivating the
4 combination of these references, any assertion of an “apparent reason” to combine must find a
5 basis in the factual record.⁶³⁰⁰ Defendants’ unsupported cobbling of selective disclosures
6 represents hindsight reconstruction.⁶³⁰¹ Defendants’ contentions are no more than an assertion
7 that certain claim elements were known in the prior art. Throughout their contentions,
8 Defendants’ selectively cite to data points in a reference without considering other disclosures or
9 even the reference as a whole. Each reference, however, must be evaluated for all that it
10 teaches.⁶³⁰² Accordingly, Defendants fail to meet their burden to establish *prima facie*
11 obviousness.

12 The Lovaza PDR fails to disclose or even suggest the claimed method of reducing
13 triglycerides in a subject with the claimed pharmaceutical composition with the specified fatty
14 acid compositions or administration period. The Lovaza PDR further does not disclose a method
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16 ⁶³⁰⁰ See, e.g., *In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the
17 formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did
18 not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply
19 the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi*
20 *Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must
21 avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to
22 select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and
23 elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp.
24 2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie*
obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding
that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been
motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

⁶³⁰¹ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under
KSR, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention
without any explanation as to how or why the references would be combined to produce the claimed invention”).

⁶³⁰² *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

1 to effect the specified TG reduction without substantially increasing LDL-C. Indeed, the Lovaza
2 PDR discloses the exact opposite, that the EPA/DHA composition contained within the reference
3 would cause a significant increase in LDL-C levels in the very high TG patient population, for
4 whom the product is indicated. At most, the Lovaza PDR discloses administration of a
5 prescription fish oil, a combination of approximately 465 mg EPA and 375 mg DHA, as an
6 adjunct to diet to reduce TG levels in adult patients with very-high (at least 500 mg/dL) TG
7 levels.

8 Defendants formulate an obviousness argument that relies on Contacos.⁶³⁰³ However,
9 Defendants fail to provide any factual or legal basis as to why Contacos discloses a claim
10 element, an “apparent reason” or motivation to combine the elements in the manner claimed,⁶³⁰⁴
11 or “a reasonable expectation of success”⁶³⁰⁵ of achieving the claimed invention.

12 Contacos disclosed administration of fish oil, pravastatin, and combination of fish oil and
13 pravastatin, but it does not disclose administration of EPA of the recited composition. Therefore,
14 Contacos fails to provide motivation to administer purified EPA to a very high TG patient
15 population and does not provide any reasonable expectation of success in lowering TG levels in
16 the very high TG patient population without increasing LDL-C. Contacos also fails to provide
17 motivation to administer purified EPA to a very high TG patient population and does not provide
18

19 ⁶³⁰³ *Id.*

20 ⁶³⁰⁴ *KSR*, 550 U.S. at 417–19; *TriMed, Inc. v. Stryker Corp.*, 608 F.3d 1333, 1341 (Fed. Cir. 2010). Hindsight may
21 not be employed to identify relevant prior art and relevant teachings therein: *Heidelberger Druckmaschinen AG v.*
Hantscho Comm. Prods., Inc., 21 F.3d 1068, 1071–72 (Fed. Cir. 1994); *Monarch Knitting Mach. Corp. v. Sulzer*
Morat GmbH, 139 F.3d 877, 881 (Fed. Cir. 1998).

22 ⁶³⁰⁵ *Proctor & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (henceforth, “P&G”);
23 *Takeda Chem. Indus. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1361 (Fed. Cir. 2007); *KSR*, 550 U.S. at 416 (a
24 combination of elements “must do more than yield a predictable result;” combining elements that work together “in
an unexpected and fruitful manner” would not have been obvious).

1 any reasonable expectation of success in lowering TG levels in the very high TG patient
2 population without increasing LDL-C.

3 The proposed combinations do not render the independent claims of the '594 Patent
4 obvious and Defendants' burden to prove otherwise is especially difficult because the PTO
5 considered Katayama, Satoh, Shinozaki, Contacos, Geppert, Kelley and Lovaza (both generally
6 and the Lovaza package insert specifically) during prosecution.⁶³⁰⁶

7 The analysis of the independent claims of the '594 Patent is incorporated into all asserted
8 claims that depend from those Claims.

9 (a) A Person of Ordinary Skill Would
10 Not Have Been Motivated to
11 Replace the Mixed Fish Oil Active
Ingredient in Lovaza with EPA of
the Recited Composition

12 For an invention to be obvious, there must have been an "apparent reason" to make it.
13 The subject matter of the '594 patent claims would not have been obvious in light of these
14 references because a person of ordinary skill would not have been motivated to purify EPA or
15 been able to reasonably expect that the claimed pharmaceutical composition would reduce TG
16 levels without an increase in LDL-C levels.

17 (i) Katayama, Satoh and/or
18 Shinozaki Do Not Disclose
19 Purported Known Clinical
Benefits of Administering
Pure EPA

20 Defendants rely on Katayama, Satoh and/or Shinozaki to demonstrate the "known clinical
21 benefits of administering pure EPA - lowering triglycerides without raising LDL-C." As

22 _____
23 ⁶³⁰⁶ See, e.g., *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012)(taking into account that "the
24 examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention.
Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear
and convincing standard came into play").

1 discussed in Section V.N.3.c.1.a.i.a.i, incorporated herein by reference, Katayama merely
2 confirms the safety of long term treatment of Epadel and its ability to lower both serum total
3 cholesterol and triglyceride levels. Katayama does not mention LDL-C levels at all, let alone
4 discuss any purported “benefits” observed related to LDL-C. Katayama does not disclose or
5 suggest that the LDL-C results obtained were a clinical benefit, nor would a person of ordinary
6 skill view these references as teaching such a benefit for very-high TG patients.

7 Satoh administered 1.8g/day of >98% EPA to patients in order to measure the effects of
8 EPA on C-reactive protein and examine how alteration of lipoprotein profile by EPA affects
9 systemic inflammation. Satoh reported a statistically significant reduction in LDL-C only when
10 compared to baseline, there was no significant effect when compared to placebo.⁶³⁰⁷

11 Defendants’ characterization of Satoh as disclosing the lowering of TG levels without increasing
12 LDL-C to be a “clinical benefit” is incorrect.⁶³⁰⁸ Satoh does not disclose or suggest that the
13 LDL-C results obtained were a clinical benefit, nor would a person of ordinary skill view these
14 references as teaching such a benefit for very-high TG patients. As discussed above, one of
15 ordinary skill in the art would not expect LDL-C to increase in a patient with TG below 500
16 mg/dL and Satoh provides no evidence to the contrary. A person of ordinary skill in the art,
17 however, would have expected that fish oils (and other TG lowering agents) would substantially
18 increase LDL-C in patients with very high TG levels. Satoh fails to provide motivation to
19 administer purified EPA to a very high TG patient population and does not provide any
20 reasonable expectation of success in lowering TG levels in the very high TG patient population
21 without increasing LDL-C.

22
23 ⁶³⁰⁷ Satoh at 145.

24 ⁶³⁰⁸ Defendants’ Joint Invalidity Contentions at 792-93.

1 Further, Satoh was a small study conducted in only Japanese patients. This study would
2 not have been extrapolated to Western populations because the Japanese diet contains much
3 more fish and has a number of other different attributes. The Japanese consume a higher amount
4 of EPA and DHA in their diets than Western populations. In fact, Defendants' own reference
5 states that the results from studies where the patient population is exclusively Japanese cannot be
6 generalized to other populations.⁶³⁰⁹ The Japanese diet comprises between 8 and 15 times more
7 EPA and DHA than typical the typical Western diet. The Western diet typically consists of
8 higher amounts of polyunsaturated omega-6 fatty acids and saturated fatty acids. Therefore, a
9 person of ordinary skill would understand that the Japanese respond differently to lipid lowering
10 agents than Westerners.

11 Shinozaki studied the long-term effect of EPA on serum levels of Lipoprotein (a) (Lp(a))
12 and lipids such as triglycerides, total cholesterol, and low density lipoprotein particles.
13 Defendants' characterization of Shinozaki as disclosing the lowering of TG levels without
14 increasing LDL-C to be a "clinical benefit" is incorrect.⁶³¹⁰ Shinozaki says nothing about an
15 LDL-C effect because it measured LDL particle number, not LDL-C. The finding disclosed by
16 Shinozaki was that "long term administration of EPA may lower Lp(a) and serum lipids."⁶³¹¹ In
17 addition to Shinozaki's lack of disclosure regarding LDL-C, Defendants identify no other basis
18 upon which a person of ordinary skill would have sought to combine the composition disclosed
19 in Shinozaki.

21 _____
22 ⁶³⁰⁹ Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to
other populations.").

23 ⁶³¹⁰ Defendants' Joint Invalidation Contentions at 792.

24 ⁶³¹¹ Shinozaki at 107-109.

1 Therefore, Katayama, Satoh and/or Shinozaki fail to substantiate Defendants’ assertion
2 that pure EPA lowers triglycerides without raising LDL-C. Further, other studies cited by
3 Defendants suggest that EPA increases LDL-C.⁶³¹² Defendants identify no other basis upon
4 which a person of ordinary skill would have sought to combine the Lovaza PDR with Katayama,
5 Satoh, Shinozaki and/or Contacos.

6 (ii) Geppert and/or Kelley Do
7 Not Disclose Purported
8 Knowledge that DHA was
9 Responsible for the Increase
10 in LDL-C

9 Defendants assert, incorrectly, that “it was known in the art as of February 2009 that
10 administration of DHA (alone or in a mixture) resulted in the negative effect of increasing LDL-
11 C levels.”⁶³¹³ Defendants’ caveat of DHA being “alone or in a mixture” is telling that it was *not*
12 known that DHA alone resulted in an increase in LDL-C levels. Further, the prior art Defendants
13 rely on to support this statement do not categorize the increase in LDL-C as a “negative effect”
14 in light of the overall impact of the disclosed composition on all lipid parameters. Further, the
15 patients in Geppert and Kelley had normal and borderline-high/high baseline TG levels,
16 respectively. As discussed above in Section III, a person of ordinary skill would not expect the
17 same LDL-C effect in patients with lower baseline TG levels—the subjects of Geppert and/or
18 Kelley—as in very-high TG patients because patients with higher TG levels had different lipid
19 responses compared to patients with lower TG levels. Patients with very-high TG levels were
20 considered fundamentally different from patients with borderline-high or high triglycerides from
21 a lipid chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint. Although a

22
23 ⁶³¹² See, e.g., Rambjor.

24 ⁶³¹³ Defendants’ Joint Invalidity Contentions at 796.

1 person of ordinary skill in the art would have expected that fish oils (and other TG lowering
2 agents) would not increase LDL-C substantially in patients with normal to borderline high TG
3 levels, a person of ordinary skill in the art would expect a substantial increase in LDL-C in
4 patients with very high TG levels.

5 Defendants rely on Geppert and/or Kelley to demonstrate that it was known that “DHA
6 was responsible for the increase in LDL-C levels.”⁶³¹⁴ Both Geppert and Kelley administer
7 DHA-rich oil that is contaminated with other saturated and polyunsaturated fatty acids.
8 Therefore, a person of ordinary skill would have known it is unsuitable for evaluating the
9 independent effects of DHA because it is not clear how much of the supplement’s effects can be
10 attributed to DHA.⁶³¹⁵ For example, Defendants’ own prior art teaches that changes in fatty acid
11 intake other than DHA, particularly palmitate, may contribute to elevations in LDL-C.⁶³¹⁶

12 In Geppert, 0.94 g/day of DHA derived from microalgae oil was administered to
13 normolipidaemic vegetarians for 8 weeks. A person of ordinary skill would not have been
14 convinced that DHA increases LDL-C based on Geppert. As Geppert acknowledges, prior
15 studies have shown “[i]nconsistent effects of DHA on LDL cholesterol.”⁶³¹⁷ Rather than reading
16 Geppert in isolation, a person of ordinary skill would have read Geppert together with the prior
17 studies cited in Geppert. As such, a person of ordinary skill would have concluded that there
18 was confusion in the art and it was unclear whether DHA increased LDL-C.

19 A person of ordinary skill would have expected that Geppert’s results would be
20 applicable to other components of fish oil such as EPA. Nothing in Geppert suggests that DHA

21 _____
22 ⁶³¹⁴ Defendants’ Joint Invalidation Contentions at 794.

23 ⁶³¹⁵ See Mori 2006 at 96.

24 ⁶³¹⁶ Maki at 197.

⁶³¹⁷ Geppert at 784.

1 was the only component of fish oil to increase LDL-C. For example, there is no data comparing
2 DHA to fish oil or EPA. In fact, Geppert discusses DHA and fish oil together when trying
3 explain the mechanism of LDL-C increase.⁶³¹⁸ A person of ordinary skill would have not
4 expected that EPA and DHA would have different effects on LDL-C based on Geppert.

5 Defendants contend that Kelley shows that DHA was responsible for the increase in
6 LDL-C.⁶³¹⁹ In Kelley, patients fasting serum TG levels of 150 to 400 mg/dL received 7.5 g/day
7 of DHA oil containing 3 g of DHA for 90 days. Kelley does not show that DHA is responsible
8 for the increase in LDL-C. Kelley suggests that increase in LDL-C is a general phenomenon
9 associated with triglyceride-lowering drugs, stating that a similar increase was induced by fibrate
10 therapy.⁶³²⁰ Further, Kelley teaches that the increase in LDL-C is not harmful when viewed in
11 context with the other lipid effects reported in the study. Kelley states that:

12 DHA supplementation may lower the risk of CVD by reducing
13 plasma triacylglycerols; triacylglycerol:HDL; the number of
14 small, dense LDL particles; and mean diameter of VLDL particles.
15 An increase was observed in fasting LDL cholesterol, but it
16 is unlikely this increase is detrimental because no increase was
17 observed in the overall number of LDL particles; actually, there
18 was an 11% reduction that was statistically not significant. The
19 reason LDL cholesterol increased despite no change in LDL
20 particle number was that the LDL particles were made larger and
21 hence more cholesterol rich by DHA treatment.⁶³²¹

22 Kelley specifically teaches that the increase in LDL-C caused by DHA supplementation
23 is unlikely to be “detrimental” because there was not a parallel increase in overall LDL particle
24 number. Kelley’s ultimate conclusion is that “[o]verall, DHA supplementation reduced the

21 ⁶³¹⁸ *Id.*

22 ⁶³¹⁹ Defendants’ Joint Invalidity Contentions at 794.

23 ⁶³²⁰ Kelley at 329.

24 ⁶³²¹ Kelley at 329

1 concentrations of atherogenic lipids and lipoproteins and increased concentrations of
2 cardioprotective lipoproteins” and that “DHA supplementation may improve cardiovascular
3 health.”⁶³²² Rather than concluding that DHA was uniquely responsible for a rise in LDL-C
4 levels, a person of ordinary skill would understand Kelley to disclose that DHA had uniquely
5 beneficial cardioprotective effects. Indeed, instead of identifying DHA as composition with
6 negative attributes, a person of ordinary skill would understand that the reference taught towards
7 the use of DHA. In addition, none of the study subjects in Kelley had a TG level above 400
8 mg/dL and, for the reasons previously discussed, a person of ordinary skill would understand the
9 very high TG patient population to be different in terms of their response to lipid therapy,
10 including administration of DHA. A person of ordinary skill in the art would have expected that
11 fish oils (and other TG lowering agents) would not increase LDL-C substantially in patients with
12 normal to borderline high TG levels, but a person of ordinary skill in the art would expect a
13 substantial increase in LDL-C in patients with very high TG levels.

14 Therefore, Geppert and/or Kelley fail to substantiate Defendants’ assertion that it was
15 known that DHA was responsible for the increase in LDL-C levels.

16 Throughout their contentions, Defendants’ selectively cite to data points in a reference
17 without considering other disclosures or even the reference as a whole. Each reference,
18 however, must be evaluated for all that it teaches.⁶³²³ As is the case with Kelley, Defendants use
19 hindsight to characterize a reference based on LDL-C levels alone without considering the other
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21
22

23 ⁶³²² Kelley at 324, 332.

24 ⁶³²³ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

1 lipid effects studied, considered and reported.⁶³²⁴ The isolated manner in which Defendants
2 select such data points is not the approach that a person of ordinary skill would have taken at the
3 time of the invention. Defendants' approach represents the use of impermissible hindsight bias.
4 A person of ordinary skill would take into consideration the entire disclosure of a reference,
5 including lipid effects other than LDL-C. In pointing only to LDL-C, Defendants ignore,
6 without explanation, the other effects of DHA that a person of ordinary skill would consider.
7 With respect to Kelley, These effects would teach a person of ordinary skill that DHA has a
8 favorable effect in hypertriglyceridemic patients.

9 Therefore, Geppert and/or Kelley fail to substantiate Defendants' assertion that it was
10 known that DHA was responsible for the increase in LDL-C levels. Further, Defendants ignore,
11 without explanation, other studies that demonstrate that DHA decreases or has little effect on
12 LDL-C levels.⁶³²⁵ Defendants identify no other basis upon which a person of ordinary skill
13 would have sought to combine the Lovaza PDR with Katayama, Satoh, Shinozaki, Contacos,
14 Geppert and/or Kelley.

15 (iv) A Person of Ordinary Skill Would Not Have
16 been Motivated to Find an Omega-3 Fatty
17 Acid "Therapy that Would Reduce TG
18 Levels in Patients with TG Levels \geq 500
mg/dL Without Negatively Impacting LDL-
C Levels."

19 Plaintiffs agree that although there was a *need* to find a therapy that would reduce TG
20 levels in patients with very-high TG levels, without negatively impacting LDL-C levels, there
21 was no motivation (or reasonable expectation of success) to find an *omega-3 fatty acid* therapy,

22 ⁶³²⁴ Kelley at 324 (providing that the objectives of the study were to determine "the effects of DHA supplementation
23 on the concentrations of apoproteins; large, medium, and small VLDL, LDL, and HDL particles; and the mean
diameters of these particles in fasting and postprandial plasma.").

24 ⁶³²⁵ See e.g., Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

1 or to modify Lovaza/Omacor, to effect a reduction in TG levels without increasing LDL-C levels
2 for very-high TG patients at the time of the invention. A person of ordinary skill in the art
3 understood that the rise in LDL-C caused by omega-3 fatty acids (or fibrates) and
4 Lovaza/Omacor was a consequence of the TG-lowering mechanism. The therapies that were
5 available at the time of the invention to treat very-high TGs were niacin, fibrates and prescription
6 omega-3 fatty acids (Lovaza/Omacor). However, niacin was associated with a highly
7 undesirable side effects—including “flushing” (or reddening of the face and other areas with a
8 burning sensation) and dyspepsia—that limited their usefulness.⁶³²⁶ Fibrates were effective at
9 reducing TGs, but they also caused an increase in LDL-C levels in patients with very-high TG
10 levels. To combat the rise of LDL-C, doctors often prescribed fibrates in combination with an
11 LDL-C lowering medication such as a statin.⁶³²⁷ However, the risk of rhabdomyolysis increased
12 five-fold if fibrates were administered with a statin.⁶³²⁸ Therefore, physicians were reluctant to
13 recommend, and patients were hesitant embrace, a combination fibrate/statin course of
14 treatment.⁶³²⁹ Finally, Lovaza/Omacor were also effective at reducing TG levels, but, similar to
15 fibrates, could cause a substantial increase in LDL-C levels for very-high TG patients. However,
16 Lovaza/Omacor could be safely administered with statins in order to mitigate increased LDL-C.

17 In any event, a person of ordinary skill in the art would have understood that omega 3-
18 fatty acids, including DHA and EPA, and fibrates cause an increase in LDL-C among very high
19

20 ⁶³²⁶ See *id.* at 991-92; McKenney 2007, at 718; ATP-III at 3315 (noting that patients often could not tolerate higher doses of niacin due to side effects).

21 ⁶³²⁷ Bays May 16, 2011 Decl., ¶ 8; Topol, at 71 (noting that in high TG patients “the addition of a statin to a fibrate is often required to achieve LDL-C and non-HDL-C goals”);

22 ⁶³²⁸ See *Id.*; McKenney 2007, at 719 (“[F]ibrates may cause rhabdomyolysis, especially when combined with statins.”).

23 ⁶³²⁹ See *Id.*, ¶ 17
24

1 TG patients, as reflected in the prior art. Accordingly, a person of ordinary skill in the art would
2 not have been motivated to look to omega 3-fatty acids in order to obtain a reduction in TGs
3 without increasing LDL-C in very high TG patients:

	LDL-C Effect	
	Borderline-High or High TG Patients	Very-High TG Patients
Fibrate ⁶³³⁰	-20%	+45%
Lovaza/Omacor ⁶³³¹	-6%	+45%

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5
6
7
8 That Epadel has been approved for decades but not approved for use in the very high TG
9 patient population prior to the invention of the asserted patents is a real-world reflection of the
10 lack of motivation. Research into the pharmaceutical uses of EPA started as early as the 1970s.
11 In 1990, Mochida Pharmaceutical, began to market Epadel, a high purity EPA drug. There have
12 been countless studies conducted which administer Epadel and report the effects observed.
13 Although a few studies administer Epadel to a patient population which included a few patients
14 with TG levels > 500 mg/dL, Defendants fail to identify a single reference directed to the
15 administration of Epadel to patients with very-high TG levels, reflecting the lack of motivation.

16 Defendants offer no “apparent reason” to administer EPA as claimed to patients with
17 fasting baseline TG levels of at least 500 mg/dl. Defendants rely on Lovaza/Omacor as the
18 starting point to “find a therapy that would reduce TG levels in patients with TG levels of at least
19 500 mg/dL without negatively impacting LDL-C levels.”⁶³³² Ironically, Lovaza/Omacor
20 significantly reduces TGs in patients with TG levels of at least 500 mg/dL but significantly

21
22 ⁶³³⁰ Tricor®, Physicians’ Desk Reference 502-505 (62d ed. 2008).

23 ⁶³³¹ Chan 2002 I at 2381 (Table 3).

24 ⁶³³² Defendants’ Joint Invalidity Contentions at 795.

1 increases LDL-C--an effect understood to be a consequence of TG reduction and the increased
2 conversion of VLDL to LDL particles.⁶³³³

3 It was well known at the time of the invention that omega-3 fatty acids, including both
4 EPA and DHA, caused significant decrease in the production of VLDL particles and a significant
5 increase in the conversion of VLDL to IDL and LDL, supporting the understanding that omega-3
6 fatty acids worked in part by inhibiting VLDL production and improving the conversion of
7 VLDL particles to LDL.⁶³³⁴ A person of ordinary skill in the art understood that EPA and DHA
8 had the *same* TG-lowering mechanism and did not differentiate between EPA and DHA when
9 discussing the TG-lowering mechanism of omega-3 fatty acids.⁶³³⁵ The discussion related to the
10 TG-lowering mechanism of omega-3 fatty acids is discussed above in Section III and
11 incorporated herein by reference.

12 In fact, it was well understood that the degree of LDL-C elevation observed with
13 prescription omega-3 therapy, such as Lovaza/Omacor, generally related to pretreatment TG
14 levels; that is, prescription omega-3 therapy, such as Lovaza/Omacor, increased LDL-C levels
15 the most in patients with the highest pretreatment TG levels.⁶³³⁶ Therefore, a person of ordinary
16 skill in the art would have viewed increased LDL-C levels caused by Lovaza/Omacor as a direct
17 consequence of lowering triglycerides in patients with TG levels ≥ 500 mg/dL. The rise in LDL-

19 ⁶³³³ See Bays 2008 Rx Omega-3 p. 402; McKenny 2007 Role of Prescription Omega-3 at 720 (finding that “[t]hese
20 results illustrate that with prescription omega-3, fewer VLDL particles are secreted into the systemic circulation, and
secreted VLDL particles are rapidly converted to LDL particle, thus explaining why LDL levels may increase in
patients with very-high triglyceride levels when given prescription omega-3 therapy”); Chan 2003

21 ⁶³³⁴ Chan 202 at 2378-84; *see also* Westphal at 917 (stating “our data confirm the well-known and pronounced
22 decrease in VLDLs after n-3 fatty acid treatment”)

23 ⁶³³⁵ Bays I, at 398; Harold E. Bays, *Fish Oils in the Treatment of Dyslipidemia and Cardiovascular Disease*, in *The
Johns Hopkins Textbook of Dyslipidemia* 245, 247 (Peter O. Kwiterovich Jr. ed., 2009 (Bays III))

24 ⁶³³⁶ See Bays 2008 Rx Omega-3 p. 402.