UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

THERMOLIFE INTERNATIONAL, LLC, and THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY, Plaintiffs, v. MYOGENIX CORP.; GNC CORPORATION; GENERAL NUTRITION CENTERS, INC.; and GENERAL NUTRITION CORPORATION, Defendants.	Case No.: 13cv651 JLS (MDD) (LEAD CASE) **MEMORANDUM DECISION AND ORDER FINDING (1) CERTAIN CLAIMS INVALID AS ANTICIPATED; AND (2) CERTAIN CLAIMS INVALID AS OBVIOUS**

The above-entitled matter came before the Court for trial without a jury on August 1–8, 2016. Tyler J. Woods of Newport Trial Group appeared on behalf of plaintiffs ThermoLife International, LLC and The Board of Trustees of the Leland Stanford Junior University (Plaintiffs). Tamany Vinson Bentz, Calvin R. Nelson, and Daniel S. Silverman of Venable LLP appeared on behalf of defendants GNC Corporation; General Nutrition Centers, Inc.; and General Nutrition Corporation. Francis DiGiovanni of Drinker Biddle & Reath LLP appeared on behalf of Vital Pharmaceuticals, Inc. John T. Gallagher of Hoffman & Baron, LLP, Arthur W. Leach, and Charles Weller appeared on behalf of defendants Hi-Tech Pharmaceuticals, Inc. and Formutech Nutrition.

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The Court heard testimony from witnesses Dr. Jeffrey S. Volek, Dr. Ranier Boger, and Dr. John P. Cooke. The Court admitted exhibits into evidence, including the depositions of Dr. Andrew J. Maxwell and Ronald Kramer, and heard closing arguments from counsel. This memorandum decision constitutes the Court's findings of fact and conclusions of law.

JURISDICTION AND VENUE

The Court has federal question subject-matter jurisdiction pursuant to 28 U.S.C. §§ 1331, 1338, and 1367. Personal jurisdiction and venue are appropriate in this judicial district because certain of the alleged acts of patent infringement have occurred in this judicial district. 28 U.S.C. §§ 1391(c) and 1400(b). Counterclaims for patent invalidity are tried under the authorization of the Federal Declaratory Judgment Act, 28 U.S.C. § 2201, *et seq.*

LEGAL STANDARD

The Court bifurcated these proceedings for purposes of invalidity, enforceability and infringement and, with the consent of the parties, consolidated these actions up to and including trial on the invalidity of the patents in suit. The sole issue tried in this proceeding is the Defendants' affirmative defense and counterclaims for patent invalidity.

Issued patents are presumed valid. 35 U.S.C. § 282. The Defendants bear the burden of proving invalidity by clear and convincing evidence. *Microsoft Corp. v. I4I Ltd. P'ship*, 564 U.S. 91, 95 (2011); *Al-Site Corp. v. VSI Int'l, Inc.*, 174 F.3d 1308, 1323 (Fed. Cir. 1999). The Defendants assert three grounds for invalidity in this action: anticipation, obviousness, and lack of enablement.[1] For both anticipation and obviousness, prior art references that were not considered by the patent examiner carry more persuasive weight than references considered by the examiner, which, by virtue of the patent having issued, were presumptively deemed not to render the invention anticipated or obvious. *Sciele*

[1] Because the Court does not reach Defendants' enablement argument, discussion of enablement law is omitted from this Order.

Pharma Inc. v. Lupin Ltd., 684 F.3d 1253, 1260 (Fed. Cir. 2012) ("[I]t may be harder to meet the clear and convincing burden when the invalidity contention is based upon the same argument on the same reference that the PTO already considered.").

I. Anticipation

Patent claims that are anticipated are invalid. 35 U.S.C. § 102. A patent is anticipated if the claimed invention was used by others in this country, patented, or described in a printed publication before the date of invention or one year before the date the patent application was filed. 35 U.S.C. § 102(a)–(b) (pre-America Invents Act).[2] Similarly, the claimed invention is anticipated if it was described in another's United States patent application published under 35 U.S.C. § 122(b) before the date of invention. 35 U.S.C. § 102(e) (pre AIA).

A prior art reference anticipates a claim if it describes the claimed invention "sufficiently to have placed a person of ordinary skill in the field of the invention in possession of it." *In re Spada*, 911 F.2d 705, 708 (Fed. Cir. 1990). That means each claim limitation must be found "either expressly or inherently in a single prior art reference." *Oakley, Inc. v. Sunglass Hut Int'l*, 316 F.3d 1331, 1339 (Fed. Cir. 2003). A claim limitation is inherent within a prior art reference when it is not stated expressly but it would nonetheless "be appreciated by one of ordinary skill in the art." *Glaxo Inc. v. Novopharm Ltd.*, 52 F.3d 1043, 1047 (Fed. Cir. 1995).

A claim limitation is inherent if it is "necessarily present" in the prior art reference. *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1343 (Fed. Cir. 2005) (citing *Schering Corp. v. Geneva Pharms., Inc.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003)).

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[2] The statutory framework for patent law, including §§ 102 and 103, was amended by the Leahy–Smith America Invents Act ("AIA"), Pub. L. No. 112–29, § 3(c), 125 Stat. 284, 287–88 (2011). For pertinent purposes here, the pre-AIA statutory framework applies to patents for which the application was filed before March 16, 2013. *Id.* at 293; *In re Giannelli*, 739 F.3d 1375, 1376 n.1 (Fed. Cir. 2014). All of the applications for the asserted patents in this case were filed before that date.

II. Obviousness

Patent claims are invalid if they cover only subject matter that would have been obvious at the time of invention to a person of ordinary skill in the art to which the patent pertains. 35 U.S.C. § 103(a) (pre-AIA). This requirement ensures that "the results of ordinary innovation are not the subject of exclusive rights under the patent laws." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 427 (2007). If the exclusivity of a patent were allowed for ordinary advances "in the normal course, . . . patents might stifle, rather than promote, the progress of useful arts." *Id.*

For a claimed invention to be nonobvious, it does not need to contain an element or claim limitation that appears nowhere in the prior art. *See id.* at 418–19. Rather, "claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." *Id.* Unlike anticipation, covered by 35 U.S.C. § 102, courts determine whether a patent claim is obvious under 35 U.S.C. § 103 when no single reference discloses each aspect or limitation of the challenged claim. The obviousness inquiry, thus, often involves combining multiple prior art references—often printed publications and other patents—and comparing them to the claim at issue. 35 U.S.C. §§ 102 & 103; *see also KSR*, 550 U.S. at 415–16. A patent claim is invalid under § 103 if, as drafted and construed, it extends to subject matter that is obvious. *KSR*, 550 U.S. at 419. When a claim combines "familiar elements according to known methods," and as a result "yield[s] predictable results," the claim is typically obvious. *Id.* at 416; *Anderson's–Black Rock, Inc. v. Pavement Salvage Co.*, 396 U.S. 57, 60–62 (1969) (holding that an invention combining a radiant heat burner and a paving machine into one device did nothing differently than if the two were used in sequence, and was therefore obvious).

When the invention solves a problem in a field in which "there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." *KSR*, 550 U.S. at 421. When the results of these known options is the "anticipated success," the subject matter is typically obvious. *Id.*

Patent invalidity is ultimately a question of law, but is predicated on factual inquiries. *Graham v. John Deere Co. of Kan. City*, 383 U.S. 1, 17 (1966). Those factual inquiries are (1) the scope and content of the prior art, (2) the differences between the prior art and the claims at issue, (3) the level of ordinary skill in the pertinent art, and (4) objective evidence of nonobviousness. *Id.*; *Dome Patent L.P. v. Lee*, 799 F.3d 1372, 1379 (Fed. Cir. 2015); *see also KSR*, 550 U.S. at 427 (noting that summary judgment of obviousness was appropriate because the content of the prior art, the scope of the patent claim, and level of ordinary skill in the art were "not in material dispute").

When all elements may be found in various prior art references, the fact finder must consider whether a person of ordinary skill in the art would have a reason to combine those references and the elements of the invention that they contain, and whether the skilled artisan would have a "reasonable expectation of success" in combining those elements. *Dome Patent*, 799 F.3d at 1380 (citing *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1164 (Fed. Cir. 2006)). One way a party challenging a patent's validity may show this reason or motivation is by identifying some "teaching, suggestion, or motivation to combine known elements" in the relevant art. *See KSR*, 550 U.S. at 418. In other circumstances, however, the reason to combine references will lie in "interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by" a skilled artisan. *Id.* at 417–18.

In some instances, the prior art will "teach away" from certain innovations, or, in other words, suggest that a certain combination or technique is unlikely to lead to a desired result. *See KSR*, 550 U.S. at 416. When the prior art teaches away from the claimed subject matter, the teaching away indicates the claimed subject matter is not obvious. *Id.* (citing *United States v. Adams*, 383 U.S. 39 (1966)) ("The fact that the elements worked together in an unexpected and fruitful manner supported the conclusion that [the inventor's] design was not obvious to those skilled in the art.").

If an accused infringer makes a prima facie showing of obviousness, objective evidence of nonobviousness, often refererred to as "secondary considerations" or the "objective indicia of nonobviousness," may rebut that showing. *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1311 (Fed. Cir. 2006) (citing *Graham*, 383 U.S. at 17–18). These considerations include commercial success, long felt but unsolved needs, skepticism of experts and unexpected results, and the failure of others. *Id.* To rebut a showing of obviousness, there must be a "nexus" between the invention claimed in the patent and the commercial success or other secondary consideration. *Id.* at 1311–12.

FINDINGS AND CONCLUSIONS

In the Pretrial Order, which the Court signed on July 29, 2016, the parties admitted to certain facts requiring no proof at trial. The Court incorporates by reference the facts admitted by the parties and set forth in the Pretrial Order. The Court's findings of fact are based upon the facts admitted in the Pretrial Order and the testimony and evidence presented at trial.

Plaintiffs assert claims from four patents in this proceeding: U.S. Patent Nos. 6,117,872 (the '872 Patent), 5,891,459 (the '459 Patent), 7,452,916 (the '916 Patent), and 6,646,006 (the '006 Patent). Stanford University owns these patents, and Plaintiff exclusively licenses them. Dr. John P. Cooke is one of the inventors for all four of the asserted patents.

Broadly speaking, the asserted patents concern administering the amino acids arginine and lysine in combination with antioxidants and other ingredients to enhance vascular function or physical performance. According to the asserted patents, this is achieved by causing the arteries to dilate, allowing greater blood flow, which allows for improved vascular function or enhanced physical performance. First, the subject ingests arginine or lysine. Those amino acids are then converted by the enzyme nitric oxide synthase in the endothelial cells lining the arteries into nitric oxide. The release of nitric oxide in the arteries then causes the arteries to dilate, allowing enhanced performance.

Nitric oxide is derived directly from L-arginine, one form of the amino acid arginine. Nitric oxide is easily converted or degraded via oxidation into nitrate, or NO2–, and nitrite, or NO3–. Neither nitrate nor nitrite have relaxing properties, and thus do not dilate the arteries. Antioxidants prevent oxidation of nitric oxide.

The '459 Patent, '006 Patent, and '916 Patent share a priority date of June 11, 1993, except that, as stipulated by the parties, the grape skin extract claims of the '006 Patent have a priority date of November 9, 1995. The '872 Patent's priority date is June 23, 1998. In the early 1990s, there was much discussion of and excitement surrounding nitric oxide in the scientific community. In fact, in 1992, *Science Magazine* dubbed nitric oxide "molecule of the year." (Tr. 27.)

It is undisputed that, as of June 1993, the scientific community was well aware of the metabolic pathway that led to endogenous production of nitric oxide. There was little doubt that the amino acid arginine was converted by the enzyme nitric oxide synthase into nitric oxide, which then caused vasodilation. However, there were differing views on whether increasing the amount of L-arginine present in the body through supplementation could actually increase production of NO. (*See* Tr. 343–44.) Research at the time suggested the amount of arginine typically present in the body would fully trigger the nitric oxide synthase enzymes on its own, such that the enzymes would already be working at essentially full capacity. (*See* Tr. 343.) This notion was borne out by tests in vitro—i.e., in a test tube or petri dish. (Tr. 344.) However, experiments involving L-arginine supplementation with subjects in vivo—conducted in living organisms—showed that supplementation actually increased production of nitric oxide because of some then-unknown conditions that existed in vivo. (Tr. 344.) The disparity between what-ought-to-have-been based on experiments in vitro and what actually occurred in vivo became known as the "arginine paradox." (Tr. 449.) This paradox was ultimately resolved by studies showing that although an enzymatic inhibitor hampers the effectiveness of nitric oxide synthase in vivo, additional quantities of L-arginine can displace that inhibitor from the enzyme and thus allow the enzyme to more effectively convert L-arginine into nitric oxide.

(*See* Tr. 451.) This hypothesis was offered by a pair of researchers as early as 1992. (Tr. 503.)

The parties agree that a person of ordinary skill in the art applicable to the patents-in-suit is an individual with a Ph.D. in biochemistry, pharmacology, nutrition chemistry, kinesiology, or the like, and at least two years of post-doctoral research or clinical work in physiology or biochemistry, or alternatively with an M.D. and two years of work experience relating to supplementation and formulation. Defendants' expert, Dr. Volek, received his Ph.D. from Pennsylvania State University and is currently a professor in the Deparatment of Human Sciences, Kinesiology Program, at The Ohio State University. (Tr. 4–5.) He researches primarily in the field of dietary supplements and exercise, and has authored or co-authored approximately 300 peer-reviewed publications. (Tr. 6.) Plaintiffs' expert, Dr. Boger, is a professor of clinical pharmacology and director of the Institute of Clinical Pharmacology and Toxicology at Hamburg University Medical Center, Germany. He received a medical doctorate in 1991 and later received specialized training in internal medicine, focusing on cardiovascular medicine. (Tr. 325.) He later obtained a Ph.D., and became an assistant professor in 1998. (Tr. 325.) In 2000, he received the title of full professor and was appointed as Chief of Clinical Pharmacology at the University of Hamburg. (Tr. 325–26.) He has authored or co-authored approximately 300 peer-reviewed publications, the majority of which focused on vascular regulation mediated by nitric oxide and the effect of L-arginine on the human body. (Tr. 328.)

The Court finds both experts qualified to testify about the patents in suit, the relevant prior art, and the person of ordinary skill in the art as of the relevant dates. Although the Court finds both experts to be generally credible, as discussed below, the Court in some instances finds the testimony of one expert or the other more entitled to greater weight or certain aspects of the expert's testimony less credible.

The Court addresses the evidence pertaining to invalidity of each of the asserted patents in turn.

I. The ’459 Patent: Anticipation by Levere

The ’459 patent, titled “Enhancement of Vascular Function by Modulation of Endogenous Nitric Oxide Production or Activity,” issued on April 6, 1999, is based on a patent application filed on November 9, 1995. It expired on June 11, 2013. Only claim 1 of the ’459 Patent is in dispute. As broken down limitation-by-limitation by the parties, it reads:

> [A] A method of improving vascular NO activity of the vascular system of a human host by enhancing endothelial NO, said method comprising:
> [B] administering orally as a dietary supplement to said host in accordance with a predetermined regimen
> [C] a prophylactic dose
> [D] in an amount sufficient to enhance endogenous endothelial NO,
> [E] L-arginine or L-arginine hydrochloride, as other than a natural food source and
> [F] in the absence of other amino acids and polypeptides as other that [sic] dietary supplements,
> [G] to enhance the level of endogenous NO in the vascular system.

(’459 Patent, Ex. 1, col. 26 ll. 38–49.) The Court construed the term, “A method of improving vascular NO activity of the vascular system of a human host by enhancing endothelial NO, said method comprising,” to require “that the method be practiced with an intent to improve vascular NO activity of the vascular system of a human host by enhancing endothelial NO,” and to “not require that the claimed method be practiced prior to physical performance.” (Claim Constr. Order 21, ECF No. 109.) The Court construed the limitation, “as other than dietary supplements” to modify both “amino acids” and “polypeptides,” so that “any amino acids other than arginine and lysine cannot be active ingredients.” (*See id.*)

As of June 1993, the relevant scientific community was well aware that L-arginine is the precursor for nitric oxide and that nitric oxide was responsible for endothelium-dependent vasodilation. (Tr. 337.) Dr. Boger testified that, as of approximately 1992, there was skepticism whether oral ingestion of L-arginine would increase nitric oxide in humans. This is because with such delivery it would have to be absorbed in the body through the

digestive tract, thus leading to the L-arginine both encountering stomach acid that could potentially degrade it and possibly being metabolized in the liver. (Tr. 340–41.)

Study at the time focused on impaired vasodilation because of certain diseases. Scientists offered two competing theories to explain impaired vasodilation, which Dr. Boger referred to as the "oxygen radical theory" and an impaired nitric oxide production theory. (Tr. 341–42.) The oxygen radical theory posited that the amount of nitric oxide produced was normal but that there were so many oxygen radicals—which can deactivate the vasodilating properties of nitric oxide—that vasodilation was impaired. (Tr. 341–42.) The impaired nitric oxide production theory was that, for some unknown reason, too little nitric oxide was being synthesized. (Tr. 341.) Of those theories, the oxygen radical theory was more widely believed at the time. (Tr. 341.)

United States Patent No. 5,217,997 (Levere) issued on June 8, 1993, based on a patent application filed on April 24, 1992. (Ex. 41.) Levere is prior art to the '459 Patent pursuant to 35 U.S.C. § 102(e). Although as of June 11, 1993 the science discussed in Levere was not completely settled—as science often is not—the Court finds that Levere discloses every element of claim 1 of the '459 Patent and would have put a skilled artisan in possession of the claimed invention.

A. *Limitation B: "administering orally as a dietary supplement to said host in accordance with a predetermined regimen"*

Levere discloses what the parties have dubbed claim limitation B, "administering orally as a dietary supplement to said host in accordance with a predetermined regimen." Levere describes administering "about 1 mg to about 15000 mg per day" (a predetermined regimen); that the "oral dosage form is preferred" (administering orally); and that L-arginine was to be administered "with food and water ad libitum" (a dietary supplement). (Levere col. 6 ll. 15–22, 32–33, col. 7 ll. 45–54.)

Dr. Boger testified that Levere would not teach a person of ordinary skill in the art that L-arginine could be administered orally because it was "unclear" whether oral administration of L-arginine would cause similar effects to intravenous or other injections,

which is largely what Levere describes in the examples. (Tr. 359.) However, where an accused infringer relies on an issued patent as prior art, "a presumption arises that both the claimed and unclaimed disclosures in a prior art patent are enabled." *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1355 (Fed. Cir. 2003). The patentee bears the burden of rebutting this presumption by a preponderance of the evidence. *Id.*; *accord In re Antor Media Corp.*, 689 F.3d 1282, 1288 (Fed. Cir. 2012). Claims 11 and 17 of the Levere patent cover oral administration and are presumed enabled. (Levere col. 12 ll. 16–17.) The Court finds that Dr. Boger's testimony that there would have been skepticism about the efficacy of oral administration based on the disclosure in Levere, when weighed against Dr. Volek's testimony that Levere teaches a skilled artisan oral administration, (*see* Tr. 57), is insufficient to rebut the presumption that oral administration is properly enabled in the Levere patent, and therefore anticipates this element in the '459 Patent.

B. *Limitations C, E, and F*

In closing arguments, Plaintiffs did not contend that Defendants had not met their burden of showing that Levere disclosed limitations C, E, and F. The Court likewise finds that the Levere patent discloses these limitations. The inventors in Levere contemplate use of their invention to stymie the "disposition of hypertensive patients to develop vascular disease," which discloses the "prophylactic dose" of limitation C. (Levere col. 1 ll. 24–27.) Levere teaches limitation E by noting that "any salt of L-arginine is suitable in the practice of the present invention" and that "L-arginine hydrochloride is the preferred salt." (Levere col. 5 ll. 44–50.) Lastly, Levere discloses limitation F, the absence of other amino acids and polypeptides as other than dietary supplements, by stating that L-arginine may be "formulated with any suitable nontoxic pharmaceutically acceptable inert carrier material." (*See* Levere col. 6 ll. 34–40.)

C. *Limitations A, D, and G: Enhancement of Endogenous Nitric Oxide*

Limitations A, D, and G pertain to the enhancement of endogenous nitric oxide. As construed in the Court's Order on Claim Construction, limitation A requires the "intent to

improve vascular NO activity of the vascular system of a human host by enhancing endothelial NO." (*See* Cl. Constr. Order 21.)

Levere discloses that the administration of L-arginine led to a reduction in blood pressure and describes the likely mechanism by which blood pressure is reduced:

> The mechanism of the blood pressure lowering effect of L-arginine is still unclear. However, while not wishing to be bound by any theory, the observation that spontaneous hypertensive rats have a diminished endothelial-dependent relaxation response and that L-arginine may be the physiological precursor of the most powerful endothelial-derived releasing factor, nitric oxide, may suggest that administration of L-arginine to spontaneous hypertensive rats increases the formation of nitric oxide and contributes to an overall decrease in peripheral vascular resistance, and therefore causes a reduction in blood pressure.

(Levere col. 7 ll. 21–32.) In the final sentence of Example 1 in the Levere patent, the inventors explain the likely reason "that L-arginine is a potent remedy in reducing blood pressure of young spontaneous hypertensive rats" is that "[t]he L-arginine effect may be mediated via generation of nitric oxide which elicits vasodilation and consequently lowers blood pressure." (Levere col. 8 ll. 37–44.) The Levere patent goes on to claim a method of administering of L-arginine "for treating high vascular resistance disorder in a mammal." (Levere col. 11 ll. 25–30.)

Prior art that discloses subject matter in somewhat equivocal terms—for example, suggesting that "[f]urther studies are needed to" determine if the subject matter disclosed is safe to administer—is sufficient to anticipate if "those suggestions [are] enabling to one of skill in the art." *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1379 (Fed. Cir. 2001); *see also Schering Corp. v. Geneva Pharm.*, 339 F.3d 1373, 1380 (Fed. Cir. 2003) ("Anticipation does not require the actual creation or reduction to practice of the prior art subject matter; anticipation requires only an enabling disclosure."). In some cases, "information arising after the critical date may show that the claimed subject matter, as disclosed in a prior art reference, 'was in the public's possession.'" *Schering Corp.*, 339 F.3d at 1380 (citing *Bristol–Myers*, 246 F.3d at 1379); *see also PharmaStem Therapeutics,*

Inc. v. ViaCell, Inc., 491 F.3d 1342, 1363–64 (Fed. Cir. 2007) (stating in the context of obviousness that "[s]cientific confirmation of what was already believed to be true may be a valuable contribution, but it does not give rise to a patentable invention") (citing *KSR*, 550 U.S. at 402–03). As noted above, where an accused infringer relies on an issued patent as prior art, the disclosures are presumed to be enabled, and the patentee bears the burden of rebutting this presumption by a preponderance of the evidence. *See Amgen Inc.*, 314 F.3d at 1355.

While the enabling disclosure in Levere is stated in equivocal terms, it nonetheless placed a person of ordinary skill in the art in possession of the invention as of June 1993. A skilled artisan who wished to reduce vascular resistance or lower blood pressure in a mammal[3] by administering L-arginine would appreciate from the Levere specification that this would be achieved by enhancing endogenous endothelial nitric oxide. The Court is not persuaded that a skilled artisan would need to appreciate to a scientific certainty that this, as opposed to the competing "renal hemodynamics" hypothesis offered by the inventors in Levere, is the mechanism by which blood pressure would be reduced for the Levere patent to enable enhancement of endogenous nitric oxide.

The parties' experts, not surprisingly, reached opposite conclusions on this point. Dr. Boger concluded that Levere does not disclose intent to enhance endothelial nitric oxide. (Tr. 361.) This opinion is predicated largely on his mistaken legal conclusion that the equivocal or hypothetical nature of Levere's disclosure of this biological process is insufficient for purposes of anticipation. As indicated above, however, the Court presumes the disclosure in Levere is sufficiently enabling to one skilled in the art because of the teaching pertaining to L-arginine's effect of enhancing endogenous endothelial nitric oxide. By contrast, Dr. Volek testified that the Levere inventors were "well aware of the effects of L-arginine on nitric oxide and that increases in nitric oxide would decrease blood

[3] The Summary of the Invention section of the Levere patent discusses using the method in "a mammalian organism, such as a human." (Levere col. 3 ll. 48–53.)

pressure, so that was the motivation or inspiration for doing these experiments." (Tr. 48.) Because Dr. Boger's testimony on this point is based on mistaken legal assumptions pertaining to interpretation of patents as prior art, the Court finds Dr. Volek's conclusions on this point more reliable.

To the extent that Dr. Boger's testimony is not based on a mistaken legal premise, the Court finds Dr. Volek's testimony more credible because it reflects a more direct reading of the Levere patent. *Hermes Consol., Inc. v. United States*, 58 Fed. Cl. 3, 8 n.7 (2003) ("[W]here there are two competing theories or explanations, all other things being equal, the simpler one is probably correct. . . . Although not a maxim of law, there is obviously much truth to this logic.") (citing Michael Shermer, *Why People Believe Weird Things: Pseudoscience, Superstition, and Other Confusions of Our Time* 1–10 (1998)). Dr. Boger's position requires him to explain why Levere's disclosure of the same metabolic process claimed in the '459 Patent does not actually disclose those claim elements. In other words, Dr. Boger was tasked with explaining why, even though the Levere patent describes the invention of claim 1, it nonetheless does not anticipate claim 1. Further, as Dr. Boger admitted on cross examination, the inventors in Levere attribute L-arginine's ability to lower blood pressure to the mechanism of increasing endothelial nitric oxide production. (*See* Tr. 426.)

Thus, a skilled artisan reading Levere would understand that the blood pressure reduction in Levere would likely be achieved through enhancement of endogenous endothelial nitric oxide. Whether the person practicing the patent emphasizes the resultant reduced blood pressure or the metabolic process that accomplishes that goal does not change whether the requisite intent existed. Regardless of how the objective is defined, Levere discloses the limitations of claim 1.

As to limitation D's requirement that the L-arginine be "in an amount sufficient to enhance endogenous endothelial NO," the Court finds that Levere discloses such an amount. In particular, Figure 1 in the Levere patent shows a reduction of blood pressure as the amount of L-arginine administered increases. (*See* Levere Fig. 1.) There can be

little doubt when comparing, for example, the data on 80 and 100 milligrams per kilogram bodyweight to the baseline of 0 milligrams per kilogram bodyweight that the supplemental dosing decreased blood pressure. (*Id.*) Levere teaches that this is mediated through enhancement of endogenous endothelial nitric oxide. (*Id.*) Further, Levere states that the "typical effective amount of L-arginine" would be in the range of 1 milligram to 1500 milligrams per day, or "more preferably about 10 mg to about 400 mg." (Levere col. 6 ll. 15–22.) The '459 Patent teaches that a "range from about .5 to 5 g, more usually from about 1 to 3 g" is a sufficient amount of L-arginine. ('459 Patent col. 10 ll. 2–5.) While the preferred ranges vary, the overall ranges the two patents teach overlap by 1000 milligrams, from 500 milligrams/.5 grams to 1500 milligrams/1.5 grams. Thus, as Dr. Volek testified, a skilled artisan would understand that Levere teaches a range that encompasses quantities of L-arginine sufficient to enhance nitric oxide production. Although Dr. Boger points out that the preferred range in Levere teaches an amount less than the disclosed effective range in the '459 Patent, the Court presumes the entire claimed range is enabled. The Court finds credible Dr. Volek's testimony that a skilled artisan would read Levere's statement that 1 to 1500 milligrams is the "typical effective amount" to mean—as Levere plainly states—that this dosage is an effective amount. The Court does not find credible Dr. Boger's testimony that Levere's teaching of a preferred range would cause a skilled artisan to think the broader range disclosed is ineffective. The Levere patent's plain statement is to the contrary. The objective evidence does not support Dr. Boger's testimony on this point, but is consistent with Dr. Volek's testimony. Limitation G in effect restates the requirements within limitations A and D pertaining to enhancing the level of endogenous NO in the vascular system.

In sum, the Court finds that Levere discloses an intent to enhance endogenous endothelial nitric oxide by administering a sufficient amount of L-arginine to achieve that objective. Levere therefore discloses limitations A, D, and G.

D. *Conclusion*

The Levere patent discloses each limitation of claim 1 of the '459 Patent. Accordingly, the Court finds this claim invalid as anticipated by Levere. Because the Court concludes that Levere anticipates claim 1, it does not consider Defendants' obviousness-based arguments addressing combinations of various references or anticipation by the Leaf reference, although the Court discusses Leaf below with respect to certain claims of the '006 Patent. *See infra* Section III.A.i.

II. The '872 Patent: Obviousness in Light of Ceremuzynski and the '459 Patent

The '872 patent, titled "Enhancement of Exercise Performance by Augmenting Endogenous Nitric Oxide Production or Activity," issued on September 12, 2000, is based on a patent application filed on June 23, 1998. It is set to expire on June 23, 2018. Plaintiffs assert independent claims 1, 7, and 12, and dependent claims 4, 5, 8, and 10 of the '872 Patent in this action.

The article "Effects of Supplemental Oral L-Arginine on Exercise Capacity in Patients with Stable Angina" (Ceremuzynski), authored by Leszek Ceremuzynski, Tomasz Chamiec, and Krystyna Herbaczynska-Cedro, was published in the American Journal of Cardiology on August 1, 1997. (Ex. 22.) Ceremuzynski is prior art to the '872 Patent under 35 U.S.C. § 102(a) because it is a printed publication in this or a foreign country predating the '872 patent's June 23, 1998 date of invention. The '459 Patent is prior art to the '872 Patent because it is a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent. 35 U.S.C. § 102(e) (pre-AIA). Taken together, these references disclose or make obvious each limitation of the asserted claims of the '872 Patent.

A. *Claims 1 and 12*

Claim 1, as broken down limitation-by-limitation by the parties, covers:

> [A] A method for enhancing physical performance of a mammal prior to said physical performance, said method comprising:
> [B] administering to said mammal prior to said physical performance as the active ingredient

> [C] an amino acid composition consisting of at least one amino acid selected the group consisting of arginine and lysine
> [D] of at least about 60 mg/kg/day within 24 h of said physical performance.

('872 Patent col. 11 ll. 55–57, col. 12 ll. 1–6.) The Court construed the limitation C of claim 1, as well as limitations in other claims containing the same language, to mean "an amino acid composition that consists of arginine, lysine, or both, as its active ingredients." (Cl. Constr. Order 20.) Claim 12 pertains to:

> [A] A method enhancing human physical performance prior to said physical performance, said method comprising:
> [B] administering to said human prior to said physical performance as the active ingredient
> [C] an amino acid composition consisting of at least one amino acid selected from the group consisting of arginine and lysine of at least about 2 g per day within 24 h of said physical performance.

('872 Patent col. 12 ll. 45–51.) Limitation A of claim 1 covers a method for enhancing physical performance of a mammal prior to the physical performance, whereas limitation A of claim 12 covers generally the same subject matter, but for a human.

The parties' experts agree that Ceremuzynski tested the effect of L-arginine supplementation on exercise performance and concluded that L-arginine supplementation improved exercise performance. (Tr. 123, 378–79.) The scope of the asserted claims in the '872 Patent covers improved exercise performance in both sick and healthy individuals, whereas Ceremuzynski pertains to improved exercise performance in sick individuals. (*Compare* '872 Patent, *with* Ceremuzynski.) However, because improving exercise performance of a sick individual would be encompassed by this claim element, it also discloses this element for purposes of obviousness. *See Bristol–Myers*, 246 F.3d at 1378 ("[I]t is axiomatic that that which would literally infringe if later anticipates if earlier.") (citing *Lewmar Marine, Inc. v. Barient, Inc.*, 827 F.2d 744, 747 (Fed. Cir. 1987)). The '459 Patent also discloses enhanced physical performance, teaching that, "[b]ecause NO is the most potent endogenous vasodilator, and because it is largely responsible for exercise-induced vasodilation in the conduit arteries, enhancement of NO synthesis could also

improve exercise capacity in normal individuals and those with vascular disease." ('459 Patent col. 2 ll. 44–49.) Accordingly, Ceremuzynksi and the '459 Patent each disclose limitation A of claim 1 and limitation A of claim 12.

Limitation B of claim 1 and limitation B of claim 12 cover administering to a mammal or human, respectively, prior to the physical performance. The L-arginine regimen described in Ceremuzynski discloses administration to humans before physical performance. (*See* Ceremuzynski at 331.)

Limitation C of claim 1 covers an amino acid composition that consists of arginine, lysine, or both, as its active ingredients. Ceremuzynski discloses using oral L-arginine capsules that appear to have no other active ingredient for bringing about the result of improved exercise performance. (*See* Ceremuzynski at 331.)

Limitation D of claim 1 covers a regimen of at least about 60 milligrams per kilogram bodyweight per day within twenty-four hours of the physical performance. Extrapolating on this claim to an average human weighing approximately 150 lbs., Dr. Volek testified—and Dr. Boger did not dispute—that limitation D of claim 1 would call for at least 4.08 grams per day. (Tr. 107–08.) Ceremuzynski describes administering "two 1-g[ram] capsules 3 times a day," i.e., 6 grams of L-arginine. Ceremuzynski therefore discloses a regimen of "at least" about 60 milligrams per kilogram bodyweight per day within 24 hours of the physical performance.

Limitation C of claim 12 mirrors limitations C and D of claim 1 except that the regimen covered is at least about 2 grams per day[4] instead of 60 milligrams per kilogram bodyweight. For the same reasons, Ceremuzynski discloses these elements.

Dr. Volek stated and the Court credits as true that, together, Ceremuzynski and the '459 Patent disclose or render obvious each limitation of claims 1 and 12 of the '872 Patent. (Tr. 144.)

[4] Limitation A of claim 12 makes clear that the 2 grams would be administered to a human, whereas the 60 milligrams per kilogram bodyweight pertains more broadly to administration to a mammal.

B. *Claim 4*

Claim 4 is dependent on claim 1, and therefore includes all the limitations of claim 1 as well as the additional limitation "wherein an antioxidant is administered to said mammal in an amount to enhance the endothelial NO." ('872 Patent col. 12 ll. 11–13.) The '459 Patent discloses this limitation by instructing that L-arginine or L-lysine could be administered "[i]n or in combination" with "other compounds, such as B6, folate, B12, or an antioxidant, which provide for short term enhancement of nitric oxide, either directly or by physiological processes . . . ." ('459 Patent abstract; *see also* '459 Patent col. 8 ll. 40–49.) Dr. Volek opined and the Court credits as true that this discloses the additional limitation of claim 4.

C. *Claim 5*

Claim 5 is dependent on claim 1, and therefore includes all of the limitations of claim 1 as well as the additional limitation "wherein said admin[i]stering comprises the inclusion of an agent further enhancing EDNO synthesis." ('872 col. 12 ll. 14–16.) The Court construed this additional limitation to mean "an additional ingredient that increases the production of nitric oxide generated by the cells lining the vascular system provided that the ingredient is not an amino acid," (Cl. Constr. Order 20).

The '459 Patent discloses this additional limitation by teaching that "other agents can be added to the oral formulation of the amino acids or polypeptides to enhance their absorption, and/or to enhance the activity of NO synthase, e.g. B6 (50-250 mg/d), folate (0.4-10 mg per daily dose), B12 (0.5-1 mg/d) or calcium (250-1000 mg per daily dose)." ('459 Patent col. 8 ll. 35–39.) The '459 Patent also states that "[t]he enhanced effect of nitric oxide may be a result of . . . providing an enzyme in the metabolic pathway to NO, particularly NO synthase . . . ." ('459 Patent col. 7 ll. 35–39.) Dr. Volek testified that a person of ordinary skill in the art would understand this passage in the '459 Patent to disclose an agent other than arginine that enhances EDNO synthesis. (*See* Tr. 133.) The Court credits Dr. Volek's testimony on this point as credible.

D. *Claim 7*

Claim 7 pertains to:

> [A] A method for enhancing human physical performance prior to said physical performance, said method comprising:
> [B] administering to said human within 6 h prior to said physical performance as the active ingredient
> [C] an amino acid composition consisting of at least one amino acid selected from the group consisting of arginine and lysine of at least about 2 g per day
> [D] in combination with an agent enhancing ENDO synthesis,[5]
> [E] as a health bar, grain or drink.

('872 Patent col. 12 ll. 19–27.) Claim 7 overlaps significantly with the limitations of claims 1 and 12, but includes additional limitations that at least about 2 grams lysine or arginine be administered within six hours of the physical performance "in combination with an agent enhancing ENDO synthesis, as a health bar, grain or drink."

Ceremuzynski discloses an L-arginine supplementation regimen that involved ingesting 2 grams of L-arginine at 9 a.m., 2 p.m., and 10 p.m. over the course of three days, followed by exercise between 9 a.m. and 10 a.m. (Ceremuzynski at 331.) Dr. Volek explained that the Ceremuzynski reference does not clarify whether the subjects, after taking L-arginine at the prescribed times for the first three days, did not take arginine on the fourth day immediately before exercise, or instead ingested arginine pills at 9 a.m., immediately before the exercise that occurred between 9 a.m. and 10 a.m. (Tr. 135–36.) If the subjects took the L-arginine supplement immediately before exercise, Dr. Volek explained, Ceremuzynski would directly disclose the "within 6 h[ours]" limitation of claim 7. (Tr. 135–36.) However, Dr. Volek stated that no matter how you read Ceremuzynski, the subjects ingested L-arginine within at least approximately eleven hours before exercise—taking 2 milligrams of L-arginine at 10 p.m. and exercising at 9 a.m. the next day. (Tr. 136.) Dr. Volek opined that a person of ordinary skill in the art reading

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[5] The Court notes that the '872 Patent refers to both EDNO and ENDO synthesis, but the litigants and experts consistently referred to EDNO synthesis. (*See, e.g.*, Tr. 132, 139.)

Ceremuzynski in 1998 would find it obvious that L-arginine would enhance physical performance if taken within six hours of exercise based on Ceremuzynski's disclosure of L-arginine within eleven hours, and that there is no "credible reason why there would be a different result." (Tr. 136.) Thus, Dr. Volek testified, a person of ordinary skill in the art would find the "within six hours" limitation obvious even if he or she read Ceremuzynski to disclose an eleven-hour lapse in time from administration to exercise.[6] (*See id.*) The Court finds persuasive Dr. Volek's testimony that, no matter how a person of ordinary skill in the art would read Ceremuzynski, the six hour limitation of claim 7 would have been obvious. The specificity of dosing, and whether the disclosures actually put one of skill in the art in possession of these limitations of the invention claimed in the '872 Patent, is discussed in greater detail below in Section II.G.

The '459 Patent discloses element D of claim 7, a "combination with an agent enhancing ENDO synthesis." That is, the '459 Patent teaches that "other agents can be added to the oral formulation of the amino acids or polypeptides to enhance their absorption, and/or to enhance the activity of NO synthase, e.g. B6 (50-250 mg/d), folate (0.4-10 mg per daily dose), B12 (0.5-1 mg/d) or calcium (250-1000 mg per daily dose)." ('459 Patent col. 8 ll. 35–39.) As Dr. Volek testified, these are agents that enhance EDNO synthesis. (Tr. 139.)

The '459 Patent also discloses the "health bar, grain or drink" limitation of claim 7 by teaching that the amino acid composition can be incorporated as "a supplement in a food, such as a health bar, e.g. granola, other grains, fruit bars, such as a date bar, fig bar, apricot bar, or the like." ('459 Patent col. 9 ll. 1–4.)

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[6] Dr. Volek referred to "ten hours," although it would actually have been at least eleven, and never discussed the possibility of twelve hours, which would be the case if a subject ingested arginine at 10 p.m. and did not exercise until 10 a.m. the next day. (*See* Tr. 135–36.) Plaintiffs did not contend that these one hour distinctions affect the obviousness analysis, and based on the discussion below pertaining to the administration protocols, the Court does not consider these slight differences significant.

E. *Claim 8*

Claim 8 is dependent on claim 7, and therefore includes all of the limitations of claim 7 as well as the additional limitation that the agent that enhances "ENDO" synthesis "comprises at least one of Vitamin A, Vitamin C, Vitamin E, selenium, carotenoid, flavanoid, L-camitine, L-creatine, and L-taurine." ('872 Patent col. 12 ll. 28–31.) The '459 Patent discloses Vitmain C, Vitamin E, or β-carotene as "agents known to protect NO from degradation." ('459 Patent col. 8 ll. 40–49.) Dr. Volek testified a skilled artisan would understand that the vitamins the '459 Patent discloses, if administered to protect nitric oxide from degradation, would be agents that enhance EDNO synthesis. (*See* Tr. 140–41.)

F. *Claim 10*

Claim 10 is dependent on claim 7, and therefore includes all of the limitations of claim 7 as well as the additional limitation "wherein said administering of said arginine and lysine is from about 2 to 12 g per day within 24 hours of said physical exertion." ('872 Patent col. 12 ll. 34–36.) Ceremuzynksi discloses administering 2 grams of L-arginine three times per day, i.e., 6 grams within a 24 hour period. (*See* Ceremuzynski at 331.) Six grams falls well within the claimed "2 to 12 g[ram] per day" range, and therefore discloses this limitation. Further, whether one reads Ceremuzynski as disclosing administration of the final 2 grams of L-arginine 0 to 1 hour before exercise or 11 to 12 hours before, it discloses "within 24 hours of said physical exertion."

G. *Chronic Versus Acute Dosing*

Although the regimen in Ceremuzynski discloses the "within 24 hours" limitations, and *may* disclose the "within 6 h[ours]" limitation, Dr. Boger testified that the claims of the '872 Patent pertain to an acute regimen, whereas the protocol in Ceremuzynski (although not quite a chronic regimen) does not teach acute dosing. (*See* Tr. 380–81.) The result, Plaintiffs urge, is that despite technically disclosing certain limitations of the '872 Patent the protocol described in Ceremuzynski would not have actually put a person of ordinary skill in the art in possession of the claimed invention.

Dr. Boger explained that a chronic regimen involves repeated or longer term administration of a drug or supplement, such that "each dose settles upon the remainder of the compound that is left over in the body from the dose before." (Tr. 381.) By contrast, an acute dose involves "administration of whatever compound to generate an immediate effect." (Tr. 380.)

As discussed above, the regimen in Ceremuzynski involved "two 1-g[ram] capsules 3 times a day for 3 days." (Ceremuzynski at 331.) Dr. Volek testified that as of June 23, 1998, a person of ordinary skill in the art would read this to be an acute, rather than a chronic, protocol. (Tr. 136.) Chronic therapy, involving repeated administrations of a substance, necessarily encompasses a series of individual administrations. The experts agreed that, generally speaking, a person of ordinary skill in the art would understand that the effectiveness of chronic administration of a substance does not necessarily show that acute administration would be effective. It is therefore conceivable that, although a chronic protocol might technically disclose an administration of a compound that, if read in isolation, appears as if it could succeed as an acute protocol, in many cases isolating such an administration from a chronic protocol would not actually teach a person of ordinary skill in the art that the isolated administration would be effective in the context of an acute protocol seeking the intended benefit. The specification of the '872 Patent, however, makes clear that this is not the case as applied to the claims at issue.

The Court begins with the presumption that the claims of the '872 Patent are enabled based on the disclosures in the '872 Patent as a whole. Notably, however, the specification does not discuss acute administration of L-arginine, but instead only chronic administration. The experts agreed that only Example 6 in the '872 Patent tested the effect of L-arginine supplementation on exercise performance—the result to which the invention of the '872 Patent is directed. (Tr. 148, 444–45.) The inventors of the '872 Patent stated in this example that the study "was designed to determine the effect of chronic enhancement of EDNO production rather than an acute effect of arginine." ('872 Patent col. 9 ll. 63–65.) Dr. Volek testified that the inventors of the '872 Patent actually "took

measures in their experiment to rule out an acute effect . . . ." (Tr. 147.) As the inventors state in the '872 Patent, that result was accomplished by replacing the test subjects' water bottles containing arginine with regular water 48 hours before treadmill testing. ('872 Patent col. 9 ll. 65–67.) Yet the claims of the '872 Patent, which are presumptively enabled by this specification, cover acute dosing. This suggests that, for purposes of L-arginine supplementation, a person of ordinary skill in the art would have little trouble extrapolating from a chronic L-arginine protocol that an acute protocol would be effective for enhancing physical performance.

Accordingly, the Court assigns greater weight to Dr. Volek's testimony that a person of ordinary skill in the art would understand the regimen described in Ceremuzynski to disclose the "within 24 hours" regimen claimed in the '872 Patent. Even Dr. Boger did not go so far as to label the Ceremuzynski protocol as chronic, instead labeling it "intermediate," i.e., somewhere between chronic and acute. (Tr. 381.) However, because a disclosure pertaining to a chronic regimen presumptively enables these acute claims, the Court finds that an intermediate regimen that literally discloses the "within 24 hours" limitations discloses these elements for purposes of obviousness. Further, the Court notes that the claims at issue do not exclude consecutive daily doses administered within 24 hours of the physical performance. Thus, because Ceremuzynski involved administration of 6 grams of L-arginine within 24 hours of physical performance, there is no reason this disclosure would not meet the within 24 hours elements for purposes of infringement if Ceremuzynski were later in time. Dr. Volek's testimony, together with the inferences drawn from the '872 Patent itself, are clear and convincing evidence that Ceremuzynski discloses the within 24 hours limitation.

Similarly beginning with the presumption that the chronic testing disclosed in the '872 Patent teaches a skilled artisan that administration of the composition within 6 hours would succeed, the Court credits as true Dr. Volek's testimony that a skilled artisan who sees the eleven or twelve hour lapse from the final administration—or possibly the administration of the L-arginine almost immediately before exercise—would find it

obvious to administer the composition within six hours. The authors fail to specify in Ceremuzynski whether the last two grams of L-arginine were administered at 10 p.m., followed by exercise at 9 a.m. or 10 a.m. the next day, or at 9 a.m. immediately before the 9 a.m. or 10 a.m. exercise. This further indicates that a skilled artisan using L-arginine supplementation to improve exercise performance would not consider this lapse in time to be a material difference that might render administration of the L-arginine significantly more or less effective for enhancing physical performance. That is, if a skilled artisan would not doubt that chronic dosing would have a similar effect to an acute dose given within six hours of the physical performance, a skilled artisan would have no trouble extrapolating from an eleven or twelve hour lapse that a dose within six hours would be effective.

As Dr. Volek testified, a skilled artisan in 1998 would see no credible reason why administration eleven hours before exercise would not enhance physical performance but administration six hours before exercise would. That rings particularly true in light of claim 12, which discloses administration of 2 grams within 24 hours as an effective regimen to enhance human physical performance. That is not to say the Court considers claim 12 as a sort of prior art to claim 7—clearly that cannot be the case—but instead that the invention claims the same result of enhanced human physical performance whether administered within 24 hours or within 6 hours. The implicit presumption in the '872 Patent that this regimen would work suggests that limiting the invention from within 24 hours down to within 6 hours does not go "to the heart of the invention" such that moving from an 11 hour time lapse to a 6 hour one would be obvious to a person of ordinary skill in the art. *See Arendi S.A.R.L., v. Apple Inc.*, --- F.3d ---, No. 2015-2073, 2016 WL 4205964, at *5 (Fed. Cir. Aug. 10, 2016). Further, a skilled artisan in 1998 would understand the mechanisms and processes by which L-arginine would be disbursed in the vascular system, and, moving from an intermediate protocol to an acute protocol, would think to administer a dose closer in time to exercise.

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That in turn suggests that, given the state of the art in June 1998, a skilled artisan would find the within 6 hours limitation of claim 7 obvious in light of the regimen described in Ceremuzynski.

H. *Motivation to Combine*

Lastly, the Court finds that a person of ordinary skill in the art in June 1998 would have been motivated to combine Ceremuzynski and the '459 Patent to come up with the invention of the '872 Patent. Dr. Volek testified that a person of ordinary skill in the art—in particular, a physician interested in improving the physical performance of patients with impaired exercise capacity—would look to a study like Ceremuzynski for its teachings about improved performance in patients with stable angina pectoris. (Tr. 125–26.) The Court finds persuasive Dr. Volek's testimony that a physician looking to improve exercise performance in a patient would look to Ceremuzynski and appreciate that L-arginine could improve performance, and that the physician preparing to treat a patient with L-arginine would be motivated to examine references, such as the '459 Patent, instructing on how to make L-arginine more effective in spurring the metabolic process that would allow enhanced exercise performance.

Further, Dr. Boger acknowledged that a skilled artisan in 1998 would combine these references because Ceremuzynski involves subjects with stable angina pectoris caused by coronary artery disease and the '459 Patent pertains to improving endothelium-dependent vasodilation, which is relevant to treatment of coronary artery disease. (Tr. 383.) Dr. Boger attempts to confine the result of this combination to a skilled artisan coming up with a "chronic dosing regimen that might help patients with coronary artery disease to receive some relief of their symptoms." (Tr. 383.) The Court does not find persuasive this narrow view of what a person of ordinary skill in the art would take away from the combination of these references. As Dr. Boger admits, the protocol in Ceremuzynski is an intermediate dose. (Tr. 381.) Dr. Volek, on the other hand, considers the protocol in Ceremuzynski to be acute. (Tr. 136.) The Court gives more weight to Dr. Volek's testimony about what a person of skill in the art would take away from the combination of Ceremuzynski and the

'459 Patent. Dr. Volek's testimony on this point is both more plausible given what the references actually teach and more internally consistent. Dr. Boger's testimony, by contrast, seeks to impose a limitation to a chronic protocol even though Dr. Boger would not characterize the regimen in Ceremuzynski as chronic. Further, as evidenced by the presumptively enabling specification of the '872 Patent, a person of skill in the art should have had little trouble understanding from information on chronic protocols that administration of the compositions encompassed within these claims would have been effective in acute doses.

I. *Conclusion*

In sum, Ceremuzynski and the '459 Patent disclose or render obvious every limitation of the asserted claims of the '872 Patent and represent a "predictable use of prior art elements according to their established functions." *See KSR*, 550 U.S. at 401. A skilled artisan in June 1998 would be motivated to combine these references to come up with the invention encompassed by these claims. The Court therefore finds Defendants have met their burden of proving by clear and convincing evidence that claims 1, 4, 5, 7, 8, 10, and 12 of the '872 Patent are invalid as obvious. Because the Court concludes these claims are obvious, it does not consider Defendants' arguments with respect to DiPasquale or lack of enablement.

III. The '006 Patent

The '006 patent, titled "Enhancement of Vascular Function by Modulation of Endogenous Nitric Oxide Production or Activity," issued on November 11, 2003, is based on a patent application filed on February 1, 2002. It expired on June 11, 2013. Plaintiffs assert claims 1, 2, 3, 4, 5, 8, and 14.

A. *Obviousness of Claims 1 and 2 in Light of Weider and/or Leaf in Combination with Fitzpatrick*

(i) *Claim 1*

As broken down by the parties limitation-by-limitation, claim 1 covers:

> [A] A composition comprising L-arginine or a physiologically acceptable salt thereof in an amount sufficient to enhance nitric oxide production and
> [B] grape skin extract,
> [C] wherein said composition is in a form suitable for oral administration selected from the group consisting of a pill, tablet, powder, or capsule.

('006 Patent, Ex. 5, col. 27 ll. 31–35.)

The article "L-Arginine Is a Precursor for Nitrate Biosynthesis in Humans," by Cynthia D. Leaf, John S. Wishnok, and Steven R. Tannenbaum (Leaf), was published in Biochemical and Biophysical Research Communications in September 1989, more than one year before the '459 Patent's June 11, 1993 priority date. (Ex. 26.) Dr. Volek testified that Leaf discloses limitation A of claim 1. (Tr. 156–57.) The Court disagrees.

Leaf discloses that L-arginine is metabolized into nitric oxide and then into nitrate in the body—or endogenously—but it does not contemplate supplementation of L-arginine to actually enhance production of nitric oxide. Rather, given what the scientific community believed about L-arginine levels in the human body in 1993, by which point it was widely accepted that this metabolic pathway existed in the body, a person skilled in the art would not understand Leaf as teaching that giving a subject more L-arginine would lead to production of a greater amount of nitric oxide. (*See* Tr. 364–69.) Although Leaf states that the subjects of that study "excreted [-5N]NO3 above the naturally occurring abundance of [15N]NO3 in the 24 hour period after the [15N2]L-arginine dose," this statement refers to the presence of isotopes used to track the molecules as they were converted from one molecule to another and eventually excreted in the subjects' urine. This sentence does not, therefore, suggest that endothelial nitric oxide activity was enhanced, but instead that the particular L-arginine molecules labeled with these isotopes were the direct precursors to the nitrate in the subjects' urine. (*See* Tr. 367–69.) In other words, the Leaf researchers showed that the labeled nitrogen went from point A to point B.

In fact, counterintuitively, one of the two subjects studied in Leaf actually displayed an overall substantial decrease in nitrate. (Leaf, Ex. 26 at 1034 tbl.I; Tr. 367–69.) The presence of the nitrate with the isotope marker increased, showing that the labeled nitrogen

was processed through the relevant metabolic pathway and ended up in the urine in the form of nitrate, but the decrease in the overall level of nitrate from that subject could actually have suggested that administering L-arginine would not enhance the overall production of nitric oxide. (Leaf, Ex. 26 at 1034 tbl.I; Tr. 367–69.) This is particularly true given the debate over the arginine paradox in that general time frame. On this point, in view of the overall nitrate levels described in this article, the Court assigns greater weight to Dr. Boger's testimony that this reference does not disclose increased production of nitric oxide, but rather shows that L-arginine was a precursor to endogenously synthesized nitric oxide. (*See* Tr. 367–69.) The objective evidence, in particular the findings in Leaf presented in Table I, corroborates Dr. Boger's testimony on this point. (*See* Leaf, Ex. 26 at 1034 tbl.I.) Accordingly, limitation A of claim 1 falls outside the scope of the Leaf reference.

The product "Joe Weider's Arginine & Lysine" was advertised, described in written publications, offered for sale, and sold in the United States more than one year before June 1993, and thus is prior art to the patents-in-suit. (*See* Ex. 29.) Articles and advertisements discussing the Weider product were published in August 1987, January 1988, and December 1987. (*See* Exs. 29, 103–05.) Dr. Volek testified that, as of 1993, a person of ordinary skill in the art would recognize that the Weider arginine capsules would enhance nitric oxide synthesis if ingested. (Tr. 155.) The capsules in the Weider product contained 1200 milligrams of L-arginine and L-lysine. (*See* Ex. 29.) Given the relevant publications and that the Weider product contained sufficient levels of L-arginine, the Court credits as true Dr. Volek's testimony on this point. Weider therefore discloses limitation A.

The article "Endothelium-Dependent Vasorelaxing Activity of Wine and Other Grape Products," by David F. Fitzpatrick, Steven L. Hirschfield, and Ronald G. Coffey (Fitzpatrick), was published in the American Journal of Physiology in August, 1993. (Ex. 24.) Because Fitzpatrick was published in 1993, more than one year before the November 9, 1995 priority date given to the grape skin extract claims in the '006 Patent, it is prior art as to those claims. Fitzpatrick discloses that "vasorelaxation induced by grape products . . .

appears to be mediated by the NO-cGMP pathway." (Fitzpatrick at 1776.) The authors go on to state:

> This study demonstrates the presence of one or more vasorelaxing components in some wines, grape juice, and GSE[, *i.e.*, grape skin extract]. The relaxations produced by grape products appear to involve the endothelium-derived relaxing factor (EDRF) . . . subsequently determined to be NO or an NO derivative.

(*Id.*) The '006 Patent cites Fitzpatrick for the premise that "grape skin extract . . . is known to enhance NO activity." ('006 Patent col. 9 ll. 18–20.) As Dr. Volek testified, Fitzpatrick discloses grape skin extract to enhance vasorelaxation involving endothelial nitric oxide, and therefore discloses limitation B. (*See* Tr. 159–60.)

Finally, the Weider product discloses limitation C because it is a capsule. (Weider, Ex. 29; *see also* Tr. 161.) In sum, the Court finds that Weider discloses limitations A and C and Fitzpatrick discloses limitation B.

(ii) *Claim 2*

Claim 2 is dependent on claim 1, and therefore includes all of the limitations of claim 1 as well as the limitation that the composition further comprises "at least one additional ingredient that enhances production of nitric oxide or that inhibits degradation of nitric oxide." ('006 Patent col. 27 ll. 36–39.) In addition to L-arginine and L-lysine, the Weider product contained Vitamins C and B6. Dr. Volek testified that Vitamin C is an antioxidant and would protect nitric oxide from degradation. (Tr. 167, 169.) Dr. Volek also testified that Vitamin B6 is a cofactor that can enhance production of nitric oxide. (Tr. 168–69.) The Court credits as true Dr. Volek's testimony that the Weider product discloses the additional limitation of claim 2. (*See* Tr. 170.)

(iii) *Motivation to Combine*

Together Weider and Fitzpatrick disclose every limitation of claims 1 and 2, and the Court finds Defendants presented sufficient evidence that as of November 1995 a skilled artisan would have been motivated to combine them. Dr. Volek testified that a person of ordinary skill in the art would have realized that nitric oxide does not last long in the body,

and would be looking for ways to prevent nitric oxide from being oxidized by free radicals, such as through antioxidants. Dr. Volek stated that grape skin extract contains antioxidants that would help protect nitric oxide. (Tr. 162–63.) The citation to Fitzpatrick on the face of the '006 Patent suggests that a skilled artisan would think to look to that reference for purposes of enhancing nitric oxide. (*See* '006 Patent col. 9 ll. 18–20 (citing Fitzpatrick).) The more difficult question is therefore whether the skilled artisan would be motivated to combine it with the Weider product to produce the invention of claim 1.

Dr. Boger asserts that what a skilled artisan at the relevant time would extract from Fitzpatrick was that it was "an experimental study that show[s] that components that you can find in red wine in principle are able to induce endothelium-dependent nitric oxide formation." (Tr. 398.) That is in fact the premise for which the specification of the '006 Patent cites Fitzpatrick. (*See* '006 Patent col. 9 ll. 18–20.) On the other hand, Dr. Volek's testimony is premised on the notion that a skilled artisan would understand from Fitzpatrick that grape skin extract would provide antioxidants that protect nitric oxide from degradation. (*See* Tr. 162–63.) The Court agrees with Dr. Volek. Although Fitzpatrick is not absolute on that premise,[7] when taken as a whole, Fitzpatrick supplies sufficient data and conclusions to motivate a skilled artisan to combine it with the Weider product.

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[7] Fitzpatrick states:

> It might be possible that the grape product could decrease degradation of basal levels of NO, perhaps acting to prevent NO destruction by superoxide . . . . We have no evidence to support these latter two possibilities, however, and they would appear to be unlikely, since basal levels of NO and cGMP are probably too low to permit the increase in NO and cGMP (caused by inhibition of NO or cGMP degradation) necessary to produce the strong relaxations seen with various grape products.

(Fitzpatrick at H776.) Fitzpatrick later states that the:

> active component responsible for endothelium-dependent relaxing activity of wine and grape juice is apparently derived from the grape skin. . . . We have little direct information on the chemical nature of the active component(s) of grape skins. The possibility that the factor is L-arginine was ruled out in preliminary experiments in which very high concentrations of L-arginine (10mM) caused only minimal relaxation . . . .

(Fitzpatrick at H776–77.) Still later, Fitzpatrick teaches, "Quercetin, a flavonoid found in grapes and possessing free radical-scavenging and lipid antiperoxidation activity (22), relaxed intact aortic rings.

Both experts have acknowledged that it is not unusual to attempt to translate results from experiments in vitro to an in vivo setting, and scientists are often motivated to find less invasive ways to deliver substances, such as orally as opposed to via injection. Thus, Dr. Boger's testimony that a skilled artisan would not think to apply the teaching of Fitzpatrick in the context of oral administration as a pill or capsule, (Tr. 399), is not particularly persuasive. After all, the observed effects of wine consumption—ingested orally—provoked the Fitzpatrick study. Nor is Dr. Boger's testimony pertaining to Weider persuasive. Dr. Boger explained that the Weider product was advertised as a supplement to increase muscle strength and muscle volume, and did not indicate that it would be useful for inducing endothelium-dependent effects. (Tr. 399.) Yet use of the Weider product may have nonetheless had endothelium-dependent effects and inherently disclosed those limitations. Ultimately, the Court is persuaded that the inherent functionality of the Weider product would put it on the radar of the person of ordinary skill relevant to this case.

Dr. Volek explained that a person of ordinary skill in the art would be motivated to combine L-arginine and antioxidants. (*See* Tr. 163.) There is no persuasive evidence that the scientist who is the skilled artisan here[8] would not look to a product that inherently disclosed endothelium-dependent effects to solve the problem addressed by the invention of claims 1 and 2. Thus, taking Weider together with Fitzpatrick as a whole discloses each limitation of claims 1 and 2, and the person of ordinary skill relevant to this case would have been motivated to combine Weider and Fitzpatrick. The Court therefore finds that Defendants have met their burden of proving by clear and convincing evidence that a

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This compound probably does not contribute significantly to the endothelium-dependent relaxing activity of grape products since *1*) it is poorly soluble in water and *2*) the relaxations were not reversed by NO synthase inhibitors," and concludes that "[f]urther work will be necessary to isolate and identify the endothelium-dependent vasorelaxing compound(s) of grape products." (Fitzpatrick at H777.)

[8] As discussed above, a person of ordinary skill in the art is "an individual with a Ph.D. in biochemistry, pharmacology, nutrition chemistry, kinesiology, or the like, and at least two years of post-doctoral research or clinical work in physiology or biochemistry, or alternatively with an M.D. and two years of work experience relating to supplementation and formulation." (Pretrial Order at 3.)

skilled artisan would be motivated to combine these references. Accordingly, the Court finds claims 1 and 2 of the '006 Patent invalid as obvious.

B. ***Obviousness of Claims 3 and 4 in Light of Levere in Combination with Werner-Felmayer and/or Fitzpatrick***

(i) *Claim 3*

As broken down by the parties limitation-by-limitation, claim 3 covers:

> [A] A composition comprising L-arginine or a physiologically acceptable salt thereof and
> [B] at least one additional compound associated with production of nitric oxide other than L-arginine or a physiologically acceptable salt thereof,
> [C] said composition excluding other amino acids which are not precursors of nitric oxide,
> [D] wherein said composition is in a form suitable for oral administration selected from the group consisting of a pill, a powder, a liquid, and a capsule.

('006 Patent col. 27 ll. 40–47.) The Court construed limitation C to mean "composition excluding any amino acid from which nitric oxide is not directly formed." (Cl. Constr. Order 21.) The Court also construed the term "compound associated with production of nitric oxide" to mean a "compound that increases nitric oxide production." (*Id.* at 22.)

Levere discloses that "L-arginine or a salt thereof may be administered to a mammalian organism by any route of administration. . . . The oral dosage form is preferred." (Levere col. 6 ll. 29–33.) This passage discloses limitation A.

The article "Pteridine Biosynthesis in Human Endothelial Cells," by Gabriele Werner-Felmayer, Ernst R. Werner, Dietmar Fuchs, Arno Hausen, Gilbert Reibnegger, Curt Schmidt, Gunter Weiss, and Helmut Wachter (Werner-Felmayer), was published in The Journal of Biological Chemistry on January 25, 1993. (Ex. 44.) Werner-Felmayer is prior art to the patents-in-suit because it was published before the earliest priority date of any of the patents-in-suit. Dr. Volek testified that Werner-Felmayer examined the role of the cofactor tetrahydrobiopterin, or BH4 for short, in the conversion of L-arginine to nitric oxide. (Tr. 185.) L-arginine is converted into nitric oxide by the enzyme nitric oxide synthase. For nitric oxide synthase to work properly, tetrahydrobiopterin must also be

present. The experiment in Werner-Felmayer confirmed that tetrahydrobiopterin was required for nitric oxide synthase to convert L-arginine into nitric oxide. (Tr. 185.)

Limitation B covers a compound other than L-arginine that increases nitric oxide production. Werner-Felmayer states that "tetrahydrobiopterin produced due to cytokine action is required for the high and long term synthesis of NO . . . ." (Werner-Felmayer at 1842.) The authors in Werner-Felmayer go on to state, "[w]e present evidence that increased intracellular tetrahydrobiopterin levels resulting from cytokine treatment significantly increase NO-mediated generation of cGMP in HUVEC." (*Id.*) Werner-Felmayer therefore discloses a compound other than L-arginine that increases nitric oxide production.

United States Patent No. 5,212,204 (Keefer) issued on May 18, 1993, and is based on a patent application filed on October 18, 1989. (Ex. 40.) It is prior art to the patents-in-suit pursuant to 35 U.S.C. § 102(e) (pre-AIA). The inventors in Keefer disclose drugs that break down into nitric oxide in the body, such as nitroglycerin. (Tr. 189–90; *see also* Keefer col. 1 ll. 12–30.) Keefer also teaches that "compounds containing the N-oxy-N-nitrosoamine group . . . wherein the compound decomposes under physiological conditions to release NO, are potent anti-hypertensives." (Keefer col. 1 ll. 30–41.) Dr. Volek testified that these compounds would break down in the body to produce nitric oxide, and Keefer therefore discloses a compound other than L-arginine that increases nitric oxide production, meeting limitation B of claim 3. (Tr. 191.)

Per limitation C, the composition must exclude any amino acid from which nitric oxide is not directly formed. Dr. Volek testified that Levere discloses this element because the inventors described administration of L-arginine with no other amino acids. (Tr. 192; *see, e.g.*, Levere, claim 1, col. 11 ll. 25–30.)

Limitation D requires that the composition be "in a form suitable for oral administration selected from the group consisting of a pill, a powder, a liquid, and a capsule." ('006 Patent col. 27 ll. 40–47.) Levere discloses that the oral dosage form is the preferred mode of administering L-arginine. (Levere col. 6 ll. 29–42.)

(ii) *Claim 4*

Claim 4 is dependent on claim 3, and therefore includes all of the limitations of claim 3 as well as the additional limitation that the composition "further comprises a predetermined regimen that provides a daily amount ranging from 1 to 12 grams of L-arginine or its physiologically acceptable salt." ('006 Patent col. 27 ll. 48–51.) Levere disclosed effectiveness of L-arginine at a dose as low as 16 milligrams per kilogram of body weight and as high as 100 milligrams per kilogram bodyweight. (Levere col. 8 ll. 10–18.) If extrapolated to a human weighing 150 lbs., or 68.2 kilograms, that would be a dose of 1.1 grams to 6.8 grams. (Tr. 196.) Levere therefore discloses the additional limitation of claim 4.

(iii) *Motivation to Combine*

Dr. Volek testified that a skilled artisan in June 1993 would have been motivated to combine the Levere, Keefer, and Werner-Felmayer references. (Tr. 193–94.) That is, a skilled artisan searching for a composition useful for "[e]nhancement of vascular function by modulation of endogenous nitric oxide production or activity," which the title of the '006 Patent suggests was the purpose of the invention, would first think to look to Levere for its teachings on the effect of L-arginine in decreasing blood pressure. (*See id.*) The skilled artisan would understand that the decrease in blood pressure was a result of the presence of nitric oxide, and would therefore look for ways to preserve or enhance the presence of nitric oxide in the body. (*See id.*) A natural place to turn would be to the enzyme that converts L-arginine into nitric oxide, and then to attempt to make that enzyme more efficient. A skilled artisan would therefore look to Werner-Felmayer's teachings about tetrahydrobiopterin's effect on nitric oxide synthase, and consider combining L-arginine and tetrahydrobiopterin or its precursor to enhance the blood pressure reduction effect of Levere. (*See id.*)

Dr. Boger testified that a skilled artisan would not combine the Werner-Felmayer and Levere references to arrive at an invention of a compound suitable for oral

administration because the cofactor Werner-Femlayer discloses, tetrahydrobiopterin, decomposes when it is exposed to gastric acid in the stomach. (Tr. 402.)

Although the Court credits as true Dr. Boger's conclusion that a skilled artisan would not think to take the teaching of Werner-Felmayer to suggest including tetrahydrobiopterin in a form suitable for oral administration, that does not mean a skilled artisan in June 1993 would be unable to take a step back in the metabolic pathway to consider a different means of delivering tetrahydrobiopterin to the endothelial cells. As Dr. Volek testified, tetrahydrobiopterin, or BH4, is derived from folate. (Tr. 193.) Patent '006 in fact envisions administering folate in one embodiment of the invention. ('006 Patent col. 8 ll. 37–40 ("[O]ther agents can be added to the oral formulation of the amino acids or polypeptides to enhance their absorption, and/or to enhance the activity of NO synthase, e.g. . . . folate (0.4-10 mg per daily dose).").) The Court finds that a skilled artisan who wished to increase the amount of tetrahydrobiopterin in a subject could, calling on her knowledge of the relevant science, extrapolate from Werner-Felmayer that administering folate could achieve the result taught in that reference. The Court credits as true Dr. Volek's testimony that a skilled artisan in June 1993 would be motivated to combine Werner-Felmayer and Levere to come up with the invention of claims 3 and 4.

Similarly, Dr. Volek testified that a skilled artisan would be motivated to combine Keefer with Levere because she would understand that nitric oxide caused vasodilation, that Keefer discloses increasing nitric oxide levels in the body through decomposition of compounds, and that Levere teaches using L-arginine to lower blood pressure and suggests that the mechanism by which this occurs is production of endothelial nitric oxide. (*See* Tr. 193–94.) A person of ordinary skill in the art would think to combine these references—they teach two different processes for increasing nitric oxide levels in blood vessels, which could work together to be "additive or even synergistic." (*See id.* at 194.) On the other hand, Dr. Boger testified that a skilled artisan would not think to combine Keefer with Levere because Keefer pertained to decomposition of other materials into nitric oxide, as opposed to synthesis of nitric oxide in the body. (*See* Tr. 402.) Although Keefer and

Levere describe increasing the amount of nitric oxide in the body through different mechanisms, the Court is not persuaded that a skilled artisan would, as a result, not think to combine these teachings. The Court adopted the broad construction urged by Plaintiffs which did not constrict compounds "associated with" production of nitric oxide to those metabolized in the endothelial cells into nitric oxide. (*See* Cl. Constr. Order 19–20.) Accordingly, the Court credits as true Dr. Volek's testimony that a person of ordinary skill in the art as of June 1993 would be motivated to combine the then well-known process of administering a compound that breaks down into nitric oxide along with administering the precursor to endogenously synthesized nitric oxide.

This testimony and these references together constitute clear and convincing evidence that a skilled artisan would be motivated to combine Levere with Werner-Felmayer and Levere with Keefer. Because each of these combinations disclose every limitation of claims 3 and 4, the Court finds that each of these combinations independently renders claims 3 and 4 of the '006 Patent invalid as obvious.

C. *Obviousness of Claims 5, 8, and 14 in Light of Levere in Combination with Werner-Felmayer, Keefer, and/or Mugge*

(i) *Claim 5*

As broken down by the parties limitation-by-limitation, claim 5 of the '006 Patent covers:

> [A] A composition comprising L-arginine or a physiologically acceptable salt thereof,
> [B] at least one additional compound associated with production of nitric oxide other than L-arginine or a physiologically acceptable salt thereof
> [C] and a compound that prevents the production of oxygen-derived free radicals, said composition excluding other amino acids which are not precursors of nitric oxide,
> [D] wherein said composition is in a form suitable for oral administration selected from the group consisting of a pill, a powder, a liquid, and a capsule.

('006 Patent col. 27 ll. 52–61.) As discussed above, Levere discloses a composition containing L-arginine or a physiologically acceptable salt thereof, and therefore discloses

limitation A. The Court construed the term "compound associated with production of nitric oxide," which appears in limitation B, to mean a "compound that increases nitric oxide production." (Cl. Constr. Order 22.) As discussed above, Werner-Felmayer and Keefer disclose this limitation.

The article by Mugge et al., "Chronic Treatment with Polyethylene-Glycolate Superoxide Dismutase Partially Restores Endothelium-Dependent Vascular Relaxations in Cholesterol-Fed Rabbits" (Mugge), was published in Circulation Research in November 1991. (Ex. 27.) Because Mugge was published in 1991, more than one year before the earliest priority date of any of the patents-in-suit, it is prior art to the patents-in-suit. Mugge studies the antioxidant superoxide dismutase, or SOD in the context of nitric oxide. (Tr. 203.) As indicated by the first sentence of the abstract, the study in Mugge addresses the problem that nitric oxide is "rapidly inactivated by superoxide radicals." (Mugge at 1293.) The Mugge authors concluded that "PEG-SOD or other antioxidants may be beneficial in clinical syndromes in which endothelial dysfunction may contribute." (Mugge at 1299.) Given that Mugge was published in 1991, Dr. Volek testified that use of materials to prevent the formation of oxygen-derived free radicals that adversely affected nitric oxide was not new or inventive as of June 1993. (Tr. 206.) Mugge therefore discloses limitation B because it teaches the use of "a compound that prevents the production of oxygen-derived free radicals" and that composition is not made up of "other amino acids which are not precursors of nitric oxide."

As discussed above, Levere discloses limitation D by stating that oral administration, such as by tablet or capsule, is the preferred mode of administering the compound. (Levere col. 6 ll. 29–42.)

(ii) *Claim 8*

Claim 8 is dependent on claim 5, and therefore includes all of the limitations of claim 5 as well as the additional limitation that the composition "is in a daily dosage form providing an amount of L-arginine or its physiologically acceptable salt in an amount ranging from about 1 to about 12 grams per daily dosage." ('006 Patent col. 28 ll. 1–4.)

As discussed above, Levere makes obvious for a human of average weight a dose of 1.1 to 6.8 grams per day, and therefore discloses doses within the range of the invention of claim 8. (*See* Tr. 209.)

(iii) *Claim 14*

Claim 14 is dependent on claim 5, and therefore includes all of the limitations of claim 5 as well as the additional limitation that "the compound that prevents the production of oxygen-derived free radicals is an antioxidant." ('006 Patent col. 28 ll. 20–22.) This claim therefore narrows the scope of limitation C of claim 5. However, the discussion in Mugge that disclosed the broader limitation of claim 5 did so by teaching that the compound is an antioxidant, and therefore also discloses the narrower limitation of claim 14. (*See* Tr. 211–12; Mugge at 1299.)

(iv) *Motivation to Combine*

Dr. Volek testified that a person of ordinary skill in the art would be motivated to combine the Levere, Werner-Felmayer, and Mugge references as well as the Levere, Keefer, and Mugge references to come up with the invention of claims 5, 8, and 14. (Tr. 208.) As previously discussed, the Court finds that a skilled artisan would combine Levere with Werner-Felmayer and Levere with Keefer. The question is therefore whether a skilled artisan in 1993 would also be motivated to combine the Mugge reference. Dr. Volek stated that, as with the prior combination, the skilled artisan would be looking for ways to make nitric oxide more effective for enhancing vascular function. If concocting a compound to achieve this purpose through enhanced nitric oxide, the skilled artisan as of June 1993 would think to add antioxidants as taught in Mugge because they were known at the time to prolong the life of nitric oxide by preventing the production of oxygen-derived radicals that scavenge nitric oxide. (*Id.*)

Dr. Boger stated that a person of ordinary skill in the art would not have been motivated to combine the teachings of Mugge with Levere and Keefer. (Tr. 407–08.) That is because the SOD taught in Mugge requires injection, and would not work for oral or dietary supplementation. (Tr. 408.) The bottom line, Boger stated, is that, while these

references "nicely point[] out the basic physiological mechanisms" as to the particular disease models studied, they do not actually "propose any kind of oral or dietary supplementation strategies." (Tr. 408.)

The Court finds Dr. Volek's opinion on this point more persuasive. Dr. Boger's opinion presumes that a skilled artisan in June 1993 could not extrapolate from the effectiveness of SOD that other antioxidants might help prevent nitric oxide from being scavenged by oxygen-derived radicals. To the contrary, a skilled artisan exploring mechanisms for promoting the presence of nitric oxide in the blood vessels would be motivated to consider the likely benefits from antioxidants, both SOD and those that might be suitable for oral administration. Dr. Volek's testimony pertaining to the state of the art in June 1993 and these references, as well as the disclosures in these references themselves, are clear and convincing evidence that a person of ordinary skill in the art would have been motivated to combine the elements of Levere, Werner-Felmayer, and Mugge—or Levere, Keefer, and Mugge—and to produce the invention of claims 5, 8, and 14 of the '006 Patent. The Court therefore finds that these claims are invalid as obvious.

D. *Anticipation of Claims 5, 8, and 14 by Weider's Arginine & Lysine Product*

Because the Court concludes that claim 5, 8, and 14 are obvious, it does not reach Defendants' argument that they are anticipated by Weider.

IV. The '916 Patent: Obviousness in Light of Levere and Keefer

The '916 patent, titled "Enhancement of Vascular Function by Modulation of Endogenous Nitric Oxide Production or Activity," issued on November 18, 2008, is based on a patent application filed on December 22, 2004. It expired on June 11, 2013.

A. *Claim 1*

As broken down limitation-by-limitation by the parties, claim 1 covers:

> [A] A method of enhancing nitric oxide production comprising orally administering to a human host in need thereof a composition comprising L-arginine or a physiologically acceptable salt thereof,

> [B] wherein (i) said composition includes an amount of L-arginine or its physiologically acceptable salt sufficient to increase the level of nitric oxide production in said human host and
> [C] (ii) said composition is a dietary or food supplement or a pharmaceutical composition in a form suitable for oral administration selected from the group consisting of a pill, a powder, a liquid, and a capsule, wherein
> [D] said administering provides a daily amount ranging from 1 to 12 grams of L-arginine or its physiologically acceptable salt and
> [E] wherein the composition further comprises at least one additional compound associated with production of nitric oxide other than L-arginine or a physiologically acceptable salt thereof.

('916 Patent col. 26 ll. 38–53.) Dr. Volek testified that Levere discloses elements A and B because the inventors, writing in the abstract of the Levere patent, describe administering an amount of L-arginine sufficient to achieve a reduction of blood pressure. (*See* Tr. 233–34; Levere abstract (discussing "administering to a mammalian organism in need of such prevention or treatment a sufficient amount of L-arginine").) The inventors in Levere noted that L-arginine is the precursor to nitric oxide and attributed the blood pressure reduction to enhanced endothelial nitric oxide production, which they stated was "the most powerful endothelia-derived releasing factor." (Tr. 234; Levere col. 7 ll. 21–32, col. 8 ll. 41–43.) Levere also states that oral administration is the preferred route, which Dr. Volek testified discloses limitation C. (Tr. 234; Levere col. 6 ll. 29–33.) As discussed above, Levere makes obvious a dosage range of 1.1 to 6.8 grams when projected to an average human based on its teaching on the quantity of milligrams of L-arginine relative to kilograms of body weight. (Tr. 238; Levere col. 8 ll. 10–18.) As Dr. Volek testified, this teaching discloses limitation D. (Tr. 238.)

Lastly, Dr. Volek testified that Keefer describes the use of various compounds that "break down and produce nitric oxide in the body." (*See* Tr. 237–38 (referring to the '916 Patent col. 26 ll. 50–54).) This discloses limitation E because those compounds are "at least one additional compound associated with production of nitric oxide other than L-arginine or a physiologically acceptable salt thereof." (*See* Tr. 237–38.) Dr. Boger stated that Keefer does not disclose this limitation. (*See* Tr. 387–88.) The main point of

disagreement between the experts is what the '916 Patent means by "production of nitric oxide." That is, the dispute appears to be over whether chemical decomposition of a compound into nitric oxide—as opposed to conversion of L-arginine into nitric oxide by the enzyme nitric oxide synthase—counts as "production."

The Court assigns greater weight to Dr. Volek's testimony and finds that claim 1 of the '006 Patent does not limit the "additional compound associated with production of nitric oxide" to a compound associated with production via conversion in the endothelial cells of L-arginine into nitric oxide. Nor does chemical decomposition of compounds in the body resulting in an increase in the level of nitric oxide fit within the term "production of nitric oxide" for purposes of the claimed invention. Tellingly, Plaintiffs argued in their Responsive Claim Construction Brief that this term was not indefinite because "L-arginine was not the only compound associated with increasing nitric oxide at the time the patents were filed . . . ; a patent filed in 1994 disclosed use of nitroglycerin to increase production of nitric oxide." (Pls.' Resp. Cl. Constr. Br. 11, ECF No. 79.) The Court, citing this very argument, held in favor of Plaintiffs that the term was not indefinite. (*See* Cl. Constr. Order 19–20.) Because Dr. Volek's testimony is consistent with Plaintiffs' position at claim construction and Dr. Boger's testimony appears tailored to avoid this claim limitation, the Court assigns greater weight to Dr. Volek's testimony and therefore concludes that Keefer discloses limitation E.

B. *Claim 2*

Claim 2 provides:

> [A] A method of enhancing nitric oxide production comprising orally administering to a human host in need thereof a composition comprising L-arginine or a physiologically acceptable salt thereof, wherein
> [B] (i) said composition includes an amount of L-arginine or its physiologically acceptable salt sufficient to increase the level of nitric oxide production in said human host and
> [C] (ii) said composition is a dietary or food supplement or a pharmaceutical composition in a form suitable for oral administration selected from the group consisting of a pill, a powder, a liquid, and a capsule, wherein

> [D] said administering provides a daily amount ranging from 1 to 12 grams of L-arginine or its physiologically acceptable salt
> [E] and wherein the composition further comprises a compound that prevents the production of oxigen-derived [sic] free radicals.

('916 Patent col. 26 ll. 54–67.) Limitations A through D of claim 2 cover essentially the same invention as limitations A through D of claim 1, and are therefore disclosed by Levere as discussed above. (*See* '916 Patent col. 26 ll. 54–67.) Limitation E varies from claim 1 to claim 2, however. In claim 2, limitation E calls for the composition to contain "a compound that prevents the production of oxigen-derived [sic] free radicals." (*Id.* at col. 26 ll. 65–67.) Dr. Volek testified that as of June 1993 the concept of using antioxidants to protect nitric oxide from degradation was very well known. (Tr. 240–41.) In fact, as Dr. Volek pointed out, (Tr. 241), the inventors of the '916 Patent stated that antioxidants should be given as part of the invention because "*it is known* that oxygen-derived free radicals (such as superoxide anion) can inactivate nitric oxide," ('916 Patent col. 9 ll. 28–29 (emphasis added)). Keefer teaches that certain compounds it discloses may be oxidized, so "an antioxidant, such as ascorbate, can be added to the carrier to increase the shelf-life." (Keefer col. 8 ll. 20–23.)

C. *Claim 6*

Claim 6 is dependent on claim 2, and therefore includes all of the limitations of claim 2 as well as the additional limitation that the "compound that prevents the production of oxygen-derived free radicals is an antioxidant." ('916 Patent col. 28 ll. 6–8.) As discussed above, the teaching in Keefer regarding preventing oxidation discloses an antioxidant. (*See* Keefer col. 8 ll. 20–23.)

D. *Motivation to Combine*

Dr. Volek reiterated his testimony pertaining to whether skilled artisans would be motivated to combine the Levere and Keefer references as of June 1993, opining that they would. (Tr. 239.) Regarding the problem solved by the invention of the '006 Patent: a skilled artisan would understand that nitric oxide caused vasodilation, that Keefer discloses increasing nitric oxide levels in the body by decomposition of compounds and protecting

compounds from oxidation by using antioxidants, and that Levere teaches using L-arginine to lower blood pressure and suggests that the mechanism by which this occurs is production of endothelial nitric oxide. (*See id.*) A skilled artisan interested in improving vascular function likely would not limit his or her endeavors to the production of nitric oxide in the endothelial cells. The Court finds Dr. Volek's testimony more reasonable and credible, and therefore assigns greater weight to it than to Dr. Boger's narrower view that a skilled artisan would not think to combine a compound that decomposes into nitric oxide with an amino acid that is enzymatically converted into nitric oxide in the endothelial cells. A skilled artisan would be looking for compounds that could work together synergistically to increase vascular function by various mechanisms. (*See id.*)

Because the Court concludes that the asserted claims of the '916 Patent are invalid as obvious in light of Levere and Keefer, the Court does not consider Defendants' argument that the claims are anticipated by Weider or obvious in light of Levere and Werner-Felmayer.

V. Secondary Considerations of Nonobviousness

Although Plaintiffs' Pretrial Memorandum emphasized the importance in this case of secondary considerations of nonobviousness such as commercial success, licensing activity, and skepticism, evidence presented at trial focused only on skepticism. Dr. Boger and Dr. Cooke testified about the skepticism Dr. Cooke faced in positing that L-arginine supplementation could actually enhance endogenous production of endothelial nitric oxide, particularly skepticism by a colleague, Dr. Harrison.

Dr. Boger testified that the scientific community, observing the arginine paradox, was skeptical that administering L-arginine as a supplement would have any effect on nitric oxide production. (*See* Tr. 343–44.) Even after 1993—for example, in 1995—members of the scientific community doubted that arginine supplementation could increase endothelial nitric oxide production. (Tr. 344.) Dr. Boger testified that he and other researchers published a study in 2007 essentially resolving the arginine paradox. The study showed that an enzymatic inhibitor hampers the efficacy of nitric oxide synthase in vivo,

and that an increased concentration of L-arginine can displace the inhibitor from the enzyme, thereby allowing it to "work better again." (Tr. 451.) At tension with the notion that scientific debate over the arginine paradox was ongoing as late as 2007 is Dr. Cooke's statement in his book, *The Cardiovascular Cure*, which suggested that a pair of researchers had offered the correct solution to the arginine paradox as of 1992. (Tr. 503.)

As discussed above, the Court finds that claim 1 of the '459 Patent is invalid as anticipated, as opposed to obvious. Secondary considerations are not an element of anticipation. *See Cohesive Techs., Inc. v. Waters Corp.*, 543 F.3d 1351, 1364 (Fed. Cir. 2008) ("[O]bviousness requires analysis of secondary considerations of nonobviousness, while secondary considerations are not an element of a claim of anticipation."). Although the Court has no reason to doubt that Dr. Harrison and perhaps other contemporaries of Dr. Cooke and Dr. Boger were skeptical that L-arginine supplementation could increase production of endothelial nitric oxide, the Court nonetheless finds that the Levere reference anticipates the invention of claim 1 of the '459 Patent, and the skepticism from certain colleagues in the scientific community does not displace that finding.

Plaintiffs have not presented additional evidence that—aside from doubt surrounding the arginine paradox as well as the competing oxygen radical theory and impaired nitric oxide production theory—the scientific community was skeptical of the efficacy of the additional limitations encompassed by the asserted claims of the '872, '006, and '916 Patents. Accordingly, the evidence of skepticism does not rebut the Court's conclusions or sufficiently diminish Defendants' evidence that certain claims of the relevant patents would have been obvious in light of the prior art.

Further, the Court finds the evidence as it relates in particular to skepticism *as of June 1993*, and by extension June 1998, unpersuasive. Defendants impeached Dr. Cooke's testimony pertaining to skepticism as of June 1993 by eliciting testimony from Dr. Cooke that his own book states that in 1992 certain researchers had posed the solution to the arginine paradox that later proved to be correct. While these researchers' hypothesis did not completely resolve the debate over the arginine paradox as of 1992, the Court finds that

it diminished skepticism, and that the degree of skepticism in the scientific community as of June 1993 was not significant enough, standing alone, to rebut the clear and convincing evidence that the majority of the asserted claims discussed above were obvious.

In sum, the evidence of secondary considerations presented at trial does not persuade the Court to change its conclusion that the inventions of claims 1, 4, 5, 7, 8, and 10 of the '872 Patent; claims 1, 2, 3, 4, 5, 8, and 14 of the '006 Patent; and claims 1, 2, and 6 of the '916 Patent are invalid as obvious.

CONCLUSION

For the foregoing reasons, the Court finds Defendants have met their burden of proving by clear and convincing evidence that: (1) claim 1 of the '459 Patent is invalid as anticipated; (2) claims 1, 4, 5, 7, 8, and 10 of the '872 Patent are invalid as obvious; (3) claims 1, 2, 3, 4, 5, 8, and 14 of the '006 Patent are invalid as obvious; and (4) claims 1, 2, and 6 of the '916 Patent are invalid as obvious.

IT IS SO ORDERED.

Dated: September 21, 2016

Janis L. Sammartino
Hon. Janis L. Sammartino
United States District Judge