2018-1295

United States Court of Appeals for the Federal Circuit

NATURAL ALTERNATIVES INTERNATIONAL, INC.,

Plaintiff – Appellant,

v.

CREATIVE COMPOUNDS, LLC,

Defendant – Appellee,

DOES 1-100, CORE SUPPLEMENT TECHNOLOGIES, INC., HONEY BADGER, LLC, MYOPHARMA, INC.,

Defendants.

Appeal from the United States District Court for the Southern District of California in Case No. 3:16-cv-02146-H-AGS, Marilyn L. Huff, Judge

REPLY BRIEF FOR APPELLANT

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CERTIFICATE OF INTEREST

Counsel for Appellant Natural Alternatives International, Inc. certifies that:

(1) The full name of every party or amicus represented by us is:

Natural Alternatives International, Inc.

(2) The name of the real party in interest represented by us is:

Natural Alternatives International, Inc.

(3) All parent corporations and any publicly held companies that own 10 percent or more of the stock of the party or amicus represented by us are: None.

(4) The names of all law firms and the parties or associates that appeared for the party or amicus now represented by us in the trial court or agency or are expected to appear in the court are:

PORZIO, BROMBERG & NEWMAN P.C.: Scott A.M. Chambers, Kevin M. Bell, Richard J. Oparil, B. Dell Chism, Caroline C. Maxwell, Matthew D. Zapadka and WILSON TURNER KOSMO LLP: Frederick W. Kosmo Jr. and Hubert Kim.

(5) The title and number of any case known to counsel to be pending in this or any other court or agency that will directly affect or be directly affected by this court's decision in the pending appeal:

Natural Alternatives Intl., Inc. v. Hi-Tech Pharmaceuticals, Inc., doing business as ALR Industries, APS Nutrition, Innovative Laboratories, Formutech

Nutrition, LG Sciences, and Sports 1; and DOES 1-100 Case No. 3:16-cv-02343-H-AGS, pending in the United States District Court for the Southern District of California.

Natural Alternatives Intl., Inc. v. Iancu, Consolidated Case Nos. 17-1962 and 17-1963, pending in the United States Court of Appeals for the Federal Circuit.

Date: July 20, 2018

/s/ Matthew D. Zapadka
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Creative Compounds, LLC	Creative
Dietary Supplement Health and Education Act of 1994	DSHEA
First Amended Complaint for Patent Infringement, *Natural Alternatives, Intl., Inc., v. Creative Compounds, LLC*, 16-cv-2146, ECF No. 48 (S. D. CA. Aug. 24, 2016)	FAC
U.S. Food and Drug Administration	FDA
United States Patent and Trademark Office Guidance on Subject Matter Eligibility	Guidance
Hi-Tech Pharmaceuticals, Inc.	Hi-Tech
Manual of Patent Examining and Procedure	MPEP
Natural Alternatives International, Inc.	NAI
United States Patent and Trademark Office	PTO
U.S. Pat. No. 5,965,596	The '596 Patent
U.S. Pat. No. 7,504,376	The '376 Patent
U.S. Pat. No. 7,825,084	The '084 Patent
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The '596 Patent, the '376 Patent, the '084 Patent, the '610 Patent, the '865 Patent, the '947 Patent collectively	Patents-on-Appeal
Plaintiff-Appellant NAI's Opening Appeal Brief	Op. Br. or Opening Brief
Defendant-Appellee Creative's Response Brief	Creative Br.

SUMMARY

The District Court erred in holding the Patents-on-Appeal were ineligible under 35 U.S.C. § 101. The District Court erred by considering that beta-alanine was the entire inventive concept of the claims. Appx7-26. The District Court further determined that the added claim elements contained nothing more than routine and conventional elements that did not add significantly more to the inventive concept. *Id*. The District Court and Creative both rely on a mischaracterization of the specification of the Patents-on-Appeal to make the latter determination, and ignore the unrebutted declaration testimony as well as other evidence that contradicts their conclusion. The present claims are directed to a patent-eligible application of beta-alanine, presented in a non-natural dietary supplement. The claims also include methods that administer the supplement at specific massive doses over a long time spans: the decision below improperly groups product and method claims together. This combination of elements is not preemptive, is not directed toward a natural phenomenon—and when considered as a whole—add significantly more to any natural concept because the elements are not routine, conventional, and well-understood. NAI submitted evidence to the District Court that supported all of these arguments, but this evidence was disregarded. The claims of the Patents-on-Appeal are all eligible under § 101.

ARGUMENT

I. EFFECTIVE AMOUNTS OF BETA-ALANINE DO NOT EXIST NATURALLY AS PART OF THE DIET OR AS A HUMAN DIETARY SUPPLEMENT.

Creative highlights its fundamental misunderstanding of the technology at issue in this case by equating the inventive concept to the understanding that "beta-alanine occurs naturally in mammals' muscle tissues as a precursor to another naturally occurring compound, carnosine." Br. at 3. Carnosine, a dipeptide, occurs in muscle but there is no evidence in the record that a measurable amount of beta-alanine is in muscle. *See In re Seaborg*, 328 F.2d 996, 999 (holding that undetectable amounts of a compound in the prior art do not anticipate claims to that compound). As claimed, beta-alanine does not naturally occur as part of a supplement that provides amounts effective to unnaturally override homeostasis and increase carnosine synthesis. Appx907-911. Ingesting beta-alanine as a human dietary supplement unconventionally and non-routinely results in a greater muscle concentration of carnosine than if carnosine (a natural dietary compound) were ingested. Appx1134, ¶¶ 20-23; Appx1158, ¶ 40. All of the evidence provided to the District Court described this mechanism and explained why this was unconventional activity. Appx905-1022, Appx1128-1141, Appx1143-1162. For example, the paresthesia (a tingling sensation) resulting from a human dietary supplement

indicates an objectively unnatural effect resulting from the claimed unnatural supplementation of beta-alanine. Appx1130-1131, ¶ 9.

New applications of naturally occurring compositions are patent-eligible. *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. 576, 590, 596 (2013). Beta-alanine contained within a human dietary supplement possesses markedly different characteristics from that which exists naturally because natural beta-alanine primarily exists as part of carnosine in food sources, and these food sources are not considered human dietary supplements, which are synthetic, human-produced products.[1] *See, e.g.*, Appx912, ¶ 13.

The claims of the Patents-on-Appeal are directed toward human dietary supplements and administration of particular unnatural amounts of beta-alanine (not in the form of the dipeptide carnosine) over an extended time period. *Id*. The dietary supplement of beta-alanine, when viewed in the context of the claims, does not occur naturally because the inventions are concerned with supplementing the diet and limited to this context. *Id*.; *see also Myriad*, 569 U.S. at 596 (method claims and applications using natural materials were not implicated by the decision). Small amounts of beta-alanine may exist naturally in the human liver (Appx909, ¶ 8) but

[1] Insulin is a compound produced naturally by the human pancreas. U.S. Patent No. 1,469,994 is directed toward insulin obtained from pancreatic glands that is used to treat diabetes. That patent, like the patents in this case, are unnatural applications of natural laws.

ingesting liver could never supply an effective amount of beta-alanine or the specific amounts as set forth in the claims because the liver's content is not effective to increase muscle carnosine content as claimed. *Id*.

The use of beta-alanine can only be considered to be a naturally occurring phenomenon if it is disembodied from the claim terms and the context of the invention, *i.e.*, ignoring the claims as a whole. The Supreme Court cautioned courts to "tread carefully in construing this exclusionary principle lest it swallow all of patent law." *Alice Corp. Pty. Ltd. v. CLS Bank Int'l*, 134 S. Ct. 2347, 2354-55 (2014) ("At some level, 'all inventions ... embody, use, reflect, rest upon, or apply laws of nature, natural phenomena, or abstract ideas.'" (quoting *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 566 U.S. 66, 70-73 (2012))).

This case is also not like *Mayo* because the inclusion of beta-alanine in the claims is more than the mere recognition of a natural law: it is an inventive application of a natural law. 566 U.S. at 80-82. Here, human manipulation was imparted to produce a beta-alanine dietary supplement, which is separate and distinct from naturally-occurring carnosine. Then, through new and useful scientific discovery, the inventors invented unnatural outcomes from administration of massive doses of beta-alanine over a long time-period to result in unnaturally high levels of muscle carnosine. Appx908-912. Whether the beta-alanine is part of a claimed composition, a treatment method, or as a method of manufacturing, it is

distinct from that which exists in nature, especially when considered in the context of the inventive concept of the claims.

II. THE DISTRICT COURT IMPROPERLY CONSTRUED THE CLAIMS AND DID NOT APPLY THE AGREED-UPON CONSTRUCTION DESPITE ITS RECITATION THAT IT WAS DOING SO.

All the parties and the District Court agreed to apply NAI's proposed claim constructions. Op. Br. at 19. The claims in the Patents-on-Appeal include the terms "human dietary supplement" or "dietary supplement" for a human. *See, e.g.*, Appx697, '376 Patent at Col. 22, ll. 45-48, Appx732, '084 Patent at Col. 22, ll. 25-42, Appx768, '865 Patent at Col. 23, ll. 4-5, Appx802, '610 Patent at Col. 22, ll. 24-37, Appx836, '947 Patent at Col. 16, ll. 1-22. That term was agreed to be construed as "an addition to the human diet, ingested as a pill, capsule, powder or liquid, which is not a natural or conventional food, meat or food flavoring extract, or pharmaceutical product which **effectively** increases the function of a tissue when administered to the human over a period of time." Appx14, n. 8 (emphasis added). If that construction is applied, the claimed invention literally cannot be construed as a natural product and must pass step one of the *Mayo*/*Alice* test. Op. Br. at 11, 17-19 (defining the *Mayo*/*Alice* test).

That point alone exemplifies the errors of Creative and the District Court. All parties and the District Court agreed to NAI's meaning of human dietary supplement

as an element of the claims. Even with evidence the functional limitations would be unmet if the natural product were provided, the District Court nevertheless concluded the claims were both directed toward a natural product and, without sufficient factual justification, the additional elements did not elevate the claims to the type of subject matter that is eligible under § 101. Appx7-26. This conclusion is incorrect.

If the District Court had applied the claim construction as agreed, it would have held that, while beta-alanine is produced in small quantities, the claimed human dietary supplements containing effective amounts of beta-alanine never occur naturally. Instead, the District Court failed to actually apply NAI's claim construction. Op. Br. at 20-21.

Furthermore, the District Court's decision did not rely on the scientific evidence supporting NAI's construction. This Court is thus left with a record that shows an undeniable error of law along with a scientific record establishing the non-natural components of the invention and the unnatural and unconventional results achieved by the specific modes of administration. The decision could have explained why the agreed-upon construction was not applied, or claim construction could have been conducted based upon factual evidence. It chose neither, leaving this Court with no option but to acknowledge the decision's legal and procedural errors. The record in front of this Court leads to one conclusion: the claims are directed to non-

natural subject matter. This is at least because the claimed human dietary supplements **never could** occur naturally because the compositions involved could only ever arise through technical, human intervention. *See Diamond v. Chakrabarty*, 447 U.S. 303 (1980); *Fromsom v. Advance Offset Plate, Inc.*, 755 F.2d 1549, 1556 n.3 (Fed. Cir. 1985) ("Only God works from nothing. Men must work with old elements."). Facts supporting these conclusions stand unrebutted.

III. THE CLAIMS ON APPEAL ARE NOT DIRECTED TOWARD A NATURAL PHENOMENON.

A. The Claimed Supplements And Methods Of Use Are Not Naturally Occurring And The Inventive Concept Is More Than Beta-Alanine.

Beta-alanine is only an aspect of the inventions and is not the sole focus of the inventions. Op. Br. at 25-49. "'[A] process is not unpatentable simply because it contains a law of nature or a mathematical algorithm.'" *Diamond v. Diehr*, 450 U.S. 175, 187 (1981) (quoting *Parker v. Flook*, 437 U.S. 584, 590 (1978)). Furthermore, Creative and the District Court improperly apply the law when concluding that the claims themselves are directed to a natural law merely because the claims contain beta-alanine as an element. *Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc.*, 827 F.3d 1042, 1050 (Fed. Cir. 2016) ("At step one, therefore, it is not enough to merely identify a patent-ineligible concept underlying the claim; we must determine whether that patent-ineligible concept is what the claim is 'directed to'"). Indeed, the claims are directed to supplements specifically formulated to increase muscle

carnosine, methods of treatment using those supplements, and methods of manufacturing those dietary supplements. They are not solely directed to beta-alanine.

The treatment methods are distinct from the claims of *Mayo*. As this Court has stated in relation to treatment methods and *Mayo*, "[t]o further underscore the distinction between method of treatment claims and those in *Mayo*, the Supreme Court noted that '[u]nlike, say, a typical patent on a new drug or **a new way of using an existing drug**, the patent claims do not confine their reach to particular applications of those laws.'" *Vanda Pharm. Inc. v. W.-Ward Pharm. Int'l Ltd.*, 887 F.3d 1117, 1135 (Fed. Cir. 2018) (quoting *Mayo*, 566 U.S. at 87) (emphasis added).

Beta-alanine supplementation is applied in a particular way so that the "claims here are directed to a specific method of treatment for specific patients using a specific compound at a specific dose to achieve a specific outcome." *Id*. at 1136. The specific methods include a method of regulating hydronium ion concentrations in a human tissue (Appx0663, '596 Patent at Col. 14, ll. 66-67) and a method of increasing anaerobic working capacity in a human (Appx0767, '865 Patent at Col. 22, ll. 55-57). The specific patients of the claims include, for example, those seeking to "promote or enhance physical prowess." *See, e.g.*, Appx0657, '596 Patent at Col. 1, ll. 17-22. The specific compound at specific doses employed by these methods includes "an amount of beta-alanine…**effective** to increase beta-alanylhistidine

dipeptide synthesis in the human tissue" (Appx0664, '596 Patent at Col. 15, ll. 1-3 (emphasis added)) and a form of beta-alanine that is "**effective** to increase beta-alanylhistidine dipeptide synthesis in the tissue" (Appx0767, '865 Patent at Col. 22, ll. 57-67(emphasis added)).[2] Compositional claims on appeal contain specific numerical doses with specific dosing regimens for these treatments. *See, e.g.*, Appx0732, '084 Patent at Col. 22, ll. 25-29; Appx0836, '947 Patent at Col. 16, ll. 1-11). The claims and analysis of *Vanda Pharm.* align nearly perfectly with the supplementation claims present here, further supporting that NAI's claims are patent-eligible.

Additionally, patents reciting processes that achieve a desired unnatural outcome, such as methods of "producing things, or methods of treating disease" are patent-eligible. *Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc.*, 827 F.3d 1042, 1049 (Fed. Cir. 2016). In so holding, this Court also said that methods that combine multiple components to form a new compound, treating headaches with aspirin, and treating cells with chemotherapy are all concepts that may contain an underlying natural process, but are not directed to a natural phenomenon and such claims are patent-eligible. *Id.* Similarly, these claims recite beta-alanine, but the claims are

[2] Although the '596 Patent and the '865 Patent do not specifically claim a numerical dose, the claim limitations require a dose "effective" to produce a desired outcome. This Court has held that "**effective**" amounts are sufficiently specific and definite. *See, e.g.*, Op. Br. at 41 (citing *Geneva Pharms., Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373, 1383-84 (Fed. Cir. 2003).

particularized applications of beta-alanine as part of a dose-specific dietary supplement with specific dose regimens, specific methods using those doses, and methods of manufacturing these compositions. The present claims are thus not directed a natural phenomenon and are patent-eligible.

B. The Combined Claim Elements—When Considered As A Whole—Add Significantly More To Any Alleged Natural Phenomenon.

After considering the properly construed claim terms and factual evidence, this Court should conclude that the claims of the Patents-on-Appeal are not naturally occurring, and even if they could be considered as such, the combination of claim elements add significantly more to any alleged natural occurring phenomenon or substance. The following chart lists some important aspects of the claims that add significantly more to any alleged natural phenomenon, which were glossed over by Creative and improperly assessed by the District Court:

Patent Claim(s)	Exemplary Terms	Type of Claim
'596 Patent, Claim 1	• A method of regulating hydronium ion concentrations in a human tissue • Effective to increase beta-alanylhistidine synthesis in the human tissue	Method of Treatment
'376 Patent, Claims 1, 5, 6	• Dietary supplement…is a supplement for humans	Composition
'084 Patent, Claim 1	• Human dietary supplement • Unit dosage of between about 0.4 grams to 16 grams	Composition

'865 Patent, Claim 1	• A method of increasing anaerobic working capacity in a human • Providing…an amount…effective to increase beta-alanylhistidine dipeptide synthesis in the tissue • The amino acid is provided through a dietary supplement	Method of Treatment
'610 Patent, Claim 1	• Use of beta-alanine in manufacturing a human dietary supplement • Mixing the beta-alanine, which is not part of a dipeptide, polypeptide or oligopeptide…in a manufacturing step of the human dietary supplement • In doses over a period of time increases beta-alanylhistidine levels in muscle tissue sufficient to delay the onset of fatigue in the human	Method of Manufacturing
'947 Patent, Claim 34	• A human dietary supplement for increasing human muscle tissue strength • A mixture of creatine, a carbohydrate and free amino acid beta-alanine that is not part of a dipeptide, polypeptide or an oligopeptide • Wherein the free amino acid beta-alanine is in an amount that is from 0.4 g to 16.0 g per daily dose • Wherein the human dietary supplement is formulated for one or more doses per day for at least 14 days	Composition

Appx643-836; *see also* Op. Br. at 35-49.

The claim terms listed above show both why the claims are specific implementations of specific doses having specific outcomes (*Vanda Pharm.*, 887 F.3d at 1136) and why the claims, when considered as a whole, provide elements that are more than routine, conventional, and well-understood. As discussed in NAI's

Opening Brief (at 25-26, 35-49) the combined elements add far more to any inventive concept beyond what could be characterized as a mere natural phenomenon. Appx905-1022; Appx1128-1141; Appx1143-1162.

Not only are the claims of the Patents-on-Appeal directed to more than a mere natural phenomenon, but the combination of elements, when considered as a whole, adds significantly more to any alleged natural phenomenon. Creative, parroting the decision below, relies heavily on the Supreme Court's decision in *Funk Bros. Seed Co. v. Kalo Inoculant Co.* to allege that the claim elements are nothing more than routine and conventional. 333 U.S. 127 (1948); *see, e.g.*, Creative Br. at 9, 30, 34-35, 39. This reliance is in error. In that case, the Court held certain composition claims unpatentable but instructed that an invention to discovery of a natural phenomenon is patentable when it comes from "the application of the law of nature to a new and useful end" or for enlargement of the range of utility for naturally occurring compositions. *Id.* at 130-31; Op. Br. at 31-32, n.4. Assuming that case even applies to § 101 and not § 103, the patent claims here satisfy both of these tests: they contain elements that provide a new and useful end that also enlarges the range of utility of beta-alanine because they greatly increase dipeptide synthesis in muscle for hydronium ion buffering or increasing muscular working capacity. Appx907-912, ¶¶ 6-14. Beta-alanine that is not present in the human-made dietary supplements and not administered as specified by the claims does not possess the range of utility

of the claimed inventions. For these reasons, *Funk Bros.* supports the patentability of the claimed inventions.

Creative also failed to satisfy its burden to prove the elements of the claims were routine, conventional, and well-understood. Whether the claim elements are routine, conventional, and well-understood is a question of fact. *Berkheimer v. HP Inc.*, 881 F.3d 1360 (Fed. Cir. 2018; *Aatrix Software, Inc. v. 12 Green Shades Software, Inc.*, 882 F.3d 1121 (Fed. Cir. 2018); Op. Br. at 18-19, 24, 42. That assertion must be proven by clear and convincing evidence. *Microsoft Corp. v. i4i Ltd. P'ship*, 131 S. Ct. 2238, 2242 (2011). Creative did not meet this burden because it failed to submit evidence to support its flawed position, despite having the opportunity to do so.

The Patents-on-Appeal do not disclose that the recited claims are mere conventional activity. The decision and Creative mischaracterize the Patents-on-Appeal, asserting, for example, that the '610 patent's specification states that "placing a natural substance into a dietary supplement to increase the function of tissues when consumed is a conventional activity." Creative Br. at 13 (quoting Appx25; *see also* Appx792 at Col. 1, ll. 41-44). The Patents-on-Appeal do not state that claimed activity is conventional. Instead, the Patents-on-Appeal state that "[n]atural food supplements are typically designed to compensate for reduced levels of nutrients in the modern human diet." *See, e.g.*, Appx792 at Col. 1, ll. 41-44.

The District Court's fundamental misunderstanding of the patent specification and technology is exemplified by its distillation of the entire inventive concept into what was contained in the very first sentence of the background section of the Patents-on-Appeal. *See, e.g.*, Appx25. The District Court did not fully consider the technology in front of it because it did not recognize that the claim elements, when considered as a whole, are not mere post-solution activity or routine and conventional. *Mayo*, 566 U.S. at 78-79.

The declaration evidence of record also comports with the disclosure of the Patents-on-Appeal. For instance, a subject wishing to increase the amount of vitamin C may take vitamin C and might expect an increase of vitamin C in the body; however, that is not how beta-alanine functions in the context of the Patents-on-Appeal. Appx1130, ¶ 7. It was not routine, conventional, and well-understood to administer massive doses of a precursor (beta-alanine) via a human dietary supplement for an extended time period to increase the amount of metabolite (carnosine) in muscle tissue. Appx914-917, ¶¶ 17-23. At the time of invention, the skilled artisan would not have found it routine, conventional, or well-understood that supplementing a precursor would result in unnatural levels of metabolic product as a new steady state in the muscle. *Id.* The claimed human dietary supplements are patent-eligible because they provided an amount of beta-alanine that could never be

achieved naturally and the administration of this amount created a definitively unnatural state in the muscle tissue.

The specific patent claims and their elements were addressed in detail in NAI's Opening Brief (at 35-48), but the following is a summary of Creative's errors.

1. The '596 Patent Is Eligible For Patent Protection.

Creative alleges the "inventors admitted in the '596 patent's specification that [the method of claim 1 of the '596 patent] is a law of nature." Creative Br. at 32. This intentional misstatement is false. Creative cites Column 2, lines 10-14 of the '596 Patent, which recites that "[i]t has been estimated that **carnosine** contributes to hydronium ion buffering capacity in different muscle fibers types; up to 50% of the total in equine II fibers." Appx0657 (emphasis added). This statement merely references some of the effects that carnosine—a chemically distinct molecule from the beta-alanine of the claim—is known to have in muscle fibers: it has no relevance to increasing the muscles' steady state amount of carnosine by unnaturally overriding the bodies' homeostatic mechanisms.

Creative also erroneously asserts that Column 4, line 58 to Colum 5, line 45 is a further admission of natural processes. Br. at 35; Appx0657. The '596 Patent emphasizes that a human-made product, such as in the claims containing specific mixtures of beta-alanine, creatine, and L-histidine, can achieve the specific objective of "increasing beta-alanylhistidine dipeptides within a muscle favorably affects

muscular performance and the amount of work that can be performed by the muscle." Appx0659, '596 Patent at Col. 5, ll. 21-35. This is analogous to the example from *CellzDirect* where cancer cells responding naturally to radiation during chemotherapy is not a natural phenomenon, even though radiation occurs naturally. 827 F.3d at 1047.

While carnosine has a buffering effect in equine muscle tissue, it was not routine, conventional, and well-understood to manufacture a human dietary supplement capable of providing massive amounts of beta-alanine and that providing massive amounts of this precursor over a long period resulted in the specific outcomes of the Patents-on-Appeal. Appx914-917. Creative made no showing in this regard. Instead, Creative misstates portions of the specifications attempting to denigrate the patents and overgeneralize the inventive concept.

Creative asserts a generic justification without legitimate legal analysis or factual basis and states that the claims of the '596 Patent are just like those in *Mayo,* asserting the claims are nothing more than the recitation of a natural law followed by the words "apply it." Creative Br. at 32; *Mayo*, 566 U.S. at 77. Creative ignores that *Mayo*'s diagnostic claims merely set forth steps for measuring thiopurine levels to make a mental determination, whereas the '596 Patent claims are treatment method claims that (1) rely on a specific chemical composition that is distinct from the chemical that produces the desired effect; (2) provide a specific unnatural

dosage; and (3) that, when administered according to the claims over long periods of time, produce a specific outcome. *Vanda Pharm.*, 887 F.3d at 1136 (The "claims here are directed to a specific method of treatment for specific patients using a specific compound at a specific dose to achieve a specific outcome" and are patent-eligible); *cf. Mayo*, 566 U.S. at 85-87. In addition, the specific dosage present in a supplement administered over a long period of time produces a transformative, unnatural outcome of regulating hydronium ion concentration. *Bilski v. Kappos*, 561 U.S. 593, 603 (2010) (holding the machine or transformation test is a useful clue to determine eligibility).

2. The '376 Patent Is Eligible For Patent Protection.

Creative asserts that composition claim 6 of the '376 Patent "satisfies step one of the *Alice* inquiry", meaning Creative believes this claim is directed to a natural phenomenon. Creative Br. at 33. Creative, like the decision, errs in this regard by breaking down each element of the claims and asserting that, because each of the elements is allegedly naturally occurring, then the entire claim must occur naturally. Creative Br. at 33; Appx9-26. This is not in accord with the *Mayo*/*Alice* analysis, which asks if the **inventive concept, not the individual parts,** are directed toward a natural phenomenon. *CellzDirect, Inc.*, 827 F.3d at 1050. Parsing the claim into its individual components and consequently finding the entire claim to be directed to a § 101 exception is the type of analysis this Court has squarely rejected. *Bascom*

Global Internet Servs. v. AT&T Mobility LLC, 827 F.3d 1341, 1345 (Fed. Cir. 2016). The inventive concept of claim 6 of the '376 Patent is not directed toward a natural phenomenon.

Creative also makes the unsupported assertion that it "is likely true of every patent found invalid pursuant to Section 101 for claiming a law of nature, and it is not sufficient alone to satisfy the Section 101 inquiry" that the claims possess elements that are not routine, conventional, and well-understood. Creative Br. at 33. This outcome is exactly what the *Mayo*/*Alice* test and progeny of § 101 cases stand for: claims that contain an inventive concept directed to a § 101 exception are patent-eligible if the claims, when assessed as a whole, contain a combination of elements that are not routine, conventional, and well-understood. Creative disagrees with this well-cemented precedent by asserting that a court finding claims eligible when they possess a combination of elements that are not routine, conventional, and well-understood would "eviscerate Section 101 and ignore this Court's and the Suupreme [sic] Court's precedents." Br. at 33. It is not clear if Creative's transposition of what the Supreme Court said is a disagreement with precedent or some other argument. Regardless, the Court stated that courts should be careful expanding the application of the exceptions to § 101 because that expansion could eviscerate patent law. *Alice*, 134 S. Ct. at 2354-55.

Furthermore, the '376 Patent's claims include a combination of elements that are not routine, conventional, and well-understood. Appx0697; Op. Br. at 37. This combination of elements has not been shown to be routine, conventional, and well-understood, especially when considering that these claim elements **effectively** increased tissue function from massive doses of these elements over an extended time under the agreed-upon claim construction. *Id*.

3. The '084 Patent Is Eligible For Patent Protection.

Creative asserts the "inventors' conventional act of placing a dosage of beta-alanine into a human dietary supplement" is "'insufficient to render the claims at issue patent-eligible even accepting Plaintiff's proposed construction for the term 'human dietary supplement.'" Creative Br. at 36 (citing Appx13-14, n.8). NAI has previously discussed the improper claim construction. Op. Br. at 39-40. Furthermore, the decision was issued prior to this Court's *Vanda Pharm.* decision. Creative ignores that case and its holding by disregarding the specificity of the composition and the dosage set forth in the claims that result in patent-eligibility. 887 F.3d at 1136 (claims are eligible when they "are directed to a specific method of treatment for specific patients using a specific compound at a specific dose to achieve a specific outcome"). Not only is this specific dosage a synthetic and unnatural form, but supplying this specific dosage as claimed results in an arrangement of non-routine, non-conventional, and non-well-understood aspects, as

demonstrated by NAI's unrefuted evidence. *See, e.g.*, Appx0731, '084 Patent at Col. 19, l. 19-Col. 21, l. 50; Appx905-918. The claims are patent-eligible.

4. The '865 Patent Is Eligible For Patent Protection.

Claim 1 of the '865 Patent provides another patent-eligible method of treatment. Appx0767, '865 Patent at Col. 22, l. 55-Col. 23, l. 5; *See Vanda Pharm.*, 887 F.3d at 1134-36. Creative's legal conclusion is that claim 1 of the '865 adds nothing more than the words "apply it" to the law of nature. Creative Br. at 37. This is not the case. Claim 1 of the '865 Patent is directed to a specific treatment method of "increasing anaerobic working capacity in a human subject", which includes a specific, effective amount of a specific combination of beta-alanine and other components that achieve the outcome of increasing the "beta-alanylhistidine dipeptide synthesis in the tissue." Appx0767, '865 Patent at Col. 22, l. 55-Col. 23, l. 5; *see Vanda Pharm.*, 887 F.3d at 1134-36. Therefore, claim 1 is not directed to a natural law.

Further, Creative asserts that the claims are directed to a natural phenomenon because "there is a direct link between carnosine concentration levels, on the one hand, and the amount of beta-alanine administered and the amount of time over which the administration takes place, on the other hand, confirms this is a natural phenomenon." Creative Br. at 39. Creative contorts the *Mayo* holding to support this conclusion by alleging these claims are the same as the diagnostic method of *Mayo*.

Br. at 39; *Mayo*, 566 U.S. at 79. These claims also differ from *Mayo* for similar reasons discussed with respect to the '596 Patent.

Creative also concludes that the components are "well-known, conventional activity [that is] not sufficient to transform the claimed law of nature into patent-eligible subject matter." Creative Br. at 37. But Creative does not support this assertion with any reference to the evidence, instead merely providing a legal conclusion devoid of the factual analysis this Court requires. *Berkheimer*, 881 F.3d at 1369. Creative cannot rely on any factual basis to support its conclusory assertions because the claim elements were not routine, conventional, and well-understood at the time of the invention. One of skill in the art would not have considered massive doses administered over a long time as unconventional because there would have been no expectation that administration of a human dietary supplement containing an unnatural amount of a synthetic human dietary supplement containing a precursor (free beta-alanine) would have led to the claimed increase in "beta-alanylhistidine dipeptide synthesis in the tissue."[3] Appx1130, ¶ 7; Appx0767, '865 Patent at Col. 22,

[3] Creative is critical of NAI's reference to "unexpected" results in its Opening Brief. Creative Br. at 23; *see* Op. Br. at 6, 15, 21, 41, 44. Although "unexpected" results are often considered in the context of 35 U.S.C. § 103, NAI explained how this consideration relates both to what is routine, conventional, and well-understood and how the Supreme Court noted that considerations of §§ 101 and 103 may sometimes overlap. Op. Br. at 41-42.

l. 55-Col. 23, l. 5. All of the evidence in the record is contrary to Creative's legal position.

Creative asserts that the claimed treatment method that includes administering enormous amounts of a synthetic, non-natural free beta-alanine merely causes the human's tissue to "continue to do what they have always done when faced with large amounts of beta alanine, without Dr. Harris or his co-inventor having exerted any effort to cause, or affect, this result." Creative Br. at 39. Creative's statements squarely conflict with *Vanda Pharm.*, 887 F.3d at 1134-36, a case it refused to cite or attempt to distinguish from the instant scenario. *CellzDirect* also instructs that claims, such as those at issue here, will always touch on a natural law. 827 F.3d at 1047. For example, claims directed toward the body's natural response from administration of chemotherapy or aspirin—just like the specific administration of the claimed dietary supplements—are the types of claims that are patent-eligible. *Id.*

5. The '610 Patent Is Eligible For Patent Protection.

Creative asserts that the manufacturing method elements of the '610 Patent "merely recite conventional manufacturing steps of supplying beta-alanine and mixing it with at least one other ingredient." Creative Br. at 41. This manufacturing method is not a natural phenomenon: free-beta alanine did not exist as the claimed dietary supplement prior to the invention. Op. Br. at 47-49. Carnosine existed as part of the diet and in the body, but the invention is not directed toward carnosine.

Creative entirely ignores this distinction, the specific claim elements, and concludes—without factual basis—that the manufacturing methods were not new or unique.

Creative then cites to Column 1, lines 41-44 of the '610 Patent, which Creative posits allegedly admits that the subject matter is "conventional activity." Creative Br. at 41. As previously discussed, that portion of the disclosure does not recite that this is conventional activity and merely acknowledges that an industry exists that creates other supplements. *See, e.g.*, Appx0757, '865 Patent at Col. 1, ll. 41-49.

6. The '947 Patent Is Eligible For Patent Protection.

Creative does not specifically address the '947 Patent or the reasons why this invention is directed toward ineligible subject matter. Op. Br. at 38-39.[4] This invention is directed toward a new, specific, non-natural composition containing free beta-alanine in a non-natural human dietary supplement intended for a specific treatment. *Id*. That composition is provided with a specific dosage with a specific

[4] Creative asserts that the '947 Patent is not part of this appeal and it does not address it in its brief. Creative Br. at 2. Creative based its own motion on the District Court's decision in The *Allmax* Case in which the '947 Patent was at issue. Appx519. The District Court's ruling, which is on appeal, invoked The *Allmax* Case and found the '947 Patent ineligible. Appx9. Creative also relied on The *Allmax* Case ruling on that patent when it "first argued that that the District Court should adopt its earlier ruling in the related case." Creative Br. at 4. Because Creative brought the eligibility of that patent into question, and resolving the eligibility of the other patents in this appeal likely resolves the eligibility question of that patent, this Court should consider all of the Patents-on-Appeal when finding them to be patent-eligible.

dosage regimens, which leads to the proper conclusion that the claimed subject matter is not directed toward a natural phenomenon. *Id.*; *Vanda Pharm.*, 887 F.3d at 1134-36. The District Court erred by holding that the combined elements of these claims were individually naturally occurring when it mischaracterized the disclosure of the patent, which led to its improper obviousness-type analysis of the claim to hold that claim 34 of the '947 was directed toward a natural phenomenon. *Id.*; *Bascom*, 827 F.3d at 1345.

Even if this unnatural composition could be considered directed toward a natural phenomenon, the specific elements including creatine, a carbohydrate, and beta-alanine with no L-histidine (an unnatural combination of features) is not a routine, conventional, and well-understood combination of elements. This is demonstrated by the specific doses and administration regimen that was determined through scientific experimentation, which created an unconventional outcome. Appx1130, ¶ 7; Appx907-919. The '947 Patent contains eligible subject matter.

7. Patents Are Presumed Valid: This Presumption Requires That A Court Rely On Clear and Convincing Evidence Of What Is Routine And Conventional.

Whether the claim elements or the claimed combination are well-understood, routine, and conventional is a question of fact. *Berkheimer v. HP Inc.*, 881 F.3d at 1368-69. That question should not be answered adversely to the patentee based on a motion to dismiss, unless the complaint, the patent, and materials subject to judicial

notice require it. *Aatrix*, 882 F.3d at 1128. "That burden is constant and never changes and is to convince the court of invalidity by clear evidence." *Am. Hoist & Derrick Co. v. Sowa & Sons, Inc.*, 725 F.2d 1350, 1360 (Fed. Cir. 1984), *abrogated on other grounds by Therasense, Inc. v. Becton, Dickinson & Co.*, 649 F.3d 1276 (Fed. Cir. 2011). Where factual issues exist regarding the validity of patent claims, a defendant must prove such facts with "clear and convincing evidence," given the presumption of validity afforded to issued patents. *See Microsoft Corp.*, 131 S. Ct. at 2242. Creative failed to satisfy this burden or address this evidentiary standard and made no attempt to cite *Berkheimer* or *Aatrix* to explain why this case is distinguished from the holdings in those cases. Furthermore, Creative provided no evidence to support its positions even though it had the opportunity to do so. Creative instead relies on attorney argument that mischaracterizes the disclosures of the patents. The District Court made these same errors (Appx9-26), and for at least these reasons, this Court should reject Creative's baseless assertions and overturn the District Court's decision.

IV. DESPITE CREATIVE'S ASSERTIONS, LACK OF PREEMPTION IS A VALID AND PERSUASIVE CONSIDERATION IN DETERMINING PATENT ELIGIBILITY.

The concept of preemption in the context of patent eligibility dates back at least to the pivotal decision in *Diamond v. Diehr*. 450 U.S. 175, 187 (1981). Similar to *Diehr*, the present inventions are not solely directed toward beta-alanine, nor do

the inventions seek to tie up any and all innovation related to beta-alanine. *Id*. In *Alice*, the Supreme Court noted that determining whether something is preemptive means the courts "must distinguish between patents that claim the buildin[g] block[s] of human ingenuity and those that integrate the building blocks into something more." *Alice*, 134 S. Ct. at 2354 (internal quotations omitted). *Alice* explained that preemption "undergirds our § 101 jurisprudence." *Id*. at 2358. The Supreme Court has never ruled that preemption is not a valid and primary concern when determining patent eligibility. And since *Alice*, this Court has looked toward preemption and acknowledged that "the principle of preemption is the basis for the judicial exceptions to patentability." *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371, 1379 (Fed. Cir. 2015).

An analysis based on preemption is instructive and justified here because it exemplifies the types of human-made products that fall within the confines of the claimed invention, demonstrating that the claimed inventions are not natural products. NAI did not and has never asserted its patents against any naturally-occurring product, nor has NAI ever asserted that its inventions are substitutable for any naturally-occurring product. Such assertions would be as absurd as the reasoning employed by Creative in its arguments to this Court. Although the District Court relied on *Ariosa* when it determined that "any potential preemption concerns are fully addressed through the Court's analysis of the [Patents-on-Appeal] under the

two-step Alice framework" and considerations of preemption were rendered moot, the District Court did not address the fact that specific implementations of natural laws can render a claim patent-eligible. Appx16 (emphasis in original) (citing *Ariosa*, 788 F. 3d at 1379 ("Where a patent's claims are deemed only to disclose patent ineligible subject matter under the *Mayo* framework…preemption concerns are fully addressed and made moot")).

While the Supreme Court has indicated that preemption is the primary and underlying concern regarding the exceptions to eligibility under § 101, in that instance, this Court tailored the analysis to say that an absence of preemption may not always carry the day in deciding patent eligibility. *Ariosa*, 788 F. 3d at 1379. Here, not only does all of the scientific evidence and proper interpretation lead to the undeniable conclusion that the claims are patent-eligible, but they are plainly not preemptive as well. This is because the inventive concepts are specific implementations and applications of natural laws that are patent-eligible. *See McRO, Inc. v. Bandai Namco Games Am. Inc.*, 837 F.3d 1299, 1316 (Fed. Cir. 2016) (holding a specific implementation of an abstract idea to be patent -eligible); *Vanda Pharm.*, 887 F.3d at 1134-36 (holding that the treatment method was not directed toward a natural phenomenon because it contained a specific compound administered at a specific dosage, for a specific outcome); *Enfish, LLC v. Microsoft Corp.*, 822 F.3d 1327, 1336 (Fed. Cir. 2016) (claims for a "specific improvement"

to computer functionality were deemed patent-eligible); *CellzDirect*, 827 F.3d at 1047 (holding that a specific method of preparing hepatocytes was not directed toward a § 101 exception). An adequately specific application of a natural law or abstract idea is not preemptive and vice versa. This is why this Court should give weight to these considerations of preemption demonstrating that these claims are patent-eligible.

The claims of the Patents-on-Appeal do not preempt any natural occurrence and use of beta-alanine. The liver's meager production of beta-alanine does not provide a human dietary supplement as defined by the claims or as would be understood by the skilled artisan in the context of the invention. Beta-alanine does not occur naturally in any non-dietary supplement to provide an effective amount that produces the unnatural results of the claims. For these reasons, the claims do not preempt the building blocks of science and are patent-eligible.

V. THE PTO GUIDANCE DOES NOT IGNORE THE *MAYO* DECISION AND PTO GUIDANCE SHOULD BE GIVEN DEFERENCE.

Creative asserts that the PTO Guidance ignores the *Mayo* decision. Creative Br. at 42-44. Although the particular guidance document containing the example cited by NAI does not specifically mention *Mayo*, the PTO created that document in consideration of that decision along with all the other decisions issued up until that time. The PTO's website makes this clear when it states the "2014 IEG guides USPTO personnel when determining subject matter eligibility under 35 U.S.C. 101

in view of decisions by the U.S. Supreme Court, including Alice Corp., Myriad, and Mayo." https://www.uspto.gov/patent/laws-and-regulations/examination-policy/subject-matter-eligibility-examination-guidance-date (last accessed July 12, 2018).

The PTO recognized that the subsequent patentability determinations would have to be made in compliance with the Supreme Court's precedent.[5] If cited Example 3 of the Guidance does not directly cite *Mayo*, this is immaterial and telling: the PTO did not believe that such claims were precluded by *Mayo*. *See* Appx1168-1171. The claims listed in Example 3 are directed toward compositions and treatment methods. Appx1169. Because of this, *Mayo* need not be applied to these claims because *Mayo* only considered claims directed toward diagnostic methods. *Mayo*, 566 U.S. at 86. In addition, the PTO's consideration of preemption is directly aligned with the Supreme Court's precedent.

The PTO does more than solely consider preemption when reviewing the claims in the examples. For example, the PTO states that "analysis of the claim as a whole indicates that the claim is focused on a process of practically applying the

[5] Creative does not cite the *Vanda Pharm*. case discussed herein, nor acknowledge that the PTO updated its guidance in view of that opinion. https://www.uspto.gov/patent/laws-and-regulations/examination-policy/subject-matter-eligibility (last accessed July 19, 2018). The PTO has updated its guidance after opinions issued by this Court but has not revised or removed the Guidance cited by NAI.

product to treat a particular disease (colon cancer), and not on the product *per se*." Appx1171. The PTO thus engaged in an analysis similar to how this Court considered the claims of *Vanda Pharm.*, 887 F.3d at 1134-36, *CellzDirect*, 827 F.3d at 1047, and *Enfish*, 822 F.3d at 1336. The District Court erred in disregarding the PTO's persuasive guidance that deserves deference and follows this Court's and the Supreme Court's precedent. *See Skidmore v. Swift & Co.*, 323 U.S. 134 (1994); Op. Br. at 49-54.

Creative also criticizes the PTO Guidance as inapplicable because it relies on the "broadest reasonable interpretation standard." Creative Br. at 44. That argument is meritless: the broadest reasonable interpretation would be more likely to ensnare ineligible subject matter. Op. Br. at 39; (citing *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005)). Because the PTO Guidance found similarly-situated claims to be patent-eligible in view of the controlling precedent, this Court should view the Guidance as informative and instructive and give the adequate deference.

VI. THIS COURT SHOULD CONSIDER THE UNIQUE IMPLICATIONS TO THE DIETARY SUPPLEMENT INDUSTRY BECAUSE PATENT POLICY HAS BEEN AN IMPORTANT ASPECT OF THE LAW.

This Court should also consider the public policy implications of the decision below. Patent law has long struck a balance between economic interests, public policy, and the incentivatization of innovation to promote the useful arts. *See* U.S. Const. art. I, § 8. cl. 8. This interplay between the grant of patent rights and the

balance of monopolies to promote this innovation is a concept that courts have considered for many years. *See* Giles S. Rich, *The Relation between Patent Practices and the Anti-Monopoly Laws*, J. Pat. Off. Soc., Vol. XXIV, No. 3, pp. 159-181 (March 1942). The existence of relationships such as these exemplifies the inextricable link between patents, the public benefits weighed against the public's removal of the right to practice the patented technology, and the surrounding economic interests. NAI does not assert that the sole basis of this Court's decision should rely on such considerations, but if the decision can be resolved in light of all of the arguments above while tipping in the favor of that which promotes the interests of the industries listed in NAI's Opening Brief, then it should do so. In considering the issues on appeal, the Court should take into account the uncertainty and need for clarity in § 101 jurisprudence, particularly in the life sciences. *See* Amicus Br. of Biotechnology Innovation Organization and Amicus Br. of Patent Law Scholars.

CONCLUSION

For the foregoing reasons, the Court should reverse the District Court's determination that the Patents-on-Appeal are invalid as ineligible under § 101.

Respectfully submitted,

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Natural Alternatives Intl. v. Creative Compounds, LLC, 2018-1295

CERTIFICATE OF SERVICE

I, Robyn Cocho, being duly sworn according to law and being over the age of 18, upon my oath depose and say that:

Counsel Press was retained by PORZIO, BROMBERG & NEWMAN P.C., counsel for Appellant to print this document. I am an employee of Counsel Press.

On **July 20, 2018** counsel has authorized me to electronically file the foregoing **Reply Brief of Appellant** with the Clerk of Court using the CM/ECF System, which will serve via e-mail notice of such filing to all counsel registered as CM/ECF users, including the following principal counsel for the other parties:

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July 20, 2018

/s/ Robyn Cocho
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