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.

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

BRIEF FOR BIOTECHNOLOGY INNOVATION ORGANIZATION AS *AMICUS CURIAE* SUPPORTING APPELLANT

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APRIL 20, 2018

CERTIFICATE OF INTEREST

Counsel for *Amicus Curiae* BIO certifies the following:

1. The full name of every party or *amicus curiae* represented by me is:

Biotechnology Innovation Organization (formerly: Biotechnology Industry Organization)

2. The name of the real party or real parties in interest (if a party named in the caption is not the real party in interest) represented by me is:

None

3. All parent corporations and publicly held companies that own 10% or more of stock in the amicus curiae represented by me are:

None

4. The names of all law firms and the partners or associates that appeared for the party or amicus now represented by me in the trial court or agency or are expected to appear in this court (and who have not or will not enter an appearance in this case):

None

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. See Fed. Cir. R. 47. 4(a)(5) and 47.5(b).

Natural Alternatives Intl., Inc. v. Hi-Tech Pharmaceuticals, Inc., Case No. 3:16-cv-02343- H-AGS (S.D. Cal.)

Date: April 20, 2018

/s/ *Melissa A. Brand*
Melissa A. Brand

Counsel for Amicus Curiae BIO

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STATEMENT OF INTEREST OF AMICUS CURIAE

The Biotechnology Innovation Organization ("BIO") (formerly: Biotechnology Industry Organization) is the principal trade association representing the biotechnology industry domestically and abroad. BIO has more than 1,000 members, which span the for-profit and non-profit sectors and range from small start-up companies and biotechnology centers to research universities and Fortune 500 companies. Approximately 90% of BIO's corporate members are small or midsize businesses that have annual revenues of under $25 million.

BIO's members are concerned that, six years after the Supreme Court decided *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 566 U.S. 66 (2012), increasing uncertainty exists about the patent-eligibility of biotechnological products that incorporate naturally-occurring substances, and of methods of using such products in therapeutic, diagnostic, or industrial processes. The unstable state of patent-eligibility jurisprudence affects modern biotechnologies ranging from biomarker-assisted methods of drug treatment to companion diagnostic tests, fermentation products, industrial enzyme technology, and marker-assisted methods of plant breeding. As developers of, and investors in, such advanced technologies, BIO members have a strong interest in clear and predictable rules of patent-eligibility. *Amicus* BIO submits this brief in the hope that it will assist the Court in the orderly development of the law in this important area.

BIO has no direct stake in the result of this appeal and takes no position on the ultimate validity of the patents at issue. Pursuant to Federal Rule of Appellate Procedure 29(a), *amicus* certifies that no counsel for a party authored this brief in whole or in part, and no such counsel or party, nor any person other than the *amicus* or its counsel, made a monetary contribution intended to fund the preparation or submission of this brief. This brief is solely the work of BIO; it reflects BIO's members' consensus view, but not necessarily the view of any individual member. Neither party to this appeal is a member of BIO. Pursuant to Federal Rule of Appellate Procedure 29(a) and Federal Circuit Rule 29(c), *amicus curiae* BIO states that all parties have consented to BIO's filing of this brief.

INTRODUCTION

This appeal is of great interest to BIO's members because it involves the application of a *Mayo/Alice* patent-eligibility analysis to manufactured articles – multi-component dosage units, such as tablets or capsules, containing biologically effective amounts of naturally occurring chemicals. Inventive preparations based on naturally-occurring substances have historically been of great importance in biotechnology, and innovation in this area has been spurred, at least in part, by the availability of patent protection. This is true for every sector of biotechnology.

Examples include vaccine antigens, crop protection products,[1] plant biotechnology and breeding,[2] industrial enzymes,[3] immunosuppressive drugs,[4] anticancer compounds,[5] and antibiotic drugs.[6]

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[1] Numerous commercial crop protection products, such as enriched or purified preparations of selected strains and combinations of *Bacillus thuringiensis* or *B. subtilis* are used in organic insect control; *B. pumilus* is used as a biofungicide. Naturally-occurring fermentation products such as spinosad and avermectin are commercially marketed for insect and mite control.

[2] Genetic elements such as promoters, intronic nucleotide sequences, non-coding RNA as well as naturally expressed sequences are widely used in plant biotechnology and breeding activities in major crops including corn, wheat, soybean, rice, tobacco, canola, potato, sugar beet, and others.

[3] Phytase, an enzyme supplement to animal feed, enhances the ability of livestock to digest phytate in grain, thus reducing environmental pollution from fecal phosphate. Progress in this area has been facilitated by the invention of a phytase enzyme from the microbe *E. coli* and patent protection of isolated DNA. *See* U.S. Patent No. 6,190,897. Glucoamylase, an enzyme from the fungus *Trichoderma reesei* that efficiently releases glucose sugars from carbohydrates, allows for better production of biofuels such as ethanol. *See* U.S. Patent No. 7,413,887.

[4] Three major immunosuppressive drugs used to prevent organ rejection of transplant recipients were all discovered in natural, soil-dwelling microbes. Cyclosporine A was first discovered in a soil sample from Norway; tacrolimus (Prograf®) is produced by the bacterium *Streptomyces tsukubaensis*, first discovered in a soil sample from northern Japan (*see* U.S. Patent No. 4,894,366), and sirolimus (Rapamune®)(*see* US patent 3,929,992) is produced by the bacterium *Streptomyces hygroscopicus*, which was famously discovered in a soil sample from Easter Island.

[5] A large proportion of early cytostatic drugs were discovered, isolated and derived from botanical or microbial sources, such as vincristine, vinblastine, vinorelbine, vindesine, camptothecin, irinothecan, topothecan, paclitaxel, docetaxel, etoposide, teniposide, doxorubicin, daunorubicin, idarubicin and epirubicin.

In the continual search for new therapies, the use of patented, naturally-occurring substances is not just a historical phenomenon but continues to be important today. For example, romidepsin was approved by the U.S. Food and Drug Administration in 2009 for the treatment of cutaneous T-cell lymphoma. It was first reported in the scientific literature in 1994 as an isolate from *Chromobacterium violaceum* from a soil sample obtained in Yamagata Prefecture, Japan (*see* U.S. Patent No. 4,977,138). Two natural marine antitumor compounds, trabectedin and aplidine (*see* U.S. Patent No. 5,834,586) were discovered in the sea squirts *Ecteinascidia turbinata* and *Aplidium albicans*, respectively. Both are in active clinical development, with trabectedin having been approved in 2007 for commercial marketing in Europe under the trade name Yondelis®. In 2012, ingenol mebutate, a natural compound extracted from *Euphorbia peplus* plants, was approved by FDA and EMA under the trade name Picato® for the topical treatment of actinic keratosis (*see, e.g.*, U.S. Patent No. 7,410,656).

As these examples indicate, preparations of novel and unobvious naturally occurring molecules continue to be an important source for drug discovery. Indeed, naturally-occurring molecules and their close derivatives have contributed an

[6] Many antibacterial and antifungal medicines were first isolated from natural sources and patented, *see, e.g.*, amphotericin b (U.S. Patent No. 2,908,611), streptomycin (U.S. Patent No. 2,449,866), actinomycin (U.S. Patent No. 2,378,876), and neomycin (U.S. Patent No. 2,799,620).

estimated 36% of all first-in-class small molecules approved by the FDA between 1999 and 2008. *See* Swinney DC and Anthony J, *How Were New Medicines Discovered?* Nat. Rev. Drug Discov. 10 (2011) 507-519. In oncology, such naturally-derived chemotherapeutic agents have been described as an important second rail in the fight against cancer that supplements the parallel development of highly-targeted oncology treatments using antibodies or fully-synthetic small molecules. *See* Basmadjian et al., *Cancer Wars: Natural Products Strike Back*. Frontiers in Chemistry 2 (2014) 1-18.

Antibiotics represent another area of drug development where naturally-derived products play an important role in addressing critical emerging medical needs. FDA antibiotic approval numbers illustrate the problem. There were 16 new systemic antibiotics approved from 1983 to 1987. Approvals declined to 10 from 1993 to 1997, to five from 2003 to 2007, and to just two between 2009 and 2012. Steve Usdin, *Antibiotics Reset,* BioCentury Nov. 19, 2012.[7] Yet, new antibiotics are urgently needed. Naturally-occurring antibacterial substances play an important role in addressing this emerging problem. Among the relatively few new antibiotic drugs that were approved during the past decade, for example, are the bacterial fermentation products daptomycin and fidaxomicin, the latter having been approved

[7] Available at: https://www.biocentury.com/biotech-pharma-news/coverstory/2012-11-19/gain-act-fda-stance-only-first-steps-to-refilling-antibiotic-pipeline-in-us-a1

as a first-in-class molecule in 2011. Over the coming decade, the importance of naturally-occurring substances as sources for new antibiotic drug development will only increase, as advances in bioprospecting, in understanding microbial physiology and bacterial biosynthetic gene clusters, and in analytical techniques provide fertile areas for critically-needed research to unlock the untapped potential of naturally-occurring antibacterial substances. *See* Wright GD, *Something Old, Something New: Revisiting Natural Products in Antibiotic Drug Discovery*. Can. J. Microbiol.60 (2014) 147-154.

Research and development within the biotechnology industry comes at a high cost, and every idea that is funded comes with a greater likelihood of failure than success. Developing a single therapy requires close to a decade of R&D, at an out of pocket cost approaching $1.4 billion. DiMasi et al., *Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs*. J. Health Econ. 47 (2016), 20-33.

Such investments are risky. For every successful biopharmaceutical product, thousands of candidates are designed, screened, and rejected after large investments have been made. Only a small minority of drugs even advance to human clinical trials and close to 90% of those fail to obtain regulatory approval. Thomas et al., *Clinical Development Success Rates 2006-2015*, BIO Industry Analysis 2016.[8]

[8] Available at:

Investment therefore is predicated on the availability of patent protection that enables biotechnology businesses to attract capital and commercial partners in order to advance basic inventions – including those based on naturally-occurring substances and processes – from the laboratory to the marketplace and ultimately to generate an expected return on investment in the form of patent-protected products or services. In the United States alone, the biotechnology industry is responsible for more than 100 billion dollars of annual research investment[9] and provides employment to more than one million individuals.[10] The overwhelming majority of this investment is through private funding.

Accordingly, it is highly important to BIO's members that investment in biotechnological innovation is not discouraged by systematically erecting special hurdles to patent protection for inventions that relate to naturally-derived substances and processes. In particular, BIO urges this Court to be conscious of the different approaches the Supreme Court has taken when it explored the patent-eligibility of processes on the one hand, and compositions and articles on the other. *Alice Corp.*

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https://www.bio.org/sites/default/files/Clinical%20Development%20Success%20Rates%202006-2015%20-%20BIO,%20Biomedtracker,%20Amplion%202016.pdf

[9] *World Preview 2017, Outlook to 2022*, Evaluate Pharma, available at http://info.evaluategroup.com/rs/607-YGS-364/images/WP17.pdf (reporting R&D in the pharmaceutical sector alone at $157 billion in 2016).

[10] *The Value of Bioscience Innovation in Growing Jobs and Improving Quality of Life*, TEConomy/BIO, available at https://www.bio.org/sites/default/files/BIO%202016_Report_FINAL_DIGITAL.pdf

Pty. Ltd. v. CLS Bank International, 134 S. Ct. 2347 (2014) provides guidance as to how to analyze process claims that implicate abstract ideas. But, *Alice* set forth only "a framework", *id*. at 2355, not "*the* framework," for an eligibility analysis that was particularly suited for the kind of claimed subject matter at issue in that case. There is little to suggest in the *Alice* decision that its mode of analysis necessarily applies in the same way to compositions or manufactures, which have developed their own line of case law. For example, none of the cases dealing with compositions and manufactures – *Assoc. for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. 576 (2013)*, J.E.M. Ag Supply, Inc. v. Pioneer Hi-Bred International, Inc.*, 534 U.S. 124 (2001)*, Diamond v. Chakrabarty*, 447 U.S. 303 (1980)*, Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127 (1948) – have applied an "inventive concept/significantly more" analysis. The *Alice* opinion does not even mention these cases, with the exception of *Myriad,* which is only cited for the truism that "[l]aws of nature, natural phenomena, and abstract ideas are not patentable." 134 S. Ct. at 2354. And, conversely, *Myriad* not only dedicates a whole section to making clear that its analysis does not implicate method claims and "applications of knowledge" (569 U.S. at 595) – it makes no mention at all of the "process" cases that feature so prominently in *Alice*: *Gottschalk v. Benson*, 409 U.S. 63 (1972), *Parker v. Flook*, 437 U.S. 584 (1978), *Diamond v. Diehr*, 450 U.S. 175 (1981), and *Bilski v. Kappos*, 561 U.S. 593 (2010). This distinction is both conspicuous and significant.

While it is true that some of the claims involved in *Alice* were formally drawn to computer-readable media and systems, the decision is by any reasonable reading a decision about process claims. The petitioner had conceded that its media claims stand and fall with the method claims. *Alice*, 134 S. Ct. at 2360. Moreover, unlike other technologies, the computer-implemented arts have long developed unique claiming practices under which process claims are commonly echoed in the form of arguably coextensive media or device claims. *Alice*'s "system" claims could thus be disposed of on the same grounds as its process claims: they were, in the Supreme Court's view, "no different in substance," i.e. they claimed the same ineligible process in a different guise. *Id.*

Thus, while the Supreme Court may have applied an "inventive concept" / "add enough" analysis when it discerned abstract ideas, laws of nature and natural phenomena in disembodied methods and processes, in instances where it encountered physical compositions and articles it engaged in a comparative exercise that queried whether the claimed thing, viewed as a whole, has a "distinctive name, character or use" compared to the natural thing (*Chakrabarty*, 447 U.S. at 309-10), has "markedly different characteristics" (*id.* at 310), enlarges its "range of utility" (*Funk Bros.*, 333 U.S. at 131), or whether the laboratory technician "created something new" (*Myriad*, 569 U.S. at 595). In each case the Court's mode of analysis was informed by, and suited to, the particular claimed subject matter at issue. For

example, it would be nonsensical to analyze a claim to an abstract idea by querying whether the claimed idea is "markedly different," has "enlarged utility," or "functions in new ways" relative to any other idea. Instead, such a claim is much more amenable to an inquiry whether the inventor has done "more than simply stating [an] abstract idea while adding the words 'apply it.'" In the same vein, a claim to a modified bacterium is clearly more amenable to a "marked differences" or "enlarged utility" analysis than it is to an analysis that asks whether the claimed bacterium is an inventive "application" of a naturally-occurring one.

Even if *Alice* could be understood to apply to compositions of matter, the Court's use of an "inventive concept" [11] approach in some cases but not in others underscores that there is no one-size-fits-all approach for satisfying § 101. Rather, the Court's varied approaches in different cases demonstrates that products containing naturally-occurring elements may be patent-eligible for a variety of different reasons, depending on the claims and facts of a given case. Nothing in *Alice* suggests that important concepts such as "distinctive name, character or use,"

[11] It is also clear that the "inventive concept" approach, even when applied, does not mean that a claim must satisfy an "obviousness" analysis as a threshold inquiry under § 101. Such a result would not only improperly render § 103 redundant, but would make the "eligibility" inquiry a "moving target" that constantly changes with the evolution of science and technology, rather than a standard based on what exists in nature, as the judicial exception was intended to be. Such a reading of the "inventive concept" approach would plainly risk "eviscerating patent law," against the Supreme Court's repeated warnings.

"markedly different characteristics," "enlarged range of utility," or the "creation of something new" should not be a primary focus for composition and manufacture claims undergoing evaluation for patentable subject matter.

In its *Myriad* decision, the most recent decision addressing the patent-eligibility of a physical thing, the Supreme Court emphasized that it neither meant to break new ground nor to revise its prior decisions. The Court's multiple cautionary statements about the narrowness of its holding and of all the questions it was explicitly *not* deciding, signal a narrow, incremental decision that should not compel broad changes in the way therapeutically and industrially useful substances and compositions are evaluated for patent-eligibility.

ARGUMENT

I. Laboratory-Created Biologically Active Compositions Are Not "Naturally-Occurring" Patent-Ineligible Subject Matter Under *Myriad*.

The *Mayo*/*Alice* framework appears to be displacing the ability of courts to first decide whether a detailed § 101 analysis is necessary at all. This is particularly true for biological innovations that inherently rely, at least in part, on natural phenomena or natural laws. But the Supreme Court has indicated that even when a claimed invention is derived from subject matter found in nature, a detailed *Mayo*/*Alice* two-step analysis may not be necessary. This makes sense. For certain claims, only minimal investigation is required to understand that the claim is directed

to a "new and useful . . . composition of matter" and does not merely claim a "natural phenomenon." *See Myriad*, 569 U.S. at 590.

The district court's analysis in this matter could have been much more succinct, asking as the Supreme Court did in *Myriad*, did the patentee create anything? *See id.* at 594-95. In *Myriad*, while the Supreme Court found certain claims to naturally occurring DNA patent-ineligible under the *Mayo* framework, the Court found claims to non-naturally occurring cDNA perfectly patent-eligible and, notably, did not implement a *Mayo* analysis in doing so. *See id.* In rejecting the petitioners' argument that cDNA should not be patent-eligible because its sequence "is dictated by nature, not by the lab technicians," the Court instructed that the key to its analysis was that the lab technician "unquestionably create[d] something new when cDNA [was] made." *Id.* at 595. The Court's approach was not new, rather, it finds its roots in long-standing Supreme Court precedent, such as, *Diamond v. Chakrabarty*, 447 U.S. 303 (1980). There, in finding claims to a modified naturally occurring organism patent-eligible, the Court asked whether the claimed subject matter constituted a "manufacture" or "composition of matter," distinct from subject matter found in nature. *Id*. at 307. The Supreme Court's long-standing approach to these types of claims is instructive: composition of matter claims requiring the work of laboratory technicians are unlikely to run afoul of § 101.

Had the district court performed this *Myriad* cDNA-type analysis for the composition claims at issue, the result would have been more straightforward, and patentees in the biotechnology space would have a clearer understanding of how their composition of matter (or article of manufacture – a pharmaceutical dosage form could qualify as either) claims will be assessed going forward. Natural Alternatives' composition claims, like *Myriad*'s cDNA claims, embody a composition of matter created by lab technicians. For example, claim 1 of the U.S. Patent No. 7,825,084 claims "A human dietary supplement, comprising a beta-alanine in a unit dosage of between about 0.4 grams to 16 grams, wherein the supplement provides a unit dosage of beta-alanine." There can be no real dispute that supplement compositions containing between 0.4 to 16 grams of beta-alanine in unit dosages do not exist in nature: they are clearly compositions manufactured in the laboratory. Like the cDNA in *Myriad*, the lab technician unquestionably created something new when she formulated the physical dietary composition according to industry quality standards, containing specific amounts of beta-alanine and other active/inert ingredients, and did so in a way that would deliver the material to the human body in a non-natural way. And like *Myriad's* cDNA, which was held to be distinct from the natural DNA from which it was derived, the unit dosage forms claimed here are distinct from the steaks, hot dogs, and chicken fingers that constitute natural dietary sources of beta-alanine for modern North Americans. Thus,

these claims should have easily passed a § 101 inquiry, for further analysis under §§ 102, 103, and 112 of the Patent Statute.

Instead, however, the result was a strained analysis under the *Mayo*/*Alice* framework that resulted in the district court developing a yet-to-be-seen test. In performing what it believed to be step one of the *Mayo*/*Alice* inquiry, the district court concluded that because "[b]eta-alanine is the only ingredient of the supplement referenced in the language of claim 1 [of the '084 patent] . . beta-alanine is the focus of the claim." *Natural Alternatives Int'l, Inc. v. Creative Compounds, LLC*, No. 16cv2146, 2017 WL 3877808, at *5 (S.D. Cal. Sept. 5, 2017) ("*NAI*"). This analysis was likewise repeated for claim 34 of U.S. RE45,947. *Id.* at *8. There was no precedential citation for this approach. And for good reason. First, this approach conflicts with this Court's guidance that "it is not enough to merely identify a patent-ineligible concept underlying the claim." *Rapid Litig. Management v. CellzDirect, Inc.*, 827 F.3d 1042, 1050 (Fed. Cir. 2016). Second, (and perhaps even more importantly), if courts are to analyze composition of matter claims reciting a naturally occurring product in this manner, they will surely always fail step 1 of the *Mayo*/*Alice* framework. If endorsed by this Court, this approach could have disastrous consequences for patents on therapeutic protein products, antibiotics, innovative crops, and industrial enzymes.

It is true that some claims to naturally occurring phenomena will fail § 101, or at least require a more searching analysis under applicable Supreme Court precedent. For example, the claims found patent-ineligible in *Funk Brothers* illustrate the distinction between the types of claims reciting naturally occurring products that require further § 101 scrutiny, and those that do not. There, the claims at issue were to nothing more than a mixture of naturally occurring bacteria. Representative claim 4 made this clear:

> An inoculant for leguminous plants comprising a plurality of selected mutually noninhibitive strains of different species of bacteria of the genus Rhizobium, said strains being unaffected by each other in respect to their ability to fix nitrogen in the leguminous plant for which they are specific.

Id. at 128 n.1. The claimed subject matter did not require the laboratory technician to create something "new." Instead, previously-used strains of different bacteria were merely aggregated in a manner that did not improve in any way their natural functioning or expand the range of their utility. *Id.* at 130-31. The "aggregation of species fell short of invention within the meaning of the patent statutes." *Id.* at 131. Thus, close inspection of the actual claims at issue in *Funk Brothers*, paired with a faithful reading of the decision, reveals that the principle set forth in that case is not that combinations of naturally-occurring things are generally ineligible (or even that they are presumed ineligible absent some additional showing). The principle set forth in *Funk Brothers* (as reiterated in and relied on for the *Myriad* decision) was

that someone cannot claim a naturally-occurring material or combination using claim limitations that define a claimed product by nothing other than its natural properties,[12] and without being able to point to a meaningful advance such as modifications that make it "function in new ways" or "enlarge its range of utilities." *See Funk Bros.*, 333 U.S. at 131.

It takes little analysis to see the distinction between this sort of claim, on the one hand, and those like the cDNA in *Myriad* and the composition of matters claims at issue in this case, on the other. The combination of strains of bacteria in *Funk Brothers* at most resulted in an improvement in packaging naturally-occurring bacteria. *Funk Bros.*, 333 U.S. at 131. While the mixtures improved the ease with which dealers could sell and farmers could buy (and use) these previously available individual inoculants, the claimed invention still failed to "satisfy the requirements of invention or discovery." *Id.* The Supreme Court had long held that mere aggregation of prior art components, without more, does not meet the requirement for "invention" as it existed at the time *Funk Brothers* was decided. *See, e.g.*, *Hailes & Treadwell v. Van Wormer*, 87 U.S. 353, 368 (1873) ("Merely bringing old devices into juxtaposition, and there allowing each to work out its own effect without the

[12] Accord *General Electric Co. v. De Forest Radio Co.*, 28 F.2d 641 (3d Cir. 1928) (claiming "substantially pure tungsten having ductility and high tensile strength"); *In re John Wesley Marden and Malcolm N. Rich*, 47 F.2d 958 (C.C.P.A. 1931) (claiming a "form of vanadium which is ductile and homogeneous"); *In Re Marden*, 47 F.2d 957 (C.C.P.A. 1931) (claiming "[as] a new article, ductile uranium").

production of something novel, is not invention."), *Reckendorfer v. Faber*, 92 U.S. 347, 357 (1875) ("There must be a new result produced by [the] union [of the lead pencil and the india rubber]: if not so, it is only an aggregation of separate elements.")[13]

But surely no one would say that the cDNA claims in *Myriad* were just an improvement in packaging the exons naturally and previously existing in human DNA. So too here, the formulation of beta-alanine into particularized dosage forms for administration as a dietary supplement cannot be said to be a mere improvement in packaging the beta-alanine that exists in the human body, particularly when there is no evidence that beta-alanine had been similarly formulated as a dietary supplement in the past. Indeed, the notion that formulating a composition for human administration could be akin to mere packaging or aggregation, like that in *Funk Brothers*, would undercut the patent-eligibility of an untold number of therapeutic products derived from nature.

Because of the difficulty courts face in deciding how to perform the *Mayo*/*Alice* step 1 analysis, guidance from this Court on when a claim warrants a *Myriad* cDNA-type analysis is needed. Indeed, Judge Linn recently acknowledged

[13] *Cf. Anderson's Black Rock, Inc v. Pavement Co.*, 396 U.S. 57, 60 (1969) ("The combination of putting the burner together with the other elements in one machine, though perhaps a matter of great convenience, did not produce a 'new or different function,' within the test of validity of combination patents.") (internal citations and quotations omitted).

that the *Mayo*/*Alice* step 1 analysis often leads to arbitrary results and the improper striking down of meritorious claims, and poses a significant danger to "some of today's most important inventions." *Smart Sys. Innovations, LLC v. Chicago Transit Authority*, 873 F.3d 1364, 1378 (Fed. Cir. Oct. 18, 2017) (Linn, J., dissenting-in-part).

This Court's precedents are illustrative of just how difficult the step 1 analysis can be in the biopharmaceutical space. In the recent *Vanda Pharmaceuticals Inc. v. West-Ward Pharmaceuticals International Ltd.* decision, the majority and dissent sharply disagreed in their step 1 analyses. 2018 WL 1770273 (Fed. Cir. Apr. 13, 2018). While the majority concluded that the claimed method for treating patients with iloperidone with differential dosages based on patient genotype was not "directed to patent-ineligible subject matter" (*id.* at *13), the dissent disagreed, stating that the majority's reliance on the claim's recitation of specific applications of the discovery improperly conflated *Mayo*/*Alice* steps 1 and 2 (*id.* at *18). This is not unlike the circumstances in *CellzDirect*, where in reversing the district court's finding of patent-ineligibility, this Court had to explain that the improved method of preserving hepatocyte cells was not "directed to an ineligible law of nature: the discovery that hepatocytes are capable of surviving multiple freeze-thaw cycles." *CellzDirect*, 827 F.3d at 1047-48. Instead, the claims were patent-eligible because

they were "directed to a new and useful laboratory technique for preserving hepatocytes." *Id.* at 1048.

Physical compositions created in a laboratory should typically require less § 101 scrutiny than even the method of treatment claims in *Vanda* and the laboratory methods of *CellzDirect* found patent-eligible. This case illustrates how district courts can easily err in a step 1 analysis by narrowly focusing on whether a laboratory-created composition nonetheless contains an ingredient derived from nature, thereby fatally subjecting the claim to a step 2 analysis. Instruction from this Court will make the patentability of such claims more predictable and provide a more efficient way for courts to address these claims.

II. Claims That Comprise a Naturally-Occurring Substance Are Not Necessarily "Directed to" Natural Phenomena or Laws of Nature Under *Mayo* and *Alice*.

Even if these types of claims are to be subjected to the *Mayo*/*Alice* framework, guidance from this Court in how to assess what these claims are "directed to," i.e., how to perform step 1, is needed. It cannot be that any claim that recites within its limitations a compound that can occur in nature is necessarily "directed to" a judicial exception to patent-eligibility, thus requiring a court to proceed to step 2. That would be in tension with the direction provided by both the Supreme Court and this Court. *CellzDirect, Inc.*, 827 F.3d at 1050 ("Under the Supreme Court's test, some claims will be 'directed to' a patent-ineligible concept and some,

necessarily, will not."). But six years post-*Mayo*, courts appear to still be struggling to apply step 1 in a consistent manner, leading to much confusion and unpredictability in the biotechnology space.

For composition of matter claims, should we always conclude that the claim is necessarily "directed to" whatever active compounds are formulated therein? That is what the district court concluded. *NAI*, 2017 WL 3877808, at *5 ("Beta-alanine is the only ingredient of the supplement referenced in the language of claim 1 . . . [t]hus, beta-alanine is the focus of the claim); *id.* at *8 (concluding that because the supplement of claim 34 contains a mixture of beta-alanine, creatine, and a carbohydrate, all of which can occur in nature, "claim 34 is directed to excluded subject matter"). But looking at just claim 34 of the '947 patent, it is apparent that a court could find that it is "directed to" several things:

- "a human dietary supplement";
- "a human dietary supplement for increasing human muscle tissue strength comprising a mixture of creatine, a carbohydrate, and beta-alanine";
- "a human dietary supplement for increasing human muscle tissue strength with a specific amount of beta-alanine";
- "a human dietary supplement specially formulated for a 14-day regimen to increase human muscle tissue strength"; or
- "a new and useful dietary supplement for increasing human muscle tissue strength."

Under *Vanda*, the correct answer of what claim 34 is "directed to" is probably something like "a human dietary supplement for increasing human muscle tissue strength comprising a mixture of creatine, a carbohydrate, and beta-alanine." C*f.*

2018 WL 1770273, at *14 ("In this case, the '610 patent claims are directed to a method of using iloperidone to treat schizophrenia."). Under *CellzDirect*, the answer may be closer to "a new and useful dietary supplement for increasing human muscle tissue strength." *Cf. CellzDirect*, 827 F.3d at 1048 ("Rather, the claims of the '929 patent are directed to a new and useful laboratory technique for preserving hepatocytes."). While these cases suggest that the district court's approach cannot be correct, they also demonstrate the absence of a useful framework for district courts assessing the patent-eligibility of biotechnological patent claims.

In contrast, there is some consensus that a framework has developed for how courts should perform the step 1 inquiry for software patents. For software patent cases, courts now ask first whether the claims at issue focus on a specific means or method that improves a particular technology. For example, in *McRo, Inc. v. Bandai Namco Games America Inc.*, this Court held the claims at issue patent-eligible because they were directed to "a specific asserted improvement" in computer animation. 837 F.3d 1299, 1314 (Fed. Cir. 2016). In so concluding, the Court emphasized that there was no evidence of record that the claims simply automate a process previously used by those in this particular area of technology. *Id.* Several cases have further elucidated this approach. *See, e.g.*, *Enfish, LLC v. Microsoft Corp.*, 822 F.3d 1327, 1337-38 (Fed. Cir. 2016) (concluding claims were patent-eligible because they were "directed to an improvement in the function of a

computer."); *DDR Holdings, LLC v. Hotels.com, L.P.*, 773 F.3d 1245 (Fed. Cir. 2014) (holding claims directed to a solution that overcomes a problem specifically arising in the realm of computer networks patent-eligible); *Trading Techs. Int'l, Inc. v. CGW, Inc.*, 675 F. App'x 1001, 1004-05 (Fed. Cir. Jan. 18, 2017) (affirming patent-eligibility of claims directed to improving the accuracy of trader transactions and recognizing that "specific technologic modifications to solve a problem or improve the functioning of a known system generally produce patent-eligible subject matter").

Not unlike other district courts looking at the patent-eligibility of life sciences patents, the district court here did not properly apply this framework to the patents at issue. The district court acknowledged that step 1 requires courts "to look at the focus of the claimed advance over the prior art to determine if the claim's character as a whole is directed to excluded subject matter." *NAI*, 2017 WL 3877808 at *4 (quoting *Affinity Labs. Of Texas LLC v. DIRECTV, LLC*, 838 F.3d 1253, 1257 (Fed. Cir. 2016)) (internal quotations omitted). But even assuming that this articulation of step 1 can be understood and is capable of reliable application, the district court engaged in no such analysis. Instead, the lower court distilled the claims to find a natural phenomenon – beta-alanine – and then proceeded to step 2 of the *Mayo*/*Alice* test. There was no assessment of, for example, whether the claimed compositions provided a benefit compared to natural sources of dietary beta-alanine, or to

previously-used compositions comprising beta-alanine, or whether the claimed compositions and methods provided a new and improved therapy. Without a more meaningful search, and without guidance from this Court, claims that involve any naturally occurring product are going to uniformly fail step 1, thus making it much more difficult for courts to find them patent-eligible.

III. Preemption Needs to Be Meaningfully Considered In Assessing Patent-Eligibility.

It appears that preemption, which features so prominently in the Supreme Court's subject matter eligibility jurisprudence, has come to be largely disregarded in assessing patent-eligibility. This is problematic given that "[t]he Supreme Court has made clear 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). In developing these judicially created exceptions, the Supreme Court was concerned about tying up the building blocks of human ingenuity in a way that would harm rather than promote the progress of science. *Alice*, 134 S. Ct. at 2354-55. Thus, while seeking to ensure that "the basic tools of scientific and technological work" remained free for the public's use, the Court carefully outlined the narrow subject matter that could not be patent-eligible, making sure that its preemption concerns did not "swallow all of patent law." *Id*. at 2354. In other words, the Court thought very carefully about why and how these judicial exceptions should exist.

While this Court explained in *Ariosa* that the absence of complete preemption does not necessarily render a claim patent-eligible, it did not clearly instruct that district courts could disregard the preemptive effect of a claim in assessing patent-eligibility. A quick search on Westlaw reveals more than 30 district court cases directly quoting this part of *Ariosa*, and a sampling of those cases reveals that courts have readily disregarded arguments concerning lack of preemption in holding claims ineligible. *See, e.g.*, *BroadSoft, Inc. v. CallWave Communications, LLC*, 282 F. Supp. 3d 771, 786 (D. Del. 2017); *My Health, Inc. v. ALR Technologies, Inc.; Orostream LLC v. ABS-CBN International*, No. 16cv535, 2017 WL 1129904, at *2 (E.D. Tex. Mar. 27, 2017); *Network Architecture Innovations LLC v. CC Network Inc.*, No. 16cv914, 2017 WL 1398276, at *6 n.3 (E.D. Tex. Apr. 18, 2017); *Appistry, Inc. v. Amazon.com, Inc.*, 195 F. Supp. 3d 1176, 1183 n.5 (W.D. Wash. 2016); *Cave Consulting Group, Inc. v. Truven Health Analytics Inc.*, No. 15cv2177, 2017 WL 6405621, at *11 (N.D. Cal. Dec. 15, 2017); *O2 Media, LLC v. Narrative Science Inc.*, 149 F. Supp. 3d 984, 995 (N.D. Ill. 2016); *Mantissa Corporation v. Ondot Systems, Inc.*, No. 15cv1133, 2017 WL 3437773, at *19 (S.D. Tex. Aug. 10, 2017). Here too, the district court refused to consider whether the narrow claims at issue – even those reciting specific formulations and dosage amounts – presented a preemption concern. *See, e.g.*, *NAI*, 2017 WL 3877808, at *7. Thus, it appears that district courts are using this Court's language in *Ariosa* to "swallow" any preemption

concerns, in tension with the very reason for which judicial exceptions to patent-eligibility were developed in the first place.

Assessing, rather than ignoring, the preemptive scope or lack thereof of a claim provides a useful tool to confirm that a patent-eligibility analysis is correct. This Court suggested as much in *CellzDirect*. There, the Court acknowledged that preemption itself is not the test for patent-eligibility, but then explained that the district court's findings that the patent claims at issue did "not lock up the natural law in its entirety" and that the accused infringer had "already managed to engineer around the patent" supported the conclusion that the claims were not directed to patent-ineligible subject matter. *CellzDirect*, 827 F.3d at 1052 (recognizing that "while pre-emption is not the test for determining patent-eligibility . . . it is certainly the concern that undergirds § 101 jurisprudence") (internal citations and quotations omitted); *see also McRo*, 837 F.3d at 1315-16 (acknowledging *Ariosa* and then proceeding to analyze the preemptive scope of the claim at issue).

Moreover, there is no clear policy support for refusing to account for a manifest lack of preemptive effect of a given claim. It is not apparent, for example, that a person of skill could not design around the claims in this case. It may be possible to use higher or lower dosage amounts, different routes of delivery, different active ingredients, longer or shorter administration periods, and so forth. And without doubt, beta-alanine and carnosine remain available to the public as building

blocks for human ingenuity going forward, even in the face of the appellant's patents. Unhesitatingly applying a test that was created to curb "preemption" against claims that do not preempt anyone will, in the long run, only lead to confusion over what is being tried to accomplish.

Finally, BIO asks this Court to consider the implications of the lower court's logic on the patentability of medical therapies. Here, NAI's inventions involve the administration of supra-normal amounts of naturally-occurring beta-alanine to increase muscle endurance in healthy humans. But in principle, there is little to distinguish this case from:

- the administration of supra-normal amounts of a natural blood-clot-dissolving enzyme to a stroke patient;
- the administration of natural amounts of growth hormone to children with dwarfism who cannot make their own;
- the administration of a naturally-occurring antiserum to a snake bite victim;
- the administration of a naturally-occurring bacterial antibiotic to treat an infection or suppress an immune response in an organ transplant recipient;
- the administration of a naturally-occurring amino acid metabolite, L-DOPA, to treat the symptoms of Parkinson's disease; and
- the administration of a naturally-occurring virus envelope protein to vaccinate women against HPV.

Examples of medical treatments that rely on the introduction, supplementation, or replacement of naturally-occurring substances in patients are too many to recount. Such treatments have saved or improved countless lives. It is inconceivable that the Supreme Court would have wanted to declare a whole class of diverse therapies off-limits for patenting on the grounds that they "merely"

involve the administration of a product of nature that, once administered, will trigger a natural physiological response that is governed by a natural law, leaving no inventive concept to support patentability. If such were the case, it is no exaggeration to say that the ability to discover and develop such therapies would be dramatically diminished.

CONCLUSION

For these reasons, BIO respectfully requests that the Court address the concerns raised herein and provide guidance on the appropriate patent-eligibility analyses for products that incorporate naturally-occurring substances, and of methods of using such products in therapeutic applications.

Respectfully submitted,

Date: April 20, 2018

/s/ *Melissa A. Brand*

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

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/s/ Simone Cintron
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