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**VIA E-MAIL ONLY**
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Michelle K. Lee
Deputy Under Secretary of Commerce for Intellectual Property and
Deputy Director of the USPTO
United States Patent & Trademark Office
401 Delaney Street
Alexandria, VA 22314

Re: **Guidance for Determining Subject Matter Eligibility of Claims Reciting or Involving Laws of Nature, Natural Phenomena, and Natural Products**

Madame Under Secretary:

The members of the BioPharma Practice Group at Harness, Dickey & Pierce, PLC ("HDP") thank the U.S. Patent & Trademark Office ("PTO") for the opportunity to submit comments regarding the March 4, 2014 PTO memorandum entitled "2014 Procedure for Subject Matter Eligibility Analysis of Claims Reciting or Involving Laws of Nature/Natural Principles, Natural Phenomena, and/or Natural Products" ("Guidance").

HDP is a global IP law firm whose clients depend on robust patent protection to support their innovative work in drug discovery, clean energy research, and many other fields of life-enhancing technology. For this reason, HDP filed an amicus brief in *Assoc. for Molecular Pathology v. Myriad Genetics,* 133 S. Ct. 2107 (2013) on behalf of five biotech companies and industry organizations urging the Court to affirm the subject-matter eligibility of cDNA and other synthetic DNA constructs.

HDP is pleased to have this opportunity to comment on the Guidance. In particular, while members of our practice group were recently in San Diego, California for the 2014 BIO International Convention, the PTO promulgated a series of seven sample claims and asked for public comment as to the patent eligibility of each proposed claim under recent Supreme Court and Federal Circuit case law. All seven of the proposed claims can be patent eligible under 35 U.S.C. §101 and applicable case law. HDP submits herewith a brief comment on the Guidance's three-step analysis, followed by reasons why each of the seven sample claims crosses the §101 threshold.

## Comment on three-step analysis

**Question #2.** The Guidance proposes (pg. 2) a flowchart with three questions to determine whether a claim is §101 eligible. The instructions accompanying this flowchart require Examiners to proceed to question #3 in circumstances in which neither legal precedent nor common sense so require, instead of simply answering question #2 in the negative. This is an important point because, as *Alice Corp. v. CLS Bank*, 134 S. Ct. 2347, 2355 (2014) makes clear, the "significantly more" inquiry only comes into play after an initial determination that "the claims at issue are directed to … patent-ineligible concepts…."

The Guidance indicates (pg. 3) the judicial exceptions to patentable subject matter under §101 "include abstract ideas, laws of nature/natural principles, natural phenomena, and natural products," and interprets (pg. 3) "natural products" to include "chemicals derived from natural sources…; foods…; metals and metallic compounds that exist in nature; minerals; natural materials…; nucleic acids; organisms…; proteins and peptides; and other substances found in or derived from nature." However, the term adopted by the Office—"natural product"—is not synonymous with "product of nature" as those words are used in *Myriad*, 133 S. Ct. at 2119 and *Diamond v. Chakrabarty*, 447 U.S. 303, 313 (1980). While some of the natural products in the quoted list certainly are "products of nature," others are not.

For example, while gunpowder may well be a "natural product" (Guidance, pg. 9), it is not a "product of nature." Unlike the borax-infused citrus of *American Fruit Growers v. Brogdex Co.*, 283 U.S. 1, 11–12 (1931), when saltpeter, sulfur, and charcoal are combined by a human agent in particular ratios, the resulting composition acquires a "new or distinctive … property [*viz.* controllable explosive potential]…[,] name [*viz.* "gunpowder"], appearance [*i.e.*, gunpowder does not look like any of its individual components], or general character…."

Similarly, "5-methyl amazonic acid" (Guidance, pg. 7, herein "5MAA") is not a "product of nature." When one applies the *American Fruit Growers* "property, name, appearance, or general character" test, one sees that not only does 5MAA have a new name, but also a new property (*i.e.*, hair growth, Guidance, pg. 8). Indeed, we believe that under the correct reading of applicable precedent, *any* structural change to a natural molecule—no matter how small, and regardless of whether the structural change imparts a new function—takes the modified molecule out of the "product of nature" category and into the realm of §101 eligibility, so long as (1) the modification does not change the first natural molecule into another natural molecule, and (2) the modification does not render the molecule without any utility.

A claim directed to a gunpowder composition or to 5MAA should be considered §101 eligible because these compositions do not exist in nature without human intervention. Humans must actively combine individual products of nature (naturally occurring saltpeter, sulfur, and charcoal) at specific ratios to form a gunpowder mixture. Humans must methylate amazonic acid at the 5-position to make 5MAA. In other words, these compositions are not *Chakrabarty*/*Myriad* "products of nature."

The appropriate inquiry under *American Fruit Growers*, *Chakrabarty*, and *Myriad* should focus on whether a claimed composition exists without human intervention. Thus, the Office's interpretation of question #2 in the Guidance should be more appropriately tailored to whether Claim 1 is directed to a "product of nature," rather than a "natural product." The analysis for both Example B, Claim 2 (Guidance, pg. 8) and Example C (Guidance, pg. 9) should stop at the question #2 step because this question can be answered in the negative.

**Question #3.** The Guidance's factor (a)/(g) inquiry (pg. 4) into whether a claimed composition is "markedly different in structure from naturally occurring products" deviates from applicable case law and is overly broad. Both *Myriad* and *Chakrabarty* distinguish a "product of nature" from a patent-eligible composition based on whether the composition possesses "markedly different characteristics from any found in nature." *See Myriad,* 133 S. Ct. at 2117 (emphasis added) (quoting *Chakrabarty*, 447 U.S. at 310). "Characteristics" refers to functional as well as structural differences. Indeed, because a compound is inseparable from its properties (*In re Papesch*, 315 F.2d 381, 391 (C.C.P.A. 1963)), the existence of a functional difference implies a structural difference, even if the precise structural difference is unknown or unspecified. Accordingly, we propose that amended factors (a) and (g) (shown in marked-up format below) would better conform to *Myriad* and *Chakrabarty*:

> (a) Claim is a product claim reciting something that initially appears to be a product of nature ~~natural product~~, but after analysis is determined to be non-naturally occurring or ~~and~~ markedly different in structure and/or function from naturally occurring products of nature.
>
> (g) Claim is a product claim reciting something that appears to be a product of nature ~~natural product~~ that is not markedly different in structure or function from naturally occurring products of nature.

Additionally, the Guidance's factor (f)/(j) inquiry (pgs. 4 and 5) requires the Examiner to determine whether given claim elements are "well-understood … in the relevant field." This consideration speaks to the state and content of the art. Art-based considerations are not supposed to form any part of the §101 inquiry. *Diamond v. Diehr*, 450 U.S. 175, 190 (1981). We urge the PTO to revise the Guidance to make explicit that §101 eligibility is distinct from—and does not overlap with—art-based considerations under §§102 and 103.

## Commentary on seven sample claims

All seven sample claims are directed to compositions of matter, so the answer to question #1 is the same for all of them: "yes." Detailed analyses of question #2 and, where appropriate, question #3 steps are presented below:

### 1. Isolated nucleic acid comprising a sequence that has at least 90% identity to SEQ ID NO:1 and contains at least one sequence modification relative to SEQ ID NO:1.

Analysis of Claim 1 requires the *a priori* / *a posteriori* distinction borrowed from PCT Rule 13. Even where a claim initially appears to be §101 eligible *a priori*, a search of the prior art may uncover grounds for a §101 ineligibility rejection *a posteriori*.

An Examiner should answer question #2 in the negative *a priori* because, just like the cDNA in *Myriad*, 133 S. Ct. at 2119, the isolated nucleic acid sequence of Claim 1 has been manipulated by human intervention, such that it differs from the naturally occurring SEQ ID NO:1 by at least one nucleotide. The *Myriad* court took pains to make clear that "the patentability of DNA in which the order of the naturally occurring nucleotides has been altered" was not at issue in that case. *Id.* at 2120. Indeed, *Myriad* makes clear that a difference of even one nucleotide is significant. "Changes in the genetic sequence … can be as small as the alteration of a single nucleotide—a change affecting only one letter in the genetic code. Such small-scale changes can produce an entirely different amino acid or can end protein production altogether …

[and] can cause disease or increase the risk of disease." *Id.* at 2112 (emphases added). Similarly, even if a Claim 1 sequence encodes the same protein as SEQ ID NO:1, the alteration of a nucleotide base may change the way in which a host organism expresses the sequence because of codon-preferences or epigenetic alterations.

In other words, Claim 1 is directed to a new, human-made molecule that differs from the "product of nature" SEQ ID NO:1. The applicant has included a *proviso* to carve naturally-occurring SEQ ID NO:1 out of Claim 1, such that only human-made nucleic acids are claimed. Under both *Myriad* and *Chakrabarty*, compositions of matter created by modifying natural materials are not "products of nature." Therefore, Claim 1 is §101 eligible *a priori* and the Examiner can stop at question #2.

Of course, as the Examiner searches the art, it is possible that a natural sequence will be found that is not identical to SEQ ID NO:1 but which is at least 90% identical to SEQ ID NO:1—*e.g.*, an orthologous gene from a closely related species. In this case, it becomes clear *a posteriori* that question #2 should be answered in the affirmative.

At this point, the Examiner should reconsider the §101 eligibility of Claim 1 and proceed to question #3. Question #3 should be answered in the negative because there are no additional elements in Claim 1 besides the product of nature (*i.e.*, the polynucleotide whose sequence is at least 90%, but not 100%, identical to SEQ ID NO:1). In this case the Examiner should reject Claim 2 for §101 ineligibility *a posteriori* and also for §102 anticipation, so long as the reference in which this natural ortholog is described is date effective. The publication date does not matter for the §101 ineligibility rejection. *Ex parte Snell*, 86 U.S.P.Q. 496, 497 (B.P.A.I. 1950).

If a §101 eligibility rejection is made *a posteriori*, the Examiner must cite the reference on which the rejection is predicated and supply a copy to the applicant. "In the prosecution of a patent, the initial burden falls on the PTO [examiner] to set forth the basis for any rejection" (brackets in original). *In re Packard*, 110 U.S.P.Q.2d 1785, 1788 (Fed. Cir. 2014). The rejection can only be made if an actual sequence with at least 90% identity to SEQ ID NO:1 is identified. It is not enough that such a sequence might exist. *Myriad*, 133 S. Ct. at 2119 n.8.

### 2. Polypeptide comprising an amino acid sequence that has at least 90% identity to SEQ ID NO:2 and contains at least one sequence modification relative to SEQ ID NO:2.

Just as with Claim 1 above, an Examiner should answer question #2 in the negative *a priori* because on the face of the claims they cannot be said to read on a natural polypeptide. However, if an art search uncovers a natural polypeptide with at least 90%, but not 100%, sequence identity to SEQ ID NO:2, then Claim 2 should be rejected as §101 ineligible *a posteriori*.[1]

### 3. A nucleic acid comprising SEQ ID NO:1 and a fluorescent label attached to the nucleic acid.

An Examiner should answer "maybe" to question #2 because Claim 3 recites two judicial exceptions—*viz.,* SEQ ID NO:1 is a naturally occurring DNA sequence, and some fluorophores are naturally occurring materials. The Examiner should proceed to question #3. Because Claim 3 is a composition claim, factors (a) and (g)—analyzed under *Chakrabarty* and *Myriad*—should control.

[1] This claim does not include the word "purified" or some such. If it did, then the considerations set forth for Claim 5 below might also be relevant.

Regarding the broadest reasonable interpretation of Claim 3, even though all DNA has some inherent fluorescence, Claim 3 cannot be reasonably construed to read on all DNA molecules. A claim construction that was expansive enough to reach all polynucleotides comprising SEQ ID NO:1 would essentially read the words "label attached" out of the claim. Therefore, when the claim as a whole is given its broadest *reasonable* interpretation, that interpretation can only reach DNA molecules with some additional, non-DNA moiety attached. Indeed, we agree with the appellant in *In re Bentwich* (Oral Argument at 3:30, *In re Bentwich*, No. 2013-1460 (Fed. Cir. May 6, 2014), *available at* http://oralarguments.cafc.uscourts.gov/default.aspx?fl=2013-1460.mp3) that a "labeled" DNA is *ipso facto* not a "product of nature" because the very word "label" signifies an alteration by a human agent. In other words, the claimed molecule necessarily comprises both a polynucleotide moiety and a distinct, but conjoined, fluorophore moiety.

The Examiner should answer question #3 in the affirmative. *Chakrabarty*'s claimed bacteria were held patent-eligible, even though *Pseudomonas* bacteria occur in nature and plasmids that encode hydrocarbon-degrading enzymes also occur in nature. Nevertheless, the physical combination of *Pseudomonas* and two plasmids is not a "product of nature." By analogy, the physical combination of DNA and fluorophore claimed in Claim 3 is also significantly different from a "product of nature" because SEQ ID NO:1 does not naturally occur with fluorescent labels attached.

*Myriad*'s cDNA was held §101 eligible because that cDNA does not occur naturally. Likewise, SEQ ID NO:1 with a fluorescent label attached does not occur naturally and exists only if a human agent attaches the fluorescent label. For at least these reasons, Claim 3 recites a product of human ingenuity that is significantly different from naturally occurring products.

### 4. A chimeric or partially humanized antibody to Antibiotic L.

An Examiner should answer "maybe" to question #2 because the broadest reasonable interpretation of "chimeric" reads on an antibody composed of naturally occurring portions of antibodies from two different species (*e.g.*, a naturally occurring coyote heavy chain and a naturally occurring human light chain). That is to say, Claim 4 reads on protein complexes assembled from "product of nature" subunits. The Examiner should proceed to question #3.

The Examiner should answer question #3 in the affirmative. Neither chimeric nor partially humanized antibodies to Antibiotic L occur without human intervention. Although the individual heavy and light chains can be "products of nature," the molecule as a whole is structurally different from any antibody found in nature.

Chimeric and partially humanized anti-Antibiotic L antibodies must be engineered by humans if they are to exist at all. The production of both chimeric and humanized antibodies requires coyote and human DNA fragments to be spliced together to create recombinant DNA not occurring in nature. Alternatively, the production requires the covalent conjugation of human and coyote heavy and light chain proteins. Neither the DNA splicing nor the peptide conjugation occur spontaneously as "nature's handiwork." Therefore, a chimeric or humanized antibody is significantly different from any naturally occurring molecule and is §101 eligible.

## 5. Purified Antibiotic L.

An Examiner should answer question #2 in the affirmative because the broadest reasonable interpretation of the claim reads on a molecule identical to the natural antibiotic. Therefore, the Examiner should proceed to question #3.

Because Claim 5 is a composition of matter claim, question #3 turns on factors (a) and (g). As an initial matter, the purified Antibiotic L of Claim 5 is structurally different from its natural cousin. The purity of the Claim 5 composition can itself be a structural difference, when purity imparts a functional difference. *In re Bergstrom*, 427 F.2d 1394, 1402 (C.C.P.A. 1970).

Although *Myriad* makes clear that mere "isolation" is not enough to make a molecule patent eligible (133 S. Ct. at 2120), that does not mean all isolated biomolecules are *ipso facto* ineligible. Courts have long recognized the §101 eligibility of isolated, natural antibiotics. Many patents concerning natural antibiotics have been litigated without a single court holding that any of them were §101 ineligible. *See Geneva Pharma. v. GlaxoSmithKline*, 349 F.3d 1373 (Fed. Cir. 2003); *In re Argoudelis*, 434 F.2d 1390 (C.C.P.A. 1970); *Pfizer & Co. v. FTC*, 401 F.2d 574 (6th Cir. 1968).

The *Myriad* court was careful to make clear that "[w]e merely hold that genes and the information they encode are not patent eligible under §101 simply because they have been isolated…." *Myriad*, 133 S. Ct. at 2120 (emphasis added). In other words, *Myriad* does not purport to disturb settled understandings about the §101 eligibility of other isolated biomolecules. Because of the presumption against *sub silentio* reversal of settled law (*Shalala v. Ill. Council on Long Term Care*, 529 U.S. 1, 18 (2000)), one should not read *Myriad* as extending to all biomolecules. Rather, with regard to molecules other than genomic DNA/RNA and prions, U.S. law still provides that if an inventor "produces an article of such purity that it differs not only in degree but in kind it may be patentable," provided that the pure composition has "a new utility." *In re Merz*, 97 F.2d 599, 601 (C.C.P.A. 1938); *accord*, *In re Bergy*, 596 F.2d 952, 972 (C.C.P.A. 1979). Neither *Merz* nor *Bergy* has been overruled,[2] so the Guidance must follow these cases.

The *Merz*/*Bergy* rule also accords with the "property, name, appearance, or general character" test from *American Fruit Growers*. *See also Myriad*, 133 S. Ct. at 2117 ("a product of human ingenuity ha[s] a distinctive name, character and use," (internal quotations and brackets omitted)). A purified composition of matter cannot be §101 eligible *simply* for being purified, but if the pure substance acquires a new property as a result of purification, then the purified composition is a product of human agency, even if the raw materials from which it was purified were merely "products of nature." Indeed, the composition of *Myriad*'s Claim 1 was not §101 eligible precisely because the gDNA constructs had no new properties ("[T]he genetic information encoded in the BRCA1 and BRCA2 genes … existed in nature before Myriad found them. Nor did Myriad create or alter the genetic structure of DNA." *Id.* at 2116).

In addition, the *Merz*/*Bergy* rule agrees with eligibility rules in other jurisdictions,[3] furthering the PTO's stated goal of harmonization across jurisdictions. *See* "Harmonization: The Time is Now" (*available at* http://www.uspto.gov/ip/global/aia_harmonization.jsp). Similarly, the current Guidance is in tension with U.S. obligations under the TRIPS agreements. *See* TRIPS

[2] *Assoc. for Mol. Pathology v. USPTO*, 653 F.3d 1329, 1352 n.7 (Fed. Cir. 2011) mistakenly asserts that *Bergy* was overruled, but this is not so. The Supreme Court dismissed *Bergy* as moot from a grant of *certiorari* (447 U.S. 303 (1980)), but a dismissal of appeal does not upset the decision below. Rather, the Court of Customs & Patent Appeals' decision in *Bergy* remains binding precedent on the Federal Circuit and the PTO.

[3] *See*, *e.g.*, EC Directive 98/44/EC (1998), paragraphs (20)–(23).

Article 27 ("[P]atents shall be available for any inventions, … in all fields of technology, provided that they are new,[4] involve an inventive step and are capable of industrial application." (*available at* http://www.wto.org/english/docs_e/legal_e/27-trips.pdf)). Given the self-stated narrowness of *Myriad*'s holding, it would be imprudent to apply *Myriad* in a manner so broad as to run afoul of U.S. treaty obligations.[5] A revised Guidance that reflected the *Merz/Bergy* rule would better serve harmonization goals and treaty obligations.

Like Bergy's prostaglandins—but unlike Myriad's gDNAs—the purified Antibiotic L of Claim 5 is significantly different from a mound of soil that happens to contain one or more Antibiotic L molecules. The purified composition is safe to administer to a patient without inducing sepsis, heavy-metal poisoning, or other such blood poisoning. In short, the composition of Claim 5, by virtue of the limitation "purified" is significantly different in kind—both structurally and functionally—from natural Antibiotic L. *Bergy*, 596 F.2d at 972 ("[T]he opening words of claim 5, 'A biologically pure culture of,'… constitute a material claim limitation."). Therefore, Claim 5 is §101 eligible as it stands.

Claim 5 variations: Even if the PTO does not agree that Claim 5 is §101 eligible, only small changes are needed to make the claim unambiguously eligible. We urge the PTO to make explicit in the next revision of the Guidance that structurally modified versions of nature-sourced proteins are *ipso facto* §101 eligible.

Illustrative examples of structural modifications that could be made to the Antibiotic L molecule that would be even more clearly §101 eligible if claimed include:

- chemical-moiety substitutions or additions to amino acid side-chains and/or to N- or C-terminal groups;
- substitution of a natural amino acid with an unnatural or synthetic amino acid;
- additional glycosylation;
- additional lipidation;
- dimerization (if Antibiotic L is naturally a monomer);
- substitution or rearrangement of amino acid sequence;
- pro-drug formation (*e.g.*, by methoxylation);
- esterification, phosphorylation, or salt-form derivatives;
- conjugation with other peptides;
- replacing multi-site stereocenters with rigid bio-isosteres; and
- a composition comprising Antibiotic L and second drug (*e.g.*, an esterase-inhibitor that prevents physiological degradation of Antibiotic L *in vivo*).

Illustrative functional examples that would be even more clearly §101 eligible if claimed include:

- method-of-use against new anti-bacterial strain; and
- therapy regimen (or kit for therapy regimen) having novel dosing or drug-use scheme.

[4] The word "new" cannot justify a *subject matter eligibility* carve-out for biomolecules under U.S. law, because "[t]he question… of whether a particular invention is novel is wholly apart from whether the invention falls into a category of statutory subject matter," (internal quotations omitted). *Diehr*, 450 U.S. at 190.

[5] Indeed, U.S. law requires that courts and agencies "avoid[] unnecessary conflict between domestic law and the international obligations of this country." *Allegheny Ludlum Corp. v. U.S.*, 367 F.3d 1339, 1335 (Fed. Cir. 2004).

### 6. Antibiotic L, which is expressed by recombinant yeast.

An Examiner should answer "maybe" to question #2 because it is unclear from the facts disclosed whether the yeast-derived Antibiotic L is identical to bacterial Antibiotic L. The Examiner should proceed to question #3.

At this point, however, the Examiner's inquiry must stop. A synthetic version of a natural composition is not §101 eligible simply because it was made by human artifice. *In re Roslin Inst.*, 750 F.3d 1333, 1337 (Fed. Cir. 2014). In other words, the process of production is, in itself, irrelevant. For the Antibiotic L of Claim 6 to be §101 eligible, the method of production must impart some discernible difference from bacterial Antibiotic L.

The PTO does not have the institutional capacity to test yeast-derived and bacterial Antibiotic L. *In re Best,* 562 F.2d 1252, 1255 (C.C.P.A. 1977). The applicant, however, could have prevented this difficulty by including data in the application as filed, proving that the yeast-derived Antibiotic L is distinguishable from bacterial Antibiotic L. Therefore, principles of fairness and efficiency—as well as long-standing PTO practice (MPEP §2112.V)—dictate that the Examiner should reject Claim 6 as *presumptively* §101 ineligible, and shift the burden to the applicant to adduce evidence (*e.g.*, mass spectroscopy data, Guthrie inhibition, *etc*.) showing that the claimed Antibiotic L is discernibly distinct from the natural Antibiotic L. If such data are supplied in a Rule 132 declaration, then the rejection should be withdrawn.

### 7. A human or fully humanized antibody to Antibiotic L.

An Examiner should answer question #2 in the negative because there is no evidence that either a human anti-Antibiotic L antibody or a fully humanized anti-Antibiotic L antibody exists as "nature's handiwork." A naturally occurring coyote anti-Antibiotic L antibody must be considerably altered to obtain a fully humanized antibody. Coyote and human DNA fragments must be spliced together to create recombinant DNA not occurring in nature. Alternatively, the CDRs of human antibodies must be enzymatically cleaved from their scaffold and replaced with coyote CDRs, which must then be covalently conjugated to the remaining human antibody structure. Both of these processes require human intervention with sophisticated molecular biological tools and methods.

Alternatively, production of a human anti-Antibiotic L antibody requires that one human inject another with Antibiotic L or an Antibiotic L antigen fragment. Once again, this process requires human agency and will not happen spontaneously as "nature's handiwork." Therefore, the Examiner should conclude that none of the molecules within the scope of Claim 7 are "products of nature." Claim 7 is §101 eligible *a priori*.

Of course, it is possible that subsequent research will reveal that human anti-Antibiotic L antibodies occur spontaneously in humans who have not been deliberately immunized against Antibiotic L. Perhaps, for example, the bacteria that produce Antibiotic L grow in mosquito salivary glands, and antigen fragments are injected into humans when the mosquitos bite, eliciting an immune response.

If so, then a §101 ineligibility rejection can and should be made *a posteriori*, provided that the Examiner supplies adequate evidence of the existence of these natural human antibodies. As noted in Claim 1 above, however, it is not enough that such an antibody *could* arise apart from human agency. The PTO has the burden in the first instance to establish that such a natural antibody *does* exist.

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Thank you for considering these comments. If you have any questions, please contact J. Timothy Keane, at 314-726-7518 or tkeane@hdp.com.

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