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VIA E-MAIL: myriad-mayo_2014@uspto.gov

The Hon. Michelle K. Lee
Deputy Under Secretary of Commerce
Acting Director
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

RE: Comments by Amgen Inc. in Response to the USPTO's Request for Comments on *Guidance For Determining Subject Matter Eligibility of Claims Reciting Or Involving Laws of Nature, Natural Phenomena, & Natural Products*

Dear Acting Director Lee:

Amgen Inc. thanks the US Patent and Trademark Office for the opportunity to provide comments to the March 4, 2014 Guidance For Determining Subject Matter Eligibility Of Claims Reciting Or Involving Laws of Nature, Natural Phenomena, & Natural Products ("the Guidance") and accompanying March 19, 2014, Training Materials ("the Training Materials") and hereby submits the following comments:

Amgen Inc. ("Amgen") is a biotechnology pioneer and, since its beginnings in 1980, has grown to be the world's largest independent biotechnology company. Amgen develops and manufactures medicines that treat serious illnesses, including approved biological and small molecule medicines such as Aranesp® (darbepoetin), Enbrel® (etanercept), Epogen® (Epoetin alfa), Krypolis® (carfilzomib), Neulasta® (pegfilgrastim), NEUPOGEN® (filgrastim), NEXAVAR® (sorafenib), Nplate® (romiplostim), Prolia® (denosumab), Sensipar®/Mimpara® (cinacalcet), Vectibix® (panitumumab), and XGEVA® (denosumab). Patent protection is a critical component in our decision to invest in the research and development of medicines like these which improve the lives of millions of patients.

I. The Guidance and Training Materials Should Be Withdrawn

While we appreciate that the Office was trying to bring consistency to patent examination in light of the Supreme Court's decision in the *Myriad* case by issuing the Guidelines, we believe that the Guidance and Training Materials misinterpret and go beyond the relevant case law and therefore respectfully request that they be withdrawn in their entirety and new guidelines issued that are more in line with the Court's decision.

Precedential court decisions relating to the patent eligibility requirement of 35 USC §101 are few in number and each is inherently fact specific and difficult to generalize. The common thread running through the opinions in these cases is that each is carefully decided on its own facts with due respect for the damaging effect that an overbroad application of the threshold patentability requirements of Section 101 would have on patent law. The Supreme Court has "cautioned that courts 'should not read into the patent laws limitations and conditions which the legislature has not expressed. … In choosing such expansive terms [in Section 101] as 'manufacture' and 'composition of matter,' modified by the comprehensive 'any,' Congress plainly contemplated that the patent laws would be given wide scope." *Diamond v. Chakrabarty*, 100 S. Ct. 2204, 2207 (1980) (citation omitted). In *Mayo Collaborative Services v. Prometheus Laboratories*, 132 S. Ct. 1289, 1293 (2012), and again in *Association for Molecular Pathology v. Myriad Genetics*, 133 S. Ct. 2107, 2116 (2013), the Court warned that "too broad an interpretation of this exclusionary principle could eviscerate patent law."

The Guidance, in contrast, imposes a fact-independent uniformity of analysis that is heedless of these warnings. The Office's own examples illustrate how this unduly restrictive interpretation of Section 101 imperils entire classes of heretofore patentable inventions, creating exactly the harm that the Supreme Court has cautioned against. For at least these reasons, we urge the Office to withdraw the Guidance.

Should the Office decline to withdraw the Guidance, we ask that the following changes be adopted to better align it with the controlling case law and to increase its clarity and usefulness.

II. Purified Products of Nature Can be Patentable Subject Matter

The Guidance's *per se* rule against patenting purified products of nature runs contrary to Supreme Court precedent and should be removed.

Myriad holds only that a genomic DNA fragment, identified and claimed solely by its sequence, is patent ineligible if the claimed sequence occurs exactly in nature. Nothing in the holding of *Myriad* suggests that every purified but otherwise unmodified product of nature is unpatentable. The Office appears to be relying on *Funk Brothers v. Kalo Inoculant*, 68 S. Ct. 440 (1948) for this proposition, but *Funk Brothers* says nothing of the sort. As quoted by the Supreme Court in *Chakrabarty*, at 2208, the *Funk Brothers* court held that the claimed combination of species of bacteria was an unpatentable product of nature because in the claimed combination "[n]o species acquires a different *use*. The combination of species produces … *no enlargement of the range of their utility*. … Their use in combination does not improve in any way their natural functioning." (Emphases added.) This is a strange comment to make if the Court had intended to simply ban all patents on purified, unmodified products, as the Guidance would. Further, the *Chakrabarty* court found that in its case, "by contrast, the patentee has produced a new bacterium with markedly different *characteristics* from any found in nature and *one having the potential for significant utility*." (*Chakrabarty* at 2208; emphases added.) *Chakrabarty* also makes reference (with no apparent disapproval) to the issuance of a patent by the Office to Louis Pasteur claiming "yeast, free from organic germs of disease, as an article of manufacture." (*Chakrabarty* at 2210 and footnote 9) Taken together, these cases are best interpreted as allowing for the patenting of purified products of nature *if* they are "made by man" and have the potential for significant utility. The courts have had ample opportunity to clearly and explicitly forbid the patenting of all purified natural products if they had wished to do so, yet they have not. Thus, the Office has no basis for forbidding the patenting of purified natural products of increased utility, such as those molecules illustrated in Example B, Claim 1, of the Guidance. The Guidance and the Training Materials should be changed accordingly.

The need for these changes is illustrated by the following examples. We urge the Office to include them in the next version of the Guidance and Training Materials.

The first example presents several variations of Example B in the Training Materials. In the first variation of this example, it is further known that the leaves of the Amazonian cherry tree contain trace amounts of cyanide. A cancer patient who eats a sufficient quantity of Amazonian cherry tree leaves to cure his cancer has a ten percent chance of dying of cyanide poisoning. The specification teaches methods for purifying amazonic acid such that it is free of cyanide and methods of using purified amazonic acid to treat cancer patients without exposing them to a risk of cyanide poisoning.

In this example, the structure of purified amazonic acid is identical to that found in nature, yet we urge that under the existing case law and on these facts, amazonic acid "substantially free of cyanide" would be found to satisfy Section 101. Surely no oncologist would consider a treatment that kills one in ten of his patients to be clinically interchangeable with a safe and effective cancer treatment, even if they share the same active ingredient.

In a second variation of this example, Amazonian cherry tree leaves do not contain cyanide or any other poison, but the amount of amazonic acid is found to vary by over a hundred fold from leaf to leaf.

It is further found that ingestion of at least a certain amount of amazonic acid is necessary to treat cancer, but that too much causes toxic side effects. The toxic effects are caused by amazonic acid itself and not by a contaminating substance that can be removed by purification.

Accordingly, the dosage of amazonic acid cannot be controlled when it is administered in the form of Amazonian cherry leaves, with the result that some patients receive a less than therapeutic dose of the drug, while others receive a toxic dose.

Both of these problems are obviated by administering a controlled dose of purified amazonic acid, resulting in more patients being successfully treated and fewer patients suffering toxic side effects.

In this variation of the example, as in the previous one, the structure of purified amazonic acid is identical to that found in nature, yet we urge that under the existing case law and on these facts, purified amazonic acid having a concentration within a specific range has properties and uses that make it patent-eligible subject matter under Section 101. Again, on these facts an oncologist would recognize that purified amazonic acid is therapeutically superior to amazonic acid in its "natural" form such that the two cannot be considered the same or equivalent in any clinically meaningful sense.

In a third variation of this example, the leaves of the Amazonian cherry tree are free of cyanide and each contains about the same amount of amazonic acid, such that a therapeutically effective but sub-toxic dose of the drug can be delivered by ingesting thirty pounds of leaves per day for at least four weeks. (These are the same facts posited by the Office's original example in the Guidance.) However, in practice it is found that the ingestion of such large quantities of vegetal matter for such an extended period causes gastrointestinal side effects that are difficult or impossible for many cancer patients to endure. These effects are caused by the sheer bulk of indigestible fiber in the leaves, not by amazonic acid itself or any other particular chemical entity. Knowing of these side effects, some patients refuse to even try this treatment. Others begin treatment but abandon it before the treatment is effective. These problems are completely avoided by the administration of a purified form of amazonic acid.

Once again, in this example the structure of purified amazonic acid is identical to that found in nature, yet we urge that under the existing case law and on these facts, purified amazonic acid having a concentration within a specific range would be found to satisfy Section 101. An oncologist would appreciate that a treatment that few patients can tolerate has a clinical benefit that is almost completely hypothetical. That hypothetical benefit becomes real, in this example, only when a purified form of amazonic acid is made available.

Another example provides a different illustration of the same point. In this example, venom from a particular species of scorpion is known to cause pain and paralysis in mammals. Applicant has found that this venom contains a variety of small peptides. Collectively, these peptides cause the pain and paralysis associated with the

scorpion's sting by inhibiting a wide range of mammalian ion channels. Applicant has, for the first time, purified one of these peptides, Peptide A, and found purified Peptide A specifically inhibits a particular type of sodium channel. Applicant has further found that purified Peptide A can be used to relieve the painful and debilitating symptoms of cerebral palsy. Venom containing Peptide A is not useful for this purpose because of the neurotoxic effects of the other peptides it contains. The chemical structure of purified Peptide A is identical to the structure of Peptide A as it occurs naturally in scorpion venom.

As with the preceding examples, purification adds a useful functionality missing from the natural product *in situ*. A neurologist would instantly recognize the profound clinical difference between scorpion venom and purified Peptide A. The case law simply provides no basis for refusing a claim to purified Peptide A under Section 101.

Another important type of invention is also denied patent protection by the Guidance, as illustrated in another example. In this example, Protein X is found in human blood. It is found that when the purified Protein X is administered at a certain dose to patients with lupus nephritis, the patients experience a clinically significant relief of their symptoms. It is found that lupus patients (like other people) normally have a certain concentration of Protein X in their blood. This normal concentration of Protein X fails to inhibit B-cell mediated immune responses. But when purified Protein X is administered to lupus patients such that the concentration of Protein X is about three times its normal concentration, Protein X inhibits B-cell mediated processes sufficiently to provide a clinically significant therapeutic benefit.

As in the previous examples, a purified natural product has a utility that it does not have in nature. In this example, it would be pointless to give a lupus patient a blood transfusion (that is, administer Protein X in its "natural" form) because doing so would not have the therapeutically necessary effect of raising the concentration of Protein X in a patient's blood to super-physiological levels. It would also expose the patient to some risk of infection by HIV, HCV, or other blood-borne illness.

Further, the precise wording of a claim is important and could distinguish the claimed subject matter from the natural product as it is found in nature (a distinction that

the claims invalidated in *Myriad*, which focused only on the information content of the recited nucleic acids, failed to make, as the Court noted). Examples of claim language that might be acceptable, depending on the specific facts of the case, include "A pharmaceutical composition comprising at least 80% amazonic acid" (in an example where Amazonian cherry tree leaves contain much less than 80% amazonic acid), "A pharmaceutical composition comprising an effective amount of amazonic acid and that is substantially free of cyanide," and "A composition comprising at least 50 mg/ml Peptide A but less than 1 mg/ml each of Peptides B, C, and D (in an example where Peptides A-D are found in a scorpion's toxin and purified Peptide A is therapeutically useful).

Each of the examples offered here illustrates a different facet of the same important principle: patentable functionality and utility can be *added* to a product of nature by *removing* it from its natural context, even without altering the chemical structure of the natural product. It is a principle that should be explicitly articulated in the Guidance and supported by examples, like those above, that discuss the importance of such factors as purity, contaminants, concentration, dosage levels, and side effects that are critical elements of real-world biomedical research but mostly ignored by the hypothetical examples in the Guidance.

This has significant practical implications. A bright-line rule against the patentability of purified natural products would frustrate the very purpose of the patent system, as predicted by the Supreme Court, by destroying the incentive to develop naturally-occurring compounds into approved pharmaceutical products. Under the proposed Guidance, there simply is no incentive for a party to invest the enormous amounts of time and resources necessary to discover, purify, study, and develop natural products—or anything that the Guidance might suggest is too close in structure to a natural product.

If a party nonetheless discovered a natural product that is useful in purified form, like one of those in the above examples, and if the Office insists that only certain structural differences qualify as "markedly different" (contrary to what we propose below in Section V), then one could imagine a scenario where the party would spend its time

and resources looking for structural variants of the natural product solely to satisfy the arbitrary requirements of the Guidance. In one such scenario, the discoverer of a natural product makes a series of slight structural variants of the product and finds that none has appreciably improved usefulness. Paradoxically, variants with larger structural changes that are measurably worse, but still useable, for the intended purpose could be "significantly different" under the Guidance and so patent-eligible. The Guidance would give the discoverer an incentive to either develop the less-effective-but-patentable variant or nothing at all, depending on the specific facts of the situation. Either way, the public good would be better served without the Guidance's distorting effect so that the discoverer would instead have an incentive to develop the purified natural product itself.

In theory, the applicant could rely on other types of claims to protect its investment, but none of these provides the scope or reliability of protection necessary to recoup the applicant's substantial investment in research and development. For example, the applicant might successfully patent a method of manufacturing or purifying the compound, but that could be designed around with relatively little effort and, as such industrial processes are carried out behind closed doors, infringing activity could go undetected. Method of treatment claims using the compound might be patentable, but there is currently great uncertainty in the law as to how and against whom such patents can be enforced. Thus, the availability of patent protection for purified natural products themselves is necessary to incentivize innovators to invest in the research and development required to bring this important class of pharmaceutical to the public.

III. Clarity and Specificity on Examiner's Prima Facie Case of Ineligibility

Next, we urge that the Guidance provide greater specificity as to what the Examiner must assert to meet the prima facie case of ineligibility. While the Training Materials indicate that speculation does not rise to the level of reasonable support for a Section 101 rejection, this is not formally incorporated into the Guidance. In particular, incorporating a specific example drawn from the facts of *Myriad* in the Guidance would guard against vague Examiner rejections and avoid needless appeals. In *Myriad,* the

cDNA claimed by respondents were determined to be patentable under Section 101 by the Supreme Court. The petitioners had unsuccessfully argued that in nature, some viruses make cDNA in their process of reproduction and as a rare side effect, some of these cDNA fragments may have been incorporated into the genome. *Myriad* at 2119, footnote 8. The petitioners did not actually produce any evidence that such process actually produced the specifically claimed sequence. With these facts, the Court found that "[t]he possibility that an unusual and rare phenomenon might randomly create a molecule similar to one created synthetically through human ingenuity does not render a composition of matter non-patentable." *Id.* Thus under *Myriad*, speculation that a sequence might have occurred through some process found in nature was not enough to demonstrate that the end result was indeed naturally occurring. The Office should follow the Supreme Court's decision. If an applicant claims a molecule having a specific sequence, the Examiners should be directed to produce documentation demonstrating that the exact sequence was previously found in nature and not simply an Examiner's speculative argument that the specific sequence could have been produced by a naturally occurring process. Similarly, claims to antibody inventions should not be rejected under Section 101 simply because immunocompromised humans or animals could in theory produce antibodies to the target. The Office should include as part of the Guidance a requirement not to speculate and provide a specific example drawn from *Myriad* directing Examiners to produce written evidence of a naturally occurring sequence or composition and not simply rely on mere possibilities.

IV. "Group Two" Factors Should Be Simplified

The Office sets forth ten factors under "Group Two" to be utilized when analyzing a claim to determine whether the claimed subject matter is "significantly different." These factors should be simplified. For example, at least four of the ten factors are opposites of each other (compare, e.g., f with j; and c with k). Analyses will be simpler with one list of factors, more akin to the *Wands* factors. It is also worth noting that the *Wands* factors were all derived from one case, *In re Wands*, 858 F.2d 731, 737 (1988). Here, the Office has cobbled together a list of phrases taken from a number of cases

that the Office has deemed relevant. If this is the Office's methodology, then it should be made clear that these factors are only exemplary and that the applicant is not required to address all or only these particular factors to the exclusion of other relevant factors. The very nature of our judicial system is that case law evolves and continues to be modified and added. Therefore, applicants should be free to address patentability using other factors that applicants believe are rooted in relevant case law, past or future but were somehow not chosen by the Office.

V. Any Claimed Structural Difference Meets the Markedly Different Test

The Guidance should follow *Myriad* to make clear that the markedly different test can be met by any structural difference between the claimed invention and the product of nature. As discussed above, the *Myriad* Court found that removal of the introns from genomic DNA created patentable cDNA:

> "[T]he lab technician unquestionable created something new when cDNA was made. cDNA retains the naturally occurring exons of DNA, but is distinct from the DNA from which it was derived. As a result, cDNA is not a 'product of nature' and is patent eligible under §101, except insofar as very short series of DNA may have no intervening introns to remove when creating cDNA. In that situation, a short strand of cDNA may be indistinguishable from natural DNA." *Myriad* at 2119.

By drawing the distinction between short strands of genomic sequence that did not have any differences in nucleotide sequence from cDNA, the *Myriad* Court clearly suggested that as long as there is even one difference in the nucleotide sequence, that difference meets the Section 101 patentability requirement. By finding a claimed structural difference, the *Myriad* Court did not need to make an additional inquiry into a difference in function. A would-be infringer could still use the naturally-occurring sequence (without the one nucleotide difference) to avoid infringement. Once Section 101 is satisfied, the Examiner can then proceed to analyze the claims for patentability

under other requirements, such as obviousness. We urge the Office to include, as a specific example, a claim directed to one nucleotide difference from the naturally occurring sequence, to make clear that any claimed structural difference meets the requirement of Section 101.

Thank you for your consideration.

Respectfully,

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