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Subject:Comments

Sir:

Sutherland Asbill & Brennan LLP ("Sutherland") thanks the United States Patent and Trademark Office ("USPTO") for the opportunity to comment on the on its March 4, 2014 Guidance Memorandum ("Guidance"). We are a multi-national firm with an established reputation across our wide range of practice groups spanning an even wider range of industry sectors. As part of our intellectual property practice, we regularly serve Fortune 100, industry leaders, sector innovators, universities and individuals worldwide in prosecuting and litigating important matters, including biotechnological patents, before the USPTO and in the federal courts. It is based on our experience with the patent system and understanding of biotechnology-related industry sectors that we respectfully submit the following comments.

To summarize, we understand that the Guidance was prompted by the Supreme Court's decision in *Association for Molecular Pathology v. Myriad Genetics, Inc.* and represents an attempt by the USPTO improve the examination of claims involving so-called "laws of nature, natural phenomena, and natural products." However, as explained in our comments below, the very analytical framework on which the Guidance is based is fundamentally flawed and must be revised. Specifically, contrary to the framework adopted in the Guidelines: (A) impermissible broaden the scope of judicially-created

exceptions to patentable subject matter; (B) misconstrue Myriad for standing for the proposition that all isolated or purified natural products are patent ineligible subject matter; and fail to meet the constitutionally-based mandate for the USPTO to promote the useful arts and sciences.

I. BACKGROUND

Under Section 101 of the Patent Act, “[w]hoever invents or discovers any new and useful ... composition of matter, or any new and improvement thereof, may obtain a patent therefor...”[1] However, in decisions such as *Bilski*,^[2] *Mayo*^[3], and recently *Myriad*^[4], the Supreme Court has created certain “judicial exceptions” to the statutory broad categories of patent-eligible subject as defined by Congress.

In *Myriad*, the Court addressed two specific questions: (1) “whether a naturally occurring segment of deoxyribonucleic acid (DNA) is patent eligible under 35 U.S.C. § 101 by virtue of its isolation from the rest of the human genome”; and (2) whether “synthetically-created DNA known as complementary DNA (cDNA), which contains the same protein-coding information found in a segment of natural DNA but omits portions within the DNA segment that do not code for proteins” was patent-eligible.^[5] The Supreme Court expressed its conclusions regarding these questions narrowly as follows:

... we hold that a naturally occurring DNA segment is a product of nature and not patent eligible merely because it has been isolated... We merely hold that genes and the information they encode are not patent eligible under §101 simply because they have been isolated from the surrounding genetic material.^[6]

Although the Court concluded that naturally occurring DNA segments are not eligible for patent

protection merely because they have been isolated, it reached the following conclusion as to whether cDNA occurs in nature:

cDNA does not present the same obstacles to patentability as naturally occurring, isolated DNA segments. As already explained, creation of a cDNA sequence from mRNA results in an exons-only molecule that is not naturally occurring cDNA retains the naturally occurring exons of DNA, but it 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.[7]

The Court’s straight-forward reasoning in finding cDNA to be man-made, and thus not a “natural product,” makes no suggestion that a more extensive analysis is to be undertaken to determine whether the cDNA is, in fact, patent eligible subject matter. Additionally, while Myriad Court reiterated that, although laws of nature, natural phenomena, and abstract ideas are long-held exceptions to patentable subject matter, these exceptions are “not without limits.”[8] Specifically, the Court pointed out that no method claims or applications of knowledge were before it, and even emphasized that it is “important to note what is not implicated by this decision.”[9]

In direct contrast to the USPTO’s analysis of the Mayo decision as supporting the Guidelines’ drastic overhaul of patentable subject matter under §101, a careful reading of the decision makes clear that the USPTO has not been charged with expanding existing, limited exceptions to patentable subject matter under §101 to also encompass, e.g., compositions of natural products or methods of treatment or drug administration. Moreover, the Court’s repeated cautionary statements regarding the limitations of its holding would suggest that the Myriad decision was in no way intended to break new ground.

II. THE USPTO’S ANALYTICAL FRAMEWORK IS FUNDAMENTALLY FLAWED

The analytical framework for the Guidance reflects the USPTO's attempt to synthesize a single test for eligibility from several independently distinct U.S. Supreme Court decisions addressing subject-matter eligibility under §101.

The Guidance's analytical framework is based on a three-inquiry analysis, the three inquiries being (1) whether the claim is directed to one of the four statutory categories of patent eligible subject matter, (2) whether the claim recites or involves a judicial exception, and (3) whether the claim as a whole recites something significantly different than the judicial exception.

For purposes of our comments, the first inquiry can essentially be considered as being satisfied based in view of the statutory categories of inventions set forth in §101. The second inquiry is broadly stated; however, the Guidance indicates that a claim is patent eligible (and the analysis is complete) if the claim does not recite or involve a judicial exception. The third inquiry requires determining whether the referenced claim as a whole recites something that is significantly different than the judicial exception.

According to the Guidance, a "significant difference" can be shown in two ways: (1) if the claim recites elements or steps in addition to the judicial exception that "practically apply the judicial exception in a significant way" (e.g., by adding significantly more to the judicial exception); and/or (2) if the claim recites features or steps that demonstrate that the claimed subject matter is markedly different from what exists in nature (and thus not a judicial exception).

In analyzing a claim under this third inquiry, the Guidance additionally sets forth twelve factors

that should be weighed in determining patent eligibility. According to the Guidance, if the majority of the

relevant factors weigh against eligibility, then the claim should be rejected as not being directed to patent eligible subject matter. In weighing the relevant factors, the Guidance states that the weight accorded to each factor will vary based on the relevant facts of the application at issue, but fails to provide any further guidance on how or to what extent the weight of each factor should be varied.

The factors that weigh in favor of patent eligibility are:

(a) the claim is a product claim reciting something that initially appears to be a natural product, but after analysis is determined to be non-naturally occurring and markedly different in structure from naturally occurring products;

(b) the claim recites elements/steps in addition to the judicial exception(s) that impose meaningful limits on claim scope, i.e., the elements/steps narrow the scope of the claim so that others are not substantially foreclosed from using the judicial exception(s);

(c) the claim recites elements/steps in addition to the judicial exception(s) that relate to the judicial exception(s) in a significant way, i.e., the elements/steps are more than nominally, insignificantly, or tangentially related to the judicial exception(s);

(d) the claim recites elements/steps in addition to the judicial exception(s) that do more than describe the judicial exception(s) with general instructions to apply or use the judicial exceptions(s);

(e) the claim recites elements/steps in addition to the judicial exception(s) that include a particular machine or transformation of a particular article, where the particular machine/transformation implements one or more judicial exception(s) or integrates the judicial exception(s) into a particular practical application; and

(f) the claim recites one or more elements/steps in addition to the judicial exception(s) that add a feature that is more than well-understood, purely conventional or routine in the relevant field.

The factors that weigh against patent eligibility are:

(g) the claim is a product claim reciting something that appears to be a natural product that is not markedly different in structure from naturally occurring products;

(h) the claim recites elements/steps in addition to the judicial exception(s) at a high level of generality such that substantially all practical applications of the judicial exception(s) are covered;

(i) the claim recites elements/steps in addition to the judicial exception(s) that must be used/taken by others to apply the judicial exception(s);

(j) the claim recites elements/steps in addition to the judicial exception(s) that are well-understood, purely conventional or routine in the relevant field;

(k) the claim recites elements/steps in addition to the judicial exception(s) that are insignificant extra-solution activity, e.g., are merely appended to the judicial exception(s); and

(l) the claim recites elements/steps in addition to the judicial exception(s) that amount to nothing more than a mere field of use.

For at least the following reasons, the analytical framework set forth in the Guidance is fundamentally flawed and should be replaced or substantially revised.

A. THE "SIGNIFICANTLY DIFFERENT" STANDARD IMPOSED
BY THE GUIDELINES IS NOT SUPPORTED BY LEGAL PRECEDENT

The Guidance characterizes the Myriad decision as "a reminder that claims reciting or involving natural products should be examined for a marked difference under Chakrabarty." According to the Guidance, Myriad reaffirms Chakrabarty's purported holding that a claimed product qualifies as patent eligible subject matter if it is a non-naturally occurring product of human ingenuity that is markedly different from naturally occurring products. Thus, the USPTO interprets Chakrabarty to require that a patent eligible product is both non-naturally occurring and is markedly different from any naturally occurring product used to produce the non-naturally occurring product.

The USPTO's interpretation of Chakrabarty in view of Myriad (as allegedly requiring that a non-naturally occurring product also have a marked difference from any naturally occurring product) forms the basis for the phrasing of the third inquiry as "whether the claim as a whole recites something significantly different than the judicial exception(s)" (e.g., a natural product). That is, the USPTO appears

to believe that the Mayo decision provides a basis for extending its interpretation of Chakrabarty to laws of nature and natural phenomena. This interpretation of Mayo is also incorrect for at least the reasons discussed further below.

In line with the USPTO's improper interpretation of Mayo, factors (a) and (g) are drawn to distinguishing non-naturally occurring products from natural products. According to the Guidance, these factors "concern the question of whether something that initially appears to be a natural product is in fact non-naturally occurring and markedly different from what exists in nature, i.e., from naturally occurring products" (emphasis in original). In the USPTO's view, Myriad merely clarifies that not every change to a natural product will result in a marked difference (and that the mere recitation of particular words [e.g., "isolated" or "purified"] in the claim does not automatically confer eligibility).

The USPTO's interpretation of Chakrabarty cannot be reconciled with the Myriad Court's reasoning for holding that Myriad's cDNA claims are directed to patent eligible subject matter. As noted supra, the Court did not find that cDNA derived by removing introns (non-coding regions) from the underlying BRCA1 and BRCA2 genes is markedly different from the underlying genes. Instead, the Court found that – to the extent that it represents a spliced version of DNA exons – cDNA is simply not a natural product, thus ending its inquiry and finding cDNA to be patent eligible subject matter under §101. As discussed further below, it is clear that the U.S. Supreme Court's finding of cDNA being patent-eligible subject matter is based on a materially different interpretation of Chakrabarty than that the USPTO's interpretation relied on as a basis for the Guidance.

1. CHAKRABARTY DOES NOT SUPPORT THE NEW "MARKEDLY DIFFERENT" STANDARD

In *Chakrabarty*, the issue was whether a genetically engineered bacterium having the capacity to degrade oil is a "manufacture" or "composition of matter" within the meaning of §101. The U.S. Supreme Court held that this bacterium is "a nonnaturally occurring manufacture or composition of matter," and thus is patent eligible subject matter under §101.[10] In arriving at this holding, the Court considered the bacterium's characteristics. Specifically, in contrasting the *Chakrabarty* bacterium to the patent ineligible mixed bacterial culture at issue in *Funk Brothers*, the Court stated that "the patentee has produced a new bacterium with markedly different characteristics from any found in nature." [11] Thus, the Court recognized that the genetically engineered bacterium had markedly different characteristics, i.e., the additional plasmids and capacity to degrade oil, from its naturally occurring counterpart. The Court determined that these markedly different characteristics showed that the bacterium is not a natural product (i.e., "not nature's handiwork"). [12]

However, the Court did not articulate a test that would require a claimed product to be both non-naturally occurring and markedly different from what exists in nature. Instead, the Court's consideration of the bacterium's characteristics merely informed the Court in making the ultimate determination of whether the bacterium is a non-naturally occurring product. That is, the Court did not find a priori that the bacterium is non-naturally occurring and then determine whether it was markedly (significantly) different from the naturally occurring bacterium from which it was derived. This distinction is very important when considering the holding of the *Myriad* decision.

2. MYRIAD DOES NOT SUPPORT THE NEW "MARKEDLY DIFFERENT" STANDARD

The Myriad decision cannot be interpreted as supporting an eligibility test that requires an otherwise patent eligible product to be both non-naturally occurring and markedly different from the natural product from which it was derived. In Myriad, the U.S. Supreme Court clearly held "that genes and the information they encode are not patent eligible under §101 simply because they have been isolated from the surrounding genetic material."^[13] Thus, the Court's narrow holding is specifically directed to the isolation of genetic material.

Genetic material poses a unique situation, because it may be the genetic information encoded by the genetic material that provides value to the isolated product (as opposed to isolation of the genetic material). Therefore, the Court cautioned against a broad reading and application of the Myriad decision.^[14] However, even if read broadly, the Myriad decision at most supports the proposition that isolation alone may be (but is not necessarily) insufficient to confer non-natural status to a natural product (depending, for example, on the characteristics of the natural product and the changes that occur during isolation).

The Court did not endorse a "markedly different" standard based on Chakrabarty. The Myriad decision discusses Chakrabarty, stating that "the Chakrabarty bacterium was new 'with markedly different characteristics from any found in nature,' due to the additional plasmids and resultant 'capacity for degrading oil.'^[15] However, this statement of fact is the only statement in the Myriad decision that makes reference to a "marked" (i.e., significant) difference. The Court does not find or even address whether isolated genomic DNA or cDNA, derived from the genomic DNA, is markedly or significantly different from the underlying (BRCA1 and BRCA2) genes. Therefore, the Myriad decision cannot reasonably be interpreted as supporting the USPTO's position that Chakrabarty requires a patent eligible product to be both non-naturally occurring and markedly different from what exists in nature.

The USPTO appears to have arrived at its "markedly different" standard by misinterpreting and mischaracterizing the holding of Myriad. In interpreting Myriad, the USPTO's fundamental flaw is finding that Myriad's genomic DNA claims are directed to non-naturally occurring products due to isolation, but that these non-naturally occurring products (i.e., isolated genomic DNA) are still not patent eligible subject matter. To attempt to reconcile this interpretation with the Court's actual holding in Myriad, the USPTO asserts that Court found that isolation is not a marked difference.

Contrary to the USPTO's analysis, the Court does not find that the recitation of "isolated" in Myriad's genomic DNA claims confers non-natural status to the genomic DNA. Instead, the Court found that Myriad's claims are not directed to a non-naturally occurring chemical product that results from isolation. Specifically, the Court expressly stated that "[n]or are Myriad's claims saved by the fact that isolating DNA from the human genome severs chemical bonds and thereby creates a non-naturally occurring molecule. Myriad's claims are simply not expressed in terms of chemical composition, nor do they rely in any way on the chemical changes that result from isolation of a particular section of DNA."^[16] Instead, the Court reads past the "isolated" language of Myriad's claims to find that "the claims understandably focus on the genetic information encoded in the BRCA1 and BRCA2 genes."^[17] Thus, the Court ignores the "isolated" language to hold that Myriad's claims are actually (in fact) directed to natural products (more specifically, genes and the information they encode). The Court does not determine whether isolation represents a marked (significant) difference.

The Myriad decision also does not discuss whether cDNA has markedly or significantly different characteristics from the underlying BRCA1 and BRCA2 genes. Instead, the Court found that that the

"creation of a cDNA sequence from mRNA results in an exons-only molecule that is not naturally-occurring." [18] According to the Court, "the lab technician unquestionably creates something new when

cDNA is made. . . . As a result, cDNA is not a 'product of nature' and is patent eligible under §101." [19] The Court made no finding that cDNA has markedly or significantly different characteristics than the underlying BRCA1 and BRCA2 genes.

Further, cDNA at least arguably does not have markedly different characteristics from the underlying BRCA1 and BRCA2 genes, because the genes and cDNA encode the exact same proteins. Only non-functional sequences (non-coding introns) are removed to create cDNA. Conversely, even if the removal of introns is a significant structural difference, the Court did not find this, nor rely on the significance of this difference, in holding that the cDNA claims are directed to patent eligible subject matter. Instead, the Myriad decision simply recognized that this cDNA is "unquestionably" new (i.e., non-natural) due to the removal of introns, ending its eligibility inquiry.

3. THE COURT ONLY REQUIRED A "NON-NATURAL" PRODUCT

As discussed supra, the correct inquiry as to subject matter eligibility under Mayo and Chakrabarty is whether the claim as a whole is directed to a naturally occurring or non-naturally occurring product. If the claim as a whole is directed to a natural product, the claim is not directed to patent eligible subject matter. Otherwise, if the claim as a whole requires something that is non-natural, the claim is directed to patent eligible subject matter. According to Myriad, claims that appear to be mere drafting attempts to claim naturally occurring genes must be further analyzed to determine whether they, in fact, are only directed to the genetic information encoded by those genes.

Thus, under a proper interpretation of the Myriad and Chakrabarty decisions, the Guidance's

third inquiry of whether the claim as a whole recites something significantly different than the judicial exception is not supported. Additionally, factors (a) and (g) of the third inquiry are not supported by these decisions, because they require an eligible product to be both non-naturally occurring and markedly different in structure from naturally occurring products. Regarding the Guidance's requirement

that the marked difference must be based on structure, Chakrabarty clearly does not support this formulation as the markedly different characteristics of the Chakrabarty bacterium were based at least as

much on function (capacity to degrade oil) as structure (additional plasmids).[20] In any event, markedly

different (structural and/or functional) characteristics merely inform whether a product is non-naturally occurring or not. They are not a separate requirement for eligibility.

B. The Guidance Provides No Useful Guidance in Its Current Form

The USPTO's flawed interpretation of Myriad and Chakrabarty results in the Guidance's analytical framework being highly susceptible to arriving at improper eligibility determinations, and thus will be unreliable and inconsistently applied in practice. In Part III, the Guidance provides Examples A-H, which include sample claims and analyses. However, to illustrate that the Guidance's analytical framework is unworkable in its current form, one only needs to evaluate Myriad's cDNA claims under the analytical framework by suspending prior knowledge that these claims were found to be directed to patent eligible subject matter by the U.S. Supreme Court.

1. The Analytical Framework Would Find cDNA To Be Patent Ineligible

The Guidance does not analyze Myriad's cDNA claims using its analytical framework. Instead, the

Guidance acknowledges that such cDNA claims are directed to patent eligible subject matter, stating that

"cDNA having a nucleotide sequence that is markedly different from naturally occurring DNA is eligible subject matter, even though the process of making cDNA is routine in the biotechnology art." However, if we suspend our prior knowledge that such cDNA claims should be found to be directed to patent eligible subject matter in accordance with Myriad, it is very likely that Myriad's cDNA claims would be found to be patent ineligible subject matter using the Guidance's analytical framework.

One of Myriad's cDNA claims recites "[t]he isolated DNA of claim 1, wherein said DNA has the nucleotide sequence set forth in SEQ ID NO:1." SEQ ID NO:1 sets forth the cDNA sequence that codes for the BRCA1 protein. *Id.* Under the Guidance's analytical framework, it is clear that the claim is directed to a composition of matter and recites something that initially appears to be a natural product, because the claim is directed to isolated DNA. Thus, the first and second inquiries would not prevent this claim from being analyzed under the third inquiry and associated factors. Importantly, the second inquiry would not resolve the issue of whether this claim is directed to patent eligible subject matter, because the Guidance generally identifies "nucleic acids" as appearing to be natural products and states that further analysis under the third inquiry is required "[i]f there is any doubt as to whether the claim recites a judicial exception (e.g., the claim recites something similar to a natural product)" (emphasis in original).

Thus, according to the Guidance, the controlling inquiry is whether the claim as a whole recites something significantly different than a natural product. To answer this question, the relevant factors must be identified and balanced. The only relevant factors are factors (a) and (g) because the claim is a product claim and does not recite elements in addition to the apparent natural product. As discussed in the Guidance, factors (a) and (g) concern the question of whether the claim as a whole recites something

that initially appears to be a natural product, but is in fact (i) non-naturally occurring, and (ii) markedly different from what exists in nature.

Before applying factors (a) and (g), it should be noted that this claim does not require any weighing of factors as factors (a) and (g) are mirror images to each other. However, the fact that this claim does not require weighing factors has the potential to cause confusion among examiners, because the Guidance calls for all relevant factors to be weighed. Thus, it is easy to envision some examiners making the mistake of weighing irrelevant factors against eligibility, because the claim does not recite any additional steps/elements in addition to the apparent natural product. However, even assuming that

factors (a) and (g) are recognized as the only relevant factors and thus weighing of factors is not required,

the Guidance's analytical framework is

highly susceptible to arriving at an incorrect eligibility determination.

For instance, applying factors (a) and (g) to the Myriad cDNA claim (by suspending prior knowledge that this claim is directed to patent eligible subject matter), one could naturally reason that the cDNA is not significantly different from the naturally occurring BRCA1 gene. Specifically, it would be reasonable to find under the Guidance's analytical framework that factor (a) is not satisfied and factor (g) is satisfied, resulting in a determination of ineligibility for isolated cDNA. Specifically, regarding factor (a), cDNA is understood in the art to mean an isolated DNA that codes for the exact same protein as the underlying gene. The difference between the isolated cDNA at issue and the BRCA1 gene is that the cDNA has been isolated from the genomic DNA and non-functional sequences (non-coding introns) have been removed from the cDNA.

While cDNA is structurally different from genomic DNA, there is no particular reason to find that

this structural difference is significant because cDNA has the exact same function as the naturally occurring BRCA1 gene. They both encode the exact same protein. Consistent with the Guidance's analytical framework, the minor structural differences of isolation and removal of non-functional regions of the BRCA1 gene taken together with the lack of any functional difference between the isolated cDNA and the BRCA1 gene fail to demonstrate that the isolated cDNA is markedly different from what exists in nature (i.e., the BRCA1 gene). Indeed, it is an exact DNA copy of an mRNA molecule. Factor (g) would then be satisfied because the cDNA is not markedly different from the BRCA1 gene or the mRNA transcript for the same reasons.

Thus, the Guidance's analytical framework can be faithfully applied to determine that Myriad's cDNA claims are patent ineligible subject matter, contrary to Myriad's holding. For at least this reason, the Guidance's analytical framework is unworkable in practice as it can be correctly applied to find ineligibility.

3. THE GUIDANCE IGNORES STRUCTURAL AND FUNCTIONAL DIFFERENCES

The analysis discussed above for determining that Myriad's cDNA claims are directed to patent ineligible subject matter is essentially the same analysis that the Guidance applies in Example E. Example E includes claim 1 that is directed to "[a] pair of primers, the first primer having the sequence of SEQ ID NO: 1 and the second primer having the sequence of SEQ ID NO: 2." The Guidance explains that SEQ ID NOs: 1 and 2 are naturally occurring DNA sequences found on a human chromosome. The Guidance recognizes that "the term 'primer' has an ordinary meaning in the art as being an isolated nucleic acid that can be used as a starting point for DNA synthesis."

In fact, a primer is understood to be a relatively short single-stranded nucleic acid molecule for priming DNA synthesis (typically for purposes of amplification) through hybridization to target DNA. With respect to the pair of primers in Example E, they would be understood to be short DNA molecules that can be used to flank/frame a region of genomic DNA to be synthesized and amplified. Thus, this pair of primers represents a combination of naturally occurring sequences that are naturally separated by an intervening DNA sequence (which intervening DNA sequence will predominantly form the target sequence to which the primers are designed to hybridize for purposes of synthesis and amplification). The primers, when taken together, are not very different from cDNA.

The main difference between cDNA derived from naturally occurring genomic sequences and a pair of primers based on naturally occurring genomic sequences is that the cDNA molecule has covalent bonds that link multiple naturally separated sequences together on a single molecule whereas the pair of primers represents two naturally separated sequences that are not covalently bonded together. However, consistent with *Myriad*, the analysis of a pair of primers should not turn on the presence or absence of covalent bonds. Whereas it might be reasonable to characterize a single primer having a naturally occurring sequence as nothing more than isolated genomic material, a pair of primers represents something much closer to cDNA. It is unclear whether a court would decide that such a pair of primers is patent eligible subject matter, but this should be left to the courts.

Regardless of whether a court would hold that these primers are patent eligible subject matter, the Guidance's factor (a) analysis for this claim does not stand up to reason and is highly arbitrary. Specifically, the Guidance states that "even though isolation structurally changes a nucleic acid from its natural state, the resultant difference (e.g., 'broken' bonds) is not significant enough to render the isolated nucleic acid markedly different, because the genetic structure and the sequence of the nucleic

acid has not been altered." However, the claim as a whole requires a combination of two primers whose sequences are naturally separated from each other on the human chromosome. Additionally, the Guidance ignores that primers are single-stranded in order to hybridize to target DNA whereas genomic DNA (and cDNA) typically exists in double-stranded form. These structural differences between a pair of primers and the naturally occurring genomic sequences must at least be considered before the pair of primers can be dismissed as not being different from naturally occurring genomic DNA, especially because these structural differences result in significant functional differences between a pair of primers and genomic DNA.

Regarding function, the Guidance's factor (a) analysis states, "[f]urther, the first and second primers have the same function as their natural counterpart DNA, i.e., to hybridize to their complementary nucleotide sequences." This finding of identical functionality between a pair of primers and the underlying genomic DNA is completely arbitrary and inconsistent with the significantly different function to which the Guidance points in other portions of Example E. It is a scientific fact that all single-stranded DNA hybridizes to complementary DNA under appropriate conditions. However, hybridization is not the function of genomic DNA per se.

Rather, genomic DNA exists to store genetic information. This fact was central to Myriad's holding "that genes and the information they encode are not patent eligible under §101 simply because they have been isolated from the surrounding genetic information." [21] Primers do not encode any significant amount of genetic information due to their small size. Rather, as shown in Example E, primers have a much different function than the storage of genetic information. Specifically, the Guidance states that a primer "can be used as a starting point for DNA synthesis," and includes claim 2 in which the primers are used in a PCR amplification method. Neither of these related functions of primers are inherent to genomic DNA. Yet the Guidance summarily dismisses the pair of primers as having the same

function as their natural counterpart DNA. This analysis simply does not stand up to reason.

For at least these reasons, it is clear that the Guidance's analytical framework is unworkable in its current form, because it is very susceptible to arriving at incorrect eligibility determinations and very susceptible to arbitrary application. To be clear, the Guidance's analytical framework can arbitrarily be made to conclude that Myriad's cDNA claims are directed to patent eligible subject matter, but regardless it should not be able to be (at least equally) reasonably and faithfully applied to arrive at the opposite conclusion. Further, the Guidance only arrives at an ineligibility determination for a pair of primers by ignoring structural and functional differences between the primers and genomic DNA. Thus, the analytical framework is unworkable in its current form.

C. FUNK BROTHERS AND MAYO ALSO DO NOT SUPPORT THE
SEPARATE "MARKEDLY DIFFERENT" STANDARD SET FORTH IN THE GUIDANCE

Neither Funk Brothers itself nor the Myriad decision's discussion of Funk Brothers supports a requirement that a claimed product be markedly (significantly) different from what exists in nature. The Guidance describes the mixed bacterial culture inoculant at issue in Funk Brothers in Example D. The Guidance even acknowledges that the Myriad Court characterized this mixed bacterial culture inoculant as being patent ineligible subject matter on the basis that "the patent holder did not alter the bacteria in any way."^[22] As this finding suggests, neither Myriad nor Funk Brothers found that the mixed bacterial culture inoculant represented a non-naturally occurring product that was insufficiently different from the naturally occurring bacteria to confer eligibility to the claim. To the contrary, both decisions simply characterize the bacteria as not being altered in any way, and thus being directed to a natural product.

As stated in Funk Brothers, "[t]he combination of species produces no new bacteria, no change in the six species of bacteria, and no enlargement of their range of utility. . . . Their use in combination does not improve in any way their natural functioning." [23] Thus, Funk Brothers suggests a much lower standard for determining eligibility than the markedly (significantly) different standard set forth in the Guidance. Specifically, Funk Brothers suggests that a natural product that has been changed in any way would be patent eligible subject matter. Further, Funk Brothers suggests that a combination of natural products with an improved or different function would be patent eligible subject matter, even if there is no change to any of the individual natural products.

The Guidance does not directly address the possibility that function alone may confer eligibility to a combination of natural products. While the Guidance bases Example D on Funk Brothers, it does not attempt to address a combination of naturally occurring bacteria (in which each individual bacterial strain is not altered in any way) that have a different functionality from their natural functionality. For instance, an appropriate example would be whether the mixed bacterial culture becomes patent eligible subject matter if the combination of bacteria was discovered to have the capacity to degrade oil (when no individual bacterial strain has this capacity). However, Example C of the Guidance appears to show that the USPTO would not consider this mixed bacterial culture with the new capacity to degrade oil to be patent eligible subject matter based on its treatment of gunpowder, which is further discussed below.

1. EXAMPLE C MISINTERPRETS FUNK BROTHERS

Example C includes a single claim directed to a fountain-style firework that comprises (a) a

sparkling composition, (b) calcium chloride, (c) gunpowder, (d) a cardboard body, and (e) a plastic ignition

fuse. The Guidance indicates that the claimed fountain-style firework is patent eligible subject matter.

However, the Guidance's analysis is almost completely superfluous, and absent assigning some factors more weight (without any indication for how to do so), results in this fountain-style firework barely

qualifying as patent eligible subject matter. This clearly illustrates that the Guidance's analytical

framework merely pays "lip service" to analyzing a

claim as a whole, contrary to longstanding patent principles.

The Guidance indicates that this claim cannot be found to be directed to patent eligible subject matter under the second inquiry (of whether the claim recites or involves a judicial exception), because

(i) calcium chloride is a naturally occurring mineral, and (ii) gunpowder is a mixture of naturally occurring saltpeter, sulfur and charcoal. Instead, in order to find that a fountain-style firework is patent eligible

subject matter, the Guidance indicates that all factors

(a)-(l) are relevant, and therefore must be analyzed and balanced to determine eligibility.

Example C illustrates several flaws in the analytical framework. For instance, this Example clearly shows that the second inquiry is not intended to be applied to the claim as a whole, defying

longstanding patent principles, because the Guidance requires analyzing a fountain-style firework (which

is clearly not a natural product) for whether it includes any naturally occurring components. Thus, the

Guidance proceeds to the third inquiry of whether the claim as a whole recites something significantly

different than the natural products. While this answer is obvious as a fountain-style firework is

significantly different from what exists in

nature, Example C proceeds to analyze every factor.

According to Example C, factors (b)-(d) are satisfied and factors (h), (i), (k), and (l) are not satisfied, which results in seven factors weighing towards eligibility. Conversely, according to Example C, factors (a), (e), and (f) are not satisfied and factors (g) and (j) are satisfied, which results in five factors that weigh against eligibility. Thus, absent assigning any additional weight to factors for eligibility (the Guidance providing no guidelines for assigning such additional weight to factors), a fountain-style firework would just barely qualify as patent eligible subject matter. This defies common sense.

Perhaps more importantly, Example C shows that the USPTO does not consider gunpowder to be patent eligible subject matter as the factor (a) analysis indicates that "calcium chloride and gunpowder as recited in the claim are not markedly different from what exists in nature." The USPTO's position regarding gunpowder is confirmed by the Training Slides for subject-matter eligibility. However, the USPTO's position is clearly contrary to the recognized historical significance of gunpowder. For instance, gunpowder has long been celebrated as one of the "Four Great Inventions" from ancient China.

Yet the Guidance's analytical framework results in gunpowder being patent ineligible subject matter despite its clear historical significance as a truly important invention. According to the Guidance, discovering that a mixture of naturally occurring saltpeter, sulfur and charcoal has the capacity to explode is not markedly different from what exists in nature. It is difficult to believe that this result was mandated by the U.S. Supreme Court in deciding *Myriad*. Instead, to arrive at this result, the USPTO clearly misinterpreted *Funk Brothers* as meaning that any mixture of natural products is patent ineligible subject matter regardless of function.

2. THE U.S. SUPREME COURT CLEARLY

DELINEATED BETWEEN MYRIAD AND MAYO

The Guidance's analytical framework conflates *Myriad* and *Mayo* contrary to the U.S. Supreme Court's clear delineation of these decisions. As discussed above, the Guidance states that a significant difference can be shown when the claim includes elements or steps in addition to the judicial exception (e.g., law of nature) that practically apply the judicial exception in a significant way, e.g., by adding more to the judicial exception. Factors (b)-(f) and (h)-(l) are primarily directed to determining whether the claim is a practical application of a judicial exception. The USPTO has derived this portion of the Guidance's analytical framework from the *Mayo* decision (as well as its discussion of prior eligibility tests, including the Federal Circuit's "machine-or-transformation test," which has been relegated to "an important and useful clue" by the U.S. Supreme Court in *Bilski v. Kappos*, 561 U.S. (2010)). However, by conflating *Mayo* with *Myriad*, the Guidance attempts to apply *Mayo* to claims that are not directed to applications of knowledge (e.g., natural laws).

The U.S. Supreme Court clearly distinguished between claims drawn to natural products and claims drawn to applications of knowledge. In *Mayo*, the Court recognized that a process claim directed to an application of a law of nature is patent eligible subject matter as long as the claimed "process has additional features that provide practical assurance that the process is more than a drafting effort designed to monopolize the law of nature itself." See slip op. at 8-9. In discussing whether the claimed process at issue is a practical application of a law of nature, the Court stated that "[t]he cases most directly on point are *Diehr* and *Flook*, two cases in which the Court reached opposite conclusions about the patent eligibility of processes that embodied the equivalent of natural laws." [24] *Diamond v. Diehr*, 450 U.S. 175 (1981), and *Parker v. Flook*, 437 U.S. 584 (1978), are both directed to process claims that recite mathematical equations. *Diehr* and *Flook* did not involve natural products.

In *Mayo*, the Court nowhere analogizes the claimed products of *Chakrabarty* and *Funk Brothers* to the claimed process at issue. Thus, the Court found no need to place *Mayo*, *Chakrabarty*, and *Funk*

Brothers under a single analytical framework. Instead, in *Myriad*, the Court clearly indicated that *Mayo* is not implicated by its decision, stating that "this case does not involve patents on new applications of knowledge about the BRCA1 and BRCA2 genes." [25] Indeed, the *Myriad* decision does not even discuss *Mayo*, which was decided in the prior year. Thus, the U.S. Supreme Court clearly delineated between the issues decided in *Myriad* and *Mayo*.

Yet the Guidance places both *Myriad* and *Mayo* under the same analytical framework. This is clearly not supported by either decision and is contrary to the Court's clear delineation between analyzing claims drawn to natural products and applications of knowledge. By conflating these two distinct decisions (and the most relevant precedent leading to these two decisions), the Guidance muddles the issues addressed by these decisions. This is clear from the inconsistent and arbitrary analyses set forth in the Guidance's Examples discussed above and below.

III. THE GUIDANCE'S REMAINING EXAMPLES

Because the Guidance's analytical framework is fundamentally flawed, the Guidance's remaining examples are either merely representative of claims at issue in one of the U.S. Supreme Court's decisions discussed above, provide no meaningful distinction from such claims, or are contrary to these decisions, rendering the examples of limited practical use. Examples A, B, and D-G of the Guidance are discussed below.

A. Example A

Example A includes claims 1 and 2. Claim 1 is clearly directed to a naturally occurring bacterial plasmid and claim 2 is directed to a genetically engineered bacterium that is non-naturally occurring due to additional plasmids and resultant additional functionality. Thus, claim 2 is squarely based on Chakrabarty. The Guidance's analytical framework is unnecessary to analyze these claims. Specifically, the naturally occurring plasmid of claim 1 has no possibility of being markedly different from what exists in nature, because the claim encompasses exactly what is in nature. On the other hand, because claim 2 is basically the Chakrabarty bacterium, it is clearly non-naturally occurring and markedly different from what exists in nature, as this was exactly what was found in Chakrabarty. Thus, Example A is of limited practical use in analyzing claims that materially depart from the issue decided in Chakrabarty.

B. Example B

Example B illustrates that the "markedly different" standard of factors (a) and (g) is unworkable in practice as it makes no usable, concrete conclusion as to when a purely structural difference rises to the level of a marked different and is contrary to both Myriad and Mayo. Claim 1 is merely based on a broad interpretation of Myriad, and thus does not show why the Guidance's analytical framework is necessary or useful. Further, for reasons discussed above, this broad interpretation of Myriad fails to consider that Myriad was decided in the context of genetic information and cautioned against extending its holding to other modified (e.g., isolated) natural products.

Claim 2 illustrates that the Guidance's markedly different standard is of no practical use and/or contrary to Myriad. Claim 2 is directed to "[p]urified 5-methyl amazonic acid." According to Example B, 5-methyl amazonic acid is a non-naturally occurring derivative of amazonic acid,

and (unlike amazonic acid) is useful for stimulating hair growth (in addition to treating breast and colon cancers). The Guidance indicates that only factors (a) and (g) are relevant, and factor (a) is satisfied. Thus, claim 2 is directed to patent eligible subject matter.

In this respect, the Guidance states that "5-methyl amazonic acid is markedly different than naturally occurring amazonic acid (because of the addition of the 5-methyl group), and this structural difference has resulted in a functional difference (5-methyl amazonic acid stimulates the growth of hair in addition to treating cancer.)" Thus, Example B makes clear that a structural difference that results in a completely new use for a compound is a marked difference. However, in practice, it would not be expected that most minor structural differences result in a completely new use for a compound. Thus, claim 2 of Example B offers limited practical guidance.

The more relevant questions (not specifically addressed in the Guidance) include whether (i) 5-methyl amazonic acid would still be deemed patent eligible subject matter if the structural difference did not result in any difference in function, or (ii) 5-methyl amazonic acid would still be patent eligible subject matter if the structural difference only slightly improved the known function of amazonic acid. To the extent that the Guidance addresses these questions, the answers appear to be "no" or "maybe," respectively. Specifically, the Guidance states that, "[w]hile a functional difference is not necessary in order to find a marked difference, the presence of a functional difference resulting from the structural difference makes a stronger case that the structural difference is a marked difference."

Assuming that derivatizing amazonic acid to have a 5-methyl group is meant to represent a very minor structural difference, it appears that the Guidance is implying that this structural difference alone would not be enough to be a marked difference. If this is the case, the Guidance should explain the USPTO's position on how this finding is consistent with Myriad's holding that cDNA is patent eligible

subject matter. As previously explained, the U.S. Supreme Court did not identify, nor rely on, any functional difference between the cDNA and the underlying BRCA1 and BRCA2 genes to arrive at its holding. Further, the Court acknowledged that cDNA is derived from the underlying genes, stating that "cDNA retains the naturally occurring exons of DNA, but it is distinct from the DNA from which it was derived." The same reasoning applies to derivatives of naturally occurring chemicals that have no functional difference from their natural counterparts.

If it is instead the USPTO's position that any minor chemical/structural difference (except isolation or purification) is a marked difference, then the requirement for a "markedly different" structure in factor (a) appears meaningless and contrary to the ordinary meaning of "markedly," as any chemical/structural difference would represent a marked difference. Further, Example B provides no guidance on whether the combination of minor structural and functional differences rises to the level of a marked difference.

Moreover, Example B's analysis of claim 3 is contrary to Mayo's finding that "a typical patent on a new drug or a new way of using an existing drug" are particular applications of natural laws. Specifically, claim 3 is directed to a method of treating colon cancer that comprises administering a daily dose of about 0.75 to 1.25 teaspoons of purified amazonic acid to a patient suffering from colon cancer for a period of time from 10 days to 20 days. According to Example B, the Applicant has discovered that amazonic acid is useful to treat colon cancer. Thus, this is clearly a new use.

The Guidance indicates that factors (b)-(f) and (h)-(l) are relevant. In this regard, the Guidance's finding that this claim is directed to patent eligible subject matter turns on the fact that the claim recites a particular dosage and treatment period. While a particular dosage and treatment period can be considered for purposes of showing a practical application, the Guidance

essentially ignores the fact that amazonic acid is being used in a new way (to treat colon cancer). As discussed above, the U.S. Supreme Court addressed this issue in Mayo. As stated by the Court, "a new way of using an existing drug" is a particular application. Thus, to the extent that the Guidance suggests otherwise, the Guidance is contrary to Mayo. Unless this issue is clarified, claim 3 of Example B is of little practical use.

C. Example D

Example D is directed to the representative claim discussed in Funk Brothers. Thus, Example D does not apply the Guidance's analytical framework to anything but a claim that has already been held patent ineligible by the U.S. Supreme Court. Thus, Example D is of little practical use and does not show why the Guidance's analytical framework is useful or necessary.

D. EXAMPLE E

Claim 1 of Example E is discussed above. Example E also includes claim 2 directed to a method of amplifying a target DNA sequence using the pair of primers of claim 1. The heating and cooling steps of claim 2 show that it is a conventional polymerase chain reaction (PCR) method known in the relevant art. The Guidance indicates that this claim is directed to patent eligible subject matter. This is clearly the correct result.

However, the Guidance's analysis is internally inconsistent and inconsistent with other examples. Claim 2 requires the use of Taq polymerase and a plurality of free nucleotides comprising adenine, thymine, cytosine and guanine. In addition to the primers, the Guidance states that "Taq polymerase is a naturally occurring bacterial enzyme, and adenine, thymine, cytosine and guanine are

naturally occurring chemicals." The Guidance indicates that factors (b)-(f) and (h)-(l) are the relevant factors. The Guidance finds that the heating and cooling steps (which contain a number of limitations that narrow the scope of the claim) are important to showing that this claim as a whole recites something significantly different from the natural products.

To arrive at this result, the Guidance refers to Taq polymerase in several factors as a limitation to the claim that is important to showing that it recites something significantly different from the natural products. However, in other examples, the Guidance does not consider the alleged natural products as being pertinent limitations and numerous factors explicitly require only evaluating elements/steps in addition to the judicial exception(s). Thus, these factors instruct examiners to ignore any role of a natural product (or other judicial exception) in limiting a claim. This is contrary to the longstanding patent principle of considering a claim as a whole.

Conversely, in considering Taq polymerase as a material limitation to the claim, the Guidance does not explain why the pair of primers is not a limitation in the claimed method that should be considered in analyzing the claim for eligibility. Specifically, the claim does not preclude others from amplifying the target DNA using other primer pairs. It is internally inconsistent to consider only one natural product and not the other (alleged) natural products recited in the claim.

Thus, the Example E analysis is internally inconsistent and inconsistent with other examples, rendering Example E of little practical use. This results from the Guidance failing to consider the claim as a whole. The claim as a whole is directed to an amplification method using a particular pair of primers. The amplification method does not occur in nature and requires human intervention to perform. Thus, such an amplification method is clearly patent eligible subject matter when the claim is considered as a whole.

E. Example F

The claim of Example F is too narrowly drafted to be of practical use, especially because the exemplary analysis raises more questions than it answers. The claim of Example F is directed to a method for determining whether a human patient has degenerative disease X that includes, among other steps, the step of "determining whether misfolded protein ABC is present in the blood sample, wherein said determining is performed by contacting the blood sample with antibody XYZ and detecting whether binding occurs between misfolded protein ABC and antibody XYZ using flow cytometry, wherein antibody XYZ binds to an epitope that is present on misfolded protein ABC but not on normal protein ABC."

The Guidance states that "the claim recites judicial exceptions, e.g., the correlation between the presence of misfolded protein ABC in blood and degenerative disease X is a natural principle, and the blood and protein ABC are both natural products." However, the Guidance further indicates that "[a] review of the specification indicates that antibody XYZ does not exist in nature, and is not purely conventional or routine in the art (as it was newly created by the inventors)." The Guidance indicates that factors (a) and (g) are not relevant, but the remaining factors are relevant and show that the claim is directed to patent eligible subject matter. This is clearly the correct result.

However, most of the analysis is superfluous and raises more questions than it answers. For example, in Example F, antibody XYZ is clearly non-naturally occurring and markedly different in structure from naturally occurring antibodies as the Guidance states that "it was newly created by the inventors."

Thus, a claim to the antibody itself would clearly be patent eligible subject matter under factor (a). It is unclear why the Guidance performs a more in-depth analysis if a method claim applies a patent eligible antibody. Additionally, at least because the specific method is limited to a diagnostic application (and/or requires flow cytometry for detection), it is unnecessary for the USPTO to further speculate in the Guidance as to whether a method claim applies to patent-eligible subject matter.

Regardless, the exemplified claim is too narrowly drafted to be of any practical use. Specifically, the Guidance does not indicate what elements/steps are necessary or unnecessary for determining patent eligibility. Due to the narrowly drafted claim of Example F, it appears that the Guidance's analytical framework is not even necessary to arrive at the finding of patent eligible subject matter.

F. Example G

Example G is of little practical use because Example G is premised on the fact that claims 1 and 2 are merely directed to something that is well-understood, purely conventional and routine in the relevant art. Specifically, Example G states that "[i]t is well-understood, purely conventional and routine in the art of treating mood disorders to expose a person to white light in order to alter their neuronal activity and mitigate mood disorders." Claims 1 and 2 merely claim this method. Claim 3 is a practical application of the well-known natural correlation because it is narrowly drawn.

However, in practice, claims based on the discovery of new natural correlations are of much more significance. Thus, if Example G was modified so that the natural correlation between white light and mitigating mood disorders was newly discovered, the important question would be whether claims 1 and 2 are directed to patent eligible subject matter. The other question that Example G raises is whether

the discovery of a naturally occurring drug to be used in a completely novel treatment method would not

qualify as patent eligible subject matter using the same analysis as set forth in Example G. For example, Example G could be modified such that it is purified (naturally occurring) amazonic acid that is newly discovered to treat a mood disorder. The question becomes whether this also represents a natural correlation. If not, why does administering a drug differ from administering white light to treat a mood disorder? Of course, the answer must be consistent with Mayo's finding that "a typical patent on a new drug or a new way of using an existing drug" are particular applications of natural laws.[26]

However, because the USPTO leaves these types of questions unanswered by premising Example G on a known natural correlation, Example G is of little practical use.

IV. Recommendations For Replacing Or Substantially Revising The Guidance

In revising or replacing the Guidance, the USPTO should be careful to (i) delineate between Myriad/Chakrabarty/Funk Brothers on one hand and Mayo on the other hand, and (ii) set forth an analytical framework that is clearly based on considering the claim as a whole.

For claims that appear to be directed to a natural product (or a mixture of natural products), the Myriad/Chakrabarty/Funk Brothers eligibility determination should focus on whether anything required by the claim is non-naturally occurring when the claim is considered as a whole. In most cases, this determination will be straightforward.

However, certain claims may require closer attention. Specifically, Myriad makes clear that an isolated nucleic acid (e.g., DNA) is not patent eligible subject matter if the claim is actually attempting to claim the associated genetic information (e.g., a human gene linked to disease). However, Myriad does

not stand for the proposition adopted by the USPTO that all isolated or purified natural products are patent ineligible subject matter, and this issue should be left for the courts to resolve. Additionally, claims that only require a mixture of natural products (i.e., no non-naturally occurring elements are required) should be further evaluated for whether the mixture has a different function from the individual natural products. If so, such claims should be found to be directed to patent eligible subject matter.

For claims that are based on a law of nature/natural principle (including mathematical principles), the Mayo eligibility determination should focus on whether the claim as a whole is directed to an application of the law of nature that does not monopolize (preempt the use of) the law of nature itself. A factor-based approach may be acceptable for this eligibility determination given the Mayo Court's characterization of precedent and the steps of the Mayo representative claim. However, the guidance should make clear that a new drug or a new way of using a new or existing drug are non-preemptive applications of natural laws. Additionally, the eligibility determination should focus on which factors may be controlling in showing non-preemptive applications of natural laws or principles.

The fact that the USPTO does not rely on readily available claims in the Guidance's examples illustrate why the Guidance provides very little practical guidance. Further, the Guidance consistently fails to address claims that represent difficult determinations. To be of practical use, any guidance must be consistent with the relevant U.S. Supreme Court decisions, base examples on real-world claims, and vary exemplary claims and fact patterns to decipher (as best as possible) the line between ineligibility and eligibility. Otherwise, as it now stands, the Guidance will cause confusion, unnecessarily protract examination, and result in a significant amount of improper ineligibility determinations. Thus, the Guidance should be replaced or substantially revised.

We appreciate this opportunity to submit our comments.

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[1] 35 U.S.C. § 101

[2] *Bilski v. Kappos*, 561 U.S. 593 (2010).

[3] *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 566 S.Ct. ... (2012).

[4] *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S.Ct. 2107 (2013).

[5] *Myriad*, 133 S.Ct. at 2111.

[6] Id. at 2120 (emphasis added).

[7] Id. at 2119.

[8] Myriad, 133 S.Ct. at 2116.

[9] Id. at 2119.

[10] Diamond v. Chakrabarty, 477 U.S. 303, 309-10 (1980) (emphasis added).

[11] Id. at 310.

[12] Id.

[13] Myriad, 133 S.Ct. at 2120.

[14] Id. at 2119.

[15] Id.

[16] Id. at 14.

[17] Id. at 14-15

[18] Id. at 16 (emphasis added).

[19] Id. at 17 (emphasis added).

[20] Throughout the Guidance, exemplary claims are evaluated for marked differences in both structure and

function. However, the Guidance only considers functional differences after determining whether there is a

structural difference.

[21] See slip op. at 18 (emphasis added).

[22] See slip op. at 13.

[23] See 333 U.S. at 131.

[24] Id. at 11 (emphasis added).

[25] See slip op. at 17 (emphasis in original).[25]

[26] See slip op. at

18.

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