The Uncertain State of Subject Matter Eligibility

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Interpretation of 35 U.S.C. 101 as to what subject matter is eligible in patent claims has recently become a controversial topic in U.S. patent law. Vague standards have left patent practitioners with an often unclear view as to how to deal with the confusing and sometimes conflicting case law and guidelines regarding subject matter eligibility. Even examiners have been struggling to understand and properly apply 101 rejections, particularly regarding claims seemingly directed to natural products or laws of nature. Various Supreme Court decisions and subsequent "interim guidelines" released by the U.S. Patent and Trademark Office ("USPTO") attempting to interpret those decisions have done little to clarify the issue. Indeed, within the past three years, the USPTO has issued five different sets of guidelines relating to subject matter eligibility with more guidelines forthcoming.

My goal here is to provide some guidance on this topic by utilizing our firm's practical experience of prosecuting patent applications in the life sciences field that have encountered 101 rejections. Selected examples of issued patent claims are provided as an illustration of useful strategies to overcome 101 rejections. However, as discussed in more detail below, the success of certain strategies can be highly dependent on the Examiner and/or the art unit.

Case law and the Mayo Framework

In 2012, the Supreme Court ruled that claims directed to using a particular biomarker as an indicator of whether a drug dose should be modified were invalid since the claims did not do "significantly more than simply describe … natural relations." *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S. Ct. 1289 (U.S. 2012). In 2013, the Supreme Court held that isolating a genomic DNA segment was insufficient to provide patent eligibility. However, cDNA, which lacks the non-coding regions of genomic DNA, was held to be patentable, as it is not naturally occurring. *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107 (U.S. 2013). In one of the most recent precedential decisions regarding subject matter eligibility, the Federal Circuit held that claims directed to a novel diagnostic method for fetal abnormalities, where paternal DNA is detected in the blood of a pregnant female, were not directed to patentable subject matter. *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371 (Fed. Cir. 2015). These decisions have significantly altered the life sciences patent landscape in recent years as 101 rejections were relatively rare in these cases prior to 2012.

When interpreting the Supreme Court's patent eligibility analysis, the USPTO developed the so-called *Mayo* test for examiners to utilize during the decision making process (see the 2014 Interim Guidance on Patent Subject Matter Eligibility). In the first step, the examiner determines whether the claim is directed to a process, machine, manufacture or composition of matter. If the answer is NO, then the claim is not eligible subject matter. If the answer is YES, then the

examiner proceeds to the next step, which is the first part of the two-part *Mayo* framework as set forth by the Supreme Court. First, the examiner determines whether the claim is directed to a law of nature, natural phenomenon, or an abstract idea (known as "judicial exceptions" to patent eligibility). If the answer to step 2A in NO, then the claim qualifies as eligible subject matter. If the answer to step 2A is YES, then the Examiner proceeds to step 2B of the *Mayo* test. In applying step 2B, the Examiner determines whether the claim recites additional elements that amount to significantly more than the judicial exception. If not, the claim is not eligible subject matter, but if YES, the claim qualifies as eligible subject matter.

So what's eligible (and what isn't)? Real World Examples

Natural Products:

The analysis of claims reciting natural products under the *Mayo* framework is relatively straightforward. It is often helpful to refer to 2014 Interim Guidance on Patent Subject Matter Eligibility ("2014 IEG") and the Nature-Based Products Examples released with the 2014 IEG for a better understanding of what the USPTO considers to be patent eligible.

A good strategy when facing a 101 rejection against a claim alleged to be directed to a natural product is to amend the claims similarly to one of the Example patent eligible claims presented in the Nature-Based Products Examples. Accordingly, U.S. Patent 9,051,562 is an excellent example of how simple amendments to product claims can confer subject matter eligibility. Claims 10 and 11 of '562 are reproduced below:

10. A recombinant polypeptide comprising an amino acid sequence as set forth by SEQ ID NO: 1 or a functionally-conservative variant thereof contained in a vector.

11. A polypeptide comprising an amino acid sequence as set forth by SEQ ID NO: 1 or a functionally-conservative variant thereof which is covalently conjugated with at least one polyethylene glycol group.

SEQ ID NO:1 corresponds to the sequence of a 'naturally occurring' bacterial methionine gamma-lyase polypeptide. The above claims were amended during prosecution to require that the polypeptide was a recombinant polypeptide contained in a vector (claim 10) or that the polypeptide was covalently conjugated with a polyethylene glycol group (PEG) (claim 11).

During prosecution, it was argued that amended claims 10 and 11 were similar to the patent eligible claims recited in Example 7 of the Nature-Based Products Examples which the Examiner found to be persuasive. These additions to the claims were sufficient to overcome the 101 rejection as they add elements which are not 'naturally occurring'. In particular, the specification defines a vector as requiring a foreign gene insert which is not naturally occurring, thus the polypeptide/vector combination is not naturally occurring. Similarly, the

polypeptide/PEG group is also not naturally occurring. Thus, the answer to Step 2A of the *Mayo* test would be NO.

Interested readers can refer to the additional product claims in U.S. Patent 9,051,562 for further examples of patent eligible claims. The reader is also referred to U.S. Patents 9,066,937 and 9,127,086 for additional examples of product claims that overcame 101 rejections. Notably, reciting an "isolated" polypeptide or nucleic acid is not enough to confer patent eligibility. However, a single point mutation in a polypeptide or nucleic acid sequence, or other chemical modification, may be enough to confer patent eligibility. When responding to a 101 rejection, it is particularly important to point out how the recited product is both structurally and functionally different from the naturally occurring product. For example, one can point out that the mutated polypeptide has an enhanced and/or different functionality as compared to the naturally occurring polypeptide.

Before the Nature-Based Products Examples were released, it appeared that Examiners were more likely to raise and maintain 101 rejections against method claims that recited natural products. After the 2014 IEG was released, however, it became clear that a method claim may recite a natural product, but is not necessarily directed to the natural product. For example, see claim 14 from U.S. Patent 9,051,562:

14. A method for treating a cancer in a subject of need thereof comprising the step of administering to said subject a polypeptide comprising an amino acid sequence as set forth by SEQ ID NO: 1 or a functionally-conservative variant thereof.

As discussed above, SEQ ID NO:1 corresponds to the sequence of a 'naturally occurring' polypeptide. Although initially rejected by the Examiner under 101, the claim was found to be allowable because the claim is not directed to the polypeptide itself, rather to a practical application of the polypeptide (i.e. to treat cancer). During prosecution, claim 14 was compared to Example 3, claim 8 of the Nature-Based Products Examples which recites a method of treating breast or colon cancer by administering amazonic acid (a natural product). This claim was determined to represent eligible subject matter because "analysis of the claim as a whole indicates that the claim is focused on a process of practically applying the product to treat a particular disease (breast or colon cancer), and not on the product *per se*." Therefore, the answer to step 2A of the *Mayo* test is NO and it is not necessary to determine if the claim recites "significantly more" than the judicial exception.

Natural Law/Phenomenon:

The *Mayo* test has been relatively simple to apply in regards to claims that are allegedly directed to natural products. However, the analysis becomes more complex in regards to claims

allegedly directed to a natural law/phenomenon, namely, in regards to claims encompassing a diagnostic method. Adding to the confusion, neither the courts nor the USPTO has provided an adequate description as to what amounts to "significantly more" than a judicial exception (i.e. Step 2B of the *Mayo* test). One, of several, claim limitations that may be enough to qualify as "significantly more" is "adding a specific limitation other than that what is well-understood, routine and conventional in the field, or adding unconventional steps that confine the claim to a particular useful application" (page 22 of the 2014 IEG).

Claims that are rejected as being drawn to a natural law/phenomenon are usually directed to some kind of diagnostic or prognostic method. For example, the claim may recite a method of diagnosing a particular disease by measuring a biomarker and comparing that measurement to a reference value to determine the disease state. Although the biomarker may be novel (i.e. it was not known in the prior art that the biomarker was predictive for the disease), an Examiner is still likely to reject the claim as being directed to the judicial exception of a "natural correlation" (i.e. the relationship between the biomarker and a disease state).

Often, in these situations, one could present an amendment that essentially converts the claim into a treatment method. For example, the claim would recite a method of treating the disease by first diagnosing the disease through measuring the biomarker level and then administering a treatment to patients determined to have the disease. This is where the 101 waters become murky. In some instances, an Examiner will find this sort of argument persuasive. See for example claim 1 of U.S. Patent 9,052,326:

1. A method of treating a cardiovascular disease in a subject having a low level of mitochondrial inhibitory factor 1 in blood, comprising:

measuring the level of mitochondrial inhibitory factor 1 in a blood sample obtained from a subject,

comparing the level of mitochondrial inhibitory factor 1 measured in the blood sample obtained from said subject to a reference value

administering to a subject, which has been identified as having a low level of mitochondrial inhibitory factor 1 as compared to the reference value, an agent that raises a level of high-density lipoprotein (HDL) in said subject, wherein said agent is selected from the group consisting of lipid-poor apoA-I, apoA-I associated with a phospholipid mixture, apoA-I mimetics and cholesteryl ester transfer protein (CETP) inhibitors,

wherein said reference value is determined

in regard to a level of mitochondrial inhibitory factor 1 present in samples taken from one or more healthy subjects, or

in regard to a level of mitochondrial inhibitory factor 1 distribution in a control population, or

by using a competitive immunoassay with a polyclonal antibody raised against human mitochondrial inhibitory factor 1, and in that case said reference value is in the range of 0.25 to 0.45 μg/ml.

Originally, claim 1 of '326 recited a method of assessing a subject's risk of having a cardiovascular disease comprising measuring inhibitory factor 1 (IF1), where the level of IF1 negatively correlated with disease risk. Essentially, the claim was directed toward a diagnostic method and was amended during prosecution to recite a treatment method. It was argued that the amended claim was not directed to a judicial exception, but to a method of treatment of a specific population, similar to Example 3, claim 8 of the Nature-Based Products Examples. It was further argued that, even if the Examiner considers the claim to be directed to the judicial exception, the claim, as a whole, is for a method of treatment that is significantly more than a natural law (i.e. a practical application of the natural law).

Accordingly, when preparing remarks in response to an office action, it is important to point out to the Examiner that method claims should be considered as a whole and not as individual steps. Indeed, page 21 of the 2014 IEG states that "Individual elements viewed on their own may not appear to add significantly more to the claim, but when combined may amount to significantly more than the exception." In this case, the Examiner recognized that, although the treatment agents recited in the claim are not novel *per se*, when the claim is considered as a whole, it is not routine or conventional in the art to use these agents to treat patients found to have a low level of mitochondrial inhibitory factor 1 in blood.

It may also be helpful to point out to an Examiner that the claim does not "tie up" the judicial exception. For example, it was argued that claim 1 of '326 does not pre-empt others from using the judicial exception since the claim does not prevent others from measuring and comparing levels of IF1 in cardiovascular disease or health, nor does it cover a wide range of treatments for cardiovascular disease that are currently available or might be developed. However, this argument is less persuasive in view of the July 2015 Update on Subject Matter Eligibility released by the USPTO. In these guidelines, the USPTO emphasizes that preemption is not a stand-alone test for eligibility. Indeed, as stated on page 8 of the July 2015 Update on Subject Matter Eligibility, "…the absence of complete preemption does not guarantee that a claim is eligible." However, arguments regarding preemption should still be presented to Examiners as it is a factor inherent in the decision-making process of the *Mayo* test.

As mentioned in the introduction, 101 analysis of claims can vary by Examiner and art unit. Claim 1 of '326 discussed above was handled by an Examiner in art unit 1675 (Small Proteins, Peptides, Proteins, Methods of Treatment, Enzymes Enzyme Assays and Plant Extracts). However, an Examiner in art unit 1653 (Fermentation and Microbiology) determined that a treatment method containing an initial diagnosis of a disease using novel biomarkers

followed by treating the patient diagnosed with the disease was not patent eligible (unlike claim 1 of ‘326 which was amended similarly). Here, the Examiner seemed to consider each step individually when stating that the diagnosis step was directed to a judicial exception and the step of treating the disease was routine or conventional in the art and thus does not add significantly more to the judicial exception. Importantly, the Examiner recognized that the method was new and unobvious since all prior art rejections were withdrawn. Thus the question remains, how is a method new and unobvious yet also routine and conventional? In any case, the lack of consistency, and not the 101 guidelines alone, is a major source of frustration among applicants and patent practitioners.

In general, converting a diagnostic claim to a treatment claim is more likely to be successful if a specific treatment agent or protocol is recited, as opposed to a general step of “treating said disease”. For example, instead of reciting a final step of “treating said cardiovascular disease in the patient determined to have a low level of IF1”, claim 1 of ‘326 recites a step of administering specific agents that raise HDL in the patient. Further, if the type of treatment depends on the level of a biomarker (e.g. a different treatment would be administered depending on a specific range of biomarker expression), then the Examiner may be more likely to view the treatment step as a meaningful limitation that goes beyond adding “insignificant extrasolution activity” to the judicial exception.

Examiners are often just as frustrated as patent practitioners with the vague 101 guidance. To address this issue, Examiners have indicated that each art unit has been provided with quality control experts with specific expertise regarding 101 issues. During telephone interviews, an Examiner will often indicate that he or she needs to consult with the quality control expert because the Examiner themselves are not sure what exactly qualifies as patent eligible subject matter. Indeed, there is often disagreement between the Examiner, his or her supervisor, and the quality control expert. For example, an Examiner and her supervisor in art unit 1643 (Antibody Engineering and Cancer Immunology) initially indicated that a diagnostic claim would be allowable under 101 as long as the claim included an active step of identifying a particular patient population. They reasoned that if there is no prior art describing this step, then it is not routine or conventional in the art. However, the next day, the Examiner indicated that “higher ups” in the USPTO determined that no more diagnostic claims would be allowed unless the method uses an entirely novel reagent. These types of contradictory interactions with the USPTO only add to the sense of uncertainty and frustration among examiners and patent practitioners.

As a final example, claim 1 of U.S. Patent 9,121,066 is presented below:

1. A method of implanting an embryo in a female undergoing in vitro fertilization, comprising the steps of:
a) collecting at least one oocyte with its cumulus cells from said female;

b) measuring, in said cumulus cells surrounding said oocyte, an expression level of each of the 5 microRNA hsa-let-7a-1, hsa-mir-182, hsa-mir-21, hsa-mir-320a and hsa-mir-210;
c) comparing the expression level of each of the 5 microRNA in the cumulus cells with control expression levels of the 5 microRNA from cumulus cells associated with competent oocytes;
d) assessing said oocyte as having a higher probability of being competent if the 5 microRNA are not differentially expressed when compared to cumulus cells associated with competent oocytes;
e) fertilizing said oocyte having a higher probability of being competent in vitro to generate an embryo; and
f) implanting said embryo in said female.

This application was handled by an Examiner in art unit 1674 (Antisense-related Nucleic Acid Compositions and Methods). Originally, the application contained claims that recited a method of selecting an oocyte that is more likely to produce viable embryos upon fertilization by measuring a set of microRNAs that were previously unknown to be related to embryo viability. The Examiner rejected the claims under 101 stating that the claims were directed to the natural correlation or relationship between the microRNAs and embryo viability. Similar to claim 1 of '326, the claim was amended to recite active steps that practically apply the judicial exception. Here, it was successfully argued that it is not routine or conventional in the art to implant an embryo based on the measurement of the expression level of a specific combination of 5 microRNAs. If the Examiner were to consider the steps individually, then he may conclude that the claim recites a natural correlation and that the additional steps of fertilizing an oocyte and implanting an embryo are routine or conventional in the art. However, in this case, the Examiner considered the claim as an ordered combination and recognized that the claim, as a whole, amounted to significantly more than the judicial exception.

The Federal Circuit's decision in *Ariosa* has been seen as a sign that diagnostic claims are no longer patent eligible. Twelve amicus briefs were filed in support of the patentee's petition for rehearing *en banc* demonstrating the importance of this decision among the patent community. The petition was ultimately denied, however, this case is still developing as the patentee may petition for a Writ of Certiorari. The Supreme Court has previously held that even if each individual step is well-known, the claim is eligible if the combination of steps, taken as a whole, is new. *Diamond v. Diehr*, 450 U.S. 175 (U.S. 1981). However, this analysis was seemingly not followed in *Ariosa* since the claimed method of detecting paternal DNA in the blood of a pregnant female was novel and certainly not routine or conventional in the art. The final outcome of *Ariosa*, whether the claims are held as invalid or not, is eagerly awaited as it would provide additional clarity to prosecution of diagnostic claims.

Conclusion

The rules surrounding 101 eligibility appear to be in flux, particularly in regards to claims

allegedly reciting natural laws or phenomenon. This uncertainty has a profound negative effect on applicants who are unsure whether it is worth pursuing patent protection of their inventions. Indeed, many applicants have significantly invested in filing diagnostic applications that were once clearly considered patent eligible. However, these applicants are now faced with an uncertain climate where 101 determinations are more of a gamble depending on who examines the application. Appealing to the Patent Trial and Appeal Board is also an expensive and daunting prospect with low chances of success. In view of standing 101 rejections, many applicants have opted to abandon their current applications while filing continuations in the hopes that, in another year or two, the 101 patent landscape will be much more defined. Indeed, the alternative, less investment in research and/or an increase in trade secrets, has the potential to disincentivize innovation thus slowing the overall progress of the biotechnology industry. In the meantime, Examiners, patent practitioners, and applicants alike await the next big court decision that may once again shift patent eligibility in favor of diagnostic-related inventions.