Supreme Court Holds Claim Invalid for Encompassing a Natural Law: Consequences for Biomarker Patents

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As many practitioners are now aware, on March 20, 2012 the Supreme Court held, in *Mayo* v. *Prometheus* ("*Prometheus*"), that claims directed to optimization of drug treatment by administering the drug and determining the level of metabolite were invalid because they encompassed unpatentable subject matter. The Supreme Court reasoned that the claims covered a law of nature and did not "add *enough* to their statements of the correlations to allow the processes they describe to qualify as patent-eligible processes that *apply* natural laws[[.]]"[1]

This decision has wide-ranging implications for the biotechnology industry and has left great uncertainty over how the Supreme Court's ruling will be interpreted by the Federal Circuit and the USPTO. In this client alert, we review the claims in *Prometheus* and provide suggestions how clients can try to prepare for and guard against rejections and claims of invalidity for unpatentable subject matter in light of the Supreme Court's decision.

I. The Prometheus Claim

Claim 1 of U.S. Patent No. 6,355,623 patent, discussed in *Prometheus,* is reproduced, below.

> 1. A method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder, comprising:
>
> (a) administering a drug providing 6-thioguanine to a subject having said immune-mediated gastrointestinal disorder; and
>
> (b) determining the level of 6-thioguanine in said subject having said immune-mediated gastrointestinal disorder,
>
> wherein the level of 6-thioguanine less than about 230 pmol per $8x10^8$ red blood cells indicates a need to increase the amount of said drug subsequently administered to said subject and
>
> wherein the level of 6-thioguanine greater than about 400 pmol per $8 x10^8$ red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.

The Supreme Court held that claim 1 and other Prometheus claims, "simply tell doctors to gather data from which they may draw an inference in light of the correlations."[2] To infringe claim 1, one must merely administer a drug to a subject with a gastrointestinal disorder and determine the level of 6-thioguanine present in the subject. No other steps are necessary. The Court stated that the "wherein" clauses, "simply tell a doctor about the relevant natural laws, at most adding a suggestion that he should take those laws into account when treating his patient."[3] It is not necessary to actually increase or decrease the dose of the drug to infringe the claim. Merely determining the level of 6-thioguanosine is enough to infringe the claim.

To determine the patentability of claim 1 of the '623 patent, the Court compared claims in *Flook* and *Diehr*.

A. *Flook*

The Supreme Court likened the subject matter of claim 1 of the '623 patent to a claim held invalid for similar reasons in *Parker v. Flook*, 437 U.S. 584 (1978) ("*Flook*"). The claim in question in *Flook* is reproduced below.

> 1. A method for updating the value of at least one alarm limit on at least one process variable involved in a process comprising the catalytic chemical conversion of hydrocarbons wherein said alarm limit has a current value of:
>
> Bo + K
>
> wherein Bo is the current alarm base and K is a predetermined alarm offset which comprises:
>
> (1) Determining the present value of said process variable, said present value being defined as PVL;
>
> (2) Determining a new alarm base B1, using the following equation:
>
> B1=Bo(1.0-F) + PVL(F)
>
> where F is a predetermined number greater than zero and less than 1.0;
>
> (3) Determining an updated alarm limit which is defined as B1 + K; and thereafter
>
> (4) Adjusting said alarm limit to said updated alarm limit value.

Claim 1 in *Flook* does more than provide instructions to use the formula recited in the claim, as step (4) provides an active adjustment step. However, the Supreme Court held that step (4) was conventional or obvious post-solution activity that any competent draftsman could add to a claim encompassing a mathematical formula in an attempt to render it patentable subject matter.[4] Likewise, the Court held that

the limitations recited in the claims in *Prometheus*, "are steps that must be taken in order to apply the laws in question, the effect is simply to tell doctors to apply the law somehow when treating their patients."[5]

B. *Diehr*

The Supreme Court distinguished claim 1 of the '623 patent from a claim held valid in *Diamond v. Diehr*, 450 U.S. 175 (1981). The claim in question in *Diehr* is reproduced below.

> 1. A method of operating a rubber-molding press for precision molded compounds with the aid of a digital computer, comprising:

- providing said computer with a data base for said press including at least, natural logarithm conversion data (ln), the activation energy constant (C) unique to each batch of said compound being molded, and a constant (x) dependent upon the geometry of the particular mold of the press,
- initiating an interval timer in said computer upon the closure of the press for monitoring the elapsed time of said closure,
- constantly determining the temperature (Z) of the mold at a location closely adjacent to the mold cavity in the press during molding,
- constantly providing the computer with the temperature (Z),
- repetitively calculating in the computer, at frequent intervals during each cure, the Arrhenius equation for reaction time during the cure, which is

$$\ln v = CZ + x$$

- where v is the total required cure time,
- repetitively comparing in the computer at said frequent intervals during the cure each said calculation of the total required cure time calculated with the Arrhenius equation and said elapsed time, and
- opening the press automatically when a said comparison indicates equivalence.

The Supreme Court held that the steps in the *Diehr* claim were different from the steps of the claim in *Flook*. The Court noted that the application of the mathematical equation claimed in *Flook* did not "explain how the variables used in the formula were to be selected, nor did the [claim] contain any disclosure relating to chemical processes at work or the means of setting off an alarm or adjusting an alarm limit."[6] In contrast, the Court held that the claim in *Diehr* added enough detail regarding limitations on specific variables that the claim as a whole satisfied 35 U.S.C. § 101. The Court held that, "when a claim containing a mathematical formula implements or applies that formula in a structure or process which, when considered as a whole, is performing a function which the patent laws were designed to protect… then the claim satisfies the requirements of § 101."[7]

C. Suggestions for Redrafting the Claims in *Prometheus*

The differences between the limitations on *Flook* and *Diehr* seem to be quantitative and qualitative. The claim in *Diehr* has many more steps than the claim in *Flook*. Further, the steps in *Diehr* are active definite steps, while the steps in *Flook* could be performed mentally and are indefinite as to how much the alarm limit should be adjusted. Thus, one approach to draft claims encompassing patentable subject matter in light of *Prometheus* would be to add steps to the claims that are active and specifically defined.

For example, one way Prometheus may have avoided the holding of invalidity of claim 1 of its '623 patent would have been to add active method steps to its claims which incorporate specific variables that are necessary to apply the scientific principle. Here the scientific principle is the variability of 6-thioguanine levels and therapeutic outcomes in subjects administered 6-thioguanine containing drugs. The variables for the specific levels of 6-thioguanine and recommendations for therapeutic responses to these levels are found in "wherein" clauses. Instead of the "wherein" clauses, claim 1 of the '623 patent could have recited the following active steps:

- increasing the amount of said drug subsequently administered to the subject when the level of 6-thioguanine is less than about 230 pmol per $8x10^8$ red blood cells;
- decreasing the amount of said drug subsequently administered to the subject when the level of 6-thioguanine is greater than about 400 pmol per $8 x10^8$ red blood cells; and
- maintaining the amount of said drug subsequently administered to the subject when the level of 6-thioguanine is greater than about 230 pmol per $8x10^8$ red blood cells and less than about 400 pmol per $8 x10^8$ red blood cells.

Thus, one strategy for drafting claims in light of *Prometheus* is to avoid "wherein" clauses like the ones in claim 1 of the '623 patent and/or add active alternative steps, at least as dependent claims, to prevent rejections of the claims as encompassing unpatentable subject matter. Effectively, this captures the ultimate treatment activity that is intended by the claim. The scientific principle is also applied to a real world condition. These active steps should include limitations on specific variables including specific active steps of action, metabolite levels, genetic mutations or phenotype expression.

II. Implications for Biomarker Patent Applications

It is unclear how the decision in *Prometheus* will be interpreted by the Federal Circuit, District Courts or USPTO. However, the decision in *Mayo v. Prometheus* may not significantly foreclose upon the ability of applicants to acquire claims to biomarker claims. Hopefully, additional guidance on this issue will be provided when the Federal Circuit reconsiders *The Association for Molecular* Pathology v. *USPTO* (*Myriad Genetics, Inc.)*, 653 F.3d 1329 (Fed. Cir. 2011) ("*Myriad"*). The Supreme Court vacated the decision in *Myriad* and has ordered the Federal Circuit to reconsider their decision in light of *Prometheus.* Claim drafting

strategy for biomarker patents will depend on how the Federal Circuit defines what constitutes scientific principle and what "sufficient" claim limitations will be necessary to make a claim encompass patentable subject matter.

A two-fold strategy could be used in drafting biomarker related claims until greater certainty is available. First, the underlying scientific principle should be defined. Second, sufficient active steps reciting specific operations that apply the scientific principle should be added to the claim.

A. Determining the Scientific Principle in Biomarker Applications

It is unknown whether a court would find that the underlying scientific principle associated with biomarkers would be the structure or sequence of the biomarkers themselves, or the actual correlation of the biomarker (s) with a disease state. Arguably, the law of nature in this instance is simply the sequence(s) of the wild-type and mutant sequences of particular genes. Under this rationale, the association of these genes or alleles with various phenotypic states is the result of cultural biases that stratify a spectrum of phenotypes into diseases and thus could not be defined as a law of nature. Alternatively, a court could argue that the correlation of a biomarker mutation with a disease state is itself a scientific principle. Thus, claim sets should contain active and specific limitations that include both possibilities.

B. Adding Active Limitations on Specific Variables

If the sequence itself is the scientific principle, then it should be enough to provide limitations to variables associating the presence of the wild-type or mutant sequence with a particular disease state. If the correlation is the underlying scientific principle, then additional steps including prophylaxis, treatment or confirmatory diagnosis may need to be added.

For example, Myriad's screening claim is reproduced below.

> 1. A method for screening a tumor sample from a human subject for a somatic alteration in a BRCA1 gene in said tumor which comprises comparing a first sequence selected from the group consisting of a BRCA1 gene from said tumor sample, BRCA1 RNA from said tumor sample and BRCA1 cDNA made from mRNA from said tumor sample with a second sequence selected from the group consisting of BRCA1 gene from a nontumor sample of said subject, BRCA1 RNA from said nontumor sample and BRCA1 cDNA made from mRNA from said nontumor sample,
>
> wherein a difference in the sequence of the BRCA1 gene, BRCA1 RNA or BRCA1 cDNA from said tumor sample from the sequence of the BRCA1 gene, BRCA1 RNA or BRCA1 cDNA from said nontumor sample indicates a somatic alteration in the BRCA1 gene in said tumor sample.

This claim could be amended as follows to make it more likely to encompass patentable subject matter if only the sequence of BRCA1 is found to be the underlying scientific principle:

1. A method for screening a tumor sample from a human subject for a somatic alteration in a BRCA1 gene in said tumor which comprises

a) sequencing the BRCA1 gene in the sample; and

b) comparing a first sequence selected from the group consisting of a BRCA1 gene from said tumor sample, BRCA1 RNA from said tumor sample and BRCA1 cDNA made from mRNA from said tumor sample with a second sequence selected from the group consisting of BRCA1 gene from a nontumor sample of said subject, BRCA1 RNA from said nontumor sample and BRCA1 cDNA made from mRNA from said nontumor sample,

wherein a difference in the sequence of the BRCA1 gene, BRCA1 RNA or BRCA1 cDNA from said tumor sample from the sequence of the BRCA1 gene, BRCA1 RNA or BRCA1 cDNA from said nontumor sample indicates a somatic alteration in the BRCA1 gene in said tumor sample.

The sequencing step distinguishes the types of mutations that are associated with breast cancer in BRCA1. There are many mutations in BRCA1 that are associated with breast cancer, so a sequencing approach is arguably a better strategy in detecting mutations that cause breast cancer. In other contexts, this step could be the use of specific primers for the detection of specific mutations.

A further step that might be included, if the underlying scientific principle is the association of mutations of BRCA1 with breast cancer, would be a treatment or subsequent confirmatory diagnosis step for subjects found to have the BRCA1 mutation. These possible limitations are presented as dependent claims below.

2. The method of claim 1, further comprising administering a treatment to the subject for breast cancer.

3. The method of claim 1, further comprising searching breast tissue in the subject for a breast cancer tumor.

These steps recite clear applications to a specific real world problem that should be practiced in light of the underlying mutation in BRCA1. Additional dependent claims could also be added to specify particular treating or searching methods. Prophylaxis claims would not apply in this context, but one could imagine a claim encompassing finding the BRCA1 mutation in healthy tissue and prophylactic steps being taken to reduce the incidence of breast cancer.

One problem with adding steps to a claim is an increase in the possibility of divided infringement. In order to have direct patent infringement, one actor must have practiced each step of the claim. More steps increase

the likelihood that multiple parties practice individual steps of the claim, but not all the claim steps. Unless there is an agency relationship of one party to another, this could prevent direct infringement of a patent claim from being found. However, the Federal Circuit is looking at the law in this area as it has ordered an *en banc* rehearing of *Akamai Technologies, Inc. v. Limelight Networks, Inc.*

Another strategy to reduce the number of steps in the claim is to couch the screening step in a treatment claim that selects a particular patient for treatment.

> 20. A method for treating cancer in a patient with a difference in the sequence of a BRCA1 gene, BRCA1 RNA or BRCA1 cDNA from a tumor sample and the sequence of the BRCA1 gene, BRCA1 RNA or BRCA1 cDNA from a nontumor sample comprising administering a therapeutically effective amount of a cancer therapeutic to the patient.

The claim provides specific remedies of treating a patient subject to a screening step. Thus, if the underlying scientific principle is the association of BRCA1 mutations with cancer, this claim should satisfy 35 U.S.C. § 101 under *Mayo v. Prometheus*.

Screening and diagnosis claims should still be patentable, in some form, in light of the holding in *Mayo v. Prometheus*. Future claims should include active steps which place specific limitations on variables concerning the correlation of a biomarker with a disease state in order to comply with § 101. If a court found that the underlying scientific theory was the sequence of the biomarker these limitations could include specific mutations, tissue types, disease states, traits of the subject and specific methods used in screening. If a court found that the underlying scientific theory was the correlation of the biomarker with a disease state, limitations involving specific methods of prophylaxis, treatment or confirmatory diagnosis may be necessary. Both types of limitations should be used, at least in dependent claims, when drafting biomarker applications until more guidance is available from the Federal Circuit and USPTO.

If you have any questions about this alert, please contact your Lathrop Gage attorney or the attorney listed above.

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[1] *See Mayo v. Prometheus*, No. 10-1150, slip op. at 8 (Mar. 20, 2012).

[2] *Id.* at 10-11.

[3] *Id.* at 9.

[4] *See, Parker* v. *Flook*, 437 U.S. 584, 590 (1978).

[5] *See, Prometheus* at 13.

[6] *Prometheus* at 12-13 *citing Diamond v. Diehr*, 450 U.S. 175, 192, n. 14 (1981).

[7] *Id.* at 192.