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PUBLIC POLICY

Federal Circuit addresses patent eligibility of companion diagnostic claims

By: Antoinette F. Konski, Jacqueline D. Wright Bonilla, and Courtenay C. Brinckerhoff

A recent Federal Court decision strengthened innovators' efforts to patent companion diagnostics and provided guidance to those seeking to patent such tools. Companion diagnostic tests guide the prescription of products in therapies such as oncology, cardiovascular disease and infectious disease to patients who are more likely to benefit from those drugs or associated therapies. These methods and tests are the work-horse of the personalized medicine industry and are increasingly used with the corresponding growth in the knowledge and understanding of differing patient responses to drugs and therapies. The patent eligibility of claims that define the relationship between a treatment or drug use to the presence or absence of a patient-specific clinical marker, gene expression level or analyte has been in question since the Supreme Court's dismissal of the grant of certiorari in *Laboratory Corp. of American Holdings v. Metabolite Labs., Inc*., 126 S.Ct. 2921 (2006) wherein Supreme Court Justice Breyer's non-binding dissent opined that similar claims were not patent eligible. However, the Federal Circuit's recent decision *Prometheus Laboratories, Inc. v. Mayo Collaborative Services*, No. 2008-1403, 2009 U.S. App. LEXIS 20623 (Fed. Cir. 2009), affirmed that such inventions are patent eligible.

In *Prometheus, supra,* the Federal Circuit addressed the issue of whether methods for determining the level of a metabolite in a patient sample and using it to select a treatment option are patent eligible. In doing so, the Federal Circuit for the first time applied the "machine or transformation" test elucidated in *In re Bilski* to the medical arts. *In re Bilski*, 545 F.3d 943 (Fed. Cir. 2008) (en banc), *cert. granted*, 129 S.Ct. 2735 (June 1, 2009). While the Federal Circuit's *"Bilski"* test for patent eligibility may be modified when the Supreme Court considers the issue this term, the *Prometheus* decision provides guidance to those seeking to patent similar methods for diagnosis and treatment.

Managing Efficacy and Toxicity

U.S. Patent Nos. 6,355,623 ("the '623 Patent") and 6,680,302 ("the '302 Patent") were at issue. The patents claim methods for calibrating the proper dosage of 6-thiopurine prodrugs for the treatment of gastrointestinal and non-gastrointestinal autoimmune diseases. The prodrugs are converted to various active metabolites in the patient which in turn not only treat the disease but also cause significant toxic side effects. The object of the claimed inventions was to calibrate dosage of the prodrugs to maximize efficacy while minimizing unwanted side effects. Claim 1 (emphasis added) of the '623 Patent was chosen as representative:

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 8 $X10^8$ 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 $X\ 10^8$ red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.

Dependent claims further provided that the level of 6-thioguanine is determined using high pressure liquid chromatography (HPLC).

Additional claims did not require the step of administering the prodrug. For example, claim 46 of the '623 Patent recites:

46. A method of optimizing therapeutic efficacy and reducing toxicity associated with treatment of an immune-mediated gastrointestinal disorder, comprising:

(a) determining the level of 6-thioguanine or 6-methyl-mercaptopurine in a subject administered a drug selected from the group consisting of 6-mercaptopurine, azathioprine, 6-thioguanine, and 6-methylmercapto-riboside, said subject having said immune-mediated gastrointestinal disorder;

wherein the level of 6-thioguanine less than about 230 pmol per 8 $X\ 10^8$ 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 $X\ 10^8$ red blood cells or a level of 6-methyl-mercaptopurine greater than about 7000 pmol per 8 $X\ 10^8$ red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.

At The District Court

Plaintiff and subsequent Appellant Prometheus marketed a PROMETHEUS Thiopurine Metabolites test covered by the '623 and '302

Patents. Defendants Mayo Collaborative Services and Mayo Clinic Rochester ("Mayo") announced an intent to use and distribute a similar test. Prometheus sued Mayo for infringement of claims 1, 7, 22, 25 and 46 of the '623 Patent and independent claim 1 of the '302 Patent. Mayo subsequently rescinded its announcement and did not launch its own test.

On cross-motions for summary judgment, claim 7 of the '623 Patent was held to be literally infringed by Mayo. Mayo thereafter moved for summary judgment that the patents in suit were invalid for failing to satisfy 35 U.S.C. § 101. The district court agreed and Prometheus appealed.

In invalidating the patents, the district court relied on an analysis outlined in a dissent authored by Supreme Court Justice Breyer in *Laboratory Corp.*, *supra*. In following Justice Breyer's reasoning, the district court held that the "determining" and "administering" steps were merely necessary data-gathering steps for use in any of the "wherein" or correlation steps. The district court thus held that the claims, only reciting correlations, were not patentable because the correlations between metabolite levels and therapeutic efficacy or toxicity, recite a natural phenomenon that wholly preempt use of the correlations.

The Federal Circuit Applies *Bilski*

The Federal Circuit began its analysis by noting the difficulty in applying the language of § 101 to a new process. The court acknowledged that while Congress intended statutory subject matter to "include anything under the sun that is made by man" (quoting *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980)), § 101 is not without limits. The Federal Circuit drew on its own "machine or transformation" test as elucidated in *In re Bilski, supra* for determining whether a process is patent eligible under § 101. The Federal Circuit stated that a claimed process is surely patent eligible under § 101 if: (1) it is tied to a particular machine or apparatus, or (2) it transforms a particular article into a different state or thing. The machine or transformation test is a 'two branched inquiry,' *i.e.*, the patentee 'may show that a process satisfies § 101 either by showing that his claim is tied to a particular machine, or by showing that his claim transforms an article.

The machine-or-transformation test has two further aspects: 'the use of a specific machine or transformation of an article must impose meaningful limits on the claim's scope to impart patent-eligibility' and 'the involvement of the machine or transformation in the claimed process must not merely be insignificant extra solution activity.

Prometheus, *supra* at *13. (citations omitted).

In applying the test to representative claim 1, the Federal Circuit found that each specific claim element satisfied the *Bilski* test, noting that the crucial error in the district court's analysis was to find that the administration and determining steps were merely to gather data, or in the language of the *Bilski* test, insignificant extra solution activities. In analyzing the

administration and determining steps, the Federal Circuit focused on the transformative characteristic of each element.

The Federal Circuit began its analysis by noting that the preamble of the claims and the specification made it clear that the object of the invention was treatment. Treatment claims, the Federal Circuit noted "are always transformative when a defined group of drugs is administered to the body to ameliorate the effects of an undesired condition." *Id.* at *23. The court also rejected Mayo's argument that the administration step disqualified the claims from the "realm of patentability" because it relied on the human body for transformation. Rather, the Federal Circuit agreed with Prometheus that: quite literally every transformation of physical matter can be described as occurring according to natural processes and natural law. Transformations operate by natural principles. The transformation here, however, is the result of the physical administration of a drug to a subject to transform – *i.e.*, treat – the subject, which is itself not a natural process.
Id. at *25.

The court further found that the determining step separately provided patent eligibility to the claimed methods because "determining the levels of [the metabolites] in a subject necessarily involves a transformation, for those levels cannot be determined by mere inspection. Some form of manipulation, such as the high pressure liquid chromatography method … is necessary to extract the metabolites from a body sample and determine their concentration." *Id.* at *26. The Federal Circuit agreed with Prometheus that "at the end of the process, the human blood sample is no longer human blood; human tissue is no longer human tissue." *Id*. "The determining step, by working a chemical and physical transformation on physical substances, likewise sufficiently confines the patent monopoly, as required by Bilski." *Id*. at *27.

The Federal Circuit also stated that the administration and determination steps in *Prometheus* were not merely only data gathering steps or insignificant post-solution activities. While these steps ultimately did gather data, they also provided more – they were steps in a treatment protocol. To further illustrate the point, the Federal Circuit distinguished its own pre-*Bilski* decision, *In re Grams*, 888 F.2d 835 (Fed. Cir. 1989), which held diagnostic claims unpatentable for failing to satisfy §101.

In *Grams, supra*, the claims under consideration were directed to diagnosing an abnormal condition in an individual by first collecting a plurality of parameters from clinical laboratory tests performed on the individual. These parameters were then evaluated by an algorithm and the identity of any abnormality, if one existed, was diagnosed. A representative claim recited the step of (a) performing a plurality of clinical laboratory tests on the individual to measure the values of the set of parameters and subsequently in steps (b) through (e) of the claim, evaluating the parameters. Although the method required the collection of clinical

information, the *Grams* court determined that the essence of the claimed process was the mathematical algorithm rather than any transformation of the tested individuals. Special note was made by the *Grams* court that the claims must be read in light of the supporting disclosure which was for the most part, was directed to the algorithm used for performing steps (b) through (e) of the claim.

By contrast, the Federal Circuit found that the administering and determining steps at issue in *Prometheus* were not merely "data gathering," but were part of treatment regimes for various diseases using particular drugs as underscored in the claims' preamble and supporting specification.

In a footnote the Federal Circuit also noted that the district court's reliance on Justice Breyer's dissent in *Laboratory Corp.*, *supra,* was misplaced. The Federal Circuit stated that the appealed claims were different from the claims under consideration in *Laboratory Corp*. claims but failed to point out the deciding differences between the *Laboratory Corp.* claims and the *Prometheus* claims. The Federal Circuit also noted the Supreme Court's dissent did not have precedential value.

The "Wherein" Clause

The Federal Circuit separately addressed the issue whether claims that encompass mental steps such as the claimed "wherein" clauses are patent eligible. The *Prometheus* court agreed with the district court that such a clause is not itself separately patent eligible, but by itself does not detract from the patentability of the claims as a whole. Thus, the Federal Circuit held that the addition of the mental step to the claimed methods does not remove the prior two steps from the realm of patentability.

When discussing the "wherein" mental steps, the Federal Circuit also stated that the district court erred in finding that the claims wholly preempt use of correlations between metabolite levels and efficacy and toxicity. The Federal Circuit concluded that the district court erroneously assumed that the claims cover the correlations themselves, once the Federal Circuit determined, as discussed above, that the claims recited transformative methods of treatment, not correlations.

Practical Application to Companion Diagnostics

The Federal Circuit's analysis in *Prometheus* and its comparison to its prior *Grams* decision is educational to those in the companion diagnostic field who seek to patent inventions or are questioning whether such patents should be pursued. *Prometheus* suggests that claimed inventions having a significant therapeutic purpose or involve the transformation of a sample are patent eligible. In *Prometheus*, the Federal Circuit emphasized the physical transformations of the administration and determining step and tied these steps to the purpose of the invention—treatment. All claims in the *Prometheus* patents recited in the preamble a method relating to treatments while the *Grams* claims recited a "method of diagnosing" a condition. Thus,

Prometheus suggests that inventions geared toward treatment are more likely to withstand a § 101 challenge.–

The Federal Circuit's findings that the "determining" step in the *Prometheus* claims "transformed" a tested bodily sample was also key to its conclusion of patent eligibility and clearly distinguished the claims from those at issue in *Grams*. For example in *Prometheus* the Federal Circuit specifically noted that "[d]etermining the levels of 6-TG or 6-MMP in a subject necessarily involves a transformation, *for those levels cannot be determined by mere inspection*." *Id.* at *26 (emphasis added). In *Grams,* by contrast, the specification had minimal disclosure on how the clinical tests were to be performed further suggesting that the invention was the algorithm. In contrast, the *Prometheus* court determined that physical manipulation and measurement must occur, e.g., by high-pressure liquid chromatography (HPLC) or other methods that involve transforming bodily samples. Notably, many of the challenged claims did not recite a specific method or means to accomplish the determining step, although the Federal Circuit credited expert testimony when finding that the "determining" step necessarily involved physical transformations. *Id.* (quoting testimony that "at the end of the process, the human blood sample is no longer human blood; human tissue is no longer human tissue").

The Federal Circuit also made clear that the mental step noted in the "wherein" clauses was not fatal to patent eligibility, provided the claim as a whole satisfied the *Bilski* machine or transformation test. Thus, claims directed to methods that include assaying a patient sample for a patient-specific biomarker or analyte by a transformative method, and then matching the results with a specific diagnostic outcome or therapeutic recommendation are likely patent eligible, at least under the guidance provided in *Prometheus*.

Thus, unless and until the Supreme Court rules on this issue, methods and tests for the companion diagnostic industry should continue to be patent eligible. Although the Supreme Court will address the patent eligibility requirement of § 101 in *Bilski*, it may not specifically address the patent eligibility of method claims that take advantage of information relating to a biomarker or analyte as it pertains to a treatment outcome or therapy. The claims at issue in *Bilski* are "business method" type claims, directed to methods of hedging the risk of bad weather through commodities trading. Thus, the Supreme Court could decide *Bilski* without discussing the issues presented in *Laboratory Corp.* or *Prometheus*. The defendants in *Prometheus* have sought Supreme Court review, however, it is possible that the Supreme Court will vacate the Federal Circuit's *Prometheus* decision and remand for reconsideration in view of its eventual opinion in *Bilski* which is scheduled for oral argument on November 9, 2009.

A Supreme Court decision on the merits as it applies to medical diagnostic tests and treatments would also preempt the recent high profile

pending litigation challenging the constitutionality of patents related to human genes filed by the Association for Molecular Pathology. *Assoc. for Molecular Pathology v. U.S. Patent and Trademark Office*, 09-CV-4515 (S.D.N.Y. 2009). Plaintiff argues that such patents violate the First Amendment and run counter to public policy in that they interfere with the free flow of information and knowledge and that patents on human genes are illegal because they are in reality "products of nature."

These civil actions add to the 2007 Congressional challenge to gene patents introduced by Rep. Xavier Becerra (CA-31) and Rep. Dave Weldon, M.D. (FL-15) under the Genomic Research and Accessibility Act of 2007. The bill seeks to end the practice of patenting any and all portions of the human genome by amending the U.S. patent code to prohibit the patenting of any nucleotide sequence or its functions or correlations, or the naturally occurring product it specifies. In introducing the Act, Rep. Becerra stated that the legislation was needed to promote a patent-free genome that does not hinder scientific research, business enterprise, or human morality.

Common among these challenges is the perception that gene patents stifle innovation and limit patient access to diagnostic tests. Contrarily, a recent report by the Office of Biotechnology Activities (OBA) of the National Institute for Health concluded that the current practice of patenting genes and genetic tests does not in and of itself, appear to stifle innovation, *See Public Consultation Draft Report on Patents and Licensing Practices and Their Impact on Patient Access to Genetic Tests*, available atoba.od.nih.gov/SACGHS/sacghs_documents.html#GHSDOC_011.

Companies working in the diagnostic and personalized medical fields are advised to “stay tuned.”