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Biotechnology
Vice Chair's Notes

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PATENTING DIAGNOSTICS AND BIOMARKERS SIX YEARS AFTER *MAYO*.

At the end of 2018, your humble Vice Chair has some thoughts to share on the topic of patenting diagnostics. How does one make sense of the decisions the courts handed down this year? These thoughts are of course purely my own, and do not reflect the position of the AIPLA or any of my clients.

DEVELOPMENTS IN 2018

This year the CAFC built on its own decisions and the Supreme Court's decisions in *Roche Molecular Systems, Inc. v. Cepheid*, *Vanda Pharmaceuticals v. Aventisub, LLC*, *and Exergen Corp. v. Kas USA, Inc.* In addition, the U.S. District Court for the District of Delaware rendered an interesting decision in *Mallinckrodt Hospital Products IP Ltd. et al. v. Praxair Distribution, Inc.* in December of 2017.

Vanda

Of these new decisions, *Vanda* is the most significant. It involved a patent for treating schizophrenia patients with iloperidone that is tied to genotyping the patient to determine the patient's tolerance for iloperidone. More specifically, the inventors discovered certain cytochrome P450 2D6 genotypes that indicate poor metabolism of iloperidone that increases the patient's risk of cardiac complications of iloperidone treatment for doses of about 12 mg/day. The claims comprised determining whether the patient had the poor metabolizer gene, administering 12 mg/day or less iloperidone if the patient has the poor metabolizer gene, but otherwise administering 12-24 mg/day iloperidone.

The CAFC found the claim to be patent eligible, essentially for the same reason that the immunization method in *Classen* was patent eligible: treating a patient according to a diagnosis is more than just the diagnosis itself. This decision squarely reaffirms *Classen*'s holding on methods of treating or preventing disease.

Roche v. Cepheid

On the other hand, in *Roche v. Cepheid*, the CAFC considered the opposite situation: a patent for a breakthrough test to detect the bacterium that causes tuberculosis and simultaneously determine the bacterium's drug resistance, but that was not coupled to any form of treatment or intervention. Specifically, the claims in *Roche* involved a PCR test for *Mycobacterium tuberculosis* that also reports certain mutations that confer rifampicin resistance, and specific primers for use in the test. The CAFC found that the primers themselves were "natural phenomena," because the nucleotide sequence was identical to natural nucleotide sequences found in *M. tuberculosis*. The CAFC then found that using the primers in PCR to detect the bacterium did not add an inventive concept to the primers themselves, because PCR is a routine procedure in medical diagnostics. In the absence of any treatment step, the claims were found invalid.

Exergen

The invention in *Exergen* was slightly different: it involved a method of calculating body temperature by measuring the peak radiant heat over the skin of an artery, and an electronic thermometer configured to execute the method. An exemplary claim reads as follows:

A method of detecting human body temperature comprising making at least three radiation readings per second while moving a radiation detector to scan across a region of skin over an artery to electronically determine a body temperature approximation, distinct from skin surface temperature.

The CAFC found this method to be patent eligible. They found the claims were directed to the law of nature that physiologic core temperature is a function of skin temperature above an artery and ambient temperature; but also found that the specific method of measuring body temperature based on these two factors, combined with the unconventional method of measuring radiant heat at least three times per second, added an inventive concept to the application of the natural law. The invention was not only the discovery of the relationship between core temperature, air temperature, and skin temperature above an artery, but it was also a new and more accurate way of measuring the skin temperature.

Mallinckrodt

A lower court made a decision at the end of 2017 that is inconsistent with *Classen* and *Vanda* in *Mallinckrodt Hospital Products IP Ltd. et al. v. Praxair Distribution, Inc.* In that case the inventors discovered that infants with impaired function of the left ventricle are at elevated risk for pulmonary edema if treated with nitric oxide (which is used to treat neonatal hypoxia). The U.S. District Court for the District of Delaware considered claims for treating hypoxic newborns using nitric oxide, if and only if an echocardiogram shows that the newborn is not also suffering from left ventricular dysfunction. The district court judge concluded that the claims were *not* eligible for patenting, because nitric oxide treatment is a conventional hypoxia treatment. *Classen*

involved conventional immunizations, administered according to a new schedule. *Vanda* involved a conventional schizophrenia treatment, administered according to new criteria. The district court's decision in *Mallinckrodt* does not seem readily reconcilable with these appellate court decisions, and could be reversed on appeal.

HOW CAN DIAGNOSTICS AND BIOMARKERS BE PATENTED NOW?

Although the CAFC has created relative certainty in terms of what can be patented, it also introduces some serious complications to obtaining effective patent rights. There are a few apparent strategies for patenting diagnostics and biomarkers, but each has attendant drawbacks.

Methods of Treatment/Prevention Tied to the Test

Classen set a precedent that methods of treatment or prevention of disease tied to diagnostic methods are eligible for patenting. The USPTO recognizes this rule in their guidance documents (see Claims 5-6 in Example 29 in "*Subject Matter Eligibility Examples: Life Sciences*"). However, claims for such methods can be complicated to enforce. In order for patent infringement to occur, the patented method must either be performed by one person in its entirety, or performed by multiple parties all under the control or direction of a single party. When a patient is treated based on the result of a diagnostic test, often the diagnostic test is performed by a contract laboratory and the treatment is provided by a physician. Physicians are unattractive targets for patent infringement lawsuits, both because they are usually the customer base of the patented product (and nobody likes to sue their customers) and because they have limited immunity from patent infringement under 35 U.S.C. § 287(c). Even if the physician ordered the test (and so the test was performed under the physician's direction and control), suing the physician might not be desirable or possible. It might be argued that the testing lab induced the physician to both order the test and administer the treatment, but such an argument failed in *Cleveland Clinic Foundation v. True Health Diagnostics LLC*.

In *Cleveland Clinic*, the Clinic had determined that lipid lowering drugs are particularly effective in patients with elevated myeloperoxidase (MPO) activity. Accordingly, their patent claimed testing a patient for MPO activity, then administering a lipid lowering drug if MPO activity was elevated. The CAFC found the claim to be patent eligible under the *Classen* rule, but found that the testing lab had not infringed. The doctor had performed the step of administering the drug, and the testing lab did not direct him to do so. This fact pattern is likely to come up in numerous situations. Accordingly, when using this approach, patents should be carefully drafted to attempt to include only steps that will be performed by one party.

Novel Way of Measuring the Analyte

As *Exergen* teaches, a novel way to measure a recognized property or analyte can still be patented, even if not tied to a diagnostic step (see Claims 3-4 in Example 29 in "*Subject Matter Eligibility Examples: Life Sciences*"). This includes new assays, reagents,

protocols, and equipment. Claims to a specific way to measure the analyte have the inherent weakness that others can simply measure the analyte in some other way to evade patent infringement. This risk can be mitigated if the test requires FDA approval, as approval can be sought only by the patented method. This tactic will not work if another party seeks separate approval using another method, so it is not foolproof.

Measuring the Analyte Without a Diagnostic Step

The USPTO has taken the position that steps to measuring an analyte can be patented, in the absence of any diagnostic or other mental steps. In Claims 1 and 7 of the USPTO's Example 29 in "*Subject Matter Eligibility Examples: Life Sciences*," steps of determining the concentration of an imaginary analyte are recited without any treatment or diagnosis step. The USPTO's analysis is that, without a diagnosis step, the claim does not involve a mental step or a natural phenomenon. So far no judicial opinions support or refute this position. Without judicial affirmation, this might be a useful secondary way to patent a diagnostic test. However, it will only be effective if the analyte has never been measured before in a patient, at least not in the manner as claimed. Otherwise the claim, although directed to patent eligible subject matter, will lack novelty. There is also significant risk that the courts might not adopt the USPTO's analysis of the eligibility of this type of claim.

Look to Foreign Markets

The complex and vague constraints U.S. courts have placed on patents for diagnostics and biomarkers are unique to the United States. Most other developed nations allow diagnostic tests to be patented in some form or another. For example, in Europe diagnostics tests may be patented, so long as they are performed outside of the patient's body. Therefore, when preparing patent applications for diagnostics tests, those hoping to enter the European market should make it clear if the test can be performed *ex vivo*. Other developed countries have their own conventions that must be considered. Overall, the difficulties of patenting diagnostic tests in the U.S. should guide the development of new tests to focus on the needs of developed countries apart from the U.S.

THE OUTLOOK FOR THE FUTURE

At present there is no immediate prospect for changes in U.S. law that would return us to the regime that was in place until the *Mayo* decision. *Mayo* and *Myriad* changed U.S. law in ways that have put us out of step with the rest of the world and in violation of the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS). Ironically, the United States expended significant diplomatic capital to create the TRIPS regime and other treaties to increase the international harmonization of patent law. Although several pro-inventor organizations have proposed legislative changes to return the U.S. to the original patent regime, none have been introduced in Congress so far. However, efforts have begun in Congress to strengthen America's patent laws by reversing certain aspects of the America Invents Act of 2011. It is

possible that amid these efforts proposals to improve patents for diagnostic tests and personalized medicine could be introduced.

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