

## The Rise Of Companion Diagnostics In Personalized Medicine

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The completion of the human genome project and the explosion of information that followed have spurred significant growth in the field of personalized medicine. Personalized medicine generally refers to “the tailoring of medical treatment to the individual characteristics, needs and preferences of a patient during all stages of care, including prevention, diagnosis, treatment and follow-up.” A key driver of personalized medicine is the identification and leveraging of novel biological indicators of disease or disease risk that will lead to development of new diagnostics (and therapeutics).

In personalized medicine, the terminology “companion diagnostic” has been adopted by the U.S. Food and Drug Administration. The FDA defines a companion diagnostic as “an in vitro diagnostic device that provides information that is essential for the safe and effective use of a corresponding therapeutic product.” The FDA has highlighted four areas in which a companion diagnostic may be essential to the safe and effective use of a therapeutic product to:



Derrick Rowe

- (1) Identify patients who are most likely to benefit from the therapeutic product;
- (2) Identify patients likely to be at increased risk for serious adverse reactions as a result of treatment with the therapeutic product;
- (3) Monitor response to treatment with the therapeutic product for the purpose of adjusting treatment (e.g., schedule, dose, discontinuation) to achieve improved safety or effectiveness; and
- (4) Identify patients in the population for whom the therapeutic product has been adequately studied, and found safe and effective, i.e., there is insufficient information about the safety and effectiveness of the therapeutic product in any other population.

### Companion Diagnostics are Central to Personalized Medicine

Because companion diagnostics provide individual, treatment-essential information, patients and health care payors (both public and private) stand to benefit significantly from the growth of the companion diagnostic device industry. These benefits include: early disease detection and risk

characterization/classification/assessment, earlier therapeutic intervention, ability to implement beneficial enhanced disease monitoring and enhanced monitoring of therapies intended for chronic use. Companion diagnostics may also identify patients for whom a therapy may be ineffective, and in turn, produce serious adverse events — thereby saving payers the burden of (i) paying for a drug that does not work and (ii) paying the costs associated with treating potentially serious side effects.

### **FDA Regulation of Companion Diagnostics**

Companion diagnostics can be: (1) laboratory developed tests (LDTs); or (2) tests which have FDA premarket approval or clearance. LDTs are in vitro diagnostic tests that are intended for clinical use and designed, manufactured and used within a single laboratory. Although the FDA asserts it has had the legal authority to regulate LDTs as medical devices since 1976, the agency initially exercised its discretion to generally not regulate LDTs. This is changing and the FDA has recently taken affirmative steps toward regulating LDTs. LDTs, although important and relatively widespread (there are an estimated 11,000 LDTs offered by 2,000 laboratories in the U.S.), are not the focus of this article. Rather, we focus on companion diagnostics that have been subject to FDA premarket approval or clearance, because these companion diagnostics will continue to increase in import in conjunction with the growth of personalized medicine and increased FDA regulation of LDTs.

For these companion diagnostics, the FDA applies a risk based approach to determine the appropriate regulatory pathway. The level of risk, together with available risk-mitigation controls, establishes whether a companion diagnostic requires a premarket approval application (PMA) or a premarket notification submission (510(k)).

For medical devices in general, including companion diagnostics, three risk classifications (Class I, Class II and Class III) determine the level of the FDA scrutiny (premarket clearance/approval) required prior to marketing. “Device classification depends on the [claimed] intended use [and indications] of the device.” Class I devices are generally considered low risk, and most Class I devices are exempt from premarket clearance requirements (e.g., submission and clearance of a 510(k) premarket notification). “Class II devices are considered to carry moderate risk and are reviewed for substantial equivalence to legally marketed products (e.g., predicate) that have clearance for the same intended use by the premarket notification or 510(k) process ...” A 510(k) submission is required for nonexempt Class I or II devices. Class III devices are considered high-risk devices that are life-saving or life-sustaining and the majority of these devices require submission of a premarket approval application.

Many companion diagnostics have been, and will likely continue to be, subject to a Class III designation: (1) because they will likely be categorized by the FDA as high-risk devices (e.g., used by health care professionals to determine if a patient should receive or discontinue a life-saving or life-sustaining drug); and (2) most will not have a predicate device to cite in a 510(k) submission. In fact, all 19 FDA approved companion diagnostic devices were approved via the PMA process. Importantly, companion diagnostics approved through the PMA process may be eligible for valuable patent term extension.

### **Companion Diagnostic Market**

Globally, the companion diagnostic device market is projected to grow from an estimated \$3.1 billion in 2014 to an estimated \$8.7 billion in 2019. Oncology, inflammation and autoimmune diseases are projected to lead the way in companion diagnostic growth. Other areas of projected interest are companion diagnostics for: anticoagulants, antipsychotics and antidepressants.

Roche Diagnostics, Abbott Laboratories, Agilent Technologies Inc., Qiagen N.V. and Thermo Fisher Scientific Inc. together accounted for an estimated 86 percent of the global companion diagnostics market in 2013. In the same year, the United States accounted for approximately 43.97 percent of the companion diagnostic market. The European Union was a close second, accounting for an estimated 38 percent of the companion diagnostic market.

### **Selected Considerations When Developing New Companion Diagnostics**

Although the market for companion diagnostic devices is projected to grow at a substantial rate, challenges exist. For example, some therapeutic product sponsors often lack expertise in co-developing novel companion diagnostics in conjunction with novel therapeutics. Also, independent developers may view companion diagnostics as a high risk investment because, in some cases, the success of a companion diagnostic device may be linked to the regulatory approval of a corresponding novel therapeutic product. On the other hand, because a companion diagnostic may allow for optimal patient selection for a given therapeutic, thereby increasing the chances that an investigational product will show substantial evidence of efficacy or increased safety, co-development of a companion diagnostic and a novel therapeutic may make it more likely that the novel therapeutic will win FDA approval and become commercially available.

In instances where the novel therapeutic and companion diagnostic may be developed by two different entities, therapeutic product sponsors should evaluate different approaches to ensure alignment of interest with the companion diagnostic developer. A therapeutic product sponsor, after conducting such an evaluation, may elect to develop its own companion diagnostic in house, partner with an established diagnostic company or acquire a diagnostic company.

In partnerships with companion diagnostic developers, therapeutic product sponsors may in some instances be reluctant to pay high premiums (e.g., development and licensing or acquisition costs) to companion diagnostic partners. This is because additional companion diagnostic devices may enter the market. For example, in the case of Herceptin, within a decade of launch, there were six different FDA-approved companion diagnostic assays that utilized different testing technologies. To accentuate the point, the 19 FDA approved companion diagnostic devices correspond to 13 therapeutic products. Therefore, therapeutic product sponsors may refuse to pay a premium. As such, some therapeutic product sponsors have preferred to structure payments to diagnostic developers as fee for service or through fixed milestone payments. However, these fee payment structures may not be enough to ensure a sufficient return on investment for the diagnostic developers.

### **Potential Patent Issues with Companion Diagnostics**

#### **Patent Eligible Subject Matter**

One way to protect companion diagnostic market share is to have a strong patent portfolio containing broad, issued claims. In view of cases such as the U.S. Supreme Court's *Mayo Collaborative Services v. Prometheus Laboratories Inc.*, 132 S.Ct. 1289 (U.S. 2012), which address when certain subject matter becomes patent eligible, developers should consult with experienced patent counsel to arrive at a strategy to optimally patent protect their companion diagnostic. Patents directed to diagnostic methods must be carefully crafted such that e.g., claims therein will obviate patent subject matter eligibility (i.e., 35 U.S.C. § 101) rejections in the U.S. Patent and Trademark Office.

## Potential Patent Infringement Issues

Where diagnostic method claims are drafted to include an assay and a treatment administration, the entity that carries out the assay may be different from the entity that administers the treatment. In such cases, the diagnostic method may not be directly infringed.

Along these lines, induced infringement may also not apply to some companion diagnostic claims. In *Limelight Networks Inc. v. Akamai Technologies Inc.* 572 S.Ct. \_\_ (U.S. 2014), the U.S. Supreme Court ruled that a defendant cannot be liable for inducing infringement unless the induced party directly infringed the patent. For these and other reasons, companion diagnostic developers should work with experienced patent counsel to obtain the best possible patent protection for their companion diagnostics.

## Conclusion

Personalized medicine, and the companion diagnostic device market, will continue to grow in size and importance to patients, health care providers and payers of health care, and the market will increase in value. Developers of companion diagnostics will invest significant developmental resources and should, therefore, consult with legal counsel to:

- (1) Craft an optimal regulatory pathway that will lead to FDA approval;
- (2) Obtain the broadest possible patent coverage; and
- (3) Maximize the benefit of any available patent term extension.

—By Vern Norviel, David Hoffmeister, Derrick Rowe and Charles Andres, Wilson Sonsini Goodrich & Rosati PC

*Vern Norviel is a partner in Wilson Sonsini's San Diego office and former general counsel and corporate secretary of Perlegen Sciences Inc.*

*David Hoffmeister is a partner in Wilson Sonsini's Palo Alto, California, office and former senior counsel for drug and device law at Syntex USA. Inc.*

*Derrick Rowe and Charles Andres are associates in Wilson Sonsini's Washington, D.C., office.*

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