Personalized Medicine, Companion Diagnostics, and NGS Diagnostic Tests

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The field of personalized medicine has been evolving ever since the Human Genome Project[1] was completed in 2003. During that program researchers identified specific genes linked to particular disease states such as the MSH2 gene with colon cancer, and variations in the FAD gene linked to Alzheimer's disease. Personalized medicine looks to exploit this information by tailoring drug therapies to a patient's gene mutation. To do this requires a diagnostic test for use by physicians to identify candidates for therapy and, specifically, what the proposed customized therapy should be. Termed Companion Diagnostics by FDA, the agency issued its first guidance[2] in August 2014 to begin to define what constitutes a companion diagnostic and its regulatory path for filing.

FDA Companion Diagnostics Guidance The FDA guidance is intended to help companies identify the need for these tests during the earliest stages of drug development and to plan for the development of a drug and a companion test at the same time. The guidance finalizes and takes into consideration public comments on the draft guidance that FDA issued in 2011.

The guidance makes several important clarifications for in-vitro diagnostic (IVD) developers and drug developers. One point states that an IVD is considered a Companion Diagnostic when the IVD is essential to the safe and effective use of the therapeutic product. The key term in this definition is "Essential." The notion of essential is defined in footnote 6 (emphasis is mine):

*"When use of a **diagnostic device** is required in the labeling of a therapeutic product (e.g., for selection of appropriate patients for therapy, or to select patients who should not use the product, or for monitoring patients to achieve safety or effectiveness), use of the diagnostic device is considered 'essential' for the purposes of this guidance. Uses of diagnostic devices that are **suggested but not required** in therapeutic product labeling are not considered 'essential.'"*

This definition answered some questions but raised others. Specifically, are personalized drug therapies that require a companion diagnostic considered a combination product in the eyes of the FDA? The guidance further addresses this question in footnote 5:

FDA expects that most therapeutic product and IVD companion diagnostic device pairs will not meet the definition of "combination product" under 21 CFR 3.2(e). It is not necessary to contact the Office of Combination Products about whether a therapeutic product and IVD companion diagnostic device pair is a combination product unless recommended by CDER, CBER, or CDRH. FDA intends to require separate marketing applications for a therapeutic product and an IVD

companion diagnostic device intended for use with that therapeutic product regardless of whether the products could constitute a combination product.

So basically the agency is stating that if the drug and diagnostic requirement meet the definition of a combination product, they will require separate regulatory submissions. However, the FDA is willing to consider a single submission combination drug on a case by case basis.

The need for a companion diagnostic clouds the regulatory pathway for personal medicine innovators because the development timelines and skill sets are quite different for drug development and IVD development. It is quite possible that a novel drug therapy could be hung up waiting for the development of its companion diagnostic. Further confusing the issue is the FDA's desire in most cases to have the diagnostic complete before the drug therapy, although they have indicated they are willing to discuss this expectation on a case by case basis.

Next generation sequencing diagnostics (NGS)

Almost all current FDA-approved in-vitro diagnostic tests (IVD) measure only a single or a limited number of substances, such as DNA or proteins. Thus, it may require several patient samples and several tests to evaluate a patient's clinical status or to determine the best therapy for the patient. In contrast to current approved IVDs, NGS diagnostics can detect over three billion bases in the human genome and may identify almost three million genetic variants in a single test. It is possible that a single NGS test could identify multiple disease states, making it difficult for the FDA to evaluate the suitability of the test. Because an NGS can analyze the whole genome, it is not necessary to know what variant you are looking for. The FDA has issued a white paper regarding NGS diagnostics and held a public workshop in February 2015 to discuss the regulatory paths forward. The FDA has approved one NGS system based upon demonstrating analytical capability and reliability in detecting a subset of variants in the genome. This approach is discussed in the white paper and is a possible way to prove reliability and capability. In the white paper the FDA asked 10 basic questions to help frame the discussion at the workshop to obtain a clearer picture of what is a fair and reasonable regulatory requirement.

Drug advances

Personalized medicine has the potential to be the biggest advance in health in many decades. To fully realize its promise will require shifting the paradigm as to how we define quality, efficacy, and safety, for both personalized drug therapies and their companion diagnostics. The FDA is continuing to refine its position on Companion Diagnostics and is working on more detailed guidance. But the agency must consider the broader implications to Laboratory Derived Tests (LDTs) within the guidance. Wall Street has bet heavily on this particular sector of biotech, creating some of the largest IPOs of 2014 and 2015. Whether the FDA and industry can navigate this complex relationship between performance, measurement, and safety will determine the likelihood of its realization.

References

1. Human Genome Project:
http://web.ornl.gov/sci/techresources/Human_Genome/index.shtml [1]
2.
http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM262327.pdf [2]

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This Regulatory Forum article appeared in the July/August 2015 issue *[3] of* Controlled Environments*.*

Links:
[1] http://web.ornl.gov/sci/techresources/Human_Genome/index.shtml?
[2] http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM262327.pdf?
[3] http://digital.cemag.us/controlledenvironments/20150708#pg16?