

The FDA and Laboratory

The Brouhaha Continues

By Neil Canavan and John McCleery

With each step forward in cancer diagnostics, a new debate ignites. In the diagnostics industry there is much debate between industry and the U.S. Food and Drug Administration (FDA) regarding regulation of Laboratory Developed Tests (LDTs). At the heart of the matter is the accuracy of the results provided by the diagnostics, what to do with the information gleaned from the tests, and whether and how to regulate these tests. With the scientific advancements being made in personalized medicine to better predict patients' responses to targeted therapies, developing and using LDTs has become increasingly important. Additionally, with the increasing hope that personalized oncology will deliver clinical benefit at the right cost to stakeholders and translate into increased value from the oncology pipeline, the stakes are quite high in this debate over regulation of LDTs.

In a recent NEJM article (July 2010), Margaret A. Hamburg, MD, Commissioner of Food and Drugs, and Francis S. Collins, MD, PhD, Director of the National Institutes of Health inferred that the field of personalized medicine cannot make good on its clinical promise if the diagnostics

being used produce inaccurate or tenuous results. In the "Paths to Personalized Medicine" article, the authors recognize that getting the right drug at the right dose at the right time to the right patients has many obstacles including, "scientific challenges, such as determining which genetic markers have the most clinical significance, limiting the off-target effects of gene-based therapies, and conducting clinical studies to identify genetic variants that are correlated with a drug response."

Currently, LDT companies must meet specific operational standards that are regulated by CMS's Clinical Laboratory Improvements Amendment (CLIA). However, some in the industry don't think that CLIA is sufficient in its scientific rigor and are requesting stricter and tighter regulation from the FDA regarding these diagnostics since their results can directly impact patient care. In March 2009, we reported on Genentech setting off a personalized oncology firestorm when the company filed a Citizen's Petition requesting that the FDA increase its regulation over the diagnostic testing industry.

That action launched a comprehensive defense by the companies developing and marketing LDTs. In a general sense, the debate revolves around the balance between proper regulation to provide scientific validity to stakeholders and the loss of incentive to innovate that could come as a result of increased regulation.

Seeking to find the right balance from these perspectives and hear from LDT stakeholders, the FDA held a public meeting in July on LDT regulation to discuss the role, if any, the agency intends to take in the future. Director of Devices and Radiologic Health, Jeffrey Shuren, MD, JD, began the hearings by stating that "Although [the] FDA has decided to exercise authority over LDTs, we have not decided how we will exercise that authority." Thus, the debate was under way and the tension between the groups was palpable.

The Background: LDTs vs IVDs

Courtney Harper, PhD, Office of In Vitro Diagnostic Device Evaluation and Safety, CDRH/FDA, provided the historical account of how the safety and effectiveness of medical devices has evolved from the Feder-

Developed Tests:

al Food, Drug, and Cosmetic Act of 1938, which extended federal control to include cosmetics and therapeutic devices, to the Medical Device Amendment of 1976 which further defined the safety and effectiveness of medical devices.

“This provided for risk-based regulation of medical devices,” she said, meaning that a regulatory difference was acknowledged between an artificial knee and a tongue depressor. Risk classification is determined by expert panels, and the designation of low, moderate, or high risk to the patient of a diagnostic test (should it fail) is associated with a relative stringency of regulation. Harper also explained the two general types of tests to which these flexible regulations apply: (a) LDTs, which in the past were understood as

tests designed and utilized by a single lab; and (b) in vitro diagnostics (IVDs) which are commercially distributed test kits.

“There’s currently a bifurcated process for getting marketing approval for these tests,” she informed. IVDs are subject to premarket approval as granted by the FDA, while LDTs need only meet CLIA criteria and are subject to further regulatory enforcement at the FDA’s discretion. The FDA regulates the IVD product itself; CLIA is only concerned with the LDT’s originating lab.

As the technology of LDTs became orders of magnitude more complex over time, the perception of risk by the FDA shifted. Initially, this resulted in adoption of the 1997 Analyte Specific Reagent (ASR) Rule, which looked to regulate not the clinical claims of the test, but the materials used in the process. Unfortunately, as Harper pointed out, “Publication of the ASR rules was followed by inadvertent or deliberate abuse of regulations.” She recapped how platforms sold

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for clinical use were merely relabeled “for research use only” thereby making them exempt from any premarket review.

Further advances in diagnostic complexities gave the FDA pause including, automated interpretation of results; “non-transparent” statistical modeling; multivariate analyses; and the ubiquitous use of de novo software (all well outside of CLIA purview). And finally, as the manufacturers of LDTs embraced a direct-to-consumer (DTC) business model, “marketed with claims that have a profound clinical impact,” noted Harper, this development started to blur the line between LDTs and IVDs, thus, a meeting inviting public comment on the issues prior to the issuance of new guidance was convened.

The Public Speaks

At the hearings, Cara Tenenbaum, Senior Policy Director for the Ovarian Cancer National Alliance stated



Cara Tenenbaum

that her concern regarding regulation “is that patients need to have accurate information. If people are misdiagnosed with ovarian cancer, or told they are having a recurrence when they are not, it can cause serious harm, not the least of which is unnecessary chemotherapy or surgery.” She pointed out that there have been some [LDTs] brought to market that are not clinically reliable, and serious errors have occurred. A bur-

den of understanding has also been foisted upon the patient, as well as the healthcare provider.

“In my organization,” she said, “we’ve had to explain to patients what tests mean, what they don’t mean, or if there is any published data [to back up a claim]. It’s difficult; I get nasty letters asking why we haven’t endorsed certain tests for which we have not seen phase 3 data.”

Coming down on the side of regulation is Richard Hockett, MD, Chief Medical Officer, Affymetrix. He asserts that “if left to our own devices, pun intended, manufacturers will push the envelope,” and under certain circumstances, this has hurt patients.” He further states, “the key is to make sure that regulation doesn’t stifle innovation.” Hockett addressed the issue of the exploita-



Richard Hockett, MD

tion of regulatory loopholes, as alluded to in the FDA’s opening remarks. “Manufacturers are now looking at the less regulated LDTs as a stepping stone to IVDs.” Reasons for this include the advent of new technologies and the expense of going all the way to FDA approval of an IVD. The Profit & Loss statement dictates seeing if the uptake of a newly developed LDT justifies investment in the regulatory process.

Any additional oversight of highly regulated labs such as the ones found at Genomic Health “must be bal-

anced with the clinical need for further innovations and patient access,” said Kathy Hibbs, Senior VP and General Counsel, Genomic Health. Hibbs cited the clinical validity of Genomic Health’s Oncotype DX genetic signature assay which is used to guide



Kathy Hibbs

treatment of breast cancer. Launched in 2004 in compliance with existing CLIA regulations, Oncotype DX has been investigated in at least 13 studies involving more than 4,000 patients; supporting data has appeared in top-shelf, peer-reviewed journals such as NEJM, and the test is now included in breast cancer treatment guidelines.

“I highlight this to make the point that any additional regulation of LDTs must recognize the value that validated tests are already providing to patients.” Going forward, the risk posed by LDT data must be balanced with the risk that such regulation will stifle innovation necessary to improve patient outcome. [Note: Oncotype DX is classified as an LDT, and the assay has not been approved by the FDA.]

Saladax Biomedical, Inc, is a company developing assays for therapeutic drug monitoring (TDM) in the field of oncology. After requesting an evaluation of a Pre-IDE (Investigational Device Exemption) for their lead diagnostic, the company received a response from the FDA that recom-



mended conducting a phase 3, prospective clinical trial. Salvatore Salamone, PhD, CEO of Saladax said, “In all my 25 years in the industry, I’ve never seen such a request of an IVD company for a TDM assay. Following this recommendation would have shut us down.”



Salvatore Salamone

In follow-up meetings with the Center of Devices and Radiological Health it was suggested that Saladax explore an LDT regulatory route, which the company eventually did. To further illustrate LDT/IVD regulatory disconnect, Salamone stated that had Saladax actually pursued IVD approval with the expensive, time-consuming phase 3 trial, the typical reimbursement for such tests would have rendered the development process untenable.

After the meeting concluded, Agendia CEO and Founder Bernhard Sixt, PhD, commented that “This [FDA] meeting was necessary because some companies crossed the line (exploiting grey areas), and this has led to frustration among those of us who have had no problem with the original legislation.” Agendia currently markets MammaPrint, a prognostic test that predicts risk of breast cancer recurrence. Although MammaPrint is considered an LDT, Sixt sought out



Bernhard Sixt

FDA clearance (which was granted) mindful of the fact that his product’s performance involved elevated risk, and unlike the experience of Saladax, the exchange of information was both fruitful, and timely, and, regarding Agendia’s other products, consistent. “In all cases we have had approvals within 5 months or less,” said Sixt, pointing out that the FDA, “never asked questions which we shouldn’t have asked ourselves.” Sixt called the

“In all my 25 years in the industry, I’ve never seen such a request of an IVD company for a TDM assay. Following this recommendation would have shut us down.”

FDA approval process cautionary but not onerous, perhaps because other currently marketed tests of what Sixt considers to be of equivalent risk have not been FDA approved.

Regarding the added cost of expanded regulations, Sixt does not see it as a deal killer. “If you look at the biotech model, smaller players are not cut out. The same should be true for molecular diagnostics.” In his view, earning approval through a consistently applied validation process ensures investor confidence—venture capitalists distinctly dislike grey areas. Sixt says he is not as concerned

with new regulations, as much as he is about clarity. “At the moment it’s unclear what regulation is...the FDA should clearly spell out what is medium and high-risk testing; and make the set of rules that already exist transparent.” He would also like to see regulations evenly applied.

Preliminary Final Recommendations

In its literature, the FDA acknowledges that there is an absence of a level playing field that creates “a disincentive to innovation by other manufacturers whose tests are approved or cleared by the agency.” Last month, two comprehensive evaluations containing recommendations for the diagnostics industry were issued by the FDA. The recommendations focused on device innovation, creating a more predictable regulatory environment, and enhancing device safety. Although the recommendations are preliminary, Shuren advised that the agency will make a decision on which recommendations to adopt, but only after a thorough review of additional comments.

The stakeholders in the oncology industry impacted by this regulation are broader than in other circumstances. Regulation of LDTs will impact on patients, private insurers, CMS, oncologists, LDT manufacturers, venture capitalists, and pharmaceutical developers and manufacturers. It is impossible to ignore the financial impact that will ripple through all these stakeholders, and yet by providing an open forum and the opportunity to consider all aspects of the debate, we can hope that the FDA will strike the right balance between regulation and innovation. **NC JM**