Regulatory & Reimbursement Policy Trends Affecting Market Access for Diagnostic Devices – Emphasis on Validity and Quality

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Advances in personalized medicine and diagnostic testing, combined with a heightened stress on value based medicine, are leading to policy changes in both the regulatory and reimbursement domains that will have a significant impact on laboratory medicine. These policy changes include:

i) Food and Drug Administration's (FDA) increased assertion of its regulatory authority over laboratory developed tests
ii) Public and private payers' introduction or enforcement of existing high evidentiary thresholds for the reimbursement of diagnostic testing and recognizing the value of analytical and clinical validity.

FDA Asserts Regulatory Authority On Laboratory Developed Tests, Stressing The Importance Of Clinical Validity And Quality

Through actions recently taken, it would appear that the Food and Drug Administration (FDA), is poised to assert its regulatory authority over in vitro diagnostics (IVD). Several developments in the recent past that include publication of related guidance documents, enforcement actions by the FDA, and public pronouncements both by the FDA Commissioner and elected representatives would indicate that FDA is laying the groundwork to issue guidance on laboratory developed tests (LDT).

On November 25, 2013 FDA released a final guidance discussing distribution of IVD devices intended for research use only (RUO) or investigational use only (IUO)[1]. The purpose of the guidance was twofold:

a) To clarify the requirements applicable to RUO or IUO IVD products
b) To mandate that labeling must be consistent with the manufacturer's intended use of the device and that manufacturers are at risk of enforcement if they encourage RUO labeled products for use in clinical diagnostic applications, thereby holding manufacturers accountable for distribution practices.

The issuance of this final guidance document followed other significant developments where, on November 22, 2013, FDA issued a warning letter to 23andMe Inc., asking it to immediately discontinue the marketing of its Saliva Collection Kit and Personal Genome Service (PGS) Kit.[2] The Agency issued this letter on the grounds that 23andMe, which claimed that its tests were exempt from regulation by virtue of their being LDT services,

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[1] Food and Drug Administration. (2013). Distribution of In Vitro Diagnostic Products Labeled for Research Use Only or Investigational Use Only – Guidance for Industry and Food and Drug Administration Staff. Retrieved from [http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm253307.htm]

[2] Food and Drug Administration. (2013). Warning Letter to 23andMe. Retrieved from [http://www.fda.gov/iceci/enforcementactions/warningletters/2013/ucm376296.htm]

was in violation of the Federal Food, Drug and Cosmetic Act by marketing a medical device subject to FDA oversight without marketing clearance or approval.

Earlier in the summer FDA Commissioner Margaret Hamburg, at the American Society of Clinical Oncology 2013, expressed concerns that, *"…LDT's have become more sophisticated and complex. Results from these tests are rapidly becoming a staple of medical decision-making…*" and the FDA *"...is working to make sure that the accuracy and clinical validity of high-risks tests are established before they come to market."*[3]

In 2010, the FDA, recognizing that the complexity of LDTs was increasing, announced that the agency was developing a guidance to actively regulate LDTs under a risk-based framework.[4] The guidance is intended to inform industry as to how LDTs would be regulated by the FDA and the requirements necessary to ensure patient safety. In addition, FDA wanted to ensure that the accuracy and clinical validity of LDTs were established before they were used in clinical decision making. The Agency claimed accuracy and validity demonstration to be outside the realm of Clinical Laboratory Improvement Amendments Act (CLIA) regulation. CLIA is administered by CMS, which sets the standards for operation of the laboratories that use LDTs as well as FDA approved tests. While this draft guidance was sent to Office of Management and Budget (OMB) by FDA several years ago, it has yet to be released.

On July 2, 2014, five US senators jointly wrote letter to the OMB asking the Office to release the FDA guidance on LDTs for public comment and feedback. In this letter, they state that "…*for years this draft guidance has languished at OMB causing continued unpredictability and uncertainty for industry, clinicians, patients and the general public."* They further stated, *"…Because these more advanced LDTs are a staple of clinical decision-making and are being used to diagnose, high-risk, and relatively common disease, it is imperative that they perform as they are expected. Incorrect results mean that patients either will not seek out the care and therapy that is needed, or will be subject to treatments that do not work or are harmful*."[5]

FDA Reviews Diagnostic Devices for Clinical and Analytical Validity

Depending on the FDA's risk-based classification of a diagnostic device, a laboratory test is either FDA cleared and found substantially equivalent to predicates or granted premarket approval as a novel safe and effective device. FDA's process requires that

[3] Turna, R. (2013). After Long Silence on LDT Regulation, FDA Commish Revives Thorny Topic at ASCO. *GenomeWeb.* Retrieved from [http://www.genomeweb.com/after-long-silence-ldt-regulation-fda-commish-revives-thorny-topic-asco]

[4] Food and Drug Administration. (2010). FDA/CDRH Public Meeting: Oversight of Laboratory Developed Tests (LDTs). Retrieved from [http://www.fda.gov/medicaldevices/newsevents/workshopsconferences/ucm212830.htm]

[5] Senator Ed Markey, Letter to Office of Management and Budget, July 2, 2014). Retrieved from [http://www.markey.senate.gov/imo/media/doc/2014-07-02_Deese_LDTs.pdf]

diagnostic devices are manufactured under Good Manufacturing Practice (GMP) as specified in Quality Systems Regulation[6]. FDA reviews a given diagnostic test for clinical validity of the claimed label; that is, the measurement of an analyte for a diagnostic claim is supported by clinical observation and studies. Importantly, FDA also requires that prior to marketing; the diagnostic device demonstrates robustness as reviewed by analytical validation studies – including reproducibility, precision, accuracy, sensitivity and specificity. Tests that do not meet certain thresholds of sensitivity and specificity may not be found approvable by the Agency. In cases where software may be a critical component of the functioning of a test and reporting of the result, FDA has specific guidance on how the software should be validated[7].

Regardless of the regulatory pathway for approval, FDA cleared/approved tests are required to be performed in a laboratory that has been certified by CLIA unless the diagnostic test is CLIA-waived. CLIA regulations require that clinical laboratories be certified by their state as well as CMS before they can accept human samples for diagnostic testing.

When authorizing a device for marketing, FDA classifies a test as low, medium or high complexity per CLIA regulations. The Agency issued a final guidance recently on standards for CLIA-waived tests, when applicable, where it stresses the importance of a "gold-standard" test for comparison.[8]

All of these actions indicate an FDA that is asserting its regulatory authority over in vitro diagnostic tests, and that it will continue to clarify its position on regulatory oversight of clinical laboratory testing.

Ensuring Device Quality and Safety through Post-Market Activities

FDA has an important role in ensuring that a medical device, once approved, is marketed for the intended use as originally claimed and that there are no failures or adverse events associated with its use.

[6] Food and Drug Administration. (2013). Code of Federal Regulations (C.F.R.) at 21 C.F.R. Part 820. Retrieved from [http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=820]

[7] Food and Drug Administration. (2002). General Principles of Software Validation; Final Guidance for Industry and FDA Staff. Retrieved from [http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm085281.htm]

[8] Food and Drug Administration. (2008). Recommendations: Clinical Laboratory Improvement Amendments of 1988 (CLIA) Waiver Applications for Manufacturers of In Vitro Diagnostic Devices. Retrieved from [http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm079632.htm]

Accordingly, medical device manufacturers must develop and implement quality systems to ensure that their products meet certain specifications and are in compliance with applicable regulatory requirements.[9] Quality system requirements for medical devices are available in the Code of Federal Regulations (C.F.R.) at 21 C.F.R. Part 820 and are applicable to device manufacturers that intend to distribute finished medical devices commercially.[6]

FDA inspects medical device manufacturers that produce FDA-regulated devices to confirm that they are complying with applicable regulatory requirements (i.e., the quality system regulation).[10] In addition to inspecting manufacturing sites where devices are produced, FDA also inspects the following: facilities where clinical trials are conducted; foreign manufacturing and processing sites for FDA-regulated devices that are sold in the United States; and imported products.

The inspections conducted by FDA vary according to FDA's regulatory needs. For example, the FDA may conduct a pre-approval inspection after a manufacturer submits an application to the Agency requesting clearance/approval for a new medical device.[10] In this circumstance, the site inspection information is used to evaluate the pending application and provide further insight into an applicant's standard operating procedures. Additionally, FDA may conduct "for-cause" inspections that are used to investigate device-related problems that have come to the Agency's attention.[11] FDA also conducts routine inspections of FDA-regulated facilities.[10] In addition to inspecting manufacturing sites where devices are produced, FDA also inspects the following: facilities where clinical trials are conducted; foreign manufacturing and processing sites for FDA-regulated devices that are sold in the United States; and products imported at the border. Following an inspection, FDA may issue an inspection report (FDA Form 483) that contains possible violations and a written establishment inspection report (EIR) in determining what further regulatory action (if any) is needed.

Payers Are Demanding Higher Evidentiary Thresholds for Diagnostic Testing

Distinct from the FDA's exercising its enforcement discretion on the regulation of laboratory developed tests, the Medicare Administrative Contractors (MACs), are taking the lead on demanding higher evidentiary standards for the payment of diagnostic tests.

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[9] Food and Drug Administration. (2014). Quality System (QS) Regulation/Medical Device Good Manufacturing Practices. Retrieved from [http://www.fda.gov/medicaldevices/deviceregulationandguidance/postmarketrequirements/qualitysystemsregulations/default.htm]

[10] Food and Drug Administration. (2014). What does FDA inspect? Retrieved from [http://www.fda.gov/AboutFDA/Transparency/Basics/ucm194888.htm.]

[11] Food and Drug Administration. (2012). Regulatory Procedures Manual: Chapter 11. Retrieved from http://www.fda.gov/downloads/iceci/compliancemanuals/regulatoryproceduresmanual/ucm074290.pdf.

The Palmetto GBA-administered MolDx pilot[12] project has focused on making coverage determinations for molecular diagnostics on the basis of 3 standards of evidence. These are: analytic validity, clinical validity, and clinical utility, all substantiated by high-level evidence. Palmetto's intent in using these 3 levels of evidence was to go beyond or supplement CLIA and other regulatory standards.

TRICARE®, the health care program serving Uniformed Service members, retirees and their families, has issued a non-coverage policy for LDTs that have not been approved or cleared through the FDA review process. In June 2014, the Department of Defense (DoD) announced a continuation of a demonstration project that will cover LDTs, but only if they meet the requirements of a hierarchy of clinical evidence. The demonstration allows LDTs priority review, but if found to lack sufficient evidence there will not be an opportunity to appeal the non-coverage decision. In its Federal Register notice, the DoD re-asserts the FDA's authority on regulating LDTs.[13]

As various public agencies and private payers come to their decisions independently, in a value-based environment, it is becoming increasingly evident that robust evidence of a test's performance and the claims made in the label are critical to ensure therapeutic validity and quality patient care.

[12] Hughes K. (July 11, 2014).MolDX May Be the Norm, but is it the Future? *Avalere Health*. Retrieved from [http://avalere.com/expertise/life-sciences/insights/moldx-may-be-the-norm-but-is-it-the-future]

[13] Department of Defense. (2014). Defense Health Agency Evaluation of Non-United States Food and Drug Administration; Approved Laboratory Developed Tests Demonstration Project. Retrieved from [https://www.federalregister.gov/articles/2014/06/18/2014-14247/defense-health-agency-evaluation-of-non-united-states-food-and-drug-administration-approved]

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