Hogan Lovells

FDA/IVD Industry Overview

Association of Medical Diagnostics Manufacturers
41st Annual Meeting
Bethesda, Maryland

Jonathan S. Kahan, Partner
Hogan Lovells US, L.L.P
jonathan.kahan@hoganlovells.com
202.637.5794

April 12, 2013

IVD Initiatives and Directions

- There appear to have been no significant new initiatives with respect to IVDs in 2013-2014
- However, there have been hints of changes and developing technologies are evident
  - Personalized Medicine and Next-Generation Sequencing
  - LDTs and possible FDA guidance
  - Companion Diagnostics as a growing trend
  - Direct to Consumer Testing issues (genetic or otherwise) - addressed through agency enforcement
  - Continued use of de novo downclassifications to advance novel, low risk products and technologies
    - CytoScan Dx Assay
    - Illumina MySeqDx Platform, as a class II exempt device
  - Recent guidances – blood glucose monitoring and RUO tests
  - Shifts in indications for use to include “wellness” conditions, in addition to diseases
- As new technologies and novel uses develop, continued flexibility and openness to dialogue by both FDA and industry will be essential

IVD Initiatives and Directions

- Personalized Medicine Report (issued October 30, 2013)
  - Personalized medicine: “use of genomic, epigenomic, exposure and other data to define individual patterns of disease, potentially leading to better individual treatment”
  - Based on product submissions and clinical studies, “the era of personalized medicine” has arrived
  - Report notes that the number of submissions to OIR involving personalized medicine has “increased by more than an order of magnitude since 2007” (Report at 54)
  - “Many of the diagnostic tests use in personalized medicine are *in vitro* diagnostics devices (IVDs)…[a] challenge associated with ensuring the safety and reliability of IVDs is that they may be marketed…as laboratory developed tests (LDTs)”
    - “While FDA…has generally exercised enforcement discretion (withheld active enforcement) over LDTs…confidence can only be assured if the diagnostic test is properly validated in the *specific therapeutic context of use*” (Report at 34)

IVD Initiatives and Directions

- Potential FDA guidance concerning the regulation of Laboratory Developed Tests (LDTs) still pending
  - FDA has indicated that it will exercise enforcement discretion with respects to LDTs using a risk based approach
  - However, when LDTs are used in conjunction with sample collection kits with a potentially "new" indication, FDA may assert its authority
    - Untitled letters and Warning Letters addressing assay "systems" (including the sample collection device and an LDT) have been issued
    - Most sample collection devices were moved to OIR for review in November/December 2013
  - Recent presubmission meeting experience with OIR suggests that until an LDT guidance document is issued, FDA is unwilling to give feedback on whether a particular LDT practice is permissible
  - In practice, FDA appears to want to avoid finding any specific LDT practice acceptable. For now, Agency will tell specific entities through enforcement actions when they have crossed a line
  - Industry not likely to see the full scope of any future LDT regulatory approach until the Guidance is issued

IVD Initiatives and Directions

- CDRH's Fiscal Year 2014 Proposed Guidance Development List
  - Final Guidance Document on In Vitro Companion Diagnostic Devices
  - Draft Guidance for Direct to Consumer (DTC) Genetic Testing: IVDs

Available at: http://www.fda.gov/medicaldevices/deviceregulationandguidance/overview/mdufaiii/ucm321367.htm

Enforcement Trends for Diagnostics

- Direct-to-consumer (DTC) genetics testing
  - FDA concern that tests based on a few genes cannot meaningfully predict diseases
  - November 22, 2013 Warning Letter to 23andMe, Inc. Saliva Collection Kit and Personal Genome Service (PGS)
    - "Some of the uses for which PGS is intended are particularly concerning, such as assessments for BRCA-related genetic risk and drug responses…because of the potential health consequences that could results from false positives or false negative assessments for high-risk indications such as these."
    - "[W]e still do not have any assurance that the firm has analytically or clinically validated the PGS for its intended uses…"

Clearance Trends

- OIVD premarket clearances increased slightly in FY2011, but have since returned to FY2010 levels
  - October 2013 to April 2014 = 146 clearances with 3 de novo reclassifications
  - October 2012 to April 2013 = 144 clearances with 1 de novo reclassification
  - October 2011 to April 2012 = 170 clearances with 2 de novo downclassifications
  - October 2010 to April 2011 = 145 clearances with 1 de novo downclassification

OIR De Novo Reclassification

- Recent de novo example:
- Affymetrix CytoScan Dx Assay (K130313) cleared January 17, 2014
  - Qualitative assay intended for the postnatal detection of copy number variations in genomic DNA obtained from peripheral whole blood in patients referred for chromosomal testing based on clinical presentation
  - "First of its kind post-natal test to help diagnose developmental delays and intellectual disabilities in children"[1]

[1] **FDA News Release (Jan. 17, 2014), available at: http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm382179.htm.**

Research Use Only and Investigational Use Only in IVDs

- FDA issued the Final Guidance "Distribution of In Vitro Diagnostic Products Labeled for Research Only Use or Investigational Use Only: Frequently Asked Questions" on November 25, 2013
  - Introduces the concept of certification programs as evidence that the manufacturer is ensuring its consumers are using the RUO or IUO product in according with its intended purpose
  - Some limits on support RUO manufacturers can provide laboratory customers
    - "provision of certain types of specialized technical support (e.g., assistance in performing clinical validations) to clinical laboratories" would be in conflict with the product's RUO or IUO labeling
  - FDA will review the totality of the circumstances when it comes to assessing whether an IVD is properly labeled as an RUO or IUO

Blood Glucose Monitoring Test Systems (BGMTS)

- FDA released two draft guidances on blood glucose monitoring
  - Draft Guidance: Self-Monitoring Blood Glucose Test Systems for Over-the-Counter Use (January 7, 2014)
  - Draft Guidance: Blood Glucose Monitoring Test Systems for Prescription Point-of-Care Use (January 7, 2014)
- Historically, FDA did not recommend different types of information in 510(k)s for BGMTS used by medical professionals as compared to over-the-counter
- New recommendations for labeling, meter performance evaluation, manufacturing controls, and cleaning and disinfection procedures are aimed to help improve accuracy and performance
- Letter of Manufacturers of BGMTS
  - FDA sent letters to manufacturers with BGMTS listed with FDA that outlined recent changes in the review of BGMTS submissions
  - "These changes were instituted in response to a critical public safety risk concerning the risk of transmission of diseases from shared use of fingerstick (lancing) device and point of care blood testing devices."
- Several companies are on the road to a fully operational, closed-loop artificial pancreas, with the CDRH issues being handled by OIR

PMA Approvals

- Recent OIR approvals include both infectious disease and cancer markers, and rely on a variety of marker types, such as antigen detection, antibody detection, and gene detection/expression
  - Elecsys HBEAG Immunoassay (P130015)
    - Hepatitis B Assay
  - MiniMed 530G System (P120010)
    - Continuous delivery of basal insulin
  - Abbott Realtime HCV Genotype II (P120012)
    - Hepatitis C Assay
  - BioMerieux Thxid Braf Assay Kit (P120014)
    - BRAF V6000E and V6000K mutations from FFPE human melanoma tissue
- Breadth and complexity of assay technologies continue to expand

Present Issues Facing the IVD Industry

- While FDA is developing an approach, companies and clinical laboratories must carefully assess when and how to launch LDTs *versus* IVDs
- FDA appears committed to regulating LDTs at some level, but practical and political considerations have resulted in delay in the issuance of OIR guidance
- FDA appears to be changing practices with respect to regulation of related products (*e.g.,* sample collection devices) in an effort to tighten the reins on LDTs
- Companion Diagnostics will be area of increasing focus

New Issues Facing the IVD Industry

- General Wellness Testing
  - Wellness tests intended to measure certain parameters of bodily function that relate to health and wellness
    - typically include a substance to be ingested/measured to produce a sample, a sample collection device, and reagents used to analyze the sample
  - Likely to be viewed by FDA as an integrated system subject to FDA regulation as a medical device or companion product (*e.g.*, with a drug or treatment aimed at improving wellness)

Conclusion

- FDA regulatory initiatives relating to IVDs have been frequent, increasing in number, and may involve legislative and refocused regulatory initiatives
- Manufacturers, laboratories, and physicians should try to keep abreast of new developments
- Where possible, trade associations, professional associations, and interested parties should make their views known about the need to continue streamlining the IVD clearance/approval process
- Agency feedback and open communication a must

www.hoganlovells.com

Hogan Lovells has offices in:

Abu Dhabi	Caracas	Ho Chi Minh City	Moscow	San Francisco
Alicante	Chicago	Hong Kong	Munich	Shanghai
Amsterdam	Colorado Springs	Houston	New York	Silicon Valley
Baltimore	Denver	Jeddah*	Northern Virginia	Singapore
Beijing	Dubai	London	Paris	Tokyo
Berlin	Dusseldorf	Los Angeles	Philadelphia	Warsaw
Boulder	Frankfurt	Madrid	Prague	Washington DC
Brussels	Hamburg	Miami	Riyadh*	Zagreb*
Budapest*	Hanoi	Milan	Rome	

* Associated offices