Hogan Lovells

FDA/IVD Industry Overview

Association of Medical Diagnostics Manufacturers
40th Annual Meeting
Bethesda, Maryland

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April 17, 2013

IVD Initiatives and Directions

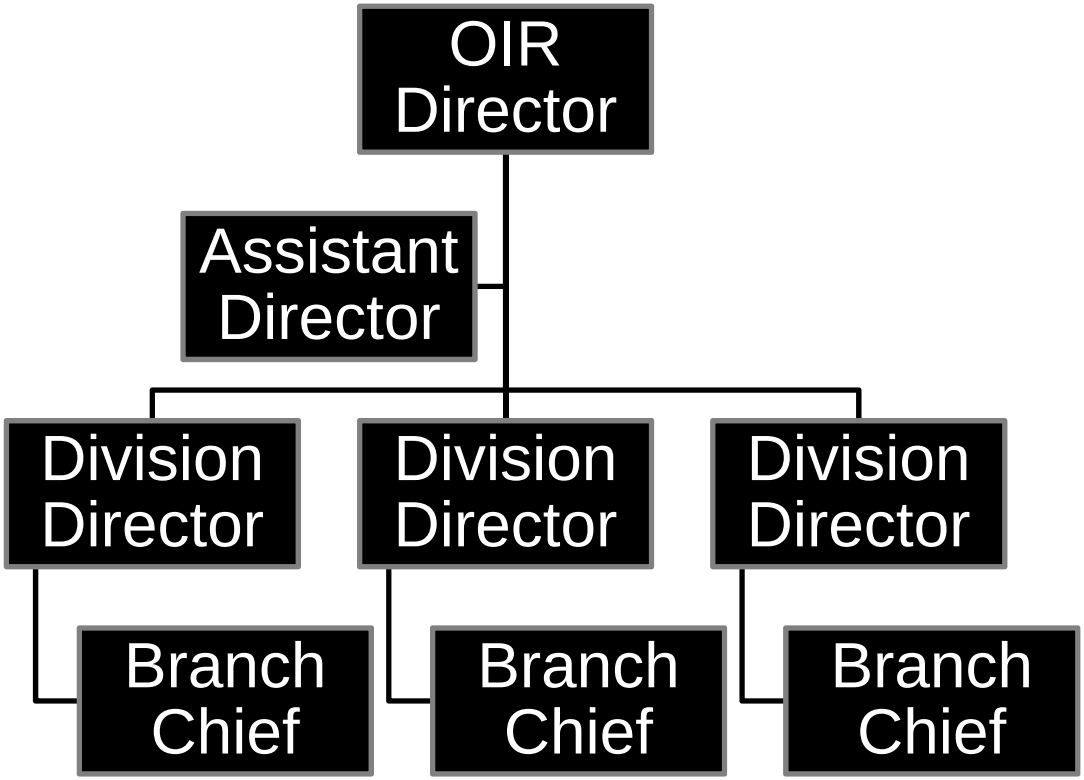
- FDA's internal regulatory process reevaluations have taken several new turns since 2012
  - Refuse to Accept Checklist now in place for 510(k) Notices
  - De Novo draft guidance creates pathway for early interactions for novel, low risk devices
  - MDUFA III timelines and "interactive" discussions during submission reviews will likely impact how submissions are reviewed and the decisions that FDA issues
    - Will fewer AI letters and less time to respond lead to an increase in NSE determinations?
- OIR, in many ways, has already employed helpful, interactive review processes
- Office's stated goals include continued open communication in regulatory applications, with focus on sound science as the norm, not the exception
- Whether OIR's historic flexibility will continue remains to be seen

Administrative Changes

- FDA re-organization led to formation of Office of In Vitro Diagnostics and Radiological Health (“OIR”)
- Change was made to allow branches within each office to focus on similar product groups
- OIR reorganized to include two new divisions with integrated regulatory responsibilities aligned by product area:
    - Division of Mammography and Quality Standards (DMQS)
    - Division of Radiological Health (DRH)

Administrative Changes

- Minimal structural changes, other than addition of Branch Chiefs, under Division Directors:



Regulatory Reality

- OIR processes generally have been more interactive and open to industry feedback (compared to ODE)
- Several review and compliance issues continue to be impacted by FDA's global shift to heightened regulatory control
  - Premarket clearances appear to have fallen to levels last seen in 2010, after an increase in FY2011(144 clearances since 10/1/2012)
  - OIR continues to utilize the de novo downclassification process, but only in 1 instance in FY2013
  - PMA and PMA Supplements remain stable in number, but with ever increasing technological complexity
  - LDT and IVDMIA issues still open and awaiting OIR guidance

Enforcement Trends for Diagnostics

- No new Warning Letters, Class 1 or Class 2 recalls, or significant new compliance initiatives
- Direct-to-consumer genetics testing - FDA has not issued any new letters to DTC genetics test facilities since early 2012
- One DTC provider is seeking FDA clearance
  - 23andMe announced in July 2012 the submission of "an initial batch of seven health-related tests to the FDA for review,"
  - Company also announced plans to submit 100 additional tests in separate installments before the end of the year (The Denver Post, http://www.denverpost.com/snowsports/ci_21191330/23andme-seeks-fda-approval-personal-dna-test#ixzz2OZ3ZZfGX)
  - No public statements since July 2012

Clearance Trends

- OIVD premarket clearances increased slightly in FY2011, but have since returned to FY2010 levels
  - 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

De Novo Reclassifications

- Per FDASIA, sponsors now can submit direct de novo petitions to FDA, requesting reclassification of their device, without first receiving NSE decision
- De novo process now referred to as “De Novo Reclassification” rather than “downclassification”
- Direct de novo petitions do not require a user fee, FDA has 120 days to review
- Given increased accessibility of de novo process, an increase in direct de novo petitions is expected
- Remains to be seen whether FDA will take swift action on such petitions

OIR De Novo Reclassification

- xTAG Gastrointestinal Pathogen Panel (GPP), a multiplex nucleic acid-based assay intended to simultaneously detect and identify multiple gastrointestinal microbial nucleic acids from human stool specimens
- OIR has indicated that neither the October 3, 2011 Draft Guidance on the De Novo Classification Process nor the March 28, 2012 final guidance on Factors to Consider When Making Risk-Benefit Determinations in Medical Device Premarket Approval and De Novo Considerations will likely change how OIR considers de novo applications

Companion Diagnostics

- 2011 Draft Guidance jointly released by CDRH, CDER, CBER
- Definition of IVD Companion Diagnostic:
  - *An IVD companion diagnostic device is an in vitro diagnostic device that provides information that is **essential for the safe and effective use of a corresponding therapeutic product** (Emphasis added).*

- *An IVD companion diagnostic device could be essential for the safe and effective use of a corresponding therapeutic product to:*
  - *Identify patients who are most likely to benefit from a particular therapeutic product*
  - *Identify patients likely to be at increased risk for serious adverse reactions as a result of treatment with a particular therapeutic product*
  - *Monitor response to treatment for the purpose of adjusting treatment (e.g., schedule, dose, discontinuation) to achieve improved safety or effectiveness*

Companion Diagnostics

- Regulatory Pathways
  - Follow current applicable regulatory requirements:
    - Medical device regulations for the IVD companion diagnostic
    - Drug and Biologic regulations for the therapeutic product application, as applicable
  - Reinforced risk-based approach to determine the need for 510(k) or PMA[1]
  - Collaborative review of the assay and the therapeutic product by relevant FDA offices

- Both IVDs and LDTs will be subject to FDA review if the test is a companion diagnostic product

[1] FDA's current experience has been that most IVD companion diagnostic devices will be Class III devices.

Companion Diagnostics

- Generally approval or clearance of the diagnostic device will be required at the same time as the therapeutic product approval.
  - Exceptions - a therapeutic product that is intended to treat a serious or life-threatening condition for which no alternative treatment exists; and
  - the benefits of the use of the therapeutic product far exceed the risks that may be presented with use of that product without an approved or cleared companion IVD.
- FDA Safety and Effectiveness Concerns
  - Analytical Accuracy – measure of expression level of marker of interest
  - Clinical Accuracy – identification of appropriate patients
  - Errors create a risk for withholding appropriate therapy or administering inappropriate therapy

Companion Diagnostic Approvals

- FDA's focus on companion diagnostics has led to two recent approvals:
  - Qiagen Manchester
  - Abbott Molecular's non-small cell lung cancer for the alk gene, to aid in identifying patients for treatment with Xalkori Crizotinib
  - Roche's COBAS 4800 BRAF v600 mutation test, to aid in selecting melanoma patients for treatment with vemurafenib
- With the growing emphasis on pharmacogenomics, we expect to see more companion diagnostic approvals and clearances, and evolving regulatory policy

Other 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
  - Abbott Architect AFP Assay (P120008)
  - Abbott Architect HBSAG Qualitative/Confirmatory Hepatitis B Test (P110029)
  - Roche Diagnostics' Cobas Ampliprep/Taqman CMV Test (P110037)
  - Roche Diagnostics' IgM anti-Hepatitis B core Antigen Test (P110022)
  - Dexcom Inc. G4 Platinum Continuous Glucose Monitoring System (P120005)
  - Siemens Total Antibodies to Hepatitis B Surface Antigen Test (P100039)
  - Gen-Probe's Progensa PCA3 Assay for Prostate Cancer Genes (P100033)
- Breadth and complexity of assay technologies continue to expand
- The number of not substantially equivalent decisions has dramatically increased across CDRH, so it can be expected that more de novo applications and PMA submissions will be filed unless CDRH takes a more flexible course on how substantial equivalence determinations are made

OIR Issued Special Control Guidances

- OIR has been busy issuing new guidances, including several special controls documents for:
  - Highly multiplexed microbiological/medical countermeasure Nucleic Acid based devices
  - Herpes Simplex Virus Types 1 and 2 serological assays
  - IVD devices for *Yersinia* spp. Detection
  - Norovirus serological reagents
- OIR appears to be focused narrowly on specific diseases and conditions, especially emerging diseases and/or bioterrorism threats

Other Guidance

- OIR issued series of non-IVD guidances in 2012, focused on radiological health issues
- In conjunction with ODE, issued administrative guidances related to third-party reviews and the eCopy program

Present Issues Facing the IVD Industry

- Companies and consultants are reporting increased premarket review times for many IVD regulatory submissions
- The criteria for determining SE have been changing, with an emphasis on reliance on “one predicate”
- Lengthening FDA review times and increase in NSE decisions for IVDs encourages movement to LDTs
- FDA has been working with stakeholders to define how LDT and IVDMIA oversight can best be implemented
- Little FDA or Industry action seen since 2010 risk-based oversight proposal

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 in an effort to tighten the reins on LDTs
- IVDMIA – Still Missing in Action
- Companion Diagnostics will be area of increasing focus

Present Issues Facing the IVD Industry

- FDA guidance and policies regarding RUO devices and materials limit the ability of equipment/analyzer manufacturers to market RUO components and instruments to users for clinical diagnostic uses (see http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM257460.pdf)
  - FDA's June 2011 guidance addresses promotional labeling and all surrounding circumstances of sales activities as indicia of the product's true intended use
  - Guidance also highlights "sales to clinical laboratories that the manufacturer knows, or has reason to know, use the IVD product in clinical diagnostic use in an investigation or otherwise, and support (including technical support) for those activities" as a relevant indicator of a new or different intended use
- When legally marketed products are promoted, labeled, sold, and intended for specific (RUO) intended uses, to what point can and will FDA seek to regulate the actions of the purchasers?

New Issues Facing the IVD Industry

Next Generation Sequencing

- FDA workshop June 2011
- Potential IVD/LDT Business Impact Due to Complexity and Challenges of NGS:
  - NGS Reagents, Instruments, Sample Collection Devices, and Analysis Methods (Bioinformatics) May Be Available only as RUO or Unapproved Devices
  - LDT Developer and Component Manufacturer May be Viewed as Joint Manufacture of a Regulated Medical Device

New Issues Facing the IVD Industry

Next Generation Sequencing

- FDA avoids IVD classification based on the technology - NGS technology is not driving FDA toward a PMA route
- 510(k), PMA and de novo processes all available
- Regulatory pathway dependent on intended use and risks associated with incorrect test results
- FDA is currently considering:
  - "Instrument only" clearances for basic NGS functions
  - Use of general controls e.g., design control and GMPs, plus some Special Controls for diagnostic clearances

New Issues Facing the IVD Industry

Bioinformatics

- FDA workshop June 2011
- Challenges identified:
  - Errors in variant calls associated with alignment against a reference genome
  - Data output
  - Data storage
- Questions remain regarding how FDA will regulate these products

Looking Ahead

- Regulatory directions are always subject to change
- LTD regulation likely is coming at some time, probably based on the risk presented by the laboratory method
- MDUFA will continue to impact FDA resources
- Review of increasingly complex IVDs and device technologies requires diversity in staff training and experience
  - Risk-based approach unchanged, but
  - Tolerance of recognized and “reasonable” risks to achieve public health benefits appears to be at a low
  - New technologies may raise new risks
  - Heightened scrutiny will impact review processes and new/modified product availability

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

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