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FDA/IVD Industry Overview

Association of Medical Diagnostics Manufacturers
39th Annual Meeting
Bethesda, Maryland

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April 19, 2012

IVD Initiatives and Directions

- FDA's internal regulatory process reevaluations, especially for medical devices, appear to have been somewhat tempered since April 2011
- OIVD seems to be more focused on issuing and updating guidance documents
- OIVD's stated goals include continued open communication and flexibility in regulatory applications, with focus on sound science as the norm, not the exception

Regulatory Reality

- OIVD processes generally appear to be 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
  - Voluntary recalls classified at highest level (class I) continue to be elevated compared to 2010 and earlier
  - Premarket clearances, however, appear to have rebounded to earlier levels
  - OIVD continues to utilize the de novo downclassification process
  - PMA and PMA Supplements remain stable in number, but with ever increasing technological complexity

Enforcement Trends for all Devices and Diagnostics

- Total number of voluntarily recalled devices and diagnostics (by product/model, not recall reports) continues to be elevated (1,311 reports in FDA database from October 2011 to April 2012) compared to 318 such recalls between October 2010 and April 2011 and only 131 recalls between October 2009 and April 2010
- 45 of the recently recalled products/models in 31 separate reports were classified as class I
- Only 1 of the class I recalls involved an IVD product

Clearance Trends

- OIVD premarket clearances have increased slightly and returned to FY2010 levels
  - October 2011 to April 2012 = 170 clearances with 2 de novo downclassifications
  - October 2010 to April 2011 = 145 clearances with 1 de novo downclassification”
  - October 2009 to April 2010 = 163 clearances with no de novo downclassifications
- Overall, we have seen
  - Increased requests for additional information from 31% of submissions in 2000 to 75% in 2011
  - Average number of review cycles to final decision has risen from 1.4 in 2000 to 2.2 in 2010
  - Percent NSE decisions has risen from 1% in 2001 to 5% in 2011 (which does not take into account the number of withdrawn submissions)

De Novo Downclassifications

- Focus Diagnostic's anti-JCv antibody detection assay, for the qualitative detection of antibodies to John Cunningham virus in patients with multiple sclerosis or Crohn's Disease receiving natalizumab therapy
- Phadia US's tryptase assay system, to aid in the clinical diagnosis of patients with a suspicion of systemic mastocystosis
- OIVD has continued to champion the use of the de novo downclassification process
- 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 OIVD considers de novo applications

Companion Diagnostic Approvals

- FDA's focus on companion diagnostics has led to two recent approvals:
  - 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

- OIVD 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
  - Roche Diagnostics' IgM anti-Hepatitis B core Antigen Test (P110022)
  - Siemens' Hepatitis B e-Antigen Test (P090024)
  - Siemens Total Antibodies to Hepatitis B Surface Antigen Test (P100039)
  - Otsuka's Pediatric Breath Test for *H. pylori* (P100025) – Note that the same product was previously cleared through the 510(k) process for adult patients
  - 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

OIVD Issued Special Control Guidances

- OIVD has been busy issuing new guidances, including several special controls documents for:
  - Herpes Simplex Virus Types 1 and 2 serological assays
  - IVD devices for *Yersinia* spp. Detection
  - Norovirus serological reagents
  - Nucleic acid-based IVD devices for the detection of Mycobacterium tuberculosis complex in respiratory specimens
- OIVD appears to be focused narrowly on specific diseases and conditions, especially emerging diseases and/or bioterrorism threats

Other Guidance

- Establishing the performance characteristics of IVD devices for the detection or differentiation of human papillomaviruses
  - OIVD is responding to recent developments in other areas, requiring sample size calculations for clinical testing that account for the increasing prevalence of HPV-vaccinated individuals

Enforcement Discretion prior to Downclassification

- December 2011 Guidance (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm283904.htm) confirmed enforcement discretion with regard to a number of IVD products
- Primarily related to clinical chemistry, hematology, and radiology devices with lengthy, safe marketing history
- All are currently class II devices for which the agency is recommending downclassification to class I and exemption from 510(k) requirements

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 OIVD guidance

Looking Ahead

- Regulatory directions are always subject to change
- LTD regulation is coming at some time, probably based on the risk presented by the laboratory method
- MDUFMA 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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