FDA/IVD Industry Overview

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IVD Initiatives and Directions

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- 2009/2010 – Public Health, Safety, and “Transparency” in Regulatory Decisionmaking
  - FDA is in the midst of significant reevaluation of regulatory review processes, especially for medical devices
    - CDRH Office of Compliance in October 2009 emphasized the need to address regulatory non-compliance more quickly and aggressively
    - CDRH Hosted a February 2010 Public Meeting addressing “Incorporation of New Science Into Regulatory Decisionmaking” where the 510(k) review process was closely scrutinzed
    - Dr. Gutierrez, upon taking the OIVD Director’s position in July 2009, expressed numerous regulatory pathway concerns:
      - “flaws in the 510(k) premarket notification program in that "substantial equivalence" allows a test maker to show its test is similar to an already cleared device in lieu of a more extensive safety and efficacy review
      - A process that “invites unwanted variability among test makers
      - Use of labeling terms, such as "sensitivity" (rate of true positives) and "specificity" (rate of true negatives) even when the terms "don't really describe what manufacturers actually proved to us."

IVD Initiatives and Directions

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- Development and regulatory review of new products, despite heightened review, is still the goal
  - Commissioner Hamburg, at the February 25, 2010 Personalized Medicine Coalition, highlighted FDA's needs:
    - to "ensure that the FDA has the scientific knowledge, tools, and standards needed to regulate these novel [personalized medicine] products"
    - to "develop a consistent, comprehensive and integrated approach to the evaluation and regulation of medical products which separately, and in combination, comprise the practice of personalized medicine"
    - Flexibility – by developing "new regulatory frameworks" that address new products
    - Collaboration – by working with academia and industry "to identify knowledge gaps and fill them; identify confidence deficits and address them"
    - Openness – by being "more transparent and endeavor[ing] to help the public understand the rationale and reasoning behind the decisions we make which have such far-reaching impacts on public health."
  - Overarching goals of the agency today continue to be guiding the approval products to ensure "a future that provides safer and more effective therapies"

IVD Initiatives and Directions

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- Tensions between safety and transparency, however, likely will arise
  - Companies and consultants are reporting increased premarket review times for many IVD regulatory submissions
  - OIVD 510(k) discussions have increasingly focused on “one predicate device, one comparator,” lessening flexibility when seeking to develop new approaches and combinations of claims
  - Reducing flexibility in 510(k) reviews has not led to an increase in de novo downclassifications (there was only 1 IVD de novo classification in FY08)
  - Recent OIVD correspondence with clients on premarket reviews, CLIA Waiver decisions, and corrections/removals has been consistently more conclusory, with little or no “rationale” or “reasoning”

IVD Initiatives and Directions

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- Significant areas likely to be impacted as we move forward include
  - Drug and device combinations, such as companion diagnostic tests
  - Laboratory developed tests and IVDMIAs
  - Areas previously subject viewed as outside the scope of FDA enforcement, such as workplace (nondiagnostic) drug testing
  - The premarket review process

Companion Diagnostics

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- OIVD has indicated that guidance is forthcoming
- Specific companion diagnostic tests and drugs historically have been approved through separate FDA pathways
  - Her2/neu and Herceptin
  - EGRF1 and Erbitux
  - Applies even when the diagnostics were developed concurrently with the therapeutic
- FDA has suggested, however, that
  - Companion diagnostics often may be combination products
  - The product's primary mode of action likely will be based on the drug component
  - Approach would likely require NDA or BLA approval, with the diagnostic test information included in the drug application

LDTs and IVDMIAs

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- Lengthening FDA review times for IVDs might encourage development of clinical laboratory services, if they are seen as a more flexible and faster pathway for bringing new healthcare technologies to patients
- FDA presentations have focused on concerns that LDTs (generally) and IVDMIAs (specifically) may present safety concerns due to a lack of established clinical utility
- Clinical laboratory oversight and accreditation bodies have suggested alternate approaches
  - CAP has recommended a risk-based approach for LDT stratification where clinical laboratories would need to establish clinical utility for some LDTs
- FDA continues to seek IVDMIA oversight, but
  - No warning letters since September 29, 2008, OvaSure correspondence
  - IVDMIA guidance still pending

Workplace Drug Testing

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- Drug testing of employees, such as SAMHSA testing programs
  - Traditionally viewed by workplace, SAMHSA, and CMS as non-diagnostic
  - Tested individuals not referred to treatment
  - Results not used for diagnosis
  - Characterized by CMS as “forensic” tests with regard to laboratory complexity categorization
  - FDA generally does not regulate forensic (defined by FDA as law enforcement) testing
- Recent OIVD statements indicate FDA concern that workplace drug tests should be regulated
  - Does FDA have authority?
    - Tests do not appear to be are not intended for diagnostic use
    - There is no direct impact on individual patient (i.e., no diagnosis of disease or condition) and little to no public health impact
  - FDA has limited resources.
  - Approach could open door to more extensive regulation of other “forensic” test areas

Premarket Review Pathways

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- 510(k) Notices
  - Flexibility in assessing technologies helped introduce novel methods
    - Culture methods compared to DNA detection
    - ELISA methods compared to PCR
  - Flexibility in reviewing combined predicates helped introduce important diagnostic tools
- FDA's new focus on single predicate devices and comparator methods may create more NSE decisions for lack of a clear predicate
  - Will OIVD recommit to the de novo downclassification process?
  - Will concerns lead to requests for expanded clinical studies and extensive additional data?

Looking Ahead

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- Regulatory directions are always subject to change
- ASRs, LTDs, and IVDMIAS will continue to be closely scrutinized
- 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

FDA and Industry

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- 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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