Multivariate Guidance

There is a lot of confusion about the regulation of diagnostic tests that are developed by, and used in, a single laboratory.

FDA believes this confusion derives in part from FDA's approach to regulation of laboratory-developed tests that use commercially available Analyte Specific Reagents (ASRs) and other commercially available, FDA-regulated components.

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FDA stated in the preamble to the final ASR rule that:

"clinical laboratories that develop [in-house] tests are acting as manufacturers of medical devices and are subject to FDA jurisdiction under the Act"
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The ASR regulations do not extend to the tests themselves:

i.e. – Laboratory developed diagnostic tests that use Class I, exempt ASRs (or ASRs created in-house) are not necessarily, by extension, Class I, exempt tests

FDA has generally exercised enforcement discretion over laboratory-developed tests

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However, IVDMIA s, a growing category of tests, include elements (e.g., complex, statistically-derived, data-driven algorithms) that are not standard primary ingredients of in-house tests that raise safety and effectiveness concerns.

Additional Concerns:

• No independent review of data sets or clinical claims
• Degree of scientific rigor varies greatly among IVDMIA s
• Some IVDMIA s offered for clinical use while still in a “research phase”

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Therefore, IVDMIA s do not fall within the scope of laboratory-developed tests over which FDA has generally exercised enforcement discretion.
The new guidance draft

**- In Vitro Diagnostic Multivariate Index Assays -**

defines a narrow niche of devices, whether commercially distributed or laboratory developed, that is subject to FDA regulation rather than enforcement discretion

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**IVDMIAs:**

- Use clinical data (from one or more IVDs assays and sometimes demographic data) to empirically identify an algorithm
  
  **AND**

  - Employ the algorithm to integrate these different data points in order to calculate a patient-specific result (e.g., a “classification,” “score,” or “index”)

  **AND**

  - The result cannot be interpreted by clinicians using prior knowledge of medicine without information from the test developer regarding its clinical performance and effectiveness

Potential examples:

- A microarray that predicts colon cancer recurrence based on an RNA expression pattern
- An assay that integrates quantitative results from 7 immunoassays to obtain a qualitative “score” that predicts a person’s risk of developing Alzheimer’s disease
- A test that integrates a patient’s age, gender, and genotype of 5 genes to diagnose cardiovascular disease
IVDMIA Clarifications

• A device may use an algorithm and not be an IVDMIA
• A device may use software and not be an IVDMIA
• A device may be multivariate and not be an IVDMIA

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Some devices that are not IVDMIA:
• Standard creatinine clearance determination
• A device that measures Total Cholesterol, HDL Cholesterol, and Triglycerides and determines LDL Cholesterol concentration via a calculation
• An assay that measures the 25 ACOG/ACMG recommended mutations to report a patient’s CFTR genotype

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Input on Guidance:
• Public meeting was held on February 8, 2007
• 31 presentations with many excellent issues raised
• Comment period on guidance closed March 5 – comments are currently being reviewed
Multivariate Guidance

- Classification and review of IVDMIAs will be risk-based by intended use
- Opportunity for Class I, II, and III indications
- IVDMIAs will be regulated the in the same manner as all other medical devices

Impact of FDA Regulation

- Independent assessment of data and labeling
- Adverse event reporting and Recalls
- Informed by evaluation standards; grounded in “least burdensome” mandate
- If focused – good science is good science

Note: If the test is already being used (or going to be used) on patients, shouldn’t data exist to show it is safe and effective?

FDA Regulatory Resources

- FDA Web page: “Device Advice” (http://www.fda.gov/cdrh/devadvice/)
- Educational outreach
  - e.g., April 17 – 18, 2007: AMDM 510(k) Workshop (http://www.amdm.org/default.cfm?id=102)
First IVDMIA Cleared for Marketing

Last month, FDA, cleared for marketing the first IVDMIA

The Agendia MammaPrint Test:

• Intended to predict the likelihood of breast cancer recurrence
• Developed and performed at a single laboratory site
• Efficient review by FDA
• Classified (de novo) into Class II
• MammaPrint can be used as a predicate device for similar IVDMIAs
• Special Control Guidance document will describe the types of information that should be submitted for these assays

Questions?

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