Oversight of Laboratory Developed Tests

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Overview

• **Background**
  - IVD regulation
  - Need for greater oversight of LDTs

• **Initial public feedback in 2010**
  - Oversight framework suggestions

• **FDA’s current proposal**
  - Continued enforcement discretion in some areas
  - Timeframe for enforcement in other areas

• **Next Steps**
  - Discussion of FDA’s current proposal
1976 – Medical Device Amendments

- Provided definition of ‘medical device’
- Defined the standard to be used
- Provided Regulatory Paradigm
- Risk-Based regulation of medical devices
Risk-Based Classification

- **Class I: common, low risk devices**
  - Most exempt from premarket submission
  - General controls

- **Class II: more complex, higher risk**
  - Premarket Notification [510(k)]
  - Substantial equivalence, special controls

- **Class III: most complex, highest risk**
  - Premarket Application [PMA]
  - Safety, effectiveness
Laboratory Developed Tests Circa 1976

- Local

- Mostly non-commercial

- Test methods generally well established, accessible

- Clinician/Pathologist/Patient relationships

- Simple software - calculations
Enforcement Discretion

- Not unique to LDTs
- Does not change the fact that the law applies
- Many different reasons for this practice (risk, history, timing, resources, etc.)
- Practices like this do occur, but may change (often because of changes in risk profile of the products)
- Policy often not written or well defined
Current Regulatory Reality

1) Commercially Distributed Test Pathway:

- "Test kit" manufactured for distribution to multiple labs
- FDA approval
- "Test kits" distributed to patients, hospital, or clinical lab
- Patient

2) Lab Developed Test (LDT) Pathway:

- Test designed, manufactured, and used in a single lab
- FDA "enforcement discretion"
- LDTs (lab developed tests) enter the market without review
- Patient
Need for Oversight

- LDTs, while offering innovations, have proliferated, essentially unregulated as devices, to a point where serious public health issues could easily arise
- CLIA “not enough” for manufacturers of LDTs
- No record of which labs offer which LDTs
- No way to distinguish a “good” lab from a “bad” one
Common Regulatory Themes

- National Human Genome Research Institute (Department of Energy & National Institutes of Health; 1997)
- Secretary’s Advisory Committee on Genetic Testing (2000)
- Secretary’s Advisory Committee on Genetics, Health, and Society (2008)
- Institute of Medicine (2012)
## Two Regulatory Paths

<table>
<thead>
<tr>
<th></th>
<th>CLIA</th>
<th>FDA</th>
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<tbody>
<tr>
<td>Research Phase</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Analytical validation</td>
<td>Post hoc sampling</td>
<td>Yes</td>
</tr>
<tr>
<td>Clinical validation</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Report Adverse Events</td>
<td>No requirement; no system</td>
<td>Yes</td>
</tr>
<tr>
<td>Transparent Results</td>
<td>No public information</td>
<td>Published review summary</td>
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Research Phase

- Investigational Device Exemption (IDE) Program for Human Subject Studies
  - Patient safety
  - Knowledge to be gained from investigation
  - Alignment with plans for later development and FDA review
CLIA: Analytical Validation

• Typically performed on inspection

• Inspectors lack expertise to cover broad menu of tests

• Validation not always simple (use of complex multi analyte systems)
CLIA: Clinical Validation

• Not a CLIA requirement
• Claims are not always supported
• Independent third party review lacking
• Analysis sometimes very complicated
CLIA: Post Market Surveillance

• Not a CLIA requirement
• No system to monitor reports
• No recall mechanism
CLIA: Transparency

• Performance and claims for LDTs difficult to obtain

• FDA issues a review summary for all IVDs it reviews
Quality Systems

• CLIA not sufficient
  - CAP
  - NYSDH
  - AABB
  - ISO15189
  - etc...
Initial Public Feedback (2010)

FDA held a public meeting PRIOR to developing the proposed regulatory oversight framework.
Initial Public Feedback (2010)

• Oversight Framework Suggestions
  - Process should allow for stakeholder input and leverage external experts
  - Should use risk-based, phased-in strategy
  - Should provide reasonable transition period
  - Should provide clear definition of LDTs
  - Registry of all tests
    - Partnerships with other agencies
  - Process to address emerging diseases/emergency situations
Initial Public Feedback (2010)

• Oversight Framework Suggestions (continued)
  - Less oversight for certain categories of tests
    • Rare Diseases
    • No FDA approved/cleared alternative
    • Hospital based tests
    • Tests with extensive peer review
    • Tests performed in accredited lab or already approved by NY state
  - Post-Market Surveillance needed to protect public health
  - Significant Education/Outreach needed
Draft Framework

- Risk-based (highest to lowest)
- Phased-in (9 years)
- Carve outs:
  - Rare Dx, unmet needs, traditional LDTs, etc
- Notification and MDR reporting
- Classification panels for new intended uses
FDA vs CLIA

- FDA regulates articles, i.e., test systems, reagents, instruments, software, etc.
- CLIA regulates laboratory operations
- Non-conflicting regulations because they are for different purposes
  - Some similarities that can be leveraged
FDA/CMS Task Force

- Senior leadership and SMEs from both Agencies
- Effort to identify similarities in regulations
- Streamline requirements for labs regulated by both CMS and FDA
- Public outreach
DTWG (Hall) Proposal

- Recognizes that laboratory developed tests can be regulated similarly to distributed tests
- Recognizes that laboratories perform some functions that distributed manufacturers do not
- Recognizes the need for all tests to be clinically valid
- Recognizes that regulation can be risk-based
Goal: Optimal Public Health

- Additional oversight:
  - Improve patient healthcare
  - Improve public health
  - Allow for timely, good innovation
Questions?

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