FDA’s Plan to Regulate Laboratory Developed Tests
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September 3, 2014
FDA’s Plan to Regulate Laboratory Developed Tests

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Background

Regulation of Test Manufacturers

FDA

???

LDT

???

Regulation of Clinical Testing Laboratories

CMS
Laboratory Developed Test

A test developed within a CLIA-certified laboratory that is used in patient management and has both of the following characteristics:

- The test is performed by the clinical laboratory in which the test was developed; and
- The test is neither FDA-cleared nor FDA-approved.
CAP Approach

- Oversight of LDTs should be strengthened through a partnership between CMS, FDA and 3rd Party Accreditors.

- Analytic and clinical validation of these tests require oversight and continued monitoring.

- Oversight should be stratified based on risk.

- Our approach recommends targeted FDA review of only high-risk LDTs.
The CAP Paradigm for LDTs…

- **LDT #1**
  - Low Risk
  - Laboratory Validates & Places in Service.
  - Accreditor Inspects.

- **LDT #2**
  - Mod Risk
  - Laboratory Validates.
  - Accreditor Reviews Before Test Placed in Service.

- **LDT #3**
  - High Risk
  - Laboratory Validates.
  - FDA Reviews Before Test Placed in Service.

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## Risk Classification Principles

<table>
<thead>
<tr>
<th>Classification</th>
<th>Principles</th>
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</table>
| Low            | • Test result is typically used in conjunction with other clinical findings to establish or confirm diagnosis.  
• No claim about test result alone determines prognosis or direction of therapy. |
| Moderate       | • Test result is typically used for diagnosis, predicting disease progression or identifying whether a patient is eligible for a specific therapy.  
• Laboratory may make claims which determine prognosis or direction of therapy. |
| High           | • Test result predicts risk, progression of, or patient eligibility for a specific therapy; AND  
• Test uses proprietary algorithms or computations such that the test result cannot be tied to the methods used, or inter-laboratory comparisons can not be performed. |
The Proposal is informed by evidence-based review and incorporates FDA and CLIA principles

- Assures analytical and clinical validity and consistency of claims with intended use;
- Least burdensome and achievable for laboratories
  - Field tested to validate principles
Elements of LDT Validation

Defining the Disorder/Test/Clinical Scenario
• Encompasses the development stage of an LDT and serves to establish a testing procedure and identify the intended use of the test.

Analytical Validity
• The test’s ability to accurately and reliably measure the analyte of interest in the clinical laboratory, and in specimens representative of the population of interest.

Clinical Validity
• The ability of a test to diagnose or predict risk for a particular health condition, measured by clinical (or diagnostic) sensitivity, clinical (or diagnostic) specificity, and predictive values.

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Proposed Regulatory Framework for Laboratory Developed Tests

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September 3, 2014
In Vitro Diagnostic tests (IVDs) are a critical component of current clinical care, influencing ca. 80% of all clinical decision-making.

Through the 1976 medical device amendments to the FFDCA, FDA has the authority to regulate all laboratory tests, regardless of whether they are commercially distributed or developed by a laboratory.

FDA is charged with ensuring that IVDs are safe and effective (do what they say they will do) for their intended use so that patients are not unnecessarily harmed.
Benefits of FDA Oversight

• Independent Premarket Review
  – Independent assessment occurs prior to clinical use of test
  – Ensures test limitations are described
  – Ensures test performance claims are supported

• Clinical Validation
  – Provide assurances that test provides clinically meaningful results

• Post Market Surveillance and Post Market Controls
  – Mechanism to assist manufacturers and FDA in identifying problems with tests and assuring the performance of the IVD through out its life cycle

• Oversight of Investigational-Stage Devices
  – Ensures patients and physicians understand the scientific evidence supporting use of a diagnostic test
Enforcement Discretion:

- **Definition:** When FDA does not enforce some or all applicable laws and regulations on certain categories of products (drugs, devices, biologics, etc.)

- **Key Points:**
  - Enforcement discretion not unique to LDTs
  - Enforcement discretion 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)
Enforcement Discretion for LDTs:

Applied to FDA requirements for:

- Registration & Listing (R&L)
- Premarket review (i.e., 510(k) or PMA)
- Quality System Regulations (QSRs)
- Medical Device Reporting (MDR) of adverse events

Which means…

- Scope of LDT use in clinical medicine unknown
- Clinical validity not necessarily demonstrated
- No systematic mechanism to detect problems when they arise
Appropriate in 1976; LDTs were:

- Local
- Mostly non-commercial
- Tests generally used FDA-approved components
- Test methods generally well established, accessible
  - Most tests were single signal tests
  - Used simple, well-defined chemical, biological, or immunological principles (IHC, RIA, etc.)
- Clinician/Pathologist/Patient relationships
- Simple software – calculations
- Performed by specialists with advanced training and require expert interpretation (karyotype, IHC)
- Small test volumes
“Traditional” LDTs

The 1976 LDT landscape is the basis of FDA’s definition of a “traditional” LDT:

An IVD that is intended for clinical use and designed, manufactured and used within a single laboratory.
LDTs Today

• Many are the same
• Still often for unmet needs, rare diseases
• Still need for expert interpretation (IHC, cytogenetics, culture, etc.)
But Also Much More

• Volume and types of LDTs has grown significantly
• Often a mechanism for market entry of novel tests
• Higher proportion in commercial labs and biotechnology companies
• Often no clinician/pathologist/patient relationship
• Tests developed for broad, commercial use
And …

• Often require complex software
• Many incorporate automated interpretation
• Tests increasingly empirical, non-transparent
• Rely on complex statistical methods
• Clinical validity not well understood
• More tests for predicting drug response, risk of disease
• Novel tests often developed by companies and “licensed” to a lab
And More

- Tests broadly advertised
- Aggressively marketed to clinicians
- DTC advertising
- Internet sales, overnight shipping
- Nationwide, international reach
## Risk Profile of Modern LDTs match IVD Kits

<table>
<thead>
<tr>
<th></th>
<th>IVD Kits ( Generally )</th>
<th>Early LDTs (Generally)</th>
<th>Many Modern LDTs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Manufacturer/Developer</strong></td>
<td>• For-profit biotech company, often w/o relationship to ordering physicians</td>
<td>• Academic/public labs w/ relationship to ordering physicians</td>
<td>• For-profit biotech company often w/o relationship to ordering physicians</td>
</tr>
<tr>
<td><strong>Intended Use</strong></td>
<td>• Diagnose/monitor/screen for rare and common diseases</td>
<td>• Diagnose/monitor rare diseases</td>
<td>• Screen for common diseases</td>
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<tr>
<td></td>
<td>• Guide critical treatment decisions</td>
<td></td>
<td>• Guide critical treatment decisions</td>
</tr>
<tr>
<td><strong>Components</strong></td>
<td>• Not FDA cleared/approved (generally) before the kit is evaluated</td>
<td>• FDA cleared/approved (generally)</td>
<td>• Use research use components, which (generally) are not FDA cleared/approved</td>
</tr>
<tr>
<td><strong>Levels of Complexity</strong></td>
<td>• Multi-signal tests</td>
<td>• Single signal tests</td>
<td>• Multi-signal tests</td>
</tr>
<tr>
<td></td>
<td>• Require information integration/quality control to ensure validity</td>
<td>• Use well-defined scientific principles</td>
<td>• Require information integration/quality control to ensure validity</td>
</tr>
<tr>
<td></td>
<td>• Novel biomarkers (previously unknown clinical significance)</td>
<td></td>
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</tr>
<tr>
<td><strong>Marketing Strategy</strong></td>
<td>• High-volume (e.g., labs, hospitals, doctors, direct-to-consumer, Internet)</td>
<td>• Tests designed for use by local doctors on local patient pop.</td>
<td>• High-volume ( e.g., labs, hospitals, doctors, direct-to-consumer, Internet)</td>
</tr>
</tbody>
</table>
Despite new public health risks, today’s LDTs are still marketed under enforcement discretion by FDA.

“test kit” manufacturer

“Enforcement Discretion”

FDA

Perform in CLIA-certified lab

Performed within same lab that developed test
Public Health Need for Greater Oversight

• Evolution of LDT technology, marketing, and business models has:
  – Increased risk associated with LDTs
  – Created gaps in LDT Oversight

• Consequences
  – Significant adverse health consequences
  – Unnecessary healthcare costs
  – Could undermine progress of personalized medicine, which depends on tests that work
Increasing Concerns About Public Health Impact of LDTs

• Incorrect diagnoses of ovarian cancer
  – Led to unnecessary surgeries to remove ovaries

• Incorrect prediction of tumor types (Duke Univ. Study)
  – Exposed some patients to ineffective therapies
  – Left other cancer patients untreated

• Incorrect diagnoses of whooping cough
  – False whooping cough epidemic at Dartmouth medical center
  – Thousands given unnecessary antibiotics and/or vaccine
  – 1,000 healthcare workers furloughed
Increasing Concerns About Public Health Impact of LDTs (cont.)

- Incorrect diagnoses of autism
  - Exposed children to ineffective treatments, and potentially harmful treatments
- Incorrect diagnoses of Lyme disease
  - Exposed patients to unnecessary antibiotics
- Incorrect information about statin response
  - Patients are being over/under-treated
- Incorrect information about heavy metal toxicity in the body
  - Patients were exposed to unnecessary, and potentially harmful therapies
- Incorrect information about breast cancer recurrence/mortality
  - 20% of HER2 testing may be inaccurate
  - High-rate of patients exposed to ineffective and expensive treatments
  - Some cancer patients left untreated
Initial FDA Approach

• Long-running discussion on need for oversight of LDTs
  – SACGHS and other recommendations for oversight in last 10-15 yrs

• Piecemeal approach
  – ASR
  – IVDMIA
Challenges faced by Historical FDA Approaches: ASR Rule

- ASR manufacturers misinterpreted the regulation and sold complete tests inappropriately as ASRs

- ASR Q&A Guidance (2007) clarified the boundaries of ASRs and the responsibilities of ASR manufacturers

- Enforcement of the ASR regulations started a resurgence of platforms and tests sold for clinical use but labeled “For Research Use Only” (RUO)

- RUO tests and instruments of uncertain quality – same situation as early 1990s
Challenges faced by Historical FDA Approaches: IVDMIAs

- IVDMIAs are complex, non-transparent and difficult to develop and validate correctly

- FDA stated that FDA premarket review and postmarket surveillance/reporting are necessary to ensure the public is protected from unsafe or inaccurate tests

- IVDMIA draft guidance stated that these devices should be subject to FDA regulation rather than enforcement discretion, even when offered as LDTs

- Publication of the IVDMIA guidance generated some controversy. FDA obtained significant public comment on both drafts of the guidance
Upcoming draft guidance is intended to initiate discussions with all stakeholders on a framework that will best serve public health.
FDA’s Current Proposal

1. Collect basic information on all LDTs through new notification process (i.e., no-fee alternative to R&L)

2. Use public process (i.e., advisory committees) to obtain input on risk and priority for regulation

3. Phase-in regulatory framework over ~9 years based on risk

4. Continue some enforcement discretion for specific categories determined by FDA to be in the best interest of public health
## Continued Enforcement Discretion

<table>
<thead>
<tr>
<th>LDTs used solely for <strong>forensic</strong> purposes</th>
<th>Notification</th>
<th>MDRs</th>
<th>Premarket Review</th>
<th>QSRs</th>
<th>R&amp;L</th>
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<tr>
<th>LDTs used in CLIA–certified, high-complexity histocompatibility labs for <strong>transplantation</strong></th>
<th>Notification</th>
<th>MDRs</th>
<th>Premarket Review</th>
<th>QSRs</th>
<th>R&amp;L</th>
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<tr>
<th>Low risk medical devices, including <strong>low risk</strong> LDTs</th>
<th>Notification</th>
<th>MDRs</th>
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<th>LDTs used for <strong>rare diseases</strong> per HUD definition</th>
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<th><strong>“Traditional”</strong> LDTs</th>
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*enforcement discretion will be applied to R&L provided notification is completed
### Notification and AE Reporting only

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<td>LDTs used in CLIA–certified, high-complexity histocompatibility labs for transplantation</td>
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<tr>
<td>LDTs used for <strong>rare diseases</strong> per HUD definition</td>
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<td>6m</td>
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**Risk-Based, Phased-In Enforcement**

<table>
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<tr>
<th><strong>Highest risk LDTs already on market</strong></th>
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<tr>
<td>LDTs with same intended use as cleared/approved companion diagnostics</td>
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<tr>
<td>LDTs with same intended use as approved Class III medical devices</td>
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<tr>
<td>Certain LDTs for determining safety and effectiveness of blood or blood products</td>
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<th><strong>Subsequent high risk categories in priority order determined by public process</strong></th>
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<tr>
<th><strong>Moderate risk categories in priority order determined by public process</strong></th>
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<tr>
<td><strong>Notication</strong></td>
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<td>6m</td>
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</tbody>
</table>
• Premarket review for all **NEW** (i.e., not currently marketed) IVDs that:
  – Have the same intended use as cleared/approved companion diagnostics
  – Have the same intended use as approved Class III medical devices
  – Certain LDTs for determining safety and effectiveness of blood or blood products
• By 6m: Notification and adverse event reporting for all **currently marketed** LDTs except:
  – those used solely for forensic purposes
  – those used in CLIA–certified, high-complexity histocompatibility labs for transplantation

• After 6m: Begin requirement for notification of all **NEW** LDTs prior to marketing
  – Includes notification for significant changes to existing LDTs
• Premarket review for currently marketed IVDs that:
  – Have the same intended use as cleared/approved companion diagnostics
  – Have the same intended use as approved Class III medical devices
  – Certain LDTs for determining safety and effectiveness of blood or blood products
• Subject to QS reg at time of PMA submission
• Subject to R&L upon PMA approval
• Publication of priority list for remaining high-risk LDTs
  – Based on public process including advisory panels
  – Publication in FDA guidance
• Premarket Review for **first prioritized high-risk group** which FDA anticipates may include:
  – Devices that act like companion diagnostics
  – Screening devices for serious diseases/conditions intended for use in asymptomatic patients without other confirmation
  – Diagnostics for certain infectious diseases with high-risk intended uses

• Subject to QS reg at time of PMA submission
• Subject to R&L upon PMA approval
• Premarket Review for all **remaining high-risk LDTs** according to priority list announced at year 2
• Subject to QS reg at time of PMA submission
• Subject to R&L upon PMA approval
• Publication of priority list for moderate-risk LDTs
  – Based on public process including advisory panels
  – Publication in FDA guidance
- Premarket Review for all moderate-risk LDTs according to priority list announced at year 4
  - FDA anticipates use of third party reviewers
- Subject to QS reg at time of 510(k) clearance
- Subject to R&L at time of 510(k) clearance
Where are we today?

Somewhere over here!

No implementation will begin prior to publication of final guidances.
What’s Next

• Publication of *DRAFT* guidances

• Solicitation of Public Input via FR Notice announcing:
  – 90 day public comment period
  – Public Workshop

  **Goal:** to work with all stakeholders to determine a framework for regulation that is in the best interest of public health

• Analysis of public input and edits to guidances