Current Proposals for Diagnostics Reform

Elizabeth Hillebrenner, Associate Director for Scientific and Regulatory Programs, CDRH, FDA
Aaron L. Josephson, Senior Director, ML Strategies LLC
Eric M. Marshall, Senior Director, Leavitt Partners LLC

Moderated by Elizabeth Richardson, Director, Health Care Products Project, The Pew Charitable Trusts
Current Proposals for Diagnostics Reform

Elizabeth Richardson, Director, Health Care Products Project, The Pew Charitable Trusts
Diagnostic Reform

Elizabeth Hillebrenner
Associate Director for Scientific and Regulatory Programs
Center for Devices and Radiological Health

May 3, 2019
Laboratory Developed Tests (LDTs)

1976
• FDA exercised enforcement discretion for LDTs because they were generally:
  • simple, relying on manual techniques used by lab personnel
  • run in small volumes by local laboratories with shared responsibility for patient outcomes
  • assembled using components legally marketed for clinical use

Today
• The landscape has evolved such that increasingly we are seeing LDTs that are:
  • more complex, sometimes including black box algorithms
  • run in large volumes as reference labs for patients from different institutions around the world
  • assembled using components intended for research use only
LDT History

1992

- Reassertion of regulatory authority over LDTs in RUO draft compliance guide

1997

- Reassertion of regulatory authority over LDTs in ASR preamble
- National Human Genome Research Institute (Department of Energy & National Institutes of Health) identifies FDA as the appropriate Agency to provide needed oversight of LDTs

2000

- Secretary’s Advisory Committee on Genetic Testing identifies FDA as the appropriate Agency to provide needed oversight of LDTs

2006

- Piecemeal LDT oversight approach: ASR and IVDMIA draft guidances released
- Comments reflected preference for overarching LDT policy

2008

- Secretary’s Advisory Committee on Genetics, Health, and Society identifies FDA as the appropriate Agency to provide needed oversight of LDTs
LDT History

2010

- Public meeting held
- Docket opened for feedback on comprehensive LDT oversight policy

2014

- LDT draft guidances released
- Docket opened

2015

- Discussion Paper Released
- DAIA discussion draft released

2015-2016

- FDA review of public comments
- FDA’s continued stakeholder engagement
- Legislative engagement (DTWG)
- Revisions to proposed FDA policy
- Congressional hearings on LDT proposals

2017

- FDA TA on DAIA
- VALID discussion draft released

2018
FDA’s August 2018 Technical Assistance

• New medical category: In Vitro Clinical Tests (IVCTs) includes LDTs and conventional IVDs

• New framework tailored to IVCTs
  • FDA jurisdiction, complementary to CLIA
  • Reasonable assurance of analytical and clinical validity (AV and CV)
  • No formal classification process; focus on where our review adds most value (e.g., high risk, novel)

• Premarket oversight:
  • ~50% exempt
  • ~40% eligible for precertification (or abbreviated premarket review)
  • ~10% subject to individual premarket review
  • Streamlined approach to modifications

• Postmarket oversight:
  • Special Rule
  • Transparency
  • Adverse event reporting
  • General authorities (e.g., recalls, corrections and removals)

• QS leverages CLIA where appropriate
## Exemptions

<table>
<thead>
<tr>
<th>Category</th>
<th>Notification</th>
<th>PreMarket Review</th>
<th>QS</th>
<th>AE Reporting</th>
<th>Labeling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grandfathered</td>
<td></td>
<td>Exempt</td>
<td></td>
<td></td>
<td>Exempt*</td>
</tr>
<tr>
<td>Pre-certified</td>
<td></td>
<td>Exempt</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td></td>
<td>Exempt</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exempt pre-enactment</td>
<td></td>
<td>Exempt</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rare disease</td>
<td></td>
<td>Exempt</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Custom</td>
<td>Exempt</td>
<td>Exempt</td>
<td></td>
<td>Exempt</td>
<td></td>
</tr>
<tr>
<td>Low volume</td>
<td>Exempt</td>
<td>Exempt</td>
<td></td>
<td>Exempt</td>
<td></td>
</tr>
<tr>
<td>PH surveillance</td>
<td>Exempt</td>
<td>Exempt</td>
<td></td>
<td>Exempt</td>
<td></td>
</tr>
<tr>
<td>Law enforcement</td>
<td>Exempt</td>
<td>Exempt</td>
<td></td>
<td>Exempt</td>
<td></td>
</tr>
<tr>
<td>Manual</td>
<td>Exempt</td>
<td>Exempt</td>
<td></td>
<td>Exempt</td>
<td></td>
</tr>
<tr>
<td>Investigational</td>
<td>Exempt</td>
<td>Exempt</td>
<td></td>
<td>Exempt</td>
<td></td>
</tr>
</tbody>
</table>

*specific disclaimer required
Precertification

• Voluntary alternative to premarket review for many IVCTs
• FDA would evaluate test developers to determine if their processes for development and validation will result in analytically and clinically valid tests
  • Full review of single representative assay to confirm
• Precertification scope:
  • Single technology and applicant-specified medical specialties
  • Not limited by intended use – a single precertification could include many different intended uses/test groups
• Eligibility
  • Developer must be in good standing
  • Tests that are first of a kind, cross-referenced, high risk, for home use or direct-to-consumer must be made eligible by FDA through regulatory pathway designation process
  • Other tests, with certain exceptions, are automatically eligible
• Once pre-certification is granted, new and modified eligible tests can be marketed without individual premarket review
• Recertification requirements
## Premarket Review

<table>
<thead>
<tr>
<th>Tests ineligible for precertification</th>
<th>Analytical Validity Review</th>
<th>Clinical Validity Review</th>
<th>QS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Raw data</td>
<td>Raw data</td>
<td>Premarket review and inspection</td>
</tr>
<tr>
<td>Tests eligible for precertification</td>
<td>Summary data</td>
<td>Summary data</td>
<td>-*</td>
</tr>
<tr>
<td>Platforms</td>
<td>Summary data from representative assay</td>
<td>-</td>
<td>-*</td>
</tr>
<tr>
<td>Collection articles</td>
<td>Summary data from representative assay</td>
<td>-</td>
<td>-*</td>
</tr>
</tbody>
</table>

*While QS may not be reviewed premarket, all IVCTs would be subject to QS requirements, unless exempt, and documentation should be available upon request or routine inspection.

Note: The data demonstrating analytical and clinical validity of a single assay could be used for any combination of the following: a premarket submission for the assay, a precertification for all eligible assays using the technology, a premarket submission for the platform, and a premarket submission for the collection article; data would need only be submitted once.
Modifications

Modification made under Precertification?
  Yes → no premarket review
  No →

Modification made under Prospective Change Protocol approved in initial submission?
  Yes → no premarket review
  No →

Modification results in:
- adverse affect on performance,
- change in performance claims,
- change in test group elements,
- test no longer complies with mitigating measures or restrictions, or
- affects the safety of an article for taking or deriving specimens from the body.

If yes → Premarket review

No
Transparency

• Comprehensive Test IT System (CTIS) would include:
  • Registration of developers and related entities
  • Notification of individual IVCTs with public transparency performance summaries
  • Electronic submission portal
  • Adverse event reporting portal
  • Identification of regulatory pathway for non-novel test groups

• CTIS would enable efficient oversight by FDA
  • Monitoring of all tests, including those introduced under precertification and the developer’s claims associated with them

• CTIS would provide transparency to patients and healthcare providers about the tests they are using
  • Ability to search for available tests based on any individual elements of a test group
  • Ability to compare performance of similar tests
Special Rule

• The shift away from premarket review for most tests necessitates clear, workable postmarket monitoring and enforcement authorities

• FDA must have the ability to address problematic IVCTs, including those that may be grandfathered

• The process would involve FDA first asking for more information, and if a finding was made based on that information, we could request that the developer provide a submission, or we could remove the test from the market, depending on the nature of the finding.

• In order to protect the public health, FDA would only invoke the special rule if:
  • There is insufficient VSE to support AV or CV (different rule for specimen collection articles)
  • Materially deceptive or fraudulent analytical or clinical claims
  • Reasonable potential the IVCT will cause death or serious adverse health consequences
Transition Period

• The period between the enactment date and the implementation date (applicability)

• Transition is needed for FDA to prepare the necessary infrastructure, issue any necessary guidances, and provide training on the new program

• LDTs during transition
  • Any LDTs introduced 90 days prior to the enactment date would be grandfathered
  • LDTs introduced between 90 days prior to enactment and the implementation date would be transitional

• IVCTs and may need a premarket submission after the implementation date (unless otherwise exempt)
  • Transitional IVCTs subject to delayed premarket review could continue to be offered for clinical use during the pendency of review to ensure no market disruption

• Conventional IVDs during transition
  • Conversion of existing approval/clearance/authorization – any IVD with an FDA approval, clearance, authorization, or licensure before the enactment date would be deemed to have an approved application after the effective date
  • Authorization during transition – IVD manufacturers would continue to seek FDA authorization under the device regulations until the implementation date, at which time such would be converted to an approval
FDA looks forward to continued engagement, at the direction of Congress, as we all work toward a legislative solution that will ensure patients have access to analytically and clinically valid in vitro clinical tests when they need them.
Current Proposals for Diagnostics Reform

Eric M. Marshall, Senior Director, Leavitt Partners LLC
|-----------------------------------|--------------------------|-------------|--------------|
| **Premarket Requirements for LDTs** | • Medical device requirements for premarket review extended to LDTs  
• Reasonable assurance of safety and effectiveness as approval standard  
• Risk-based classification based on the availability of controls using existing medical device classification system | • Creates new category under FDCA for in vitro clinical tests (IVCTs)  
• Reasonable assurance of analytical and clinical validity established as standard for approval  
• Adopts risk-based classification system based upon patient risk  
• Premarket review for high-risk IVCTs  
• Streamlined submissions for moderate-risk IVCTs  
• Registration and listing for low-risk IVCTs | • Creates new category under FDCA for in vitro clinical tests (IVCTs)  
• Reasonable assurance of analytical and clinical validity established as standard for approval, and safety as applicable  
• Attempts to eliminate risk-based classification, establishing 2 to 4 classes  
• Creates voluntary precertification pathway |
| **Premarket Requirements for IVDs** | • Regulated as medical devices subject to all classification, premarket, and other device requirements  
• No significant changes to medical device requirements as applied to IVDs | • Establishes expedited “approval with confirmatory post-market obligations” pathway for unmet need and clinically significant advantage | • To-be-defined alternative pathway for breakthrough IVCTs and IVCTs that provide a clinically meaningful advantage |
| **Special Pathways** | • Standard device pathways available | • Continued enforcement discretion for LDTs for:  
• Unmet need LDTs  
• Rare disease LDTs  
• “Traditional” LDTs | • Device-like post-market requirements with some summary reporting |
| **Post-Market Obligations** | • IVDs regulated as medical devices subject to all post-market requirements  
• LDTs not subject to FDA post-market requirements  
• Medical devices post-market requirements extended to LDTs, including adverse event reporting, corrections and removals, and modification requirements  
• Tailored modification requirements based on changes to intended use or meaningful clinical impact  
• Quarterly adverse event summary and trend reporting | | • No changes to CLIA  
• Instructs FDA to avoid duplicative requirements |
| **CLIA** | • Test services regulated by CLIA  
• No changes to CLIA | • Harmonizes CLIA and FDA requirements  
• Modernizes CLIA requirements to CAP standard | |
Current Proposals for Diagnostics Reform

Aaron L. Josephson, Senior Director, ML Strategies LLC
• Elizabeth: brief history followed by overview of FDA TA & VALID Act
• Eric: DTWG proposals/history
ACLA Response to VALID

1. Diagnostics are services and should not be regulated as or like medical devices
2. Legislation should allow for grandfathering and transitional tests so as not to disrupt patient access
3. Model should balance regulatory oversight with innovation

ACLA represents labs, whose tests have been subject to FDA enforcement discretion.
Service vs. Product

1. Diagnostics are services and should not be regulated as or like medical devices
   • To that end, ACLA proposes:
     – Separate FDA Center to regulate diagnostics or separate office with management and staff with experience specific to labs
     – “An LDT is essentially a service, while an IVD is a tangible product.”
     – Based on latest VALID Act, Congress does not agree with these positions
Patient Access

2. Legislation should allow for grandfathering and transitional tests so as not to disrupt patient access.

To that end, ACLA proposes:

- A 5 year default transition period between enactment and effective date unless regulations are promulgated earlier.
- No lab tests should be subject to device provisions at any time.
- Support for grandfathering of tests performed in a CLIA-accredited high-complexity laboratory under common ownership with the high-complexity lab in which the IVCT was developed.
- There is too much discretion given to FDA to begin oversight of grandfathered tests if the agency has “reason to believe” there is insufficient evidence to support analytical and clinical validity.
  - The burden should be on FDA to show that the test does not meet standards of analytical and clinical validity.
- Modifications to grandfathered tests should be limited to modifications with a significant clinical impact or that change the intended use.
Balance Oversight and Innovation

3. Model should balance regulatory oversight with innovation
   • To that end, ACLA proposes:
     – Better delineation between CLIA requirements and QSR
     – VALID excludes lab operations from quality system requirements but should be excluded from the entire Act
     – ACLA agrees that summary information generally will be sufficient to support approval of most tests but language in VALID granting FDA significant discretion to require raw data could limit innovation by creating uncertainty for the type of data needed to support approval
     – Scope of precertification should not be limited to a single technology
AdvaMedDx Response to VALID

1. Clarification of terms
2. Technical changes that appear consistent with intent
3. Precertification should include multiple technologies (same as ACLA)

AdvaMedDx represents IVD manufacturers, who have been subject to FDA regulation and want to see all diagnostics regulated consistently regardless of where the test is developed.