FDA Regulation of Laboratory Developed Tests

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Disclosures

- Clinical Laboratory Improvement Advisory Committee
- Association for Molecular Pathology
  - Chair, Professional Relations Committee
  - Board of Directors
  - Economic Affairs Committee
  - Strategic Opportunities Committee
- College of American Pathologists
  - Economic Affairs Committee
  - Checklist Committee
  - Pathology Coding Caucus
- American Medical Association
  - Molecular Pathology Advisory Group
  - CodeBridge Mapping Panel

Laboratory Stakeholders

- Hospital and health system laboratories
  - hospital outreach programs
- Small independent laboratories
- Large independent laboratories
- “Advanced Diagnostic Laboratory Test” providers
- In vitro diagnostic kit manufacturers

IVD vs. LDT

- Laboratory Developed Test (LDT): A clinical laboratory procedure that is developed, validated, performed, continually monitored, and improved upon by and within a single laboratory for use with its own patients. Services regulated by Centers for Medicare and Medicaid Services (CMS) and States.
- In Vitro Diagnostic Test (IVD): A diagnostic test kit that is designed, developed, manufactured, packaged, sold and distributed in interstate commerce to many labs throughout the United States and the world. Products regulated by Food and Drug Administration.

FDA Regulation of LDTs

- On July 31, 2014, FDA notified Senate Committee on Health, Education, Labor and Pensions and House Energy and Commerce Committee of intent to issue draft framework for regulation of LDTs
  - 2 draft guidance documents published on October 3, 2014
  - Public workshop on January 8 – 9, 2015
  - Public workshop on regulation of NGS tests on February 20, 2015

FDA has historically regulated medical device manufacturers
FDA proposing to regulate clinical laboratories as medical device manufacturers

Clinical Laboratory Improvement Amendments (CLIA)

FDA Regulation of LDTs
- Current medical device regulatory framework established by 1976 amendments to Food, Drug, and Cosmetic Act - several subsequent modifications
- FDA claims authority to regulate LDTs
- Jurisdiction is disputed
- FDA claims to have exercised policy of enforcement discretion - uncertainty regarding FDA’s right to regulate LDTs - statutory constraints against interfering with the practice of medicine - resource limitations - disagreement about the need for FDA intervention - potential adverse impacts on patient access

FDA Risk-Based Device Classification
- **Class I (low risk)**
  - subject to “general controls” applicable to all devices
  - include adulteration and misbranding provisions, registration and listing, records and reports, and good manufacturing practices
- **Class II (intermediate risk)**
  - subject to premarket notification under §510(k) FDCA
  - FDA “clears” after demonstration of “substantial equivalence” to class I or class II “predicate devices” based on intended use
  - may require special controls such as performance standards, postmarket surveillance, patient registries, guidelines, and recommendations.
- **Class III (high risk)**
  - subject to premarket approval
  - requires demonstration of safety and effectiveness
  - typically requires data obtained from clinical trial

New Device Introduction
- **By default placed into Class III**
  - manufacturers can request immediate placement into Class I or Class II through “de novo” 510(k) process
- Relatively few cleared or approved molecular pathology tests - dynamic nature of technologies - low reimbursement for diagnostics tests - effectiveness and ease of implementation of LDTs - limited potential volumes for many assays - costs and restrictions posed by FDA submission - multiple possible specimens or indications for many tests, which if not mentioned in the label subjects laboratories LDT validation requirements

FDA Requirements
“LDTs for Unmet Needs”
- ‘Device’ meets definition of LDT
- No FDA cleared or approved IVD for specific intended use
- Device ‘manufactured’ and used by healthcare facility for patient of facility or health system

Premarket Review
- Premarket approval (PMA)
- Clearance through 510(k) process

Premarket Approval (PMA)
- Class III devices
- Must be supported by valid scientific evidence demonstrating safety and effectiveness of the device for its intended uses
- Typically include results of extensive clinical trials, bench tests, laboratory studies, animal studies, and references to any standards relevant to a device’s safety or effectiveness
- Complete description of device and components
- Detailed description of the methods, facilities, and controls used to manufacture the device
- Proposed labeling and advertising literature
- Training materials
- Published and unpublished literature concerning prior uses
- Bibliography of published reports known not submitted regarding safety and effectiveness

510(k) Premarket Notification Process
- Involves comparison of new device to one or more legally marketed devices ("predicate device(s)"
- Required to file 510(k) notification prior to:
  - Initial marketing of device
  - Making change or modification to cleared device that could affect safety or effectiveness
  - Making change or modification to intended use of previously cleared device
- Manufacturers submit at least 90 days prior to intended introduction into the market
  - Marketing requires FDA order stating that device is substantially equivalent to a legally marketed predicate device

“Substantial Equivalence”
- Same intended use as predicate; and either
- Same technological characteristics as predicate device; or
- Different technological characteristics, but information submitted must not raise new questions of safety and effectiveness and must demonstrate substantial equivalence
- Determination based on device’s proposed labeling

Contents of 510(k)
- Device Name
- Identification
- Registration Number
- Classification
- Description
- Substantial Equivalence Comparison
- Software
- Standards
- Clinical Data
- Performance
- Biocompatibility
- Sterility
- Labeling
- Class III Certification and Summary
- 510(k) Summary Statement
- Truthful and Accuracy Statement
Medical Device Reporting (MDR)

- FDA currently enforces MDR provisions applicable to device user facilities against clinical laboratories
  - must report deaths to FDA and manufacturer
  - must report serious injuries to manufacturer
- FDA intends to enforced medical device reporting requirements on LDPs (21 C.F.R. 803 Part E)
  - requires manufacturer to submit reports to FDA when become aware of information that reasonably suggests device may have caused or contributed to a death or serious injury
  - or has malfunctioned and malfunction would be likely to cause or contribute to a reportable death or serious injury should it recur

“Caused or Contributed to”

- “a death or serious injury was or may have been attributed to a medical device, or that a medical device was or may have been a factor in a death or serious injury, including events occurring as a result of failure, malfunction, improper or inadequate design, manufacture, labeling, or user error” (21 C.F.R. 803.3)

“Serious Injury”

- Injury or illness that:
  - is life-threatening;
  - results in permanent impairment of a body function or permanent damage to body structure; or
  - necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure (21 C.F.R. 803.3)

“Malfunction”

- The failure of a device to meet its performance specifications or otherwise perform as intended (21 C.F.R. 803.3)
  - Performance specifications include all claims made in the labeling for the device
  - The intended performance of a device refers to the intended use for which the device is labeled or marketed

MDR Procedures

- Clinical laboratories must develop, maintain, and implement written MDR procedures (21 C.F.R. 803.17)
  - Include internal systems that provide instructions for:
    - timely and effective identification communication
    - evaluation of events that may be subject to MDR requirements
    - standardized review protocol or procedure that assists in determining when an event meets MDR reporting criteria
    - timely transmission of complete MDR reports to FDA
  - Include instructions for addressing documentation and record keeping requirements for:
    - information evaluated to determine if an event was reportable
    - all medical device reports and information submitted to FDA
    - information evaluated for the purpose of preparing submission of annual reports
    - systems ensuring access to information that facilitates timely follow-up and inspection
- Laboratories must establish and maintain MDR event files required by 21 C.F.R. 803.17

Quality System Regulations (QSR)

- Medical device amendments require promulgation of “regulations requiring that the methods used in, and the facilities and controls used for, the manufacture, pre-production design validation (including a process to assess the performance of a device but not including the evaluation of the safety or effectiveness of a device), packing storage, and installation of a device conform to current good manufacturing practice, as prescribed in such regulations, to assure that the device will be safe and effective and otherwise in compliance with this Act” (21 U.S.C. § 360(j)(1)(a))
  - Regulations require quality system in place for design, manufacture, packaging, labeling, storage, installation, and servicing of finished medical devices
GMP Required Procedures

- Management responsibility
- Quality audits
- Personnel (and training)
- Design Controls
- Document Controls
- Purchasing Controls
- Device Identification and Traceability
- Production and Process Controls
- Inspection, Measuring and Test Equipment
- Process Validation
- Receiving, In-Process, and Finished Device Acceptance
- Nonconforming Product
- Corrective and Preventive Action (CAPA)
- Device Labeling and Packaging
- Device Handling, Storage, Distribution and Installation
- Device Recordkeeping
- Complaint Handling
- Servicing
- Statistical Techniques
- Comply with regulations applicable to operations
- Component manufacturers and third party servicers not covered
- Several guidance documents interpret

Timeline for implementation

- 6 months: Registration and listing / modification
- Begin advance warning & approval
- 1 year: FDA to announce priority list of high risk LDTs
- 2 years: FDA to announce priority list of moderate risk LDTs
- 3 years: FDA to announce priority list of low risk LDTs
- 4 years: FDA to begin enforcing premarket review of high risk LDTs
- 5 years: FDA to begin enforcing premarket review of moderate risk LDTs

Next Generation Sequencing

- Effects of FDA Guidance
  - The number of existing LDTs and lack of apparent exemptions suggest implementation would result in significant financial consequences for large reference laboratories
  - As written could cause discontinuance of many LDTs
  - Hospital and health system laboratories could potentially avoid some regulation by using FDA kits when available and restricting testing to institution’s patients
  - Serious concerns about use of NGS for molecular oncology testing
  - Advanced diagnostic laboratory tests (ADLT) undergo
    - significant cost burdens
    - potential impact on claims
  - IVD manufacturers possibly stand to gain as strong incentives to use kit, but
    - modifications of FDA-cleared/approved kits?
    - preservation of local testing?

Legal Challenges?

- Laboratory Testing Services
  As The Practice Of Medicine Cannot Be Regulated As Medical Devices

- LabCorp Taps Paul Cormier, Laurence Tribe For FDA Battle

- Roche

- LabCorp
Conclusions

- Potentially enormous change in regulatory oversight of clinical laboratories
  - could eliminate key testing in laboratories across the country creating serious concerns about patient access
  - major potential threat to continued advancement and innovation in molecular pathology
  - serious concerns about use of NGS in oncology
- Stakeholders jockeying for position in order to gain competitive advantages poses additional threats
- Preservation of CLIA-centric oversight framework likely continues to be best approach to ensure persistent patient benefits, innovation, and high quality laboratory testing