Disclosures

Professor of Practice – University of Minnesota Law School
- Teach FDA and related classes
- Supported in part by NIH and NSF grants

Partner – Leavitt Partners
- Develop policy solutions to FDA challenges
- Coalition management
- Consulting and strategic advising

CEO – MR3 Medical LLC
- Start up medical device company
- Probably PMA pathway if product successful
1. Background and current situation
2. DTWG output
3. Current proposed structure
4. Next steps
   - Congress
   - FDA
FDA Regulation of IVDs as Medical Devices

Mounting pressure to regulate LDTs
- Patient groups, FDA, industry, etc.
Counter pressure to rely on CLIA and state oversight
- labs, AMCs, physician groups
Various efforts to resolve issue unsuccessful over 15+ years
Proposed legislation
2014 - FDA issues two draft guidances
Major firestorm
ACLA ready to sue
Guidances probably go final in 2016
The FDA regulates in vitro diagnostics as medical devices.

The term “device” . . . means an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is—

(2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or

21 U.S.C. § 321(h)
**In vitro diagnostic products** are those reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequela. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body. These products are devices as defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act (the act), and may also be biological products subject to section 351 of the Public Health Service Act.

21 C.F.R. § 809.3(a)
Enforcement Discretion of LDTs

- FDA defines a laboratory developed test (LDT) as an IVD that is intended for clinical use and designed, manufactured and used within a single laboratory.
- FDA has asserted enforcement discretion with regard to LDTs since 1976.
  - Has generally not enforced applicable FDCA provisions
  - Developed as a matter of general practice
  - Most were well-characterized or intended for use in diagnosing rare diseases or meeting other local needs
FDA’s Move to Enforce Device Requirements

- On October 3, 2014 FDA issued two draft guidances setting out its intent to enforce and apply device regulations to LDTs:
  - Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)
  - FDA Notification and Medical Device Reporting for Laboratory Developed Tests (LDTs)
- These followed years of discussion
FDA’s Move to Enforce Device Requirements

• Strong stakeholder reaction to the draft guidances
  • General support from traditional IVD manufacturers and some patient groups
• General opposition from lab and professional societies
  • Legal challenges to FDA’s authority and process
  • Operational impact and burden
• Burden concerns
  • Impact on innovation
  • 30,000-100,000 LDTs may exist
FDA’s Move to Enforce Device Requirements

Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)

- Risk-based framework with premarket and post-market device requirements
- High-risk tests: Premarket review and QSR requirements begin 12 months after publication and phased-in over 4 years
  - Existing tests remain on market during review
- Moderate-risk test: Premarket review and QSR requirements begin 5 years after publication of the final guidance and phased-in over 4 years
- Continued enforcement discretion with regard to premarket submissions and QSRs for:
  - Low-risk LDTs (Class I devices)
  - LDTs for rare diseases
  - “Traditional LDTs”
  - LDTs for unmet needs
Legal Challenges to FDA’s Authority

FDA is only authorized to regulate “articles” as devices.

“‘Device’ . . . means an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory . . . .” 21 U.S.C. § 321(h).

**LABS**: LDTs are processes and methodologies, not articles.

**FDA**: The inclusion of “in vitro reagent” is intended to make clear that LDTs are devices.

*United States v. Regenerative Sciences, LLC*, 12-5254 (D.C. Cir. 2014)

- An article generated as part of a medical process can be separated from that process and regulated by FDA.
- “Notwithstanding appellants’ attempt to characterize this case as an effort by the FDA to ‘restrict[] the use of an autologous stem cell procedure,’ . . . the focus of the FDA’s regulation is the Mixture. That is, the FDA does not claim that the procedures used to administer the Mixture are unsafe; it claims that the Mixture itself is unsafe. Appellants’ arguments about the practice-of-medicine exemption are therefore wide of the mark.”
Legal Challenges to FDA’s Authority

Premarket submissions are only required for devices introduced into interstate commerce for commercial distribution.

*Each person . . . who proposes to begin the introduction or delivery for introduction into interstate commerce for commercial distribution of a device intended for human use shall, at least ninety days before making such introduction or delivery, report to the Secretary . . . .” 21 U.S.C. § 360(k).*

<table>
<thead>
<tr>
<th>LABS: The LDT process does not move in interstate commerce and is not commercially distributed.</th>
<th>FDA:</th>
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<tbody>
<tr>
<td>• Promoting or offering test is not enough to establish interstate commerce.</td>
<td>• LDT components move in interstate commerce.</td>
</tr>
<tr>
<td>• Test results are not commercially distributed; they are communicated to the physician and/or patient.</td>
<td>• LDTs are commercially offered.</td>
</tr>
</tbody>
</table>

*United States v. Regenerative Sciences, LLC, 12-5254 (D.C. Cir. 2014)*

- If a component of an article is in interstate commerce, the article is in interstate commerce.
- “Appellants read § 331(k) to require that the entire Mixture have been shipped in interstate commerce. They contend that merely using an ingredient that travelled in interstate commerce—here, doxycycline—is insufficient to trigger the bar. We disagree. Not only does the FDCA define the term “drug” to include a drug’s components, but to interpret § 331(k) as appellants suggest would severely narrow a statutory scheme designed to regulate the safety of drugs at every stage of their distribution. . . . .”
Legal Challenges to FDA’s Authority

FDA is statutorily prohibited from regulating the practice of medicine.

“Nothing in this chapter shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner‐patient relationship.” 21 U.S.C. § 396.

LABS: The LDT process is performed at the request of an individual doctor, within the context of a doctor‐patient relationship, to inform diagnosis and treatment decisions, and therefore regulation of the process would interfere with the practice of medicine.

FDA: FDA seeks to regulate the design of the LDT, not the process of performing it or interpreting the results.

*United States v. Regenerative Sciences, LLC, 12-5254 (D.C. Cir. 2014)*
- Regulation of an article used in the practice of medicine is distinct from the practice of medicine.
Additional lab arguments:

- Rule of lenity
- Clear, detailed regulation of the testing process under CLIA makes clear Congress did not intend for FDA regulation of LDTs.
Legal Challenges to FDA’s Authority

Substantive rules require notice and comment; interpretive rules do not.

Administrative Procedures Act (5 U.S.C. § 553)

- Substantive rules may only be promulgated after notice and comment.
- “Interpretative rules, general statements of policy, [and] rules of agency organization, procedure, or practice” do not require notice and comment.
- An agency must consider and respond to relevant and significant comments.
- Executive Orders 12866 and 13563 require economic impact assessment as part of notice-and-comment rulemaking.

LABS: Even if LDTs are devices, FDA may only impose it’s proposed scheme through notice-and-comment rulemaking.

FDA: The draft guidances amend enforcement discretion that was established without notice-and-comment rulemaking. Mortgage Bankers case
Legal Challenges to FDA’s Authority

Substantive rules require notice and comment; interpretive rules do not.

The substantive-interpretive line is difficult to draw.

- Intent to create new rights or duties (Orengo-Caraballo, 11 F.3d 186, 195 (D.C.Cir.1993))
- Stated intent not dispositive (Chamber of Commerce v. OSHA, 636 F.2d 464, 468 (D.C.Cir. 1980))
- Whether duty is fairly encompassed within interpreted statute or regulation (Kelley v. EPA, 15 F.3d 1100, 1108 (D.C.Cir.1994))
- More likely to be substantive if underlying statute is vague or general (e.g., “fair” or “equitable”) (United States v. Picciotto, 875 F.2d 345, 348 (D.C.Cir.1989))


- “Because an agency is not required to use notice-and-comment procedures to issue an initial interpretive rule, it is also not required to use those procedures when it amends or repeals that interpretive rule.”
Possible Approaches Going Forward

FDA intends to finalize guidances in 2016

• Let FDA finalize the guidances
  • Sue
  • Risk, uncertainty and cost
  • Consider legislation in 2017 or 2018
• Congressional and stakeholder pressure to delay the guidances
  • Political challenges and changing political dynamics
  • Delay the inevitable
  • Consider legislation in 2017 or 2018
• Find a legislative solution in 2016
  • Balance interests:
    • Address FDA, industry, labs, patient groups, political needs
    • Provide certainty
DTWG Background

Diagnostic Test Working Group
Created November 2014 by Leavitt Partners
Small group
Balanced industry and laboratory members
Thought leaders (including MDs)
Currently 9 members
“Fast fail” model
Complete confidentiality
Arrived at two consensus documents (the “white papers”) – March and October 2015
Possible Legislative Approaches

- AdvaMed type approach (close to FDA)
- ACLA concepts
- Utilize a system closer to the EU
- Professional society proposals (generally similar)
  - AMA
  - CAP
  - AMP
  - ACMG
- DTWG
DTWG Foundational Philosophy

- Patient comes first
- IVCTs are not the same as therapeutic devices
- Same activity/same regulation
- Risk based system
- Only one regulatory oversight system for one activity
  - No duplication or overlap
- Efficiency in the system
  - Eliminate non-value added requirements
- Advance innovation
- Certainty
- Not bound by current systems
Key Concepts

• Separate IVCTs from “medical devices”
• Jurisdiction
  • FDA, CLIA and practice of medicine
• Risk Classification
• Submissions
  • Process, standard, and contents
  • Three classes but no 510(k)
• Special Categories
  • Rare disease, unmet needs and significant clinical advancement
  • AWCPO
• Post-market
  • Studies, reporting and recalls

• Transition and Grandfathering
  • CLIA modernization
Excluded Concepts

• Two agencies regulating the same test
• Duplicative jurisdiction
• Technology specific provisions
  • No specific NGS rules
• Disease specific provisions
• Special rules based on entity type
• Excluded clinical utility from FDA oversight
• Did not specifically address reimbursement challenges
• Excessive reliance on enforcement discretion
• Submissions for existing tests
• Patent exclusivity approaches
## Jurisdiction

<table>
<thead>
<tr>
<th>IVCT Process Activities</th>
<th>Jurisdiction</th>
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<tbody>
<tr>
<td><strong>Test Development</strong></td>
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<tr>
<td>1. IVCT Design</td>
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<tr>
<td>2. IVCT Development</td>
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<tr>
<td>3. IVCT Validation</td>
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<tr>
<td>4. Preparation of reagents and other materials for use in more than one CLIA facility or by a third-party</td>
<td>FDA</td>
</tr>
<tr>
<td>5. Preparation of reagents and other material for use in one CLIA facility</td>
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<tr>
<td><strong>Laboratory Operations</strong></td>
<td></td>
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<tr>
<td>6. Development of lab SOP, verifying lab performance</td>
<td>CMS</td>
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<tr>
<td>7. Pre-analytical Processes</td>
<td></td>
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<tr>
<td>8. Performing the IVCT</td>
<td></td>
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<tr>
<td>9. Reporting the IVCT Output</td>
<td></td>
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<tr>
<td><strong>Medical Application</strong></td>
<td></td>
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<tr>
<td>10. Interpretation and Consultation</td>
<td>States</td>
</tr>
</tbody>
</table>
Key Jurisdiction points

• FDA regulates IVCTs under new system
  • Traditional IVCTs – e.g. test kits or “finished products”
  • Laboratory Developed Protocols
    • Defined boundary with laboratory operations/CLIA
  • Finished product does not include ASRs
  • Components under quality systems
• Devices regulated under existing systems
• CLIA Regulates
  • Laboratory operations
  • Purchasing
  • Test reporting
Risk Classification Concepts

- Based on risk to patient; not risk of technology
- Designed to be evolutionary
- Includes:
  - Impact of wrong result
  - One or multiple determinates
  - Level of experience with technology or test
  - “Mitigations” or “risk reduction factors”
  - User environment
  - Remoteness of risk
- Based on intended use
- Three classes
Risk Classification

Proposed IVCT Classification Flowchart

Clinically significant inaccurate result for developer’s stated intended use

When used as intended in medical practice, an undetected inaccurate result causes:
- Minimal/no harm,
- Immediately reversible harm, or
- No disability.
- Or—
  There is a remote risk of any adverse patient impact or adverse public health impact caused by such an inaccurate result.

Is:
- Well-characterized technology and well-characterized clinical use; or
- Clinical presentation; or
- Other tests (e.g., confirmatory or adjunctive); or
- Materials standard; or
- Other factors; and/or
- “Mitigations” available to prevent or detect the clinically significant inaccurate result, or otherwise mitigate the risk?

Yes → Low-Risk Test
No → Moderate-Risk Test

When used as intended in medical practice, an undetected inaccurate result causes:
- Non-life threatening injury,
- Injury that is medically reversible, or
- Delay in necessary treatment.

Is:
- Well-characterized technology and well-characterized clinical use; or
- Clinical presentation; or
- Other tests (e.g., confirmatory or adjunctive); or
- Materials standard; or
- Other factors; and/or
- “Mitigations” available to prevent or detect the clinically significant inaccurate result, or otherwise mitigate the risk?

Yes → Moderate-Risk Test
No → High-Risk Test

When used as intended in medical practice, an undetected inaccurate result causes serious or irreversible harm, or death, to the patient or public based on failure to treat, incorrect treatment, invasive procedures, or prolonged disability.

Figure 3
• High Risk: An IVCT for which a clinically significant inaccurate result for the intended use would cause serious or irreversible harm, or death, to the patient or public based on failure to treat, incorrect treatment, invasive procedures, or prolonged disability if such inaccurate result were undetected when used as intended in medical practice. **However, such an IVCT is a moderate-risk IVCT if mitigating factors are available to prevent or detect the clinically significant inaccurate result or otherwise mitigate the risk.**

• Moderate risk: An IVCT for which a clinically significant inaccurate result for the intended use would cause non-life-threatening injury, injury that is medically reversible, or delay in necessary treatment if such inaccurate result were undetected when used as intended in medical practice. However, such an IVCT is a low-risk IVCT if mitigating factors are available to prevent or detect the clinically significant inaccurate result or otherwise mitigate the risk.
Submissions

- New standard: *Reasonable assurance of analytical validity and clinical validity for the intended use*.

- Submission processes
  - Analytical and clinical validity
  - 120 day/75 day review periods
  - No RTA processes or hold
  - Role of “valid scientific evidence”
    - Broad definition

- No 510(k) process

- No submission for low risk

- Streamlined submission content
  - Limited raw data or manufacturing information
  - More summary reports for moderate risk
  - No pre-approval inspections
Modifications

• Only submit modifications if
  • New intended use
  • “Meaningful clinical impact”
  • Increased role of V & V to reduce submission numbers
• Specimen and stability changes don’t trigger submissions
• Developer responsible for submissions
• Reduction in number of submissions
• Critical issue for all stakeholders
Special Categories

- Rare disease:
  - 8,000 incidence
  - 50,000 prevalence
- Unmet need
- Meaningful clinical benefit
- Approval with confirmatory post-market obligations (“AWCPO”)
- Faster pathways/post-market data collection
Post-Market

- Streamlined adverse event reporting
- Greater use of summary reporting
  - Quarterly summary reports for most “MDRs”
- Standard recall provisions
  - Faster FDA classification
- Defined and limited authority to require post-market data collection
- Eliminated “conditions of approval”
- Standard adulteration and misbranding provisions
- Hybrid inspection processes
Grandfathering, Transition and Misc.

- IVCTs on market 90 days before legislation grandfathered in
- Limited authority for informational submission after 4 years
- 180 day listing requirement
- 4 year transition period
  - 2 years for regulation develop
  - 2 years to come into compliance
- New center/super office
- Use existing UDI
- Use of experts (internal and advisory)
- Training and education
- Export and reimbursement
CLIA Modernization and Other Elements

- Modernized and harmonized CLIA key elements
- Provide better coverage of laboratory operations
- Enhanced quality requirements
  - Includes change control, CAPA, validation and verification, proficiency testing, etc.
- Preemption of different state systems
- Third party accreditation
- User fees
Next Steps

• Leg text released in June and October 2015
• Stakeholder discussions ongoing
  • Collecting comments now
  • FDA and HHS heavily engaged
  • Growing (but not universal) consensus
• House Energy and Commerce consideration of final bill
  • Markup with subcommittee - May
  • Full committee consideration
• Senate HELP
  • Current situation
  • Next steps
• Is 2016 possible? Yes.
Questions
### FDA’s Move to Enforce Device Requirements

#### How oversight would change after FDA finalizes LDT guidance

<table>
<thead>
<tr>
<th>Type of laboratory-developed test</th>
<th>Notification</th>
<th>Adverse-event reporting</th>
<th>Premarket review</th>
<th>Quality system regulations</th>
<th>Registration &amp; listing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Used solely for forensic purposes</td>
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<tr>
<td>Used in CLIA-certified, high-complexity HLA labs for transplantation</td>
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<tr>
<td>Low-risk medical devices, including low-risk LDTs</td>
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<tr>
<td>Used for rare diseases (&lt;4,000 cases per year nationwide)</td>
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<tr>
<td>“Traditional LDT” (uses only legally marketed components and in patient care within one health care organization)</td>
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<tr>
<td>Used for “unmet needs” because there’s no FDA-cleared/approved test; limited to use in one health care organization</td>
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<tr>
<td>Highest-risk LDTs (same use as cleared/approved companion diagnostics, or class III device, or used to determine safety and effectiveness of blood or blood products)</td>
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<tr>
<td>Other high-risk types of tests in priority order determined by public process</td>
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<tr>
<td>Moderate-risk types of tests in priority order determined by public process</td>
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</table>

Comply within 6 months

- Not required

If new test, submit immediately; if already on market, within 1 year

Submit within 2–5 years

Submit within 5–9 years

Upon submission for premarket approval

Upon premarket approval

Not required if labs complete LDT notification process

Credit: Dr. Jack Snyder, RAC, DABT, CPI, CPE, CATO Research Washington