Laboratory Developed Tests
A Regulatory History and Update

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OBJECTIVES
• Identify regulatory authority for reagents under the Medical Device Amendments (MDA)
• Assess the requirements for assay validations under the Clinical Laboratory Improvement Amendments of 1988 (CLIA’88)
• Appraise current regulatory efforts regarding LDTs at the federal level

OUTLINE
• Background
• History of Federal Regulations
  “How we got here”
  - Medical Device Amendments of 1976 (MDA)
  - Clinical Laboratory Improvement Amendments of 1988 (CLIA’88)
• LDT Turning Point (1992-1998)
• Possible Regulatory Oversight (2010-2017)
  “What Now?”

DISCLOSURES
• University of Utah
  – Associate Professor (Clinical)
• ARUP Laboratories
  – Medical Director, ARUP Automated Core Laboratory
  – Vice President | Section Chief, Clinical Chemistry
  – Oversight over LDTs

The views presented are my own and are not meant to be representative of my employer
Federal Statutes

1906  Pure Foods and Drugs Act

1938  Federal Food, Drug, and Cosmetic Act (FFDCA; “The Act”)

1976  Medical Device Amendments (MDA)

Pure Foods and Drugs Act

1906  Pure Foods and Drugs Act
Prohibited misbranded and adulterated foods, drinks, and drugs in interstate commerce

“Wiley Act”
Dr. Harvey Washington Wiley
Chief Chemist
U.S. Department of Agriculture
Bureau of Chemistry

BUT: burden placed on the government to prove misbranding or adulteration

1938  FFDCA
Manufacturers were required to show that a drug was safe before it could be marketed

Regarding DEVICES
Prohibited misbranding and adulteration of “devices”
Defined device as:

*Instruments, apparatus, and contrivances, including their components, parts, and accessories, intended (1) for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; or (2) to affect the structure or any function of the body of man or other animals. [Sec. 201(h)]

BUT, it did NOT provide a comprehensive regulatory system for medical device safety, efficacy, or evaluation

1937 - Sulfanilamide Tragedy

1969 - Bacto-Unidisk Case

Regulatory Standards (1940-1970)

United States v. Bacto-Unidisk
394 U.S. 784 (1969)

The Secretary of Health, Education, and Welfare had the authority to regulate the device as a drug such that the “Secretary can subject it to pre-market clearance regulations”
1969 – Consumer Protection

Special Message to Congress on Consumer Protection
October 30, 1969

President Richard Nixon

“certain minimum standards should be established for such devices” and “a thorough study of medical device regulation” would be undertaken by the Department of Health, Education, and Welfare

1970s – Food and Drug Administration

January 1972 FDA NOTICE Released

They would “in the near future propose regulations governing in vitro diagnostic products” which include “reagents, instruments, and kits”

August 1972 FDA NOTICE OF PROPOSED RULEMAKING

Asserted jurisdiction over in vitro diagnostic products stating that they are medical drugs or devices under FFDCA

1970 – “Cooper Committee Report”

Study Group on Medical Devices
Department of Health, Education, and Welfare.

Medical Devices: A Legislative Plan.
September 1970.

Proposed broad recommendations for review and categorization of medical devices and establishment of performance standards.

Dr. Theodore Cooper (1929-1993)
Director of the National Heart and Lung Institute

1970s – Food and Drug Administration

1973 FDA Releases Response to Comments of Proposed Rules

Reiterated its authority


• Re-codified in March 1974 [21 CFR § 328]
• Re-codified in February 1976 [21 CFR § 809]
• Amended in February 1980 [45 FR 7484]

Who Cares?

In Vitro Diagnostic Product

Definition: “In Vitro Diagnostic Product”

“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 sequelae. 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)…”

1973 - Senate Hearings

U.S. SENATE - September 1973
Hearings before the Subcommittee on Health of the Committee on Labor and Public Welfare United States Senate

“Medical Device Amendments, 1973”

3 Proposed Bills – S. 2368; S. 1446; S. 1337

• Strong focus on conventional devices (IUDs)
• There was testimony that in vitro diagnostics were devices
• “Custom devices” were discussed (in the context of dental implants)
• The concepts of LDTs or “home-brew” testing NOT discussed
1975 – House of Representatives

U.S. House - September 1975

Hearings before the Subcommittee on Health and the Environment of the Committee on Interstate and Foreign Commerce.

Similar content to 1973 Senate hearings

Testimony from Dr. Theodore Cooper

"It should also be made clear that FDA would be able to take necessary action to curb a practitioner’s use of a custom device as a course of conduct on a number of patients, where this use is repeated to such an extent that the practitioner is in effect conducting unsupervised experiments, or allowing the marketing of a product that would otherwise be unlawful"

LDTs or “home-brew” testing NOT discussed

Medical Device Amendments of 1976

An act “to amend the Federal Food, Drug, and Cosmetic Act [FFDCA; 1938] to provide for the safety and effectiveness of medical devices intended for human use, and for other purposes”

- Authorized FDA to regulate in vitro diagnostic devices
- Established Device Classes (risk based):
  - Class I, General Controls (lowest risk)
  - Class II, Performance Standard (moderate risk)
    - Subject to General and Special Controls
    - Premarket notification (510k) "clearance"
  - Class III, Premarket Approval (highest risk); PMA; “approval”

Medical Device Amendments of 1976

- Includes Amendment to Section 201
  - (B) Section 15(d) of the Federal Trade Commission Act is amended to read as follows:
    - (d) the term ‘device’...means an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article...

Statute

...which is:
- (2) intended for use in the diagnosis of disease or other condition, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals...

In Vitro Reagents are Devices

Medical Device Amendments of 1976

The statute...

- DOES NOT specifically discuss the “concept” of LDTs
- DOES include several concepts that should be considered if the FDA were to regulate LDTs
  1) Records and reporting requirements
  2) Custom devices

1) MDA – Records and Reports

Prescribed regulations...

"shall not impose requirements unduly burdensome to a device manufacturer, importer, or distributor taking into account his cost of complying with such requirements and the need for the protection of the public health and the implementation of this Act..." [SEC. 519 (a)].

Exemption from reporting...

"any practitioner who is licensed by law to prescribe or administer devices intended for use in humans and who manufactures or imports devices solely for use in the course of his professional practice..." [17; SEC. 519 (b) (1)].

What is the professional practice of clinical pathology?

2) MDA – Custom Devices

Statute

"in order to comply with the order of a physician or dentist (or other specially qualified person designated under regulations)..." "necessarily deviates from an otherwise applicable performance standard..." if

- The device is not generally available in finished form for purchase or for dispensing upon prescription AND is not offered through labeling or advertising by the manufacturer, importer, or distributor thereof for commercial distribution, AND
- Such device...
  - (A)(i) is intended for use by an individual patient named in such order of such physician or dentist (or other specially qualified person so designated) AND is to be made in a specific form for such patient, OR
  - (i) is intended to meet the special needs of such physician or dentist (or other specially qualified person so designated) in the course of the professional practice of such physician or dentist (or other specially qualified person so designated), AND
  - (B) is NOT generally available to or generally used by other physicians or dentists (or other specially qualified persons so designated)" [17, SEC. 520 (b)]
**1977 Final Rule – Establishment Registration**

**Persons EXEMPT from Registration**

“(i) Persons who dispense devices to the ultimate consumer or whose major responsibility is to render a service necessary to provide the consumer (i.e. patient, physician, laymen, etc.) with a device or the benefits to be derived from the use of a device; for example, a...clinical laboratory”

**“Is LDT Notification de facto registration?”**

If YES, then Draft Guidance can’t change this – requires Notice and Comment Rulemaking.

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**1976-1992**

- For 16 years after passage of the Medical Device Amendments, the FDA did not (at least publically) assert any authority over LDTs
- In practice, there were two “pathways” for laboratory testing:
  - Commercially Distributed Pathway (regulated by the FDA)
  - LDTs (not regulated by the FDA)

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**Current Regulatory Reality**

1) Commercially Distributed Test Pathway:

2) Lab Developed Test (LDT) Pathway:

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**CLIA’88**

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**1967 – Partnership for Health Amendments**

**Clinical Laboratory Improvement Act of 1967**

- Licensing program for clinical laboratories involved in **interstate commerce**

  “No person may solicit or accept in interstate commerce, directly or indirectly, any specimen for laboratory examination or other laboratory procedures, unless there is in effect a license...”  
  [p536]

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**CLIA’67 - Consequences**

- **Fragmented** system
- Didn’t apply to ALL clinical laboratories
- **Physician office laboratories** were excluded

Different **quality requirements** for different types of laboratories led to growing national concern over laboratory quality (e.g. PAP smears)
1988 – House of Representatives #1

U.S. House - 1988

“Deadly Mistakes: Are Laboratory Results Reliable”

LDTs not discussed!

1988 – House of Representatives #2

U.S. House - 1988

“Clinical Laboratories”

LDTs not discussed!

1988 – Senate Hearings

U.S. Senate - 1988

“Health Care Financing Administration’s Management of Medical Laboratories”

LDTs discussed once in testimony!

12 years after MDA passage!

1988 – Senate Hearings

U.S. Senate - 1988

Written testimony of Dr. Herbert W. Dickerman
Director of the New York State Wadsworth Center for Laboratories and Research

Describing the Federal program for laboratory regulation...

“while FDA requirements must be met if a kit or reagent is to be commercially marketed, labs that use their own techniques and reagents need no approval” (p235).

CLIA – PERFORMANCE SPECIFICATIONS

42 CFR 493.1253 · Standard: Establishment and verification of performance specifications

(2) Establishment of performance specifications. Each laboratory that modifies an FDA-cleared or approved test system, or introduces a test system not subject to FDA clearance or approval (including methods developed in-house and standardized methods such as test book procedures), or uses a test system in which performance specifications are not provided by the manufacturer must, before reporting patient test results, establish for each test system the performance specifications for the following performance characteristics, as applicable:

[a] Accuracy;
[b] Precision;
[c] Analytical sensitivity;
[d] Analytical specificity to include interfering substances;
[e] Intra- and inter-laboratory variability of test results for the test system;
[f] Reference intervals (normal values);
[g] Any other performance characteristic required for test performance.

Regulation NOT Statute

Clinical Laboratory Improvement Amendments of 1988 (CLIA ’88)

“An amendment to the Public Health Services Act (PHSA) in which Congress revised the federal program for certification and oversight of clinical laboratory testing”

- Quality standards
- Certification program

- All facilities in the United States that perform laboratory testing on human specimens for health assessment or the diagnosis, prevention, or treatment of disease are regulated under [CLIA]”
1992

1992 – Citizen Petition to CPG

October/December 1992 – Citizen Petition filed by Hyman, Phelps & McNama (law firm representing “laboratories that would be affected”)

“...request that the Commissioner of Food and Drugs not regulate as medical devices assays developed by clinical reference laboratories strictly for in-house use”

Grounds

• Inconsistent with CLIA
• FDA lacks Statutory Authority to Regulate In-House Assays
• CPG Would Violate the Administrative Procedure Act
• CPG Would Diminish the Quality of Health Care

1992 – FDA Draft CPG


“It has come to the attention of the FDA that laboratories have been manufacturing, “home brew” products, either from products already on the market, or from components, and utilizing these unapproved products for diagnostic purposes. These products are subject to the same regulatory requirements as any unapproved medical device not identified in Attachment A.”

1997 – Analyte Specific Reagent (ASR)

Federal Register 21 CFR Parts 809 and 864; Medical Devices: Classification / Reclassification; Restricted Devices; Analyte Specific Reagents (FINAL RULE)

III. Response to Comments

General Comments, Comment 9 (about device classification)

“FDA appreciates the concerns raised about the development of in-house tests and the current marketing of test services based on tests that have not been reviewed independently for safety and effectiveness. FDA believes that clinical laboratories that develop such tests are acting as manufacturers of medical devices and are subject to FDA jurisdiction under the act.”

Response to Comment in Federal Register
Jonathan R Genzen - LDT

2010

2010 – July 19-20th, FDA Public Meeting

Jeffrey Shuren, Director of the Center for Devices and Radiological Health, announced that FDA intends on regulating all LDTs
- Moving from “enforcement discretion” to “exercise oversight”
- FDA plans to issue Guidance Document instead of Notice and Comment Rulemaking

Rationale Provided:
- Volume and types of LDTs have grown. Now commercial labs and/or biotechnology companies.
- LDTs have evolved to be more like commercial in vitro devices. Not just regional with direct contact to ordering clinician.
- LDT route to market presents a favorable business model and driving venture capital funding for clinical diagnostics; competitive disadvantage to FDA premarket review.
- Some LDTs aggressively marketed directly to clinicians via internet.
- Public needs assurances that LDTs are sound and reliable.

Draft Guidance vs Notice and Comment

2010

Policy vs Practice

Timeline
- Clearly had a practice of not exercising oversight
  - Claim that authority existed since 1976
  - Did not recognize issue until 1992
  - Did not announce intention until 2010

2010-2014

- 2010 onward – FDA Created Draft Guidelines
- August 2013 – Nine Democratic Congressmen wrote letter to OMB urging release:
  “We have reached a critical point in the development of advanced diagnostics at which it has become essential that FDA move this guidance forward to ensure appropriate and efficient oversight of safe and effective diagnostics.”
- July 11, 2014 – Five Democratic Senators wrote letter to OMB urging release, stating
  “For years this draft guidance has languished at OMB causing continued unpredictability and uncertainty.”
- July 31, 2014 – FDA Notified Congress of its intent to release the Draft Guidance documents

October 3, 2014

OMB review not publically available

2010

2010

2010

2010

2010

2010
**Framework for Regulatory Oversight**

- "Notification" to FDA of all LDTs
- Medical device reporting (e.g., adverse events)
- Enforcement discretion for forensic LDT and HLA/transplant
- Enforcement discretion (with respect to premarket review requirements) for low-risk LDTs; Traditional LDTs, LDTs used for rare diseases, and "LDTs for Unmet Needs"
- Risk-based, phased-in approach to enforcing the premarket review requirements for other high-risk and moderate-risk LDTs
- Use of clinical literature to support a demonstration of clinical validity
- Third-party review for many moderate risk LDTs
- Phased-in approach to enforcing the Quality System (QS) regulation

**U.S. House of Representatives**

The Energy and Commerce Committee

- Sep 9, 2014: Hearing on FDA Draft Guidance
- Dec 2014: White Paper Seeking Feedback for 21st Century Cures (11 Qs)
- Jun 2015: Draft Bill Circulated for NEXZ Regulation (i.e., DPA)
- Oct 2015: Updated LDT Draft Bill (would create new FDA center for NICE) (PDF 24hrs prior released: "20 Case Studies"

**January 8-9, 2015 – FDA Public Workshop**

**"Laboratory Developed Tests"**

**FDA Public Workshop (Bethesda, MD)**

- Overview of Proposed Framework
- Components of a Test and LDT Labeling Considerations
- Clinical Validity and Intended Use
- Categories for Continued Enforcement Discretion
- Notification and Adverse Reporting
- Public Process for Classification and Prioritization
- Quality System Regulation
- Public Comments (~40 different individuals/organizations)

**April 19, 2016**

**Laboratory Developed Tests.**—The FDA’s draft guidance issued on October 3, 2014, titled “Framework for Regulatory Oversight of Laboratory Developed Tests” (LDTs), puts forth a proposed regulatory framework that is a significant shift in the way LDTs are regulated. Such a shift deserves input from the public, and Congress has been working with stakeholders, constituencies, and the FDA to find common ground on regulating LDTs. The FDA’s guidance circumvents the normal rulemaking process and changes expectations for patients, doctors, and laboratories for the first time since the Clinical Laboratory Improvement Amendments Act was passed in 1988. The Committee directs the FDA to suspend further efforts to finalize the LDT guidance and continue working with Congress to pass legislation that addresses a new pathway for regulation of LDTs in a transparent manner.
Pro-Industry? Anti-Regulation?

On the issue of FDA regulation of LDTs, can you be both?

January 2017
- Discussion Paper on Laboratory Developed Tests (LDTs), FDA’s “synthesis of feedback” received during the public comment period and stakeholder engagement; FDA’s “current thoughts”

March 2017
- Diagnostic Accuracy and Innovation Act (DAIA) Discussion draft was made available for public comment from two members of the House Energy and Commerce Committee, Subcommittee on Health

Diagnostic Accuracy Innovation Act (DAIA)

In Vitro Clinical Tests (IVCTs)

Risk Classification

High Risk  Medium Risk  Low Risk

Would a clinically significant inaccurate result for the intended use cause serious harm?

Do risk reducing factors have the capacity to prevent or detect such inaccurate result or otherwise mitigate the risk?

Is the risk of adverse patient impact remote?

Reasonable assurance of analytical and clinical validity?

Valid scientific evidence?

Questions
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