



FDA's History with Lab Developed Tests

**Public Meeting on Oversight of
Laboratory Developed Tests
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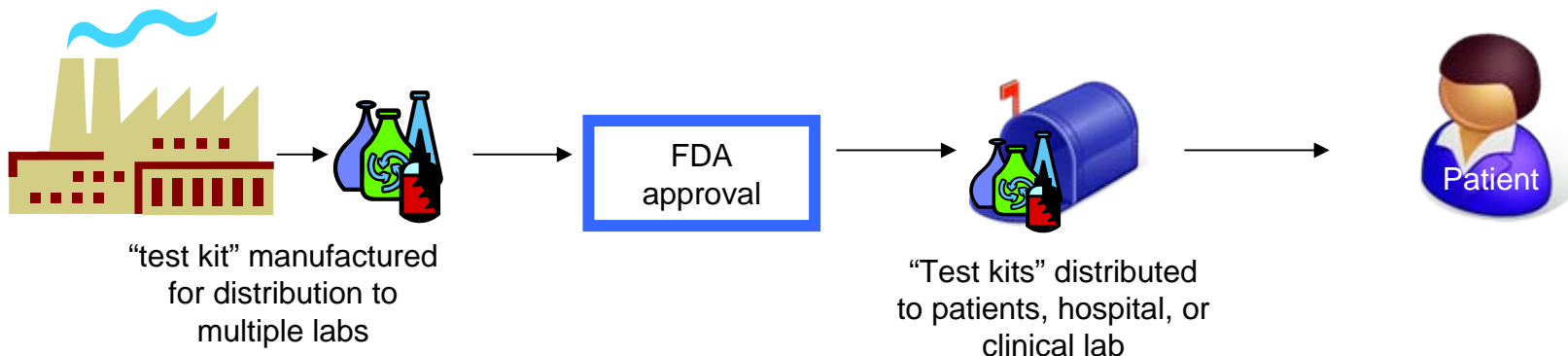
FDA Regulation of Medical Devices

1976 – Medical Device Amendments

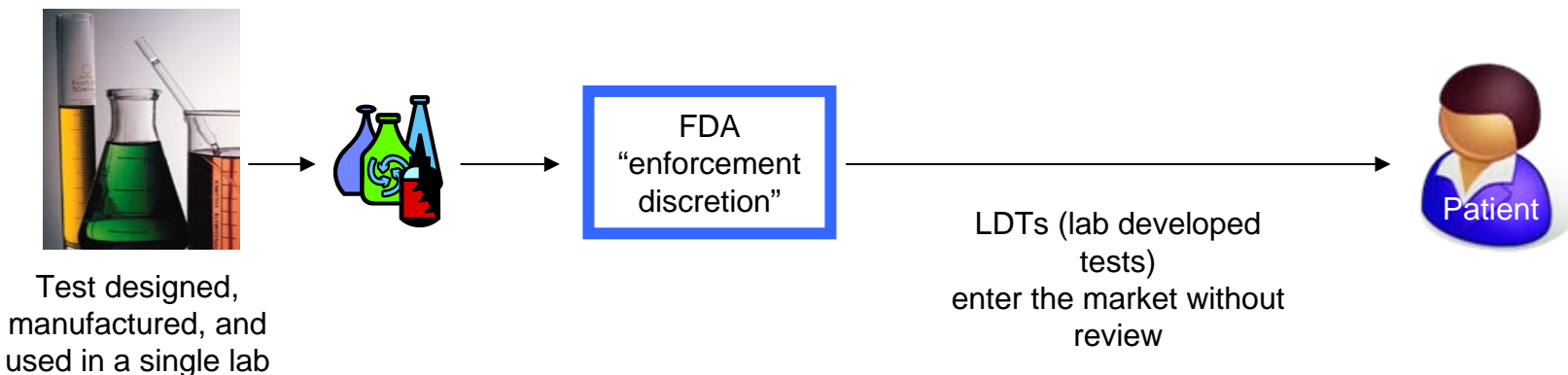
- Provides definition of ‘medical device’
 - regulation provides definition of ‘*in vitro* diagnostic test’
- Provides for Risk-Based regulation of medical devices
 - Knee implant ≠ toothbrush
 - Built-in flexibility for application of regulatory requirements
- Required phased-in regulation over the first several years
 - Regulations created for patient protection, premarket review, postmarket surveillance, enforcement, etc.
 - Classification panels for existing devices
 - Time for manufacturers to come into compliance

Lab Developed Tests

1) Commercially Distributed Test Pathway:



2) Lab Developed Test (LDT) Pathway:





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

- 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)

LDTs - Then

- Local
- Mostly non-commercial
- 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
- Tests usually for diagnosis or monitoring
- Often for rare diseases, unmet needs
- Performed by specialists with advanced training and require expert interpretation (karyotype, IHC)
- Small test volumes

The Evolution of LDTs

The 1990's:

- Human Genome research led to increased attention on genetic testing
 - All clinical genetic tests were LDTs
 - DNA testing became more practical and technologies made tests easier to develop
- Widespread use of research grade reagents for clinical use
- Questions arose about proper oversight of genetic tests and LDTs
- Some calls for increased oversight
- Others stated that no FDA regulation needed
 - Oversight would stifle innovation
 - CLIA regulation of labs was enough
- First written statements by FDA on authority over LDTs



The Evolution of LDTs

The ASR Rule - 1997

- FDA chose to regulate "the primary ingredients of most in-house developed tests" rather than the LDTs themselves
- Sought to ensure the quality of the test components, and to continue enforcement discretion for LDTs
- FDA stated that if the risks of LDTs change, FDA may require increased regulation of LDTs in the future

The Evolution of LDTs

The 2000's:

- Molecular testing platforms developed and improved at a fast pace
- Multiplex testing became easy to do (difficult to validate for clinical use)
- Tests became more complex and manufacturers / labs began to introduce higher risk products as ASRs or LDTs
- 2001 - SACGT – Released Recommendations of Genetic Testing Oversight
“the Food and Drug Administration (FDA) should be involved in the review of all new genetic tests regardless of how they are formulated and provided”

The Evolution of LDTs

- Publication of the ASR Rule was followed by inadvertent or deliberate abuse
- 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 in early 1990’s

The Evolution of LDTs

IVDMIA Draft Guidance (2006)

- IVDMIAAs are complex, non-transparent, and difficult to develop and validate correctly
- Most IVDMIAAs are marketed with claims that have a profound clinical impact (e.g., cancer diagnosis/prognosis, Alzheimer's disease risk, stroke risk, etc.)
- 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 laboratory developed tests
- Publication of the IVDMIA guidance generated some controversy. FDA obtained significant public comment on both drafts of the guidance

The Evolution of LDTs

- Genetic Tests Offered directly to consumers (DTC) by 2006
 - Mostly fringe “nutritional genetic” tests at first
 - GAO Investigated Direct to Consumer (DTC) Genetic Testing companies
 - FDA, CDC, FTC Published Cautionary statement on DTC Genetic Tests
- DTC Genetic Testing Moved into Higher Risk Clinical Claims starting in 2008
 - Proliferation of companies offering genome scans and SNP tests to consumers to predict risk for many clinical diseases
 - Generated much public discussion in genetic testing communities



LDTs - Now

- Many still performed that were performed 30 years ago
- Still often for unmet needs, rare diseases
- Still need for expert interpretation of traditional LDT types (IHC, cytogenetics, etc.)



LDTs - Now

- 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
- Tests broadly advertised
 - Aggressively marketed to clinicians
 - DTC advertising
 - Internet sales, overnight shipping
 - Nationwide, international reach

LDTs - Now

- Often require complex software
- Many incorporate automated interpretation, no competent human intervention for test 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
- “LDT” is self-determined – may not always be lab-developed



Clinical Laboratory Improvement Amendment of 1988 (CLIA)

Implemented increased oversight of laboratory testing:

- Certification process
- Accreditation requirements
- Periodic inspections
- Education and training requirements
- Proficiency testing

Focus is on the quality of the lab performing the tests, not on the tests themselves

CLIA regulation of labs and FDA regulation of tests are complementary for diagnostic testing



	FDA	CMS (CLIA)
Registration/Listing	Registration of establishment Publicly available listing of marketed tests	Registration and certification of Lab Lists of tests maintained by CMS (not currently publicly accessible)
Analytical validation	Premarket review of analytical data for Class II and Class III tests	Sampling after marketing during periodic laboratory inspections
Clinical validation	Premarket review of clinical claims for Class II and Class III tests; Postmarket surveillance of clinical claims for Class I tests	Not required
Quality System	GMPs, QS Regulations Assessed by inspection	Laboratory Quality system Assessed by inspection
Design Controls	Required for Class II and Class III tests and all other devices with software	Not required. Software not addressed by CLIA.
Adverse Event Reporting	Yes	No
Postmarket surveillance	Yes	No
Recalls	Yes	No



The Potential Risks of Insufficient Oversight

Under the current LDT pathway:

- Clinical validation (i.e., whether the test works as claimed) is not required
- No independent premarket review of data and claims
- Used for patients while still researching clinical utility (no informed consent)
- No post-market reporting/recall requirements
- Industries that engage the FDA regulated pathway are at a commercial disadvantage
- Lack of regulatory clarity adds business risk/uncertainty

The Potential Risks of Insufficient Oversight

Tests without sufficient oversight can lead to incorrect diagnoses

FDA has observed the following in LDTs in recent years:

- Faulty data analysis
- Exaggerated clinical claims
- Fraudulent data
- Lack of traceability/change control
- Poor clinical study design
- Unacceptable clinical performance



Current Landscape

- SACGHS – Released Recommendations of Genetic Testing Oversight - Recommended that that FDA address all lab tests using risk based approach (2008)
- AHRQ – Published draft Technology Assessment on Quality, Regulation and Clinical Utility of Laboratory-developed Tests (2010)
- Congressional Interest
 - Diagnostic Test Oversight
 - Personalized Medicine
 - DTC testing



Current Landscape

- Move toward Personalized Medicine
 - Increased use of lab tests in clinical care
 - Companion Diagnostics increasingly developed – different risks
- New Business Models
 - LDT viewed as ‘easier’ route to market
 - Driving VC funding decisions



Current Landscape

- Genentech petition
- Laboratory and Manufacturer Groups proposed alternatives to traditional FDA regulation:
 - ACLA
 - AdvaMed
 - Coalition for 21st Century Medicine
 - College of American Pathologists
 - etc...
- In the past few years many groups have modified their positions/thinking on the need for oversight of LDTs and how it could be accomplished



Today

- LDTs largely still considered important and beneficial
- Increased FDA oversight over LDTs
 - Under discussion for over 20 years
 - need for change recognized several years ago
- ASR regulation, IVDMA guidance – understood a need for modified oversight policies
- “Piecemeal” approach - not predictable, transparent enough

Question = What should FDA be doing in 2010?