# A New Era

## FDA Regulatory Oversight of Laboratory Developed Tests (LDTs)

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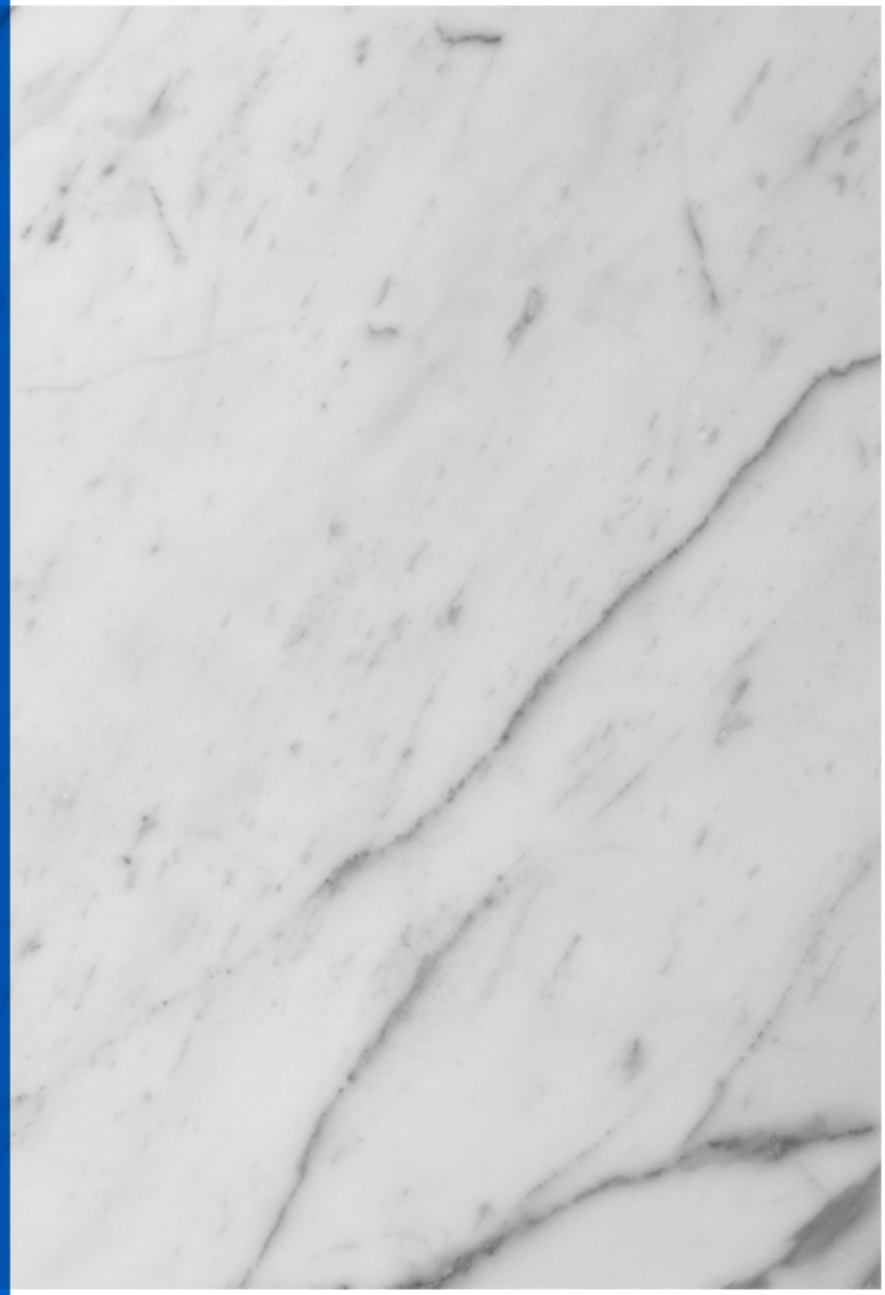

## In Vitro Diagnostic (IVD)

- 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….(21 CFR 809.3(a))

## Laboratory Developed Test (LDT)

- Used to detect a wide variety of analytes (such as proteins, chemical compounds, or DNA) in a sample taken from the human body

# Diagnostic Tests

- The use of tests even diagnostic tests to support medical decision making is not new
- Extraordinary advances across multiple scientific fields are leading to an explosion of diagnostic tests
  - Laboratory Developed Tests
    - Prognostic
    - Preventive Medicine
    - IVF and genetic testing of embryos
- Appropriate oversight of these tests has a long history of debate
  - http://www.genome.gov/10001733 (1997)
  - http://www4.od.nih.gov/oba/sacgt/reports/oversight_report.pdf (2010)
  - http://oba.od.nih.gov/oba/SACGHS/reports/SACGHS (2008)
- FDA's enforcement priorities …***SHIFTING***

# IVDs

- IVDs meet the definition of device under the Medical Device Amendments (MDA) to the FFDCA of 1976
- The term “device” means an instrument,…implant, in vitro reagent, or other similar or relate 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…

# LDTs

- FDA defines LDTs as a subset of IVDs which are designed, manufactured, and offered for clinical use by a **single laboratory.**
- FDA’s authority to regulate LDTs is *based* in the Medical Device Amendments of the FFDCA of 1976

# Regulatory History Over LDTs

- FDA has generally not enforced premarket review and other FDA regulatory requirements for LDTs
- Adopting instead a policy of “enforcement discretion” over labs and LDTs “because they were relatively simple, low-risk tests performed on a few patients being evaluated by physicians at the same facility as the lab”
- Primary regulation under Clinical Laboratory Improvement Amendments (CLIA) administered by CMS

# Regulatory History Over LDTs

- Primary regulation under Clinical Laboratory Improvement Amendments (CLIA) by CMS
  - CLIA establishes quality standards for laboratory testing and an accreditation program for clinical laboratories
  - CLIA requirements vary according to technical complexity in the testing process and risk of harm in reporting erroneous results
    - Waived tests
    - Tests of moderate complexity
    - Tests of high complexity

# New Era of Regulatory Power

- Today's LDTs are "more sophisticated and complex…becoming a staple of medical decision making…some people using the tests to decide whether to take preventive action"
- FDA has ***shifted*** to more active approach to regulation of LDTs under a phased-in risk-based framework
- Raises regulatory, policy, public health and legal questions
- Risks and problems are overshadowing the benefits and rigor of LDTs

# FDA Identified Problems with High Risk LDTs

- Claims not adequately supported with evidence
- Lack of appropriate controls yieldng erroneous results;
- Falsification of data
- Initiation of unnecessary treatment or delay or abandonment of treatment leading to illness or death

# FDA Is Aware Of Faulty LDTs

- Patients being over or undertreated for heart disease
- Cancer patients being exposed to inappropriate therapies or not getting effective therapies
- Incorrect diagnosis of autism
- Unnecessary antibiotic treatements
- Exposure to unnecessary, harmful treatments for certain diseases such as Lyme disease

# Time for Change: FDA Takes Action

- October 3, 2014 “Framework Guidance” describes a risk-based framework for the LDTs subset—guidance is geared to clinical laboratories that manufacture LDTs aka medical device manufacturers under the FD&C Act
  - FDA’s priorities for enforcing premarket and post market requirements and phase in enforcement
- October 3, 2014 draft guidance document FDA Notification and Medical Device Reporting for LDTs
  - Notification process and reporting requirements for clinical labs

# Key Dates For The Calendar

- October 23, 2014
  - Public Webinar hosted by FDA to answer questions about the draft guidance documents, pre-registration not required
- November 4-5, 2014
  - Public workshop and webcast hosted by the CDC and the Centers of Medicare and Medicaid Services (CMS)
- January 30, 2015
  - End of comment period draft guidance docs

# New Era: Framework Guidance

- Risk-based approach
- Captures LDTs into three groups
  - No regulation (enforcement discretion)
  - Partial regulation (partial enforcement discretion)
  - Full regulation

# LDT Group 1 – Enforcement Discretion

- Type of LDTs
  - LDTs solely for forensic (law enforcement) purposes
  - Certain LDTs for transplantation when used in CLIA-certified, high-complexity histocompatibility laboratories
- No Regulatory Requirements

# LDT Group 2 – Partial Regulation

- Type of LDTs
  - Low-risk LDTs
    - Equivalent to class I devices
  - LDTs for rare diseases
    - Perform fewer than 4,000 tests per year
  - Traditional LDTs
    - The type of LDTs that were available when FDA began its policy of exercising enforcement discretion over LDTs
  - LDTs for Unmet Needs
    - When there is no FDA-approved or cleared equivalent device available

# LDT Group 2 – Partial Regulation

- Regulatory Requirements
  - Notification of FDA
    - Alternative to establishment registration and listing
    - No user fees
  - MDR Reporting
    - Report adverse events (death, serious injury and malfunctions that could lead to the same) to FDA within defined timeframes
  - Recall Reporting
    - Reporting of certain corrections and removals of LDTs to FDA
  - No Premarket submission and no compliance with Quality System Regulation
    - Provided the laboratory notifies FDA of the test

# LDT Group 3 – Full Regulation

- Type of LDTs – High and Moderate Risk tests
  - Highest Risk
    - LDTs with the same intended use as a cleared or approved companion diagnostic
    - LDTS with the same intended use as an FDA-approved Class III device
    - Certain LDTs for determining safety and effectiveness of blood or blood products
  - Other High Risk
    - Those classified as Class III devices
  - Moderate Risk
    - Those classified as Class II devices
- LDTs of these types would be grandfathered until a premarket submission is required

# LDT Group 3– Full Regulation

- Regulatory Requirements
  - Notification
  - MDR Reporting
  - Recall Reporting
  - Premarket submission
    - PMA or 510(k), as applicable
  - Compliance with Quality System Regulation
    - After PMA is submitted or 510(k) clearance is obtained

# Proposed Implementation: 6 Months – 9 Years

- 6 Months
  - All labs must notify FDA of their LDTs
  - Adverse event reporting for LDTs begin
- 12 Months to year 5
  - Premarket submission for High Risk LDTs phased in
- Year 5 through 9
  - Premarket submission for Moderate Risk LDTs phased in
- Compliance with the QSR applies after the LDT is submitted for PMA approval or 510(k) clearance is obtained

# 120-Day Comment Period

- Ends January 30, 2015
- FDA has specifically requested public comment on, among other things:
  - Whether the healthcare system criterion in the traditional LDT and LDT for unmet needs can be omitted.
  - Standard for determining if an LDT is for a Rare Disease (e.g., use of the HUD standard or an alternative standard.
  - Quality System Regulation phase-in timeline.
  - Notification – whether a single notification from a healthcare system is sufficient if the test is being run in multiple labs and whether some LDTs should not require registration and listing.

# Questions About FDA Regulatory Oversight and Best Practices

Common Concerns About:

- FDA regulation of IVDs and LDTS

- how to prepare and what to expect during the FDA proceedings

- preparing and submitting comment

- conducting a risk based analysis

- mitigating risk and preparing for possible litigation

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## FDA Regulatory Oversight of In Vitro Diagnostic Devices (IVDs) and Laboratory Developed Tests (LDTs)

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