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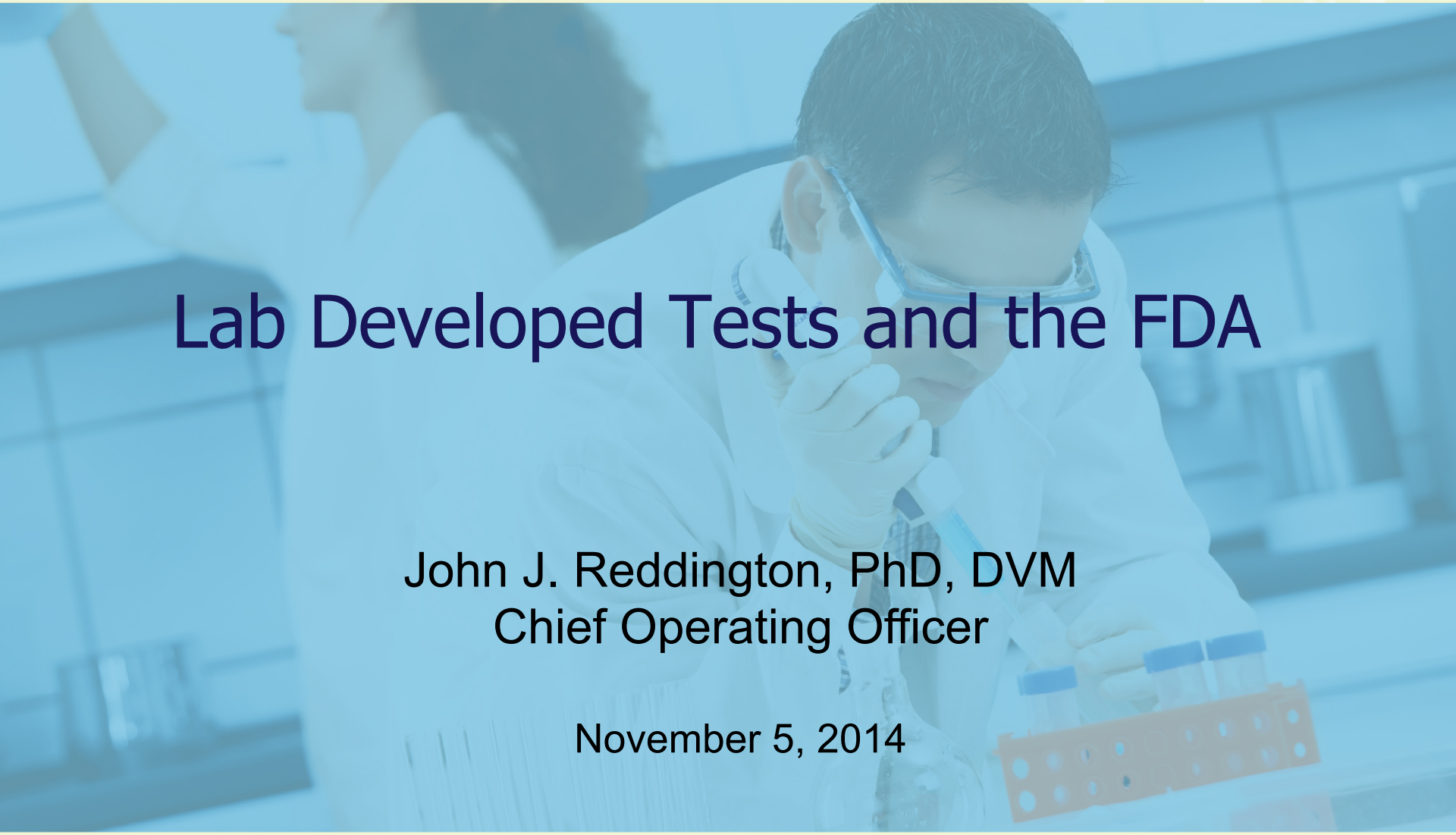

Lab Developed Tests and the FDA

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November 5, 2014

Overview

- What is an LTD and how is it different than a RUO, IUO or IVD?
- How have they been regulated to date?
- How will the FDA oversight change the future of LDTs?
- What is the timeframe for compliance with the new FDA Guidance?

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Changing Regulatory Oversight of LDTs

- "As required by Section 1143 of the Food and Drug Administration Safety and Innovation Act (FDASIA), **signed into law by the President on July 9, 2012, the Food and Drug Administration (FDA) is providing notification** to the Committee on Health, Education, Labor and Pensions and the House Committee on Energy and Commerce of **its intent to issue draft guidance entitled *Framework/or Regulatory Oversight of Laboratory Developed Tests (LDTs).*"**

Research Use Only (RUO) & Investigational Use Only (IUO)

- May be used in research or investigations on human samples that may eventually lead to their clearance or approval for clinical diagnostic use.
- May be marketed for and used in the research and investigation of other FDA-regulated products.
- Manufacturer of an IUO IVD product is not necessarily the sponsor of a clinical investigation that uses such an IVD product in a study.
- Manufacturer may legally distribute without FDA premarket review, as long as labeled:
  - ***"For Research Use Only. Not for use in diagnostic procedures."***
  - ***"For Investigational Use Only. The performance characteristics of this product have not been established."***

FDA's View of RUO Products in LTDs

- FDA fully supports the use of IVD products labeled RUO for research purposes, but since these products may not be manufactured in accordance with current Good Manufacturing Practice (cGMP) and their performance characteristics have not been established
- Believe they present a serious potential risk to the public health when used in clinical laboratories to generate tests results intended for patient management.
- FDA would consider promotion of IVD components, instruments, or reagents labeled RUO or IUO for use in an LDT conflicts with RUO and IUO labeling, which may render the device misbranded.

FDA Oversight of LDTs

- In the past, LDTs were referred to as “home brew” or “in-house” devices.
  - The term “laboratory developed test” and its acronym “**LDT**” replaced “home brew” over time, but the regulatory considerations are not affected by the change in terminology.

- FDA defines the term *laboratory developed test* (***LDT***) as an IVD that is intended for clinical use and designed, manufactured and used within a single laboratory

- CLIA requirements address the laboratory’s testing process (i.e., the ability to perform laboratory testing in an accurate and reliable manner). Under CLIA, accreditors do not evaluate test validation prior to marketing nor do they assess the clinical validity of a **LDT**.

Laboratory Developed Tests – Current Numbers

- Over 11,000 LDT's used in CLIA Certified Laboratories as of 2012
- Estimated that there are more than 800 new tests developed annually
  - Mayo Laboratory alone develops over 80 per year
- FDA wants to enforce its regulatory approval system for all existing and new LDTs, regardless of their risk
- FDA estimated that it can approve between 13 and 20 LDTs per year with current resources
- Would have made more sense to give CMS/CLIA/CAP additional resources to implement its recommended system

Current Oversight by CMS, CLIA and CAP

- CMS – Center for Medicare and Medicaid Services regulates all laboratory testing (except research) performed on humans in the U.S. through Clinical Laboratory Improvement Amendments of 1988 (CLIA)
- The Division of Laboratory Services, within the Survey and Certification Group, under the Center for Clinical Standards and Quality (CCSQ) has the responsibility for implementing the CLIA Program.
- CAP – College of American Pathologists, performs regulatory oversight of CLIA program, including proficiency testing and Accreditation
- CMS/CAP/CLIA covers approximately 244,000 laboratory entities (assays)

College of American Pathologists (CAP)

- Organization with more than 18,000 board-certified pathologists
- CAP's Laboratory Improvement Programs initiated 65 years ago, currently in 100 countries, accrediting 7,600 laboratories and providing proficiency testing to 20,000 laboratories worldwide.
- CAP President Gene Herbek, MD "The CAP will work to ensure LDT oversight assures quality laboratory testing for patients in a manner that is consistent with principles outlined by the CAP. The proposed FDA guidance embodies a number of those key principle……CAP will provide its recommendations and propose changes to improve the guidance during the public hearing and comment period.“

The Battlegrounds

- Under the FD&C Act, the FDA assures both the analytical validity (e.g., analytical specificity and sensitivity, accuracy and precision) and clinical validity of diagnostic tests through its premarket clearance or approval process.

- In addition to premarket review, FDA requirements provide other controls to ensure appropriate design, manufacture, and safety and effectiveness of the device.

- As a result, while CLIA oversight is important, it alone does not ensure that LDTs are properly designed, consistently manufactured, and are safe and effective for patients.

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FDA's View of Enforcing New Guidance

- FDA has determined that many modern LDTs are:
  - • manufactured with components that are not legally marketed for clinical use
  - • offered beyond local populations and manufactured in high volume
  - • used widely to screen for common diseases rather than rare diseases
  - • used to direct critical treatment decisions (e.g., prediction of drug response)
  - • highly complex (e.g., automated interpretation, multi-signal devices, use of non-transparent algorithms and/or complex software to generate device results)
- FDA recognizes that, as with all IVDs, there is a wide range of risks associated with the wide variety of LDTs.
- FDA believes that a risk-based approach to regulatory oversight of LDTs is appropriate and necessary to protect patient safety.

Risk-Based Approach toward Oversight of LDTs

- Medical devices are classified as Class I, II or III
  - Class I devices, which are subject only to general controls, generally represent the lowest-risk category of devices
  - Class III devices, which are subject to general controls and premarket approval, generally represent the highest-risk devices.

- FDA will consider several factors including whether the device is intended for use in high risk disease/conditions or patient populations, whether the device is used for screening or diagnosis, the nature of the clinical decision that will be made based on the test result.

- **To provide additional clarity, FDA intends to issue draft guidance to describe what the Agency considers generally to be Class I, II or III within 18 months of finalization of this guidance**.

Low Risk LDT

- FDA intends to exercise enforcement discretion for applicable premarket review requirements and quality systems requirements, but enforce other applicable regulatory requirements including registration and listing (with the option to provide notification) and adverse event reporting.
- Low-risk LDTs (Class I devices).
- LDTs for rare diseases (<4,000 patients) and "Traditional LDTs" (existed when the enforcement discretion policy was initially implemented, 1976).
- • "LDTs for Unmet Needs," when no FDA-approved or cleared equivalent device is available

Moderate Risk LTDs

- For other moderate and high risk LDTs, FDA intends to enforce applicable regulatory requirements, including registration and listing, adverse event reporting, premarket review, and quality system requirements.

- *Moderate-risk LDTs (Class II medical devices)*: Registration and listing and adverse event reporting begin six months after this guidance is finalized. *Premarket review requirements begin after the high-risk* (Class III) LDTs are completed, meaning 5 years after the guidance is finalized, and phase-in over 4 years (9 years total).

- FDA intends to utilize FDA-accredited third party review of premarket submissions as appropriate

High Risk LDTs

- *High-risk LDTs (Class III medical devices)*: Registration and listing and adverse event reporting begin six months after this guidance is finalized.

- Premarket review requirements begin 12 months after this guidance is finalized for the highest risk devices and phase-in over 4 years for the remaining high-risk devices (5 years total).

- Devices would remain on the market during review and FDA's consideration of applications. FDA's focus on high-risk devices begins with the following:
  - a) LDTs with the same intended use as a cleared or approved companion diagnostic;
  - b) LDTs with the same intended use as an FDA-approved Class III medical device; and
  - c) certain LDTs for determining the safety or efficacy of blood or blood products

Timeline for Implementation

- *Registration and Listing/Notification and Adverse Reporting*: Six months after this guidance becomes final, manufacturers of LDTs should notify FDA if they are developing LDTs and must begin to report significant adverse events to FDA.

- *Premarket Review*: FDA intends to phase-in enforcement of premarket review requirements for relevant LDTs over an extended period of time. The phased-in enforcement, starting with the highest-risk devices will begin 12 months after the guidance becomes final.
  - Class III/High Risk: Within 5 years of finalization of the guidance
  - Class II/Moderate Risk: Within 9 years of finalization of the guidance

Main Elements of FDA's Framework for Regulatory Oversight

- Notification to FDA of LDTs manufactured by a laboratory or Registration and Listing
- Medical Device Reporting Requirements (MDR) for LDTs (e.g., adverse event reporting)
- Continued 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

Main Elements of FDA's Framework for Regulatory Oversight

- Use of clinical literature to support a demonstration of clinical validity, which FDA expects would reduce the need for additional clinical studies to show clinical validity for LDTs where the analytes/markers that are measured/assessed have had their clinical validity established in the literature
- Facilitation of third-party review for many moderate risk LDTs
- Phased-in approach to enforcing the Quality System regulation
- Continued enforcement discretion for premarket review of Class I LDTs

LDT Devices of Higher Concern to the Agency

- *(1) Devices that act like companion diagnostics*
- *(2) Screening devices for serious diseases and/or conditions intended for use in asymptomatic patients with no other available confirmatory diagnostic product or procedure, such as screening device for malignant cancers*
- *(3) Diagnostic devices for certain infectious diseases with high-risk intended uses*

Clinical Implications

- ***Clinical Investigations***
  - FDA intends to continue to enforce investigational device requirements under 21 CFR Part 812 for all clinical investigations of LDTs that are conducted under clinical protocols that require institutional review board approval. Before conducting a investigation, clinical laboratories must follow applicable requirements in 21 CFR Part 56 for institutional review board (IRB) approval.

- ***Evaluation of Clinical Validity of LDTs***
  - FDA expects that for many LDTs, clinical validity has already been established in literature. FDA may still require studies demonstrating device performance (e.g., analytical evaluations) but generally intends to rely on the scientific literature to support clinical validity if appropriate.

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Third Party Review

- FDA has an established third party review program for eligible medical device.
- For LDTs, FDA envisions that the Agency would generally review PMAs for high risk (Class III) LDTs
- Third parties would generally review the 510(k)s for lower risk (Class II) LDTs.
- FDA seeks to work with interested parties that have experience with laboratories and can meet FDA requirements for third party reviewers.

Summary

- To date, the FDA has exhibited “discretionary oversight” of LDTs
- CMS/CAP/CLIA has filled the void by providing proficiency testing and regulatory oversight
- The FDA intends to issue new guidance within the next 18 to 24 months, at which time they will take an active role in registering and regulating risk-based LDTs
  - Class I (Low Risk): will exercise enforcement discretion
  - Class II (Moderate Risk): Registration and listing and adverse event reporting begin six months after this guidance is finalized. Premarket review requirements begin 5 years after the guidance is finalized, and phase-in over 4 years (9 years total).
  - Class III (High Risk):Premarket review requirements begin 12 months after this guidance is finalized for the highest risk devices and phase-in over 4 years for the remaining high-risk devices (5 years total).
- CAP/CLIA will maintain oversight in the interim

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Thank You!

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