

# **FDA Perspectives on Diagnostic Test Quality in Newborn Screening**

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Genetic Testing Symposium  
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# Agenda

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- Regulation of IVDs
- Laboratory Developed Tests
- ASRs
- IVDMIAs
- Current Status

# Medical Device Amendments of 1976

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Regulation of all Medical Devices includes:

- General controls
- Registration and listing
- Good manufacturing practices
- Reporting of adverse events
- Risk based regulation by intended use

# IVDs

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FDA is concerned that diagnostic tests are reliable and that patients and health care professionals understand both the value and the limitations of such testing

# Intended Use

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**FDA regulatory requirements are driven by the intended use of the device**

The claims made in the intended use will determine the type of review and the types of studies that are necessary - This can be independent of the technology or assay format

# Intended Use

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FDA Regulates IVDs by the risk of an incorrect result:

**Class I** – Low risk – Usually exempt from Premarket FDA review

**Class II** – Moderate risk – Risk of an incorrect result can be mitigated by Special Controls

**Class III** – High risk – a false result may result in serious injury or death

# Intended Use

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“Moderate Risk” intended uses usually require premarket review in the form of a premarket notification [510(k)] submission

- The company submits information describing how the device is “substantially equivalent” to legally marketed devices
- Submissions may include clinical data

# Intended Use

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“High Risk” intended uses require premarket review in the form of an application for Pre-Market Approval (PMA)

- This sometimes includes devices with new technologies / methodologies
- The company submits information describing the safety and effectiveness of the device, usually including the device performance in clinical trials

# Intended Use

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**De novo classification** – FDA can classify certain novel devices as “moderate risk” if enough information is available

- Allows for mitigation of potential risks by the creation of Special controls, including Guidance documents
- Allows for the clearance of similar devices via the 510(k) process in the future
- Encourages the submission of new and innovative products because of the lower regulatory threshold

# Intended Use

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- Carefully define the intended use population(s)  
(e.g., some biomarkers may have low prevalence in certain populations - many patients may need to be tested for statistical significance)
- The type of review [510(k), PMA, etc.] and the types of validation studies that are needed depend on the claims that are made in the intended use

# Analytical Performance

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- Precision / Reproducibility
- Accuracy
- Limit of Detection
- Potential Interferences
- Etc...

# Analytical Performance

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## Precision / Reproducibility:

- Studies should demonstrate that the intended users can get reliable results
- Reproducibility at external sites for commercially distributed devices
- Should use clinical samples when possible through all pre-analytical and analytical steps
- User training should be the same for studies as for marketed assay

# Analytical Performance

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## Accuracy:

- Real clinical samples
  - Retrospective samples, appropriately collected and stored
  - prospectively collected samples
- Compare assay results to:
  - predicate device results (510(k) only)
  - a gold standard method (510(k), PMA, or de novo)
  - Clinical diagnosis

# Clinical Performance

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- Clinical performance – clinical validity
  - Device must have a clinical indication/clinical utility
- May be based on:
  - Existing clinical data
  - New clinical trial data
  - Review of information in the literature
  - Current clinical knowledge

# Clinical Performance

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## Examples:

- CFTR mutations (ACOG/ACMG recommended)
  - literature validation likely to be acceptable
- Mutations in a novel gene to predict risk of developing cancer
  - most likely needs clinical study data

# Software

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Software in medical devices should be developed under Design Controls

- Follow the FDA guidance for premarket submission requirements for devices containing software
- Follow the FDA guidance for off-the-shelf software

# Laboratory Developed Tests

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Currently, IVDs have 2 paths to market:

- Traditional, commercially distributed test
- Laboratory Developed test (LDT)

# Laboratory Developed Tests

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- Some diagnostic tests are created in a single laboratory for use only in that laboratory
- Also called “Homebrew tests” or “In-house Tests”
- The use of laboratory developed tests is a well established practice
- A broad menu of tests are offered in this manner

# Laboratory Developed Tests

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- Laboratory personnel and practices subject to CLIA (CMS)
- Analytical performance validation is required for CLIA
- Clinical validation not required under CLIA
- A lab Quality System is required
- Limited post-market reporting requirements

# Laboratory Developed Tests

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Laboratories using commercial IVDs are required to:

- Report deaths to FDA
- Report serious injuries to the test manufacturer and/or FDA

Other device issues should be reported to the manufacturer, although this is not a requirement for labs.

Test manufacturers use complaints to track device problems so that they can fix them.

# LDTs – not trouble free

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- Different regulatory threshold than FDA reviewed tests – non-parity
  - No premarket review
  - No independent research phase
  - No requirement for clinical validity
- Varying quality in test development and validation

# LDTs – not trouble free

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Early/mid-1990's:

- Widespread promulgation of RUO/IUO devices for clinical use
- Increased attention on genetic testing -- human genome project

# Analyte Specific Reagents (ASRs)

FDA has stated that "clinical laboratories that develop [in-house] tests are acting as manufacturers of medical devices and are subject to FDA jurisdiction under the Act"

However, FDA has generally exercised enforcement discretion over LDTs, and not actively regulated them

Instead, FDA decided to try to ensure the quality of the reagents used in LDTs.

So, FDA created the ASR Rule (1997)

# Analyte Specific Reagents

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ASR = Analyte Specific Reagent

Rules published 1997

21 CFR 864.4020, 809.10, and 809.30

“Analyte specific reagents (ASR's) are antibodies, both polyclonal and monoclonal, specific receptor proteins, ligands, nucleic acid sequences, and similar reagents which, through specific binding or chemical reaction with substances in a specimen, are intended for use in a diagnostic application for identification and quantification of an individual chemical substance or ligand in biological specimens.”

# Analyte Specific Reagents (ASRs)

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- Desire to ensure that reagents used in laboratory developed tests for clinical use are manufactured using cGMP
- Deliberate effort to create safe harbor for laboratory developed tests
- Assure transparency in labeling – responsible party is the lab, not the manufacturer

# ASR: Impact on Manufacturers

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ASR manufacturers:

- Required to register and list
- Required to meet GMPs
- Required to report adverse events
- Restricted distribution, use, and labeling  
(see 21 CFR 809.10, and 809.30)

# ASR Rule -Unexpected Consequences

- Publication of the ASR Rule was followed by inadvertent or deliberate abuse
- ASR manufacturers were promoting products as ASRs that were inconsistent with the definition of an ASR as outlined in 21 CFR 864.4020
- IVD “Kits” were labeled and Listed as ASRs to skirt FDA oversight

# LDTs

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Recently, OIVD has released 2 draft guidance documents that are LDT-related:

- ASR Q&A Guidance
- IVDMIA Guidance

# ASR Q&A Guidance (2006)

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## Draft Guidance - Commercially Distributed Analyte Specific Reagents (ASRs): Frequently Asked Questions

Published September 7, 2006

(<http://www.fda.gov/cdrh/oivd/guidance/1590.pdf>)

- Intended to clarify the definition of an ASR and limitations on marketing of ASRs
- Not intended to eliminate legitimate homebrew testing
- Labs must be able to take responsibility for the design and validation of the test – not possible with “kits” or “pseudokits”

# ASR Guidance

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- Examples of ASRs:
  - a single antibody
    - e.g., an anti-troponin I antibody
  - a single nucleotide primer
    - e.g., a forward primer for amplification of the  $\Delta F508$  locus of the CFTR gene
  - a single purified protein or peptide
    - e.g., purified estrogen receptor protein

# ASR Guidance

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- Examples of entities that are not ASRs:
- Multiplexed reagents
- Test systems
  - e.g., when it some or all of the products needed to conduct a particular test and/or has instructions for use.
- Control material
- Products that have specific performance claims, or procedural instructions, or interpretations for use.
- Reagents that are extensively processed
  - e.g., arrayed on beads
- Reagents offered with software for interpretation of results.
- Other products that do not meet the ASR definition
  - e.g., software for interpretation of assay results, microarrays, etc.

# Multivariate Guidance

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## IVDMIAs:

a growing category of tests, include elements (e.g., complex, statistically-derived, data-driven algorithms) that are not standard primary ingredients of LDTs that raise safety and effectiveness concerns.

## Additional Concerns:

- No independent review of data sets or clinical claims
- Degree of scientific rigor varies greatly among IVDMIAAs
- Some IVDMIAAs offered for clinical use while still in a “research phase”

# Multivariate Guidance

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The new guidance draft

- **In Vitro Diagnostic Multivariate Index Assays** -  
defines a narrow niche of devices, whether  
commercially distributed or laboratory  
developed, that is subject to FDA regulation  
rather than enforcement discretion

# Multivariate Guidance

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## **IVDMIAs :**

- Use clinical data (from one or more IVDs assays and sometimes demographic data) to empirically identify an algorithm

**AND**

- Employ the algorithm to integrate these different data points in order to calculate a patient-specific result (e.g., a “classification,” “score,” or “index”)

**AND**

- The result cannot be interpreted by clinicians using prior knowledge of medicine without information from the test developer regarding its clinical performance and effectiveness

# Multivariate Guidance

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## Potential examples:

- A microarray that predicts colon cancer recurrence based on an RNA expression pattern
- An assay that integrates quantitative results from 7 immunoassays to obtain a qualitative “score” that predicts a person’s risk of developing Alzheimer’s disease
- A test that integrates a patient’s age, gender, and genotype of 5 genes to diagnose cardiovascular disease

# Multivariate Guidance

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## **Some devices that are *not* IVDMIAs:**

- Standard creatinine clearance determination
- A device that measures Total Cholesterol, HDL Cholesterol, and Triglycerides and determines LDL Cholesterol concentration via a calculation
- An assay that measures the 25 ACOG/ACMG recommended mutations to report a patient's CFTR genotype

# Multivariate Guidance

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- Classification and review of IVDMIAs will be risk-based by intended use
- Opportunity for Class I, II, and III indications
- IVDMIAs will be regulated the in the same manner as all other medical devices

# Impact of FDA Regulation

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- Independent assessment of data and labeling
- Adverse event reporting and Recalls
- Informed by evaluation standards; grounded in “least burdensome” mandate
- If focused – good science is good science

Note: If the test is already being used (or going to be used) on patients, shouldn't data exist to show it is safe and effective?

# First IVDMIA Cleared for Marketing

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In February, FDA, cleared for marketing the first  
IVDMIA

## The Agendia MammaPrint Test:

- Intended to predict the likelihood of breast cancer recurrence
- Developed and performed at a single laboratory site
- Efficient review by FDA
- Classified (*de novo*) into Class II
- MammaPrint can be used as a predicate device for similar IVDMIAs
- Special Control Guidance document will describe the types of information that should be submitted for these assays

# Current State of Affairs

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- Industry seeking regulatory parity between IVDs and LDTs
- Consumer advocates seeking more comprehensive regulatory assurance of LDTs
- Commercial Laboratories seeking predictability, some favor CMS regulation over FDA regulation
- Congress concerned with issues

# Current State of Affairs

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- Secretary Leavitt Priority – Personalized Medicine
- GAO report and Hearing of the Senate Committee on Aging
  - Direct-to-Consumer Genetic tests
  - Nutrigenetic Tests
- Kennedy/Smith Bill
  - Laboratory Test Improvement Act
  - Calls for FDA regulation of LDTs
- Obama Bill
  - Personalized Medicine
  - Pharmacogenomics

# Current State of Affairs

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- FDA is considering options
- FDA is seeking input from all stakeholders
- FDA resources are limited

# Questions?

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