Overview of Genetic Testing from the FDA Regulatory Perspective

Clinical Laboratory Improvement Advisory Committee Meeting

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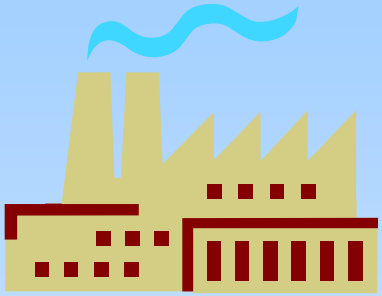
Laboratory Developed Tests

Currently, IVDs have 2 paths to market:

- Traditional, commercially distributed test
- Laboratory Developed test (LDT)
  "Homebrew tests" or "In-house Tests"

IVDs – Dual Path



"test kit" manufacturer

lab

FDA

CLIA

Laboratory Developed Tests

- The use of laboratory developed tests is a well established practice
- A broad menu of tests are offered in this manner

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

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)

- 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 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

ASR Q&A Guidance (2006)

Draft Guidance - Commercially Distributed Analyte Specific Reagents (ASRs): Frequently Asked Questions

Published September 7, 2006

- 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”

Revised ASR Guidance

FDA received more than 30 comments

- Appreciation of publication of guidance document and clarifications of the ASR rule
- Enforcement of ASR regulations will stifle innovation and impede rare disease testing
- The clarification that a reagent containing "multiple moieties" is not an ASR is too restrictive
- Transition period needed

IVDs – Unequal Regulation

	CLIA	FDA
Research Phase	No	Yes
Analytical validation	Post hoc sampling	Yes
Clinical validation	No	Yes
Report Adverse Events	No requirement; no system	Yes
Transparent Results	No public information	Published review summary

LDTs – not trouble free

- Widespread promulgation of RUO phase and IUO phase devices for clinical use
  - New biomarker tests, often offered in RUO phase
- Clinical Validity is sometimes unknown
- Many have high risk indications
- Many being introduced to direct drug treatment
- Increased attention on genetic testing -- human genome project

LDTs – not trouble free

- Quality of labs varies
  - → Training of lab directors and staff varies
  - → No PT programs or even material for new tests
- Non-transparency in validation of LDTs

IVDMIA Update

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

- No independent review of data sets or clinical claims
- Scientific rigor varies greatly
- Some offered for clinical use while in “research phase”

IVDMIA Guidance

- Original draft guidance published September 7, 2006
- Public Meeting held February 8, 2007
- 180 day comment period
- FDA received more than 60 comments

IVDMIA Guidance

- FDA published a revised draft guidance on July 26, 2007
- Comment Period of 30 days has been extended for 30 more days.
- FDA will determine the next steps after careful consideration of the comments it receives

Revisions based on Comments

- Need for clearer definition of terms

  Definition clarified and simplified, with examples

- Need for clarification of FDA regulatory process

  Appendix added to provide clarity on labeling and regulation of devices

- Concern over chilling of new technology for diagnostic use

  Clarifies the flexible regulatory mechanisms that are in place to handle the iterative nature of medical devices

- Concern over impact on rare disease testing

  Exercise enforcement discretion and not require premarket review for LDT IVDMIAs intended for rare disease testing

Revisions based on Comments

- Need transition period for compliance

  FDA will exercise enforcement discretion during transition period

- Clarify how labs can implement FDA's QS Regulation

  FDA intends to issue guidance to assist laboratories that manufacture IVDMIAs in complying with the QS regulation

- Clarify postmarket requirements

  Revised guidance provides additional clarity in this area

Current State of Affairs

- 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

- 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

Personalize Medicine Commissioner's Priority

- Co-development
- Pharmacogenomics
- Development and validation of new biomarkers

Current State of Affairs

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