# FDA – Clarifications of the Current Regulatory Paradigm

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# Medical Device Amendments of 1976

Regulation of all Medical Devices includes:

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

# Premarket Review

All In Vitro Diagnostic Devices must establish adequate:

- Analytical performance – test accuracy
- Clinical performance – how to interpret test signal
- Labeling – adequate instructions for use

# Laboratory Developed Tests

- Some diagnostic tests are created in a single laboratory for use only in that laboratory
- Also called “Homebrew 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 – not trouble free

- Different regulatory threshold than FDA reviewed tests – non-parity
- No premarket review
- No independent research phase
- No requirement for clinical validity
- Some very colorful players – recent GAO report and Congressional hearing

# Analyte Specific Reagent Rule

To ensure the quality of reagents used in laboratory developed tests, FDA created the ASR Rule (1997)

- Incremental increase in regulation
- Achieved by a regulatory Down-classification
- 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

# Preamble to ASR Rule

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

# 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.
- “Kits” disguised as ASRs to skirt FDA oversight
- Test optimization and implicit claims

# ASR Q&A Guidance (2006)

- Intended to clarify the definition of an ASR and limitations on marketing of ASRs - not new in substance, spirit, or meaning, and include examples
- 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”

# ASRs vs. Tests

Class I exempt ASR ≠ exempt Test:

- Laboratory developed tests that use Class I, exempt ASRs (or ASRs created in-house) are not necessarily, by extension, Class I, exempt tests – it depends on what they are used for

- FDA has generally exercised enforcement discretion over laboratory-developed tests

# Multivariate Guidance (2006)

IVDMIAs:

- a growing category of tests that include elements that are not standard ingredients of in-house tests
- raise safety and effectiveness concerns

Therefore, IVDMIAs do not fall within the scope of laboratory-developed tests over which FDA has generally exercised enforcement discretion

# Multivariate Guidance

The new guidance draft

**- In Vitro Diagnostic Multivariate Index Assays -**

defines a a narrow niche of devices, whether commercially distributed or laboratory developed, that is subject to FDA regulation rather than enforcement discretion

# Multivariate Guidance

**IVDMIAs :**

- Use clinical data to empirically identify an algorithm

**AND**

- Employ the algorithm to calculate a patient-specific result
  (e.g., a "classification," "score," or "index")

**AND**

- The result cannot be interpreted by well trained health care provider without help of test developer

# IVDMIA Clarifications

- A device may use an algorithm and not be an IVDMIA
- A device may use software and not be an IVDMIA
- A device may be multivariate and not be an IVDMIA
- If in doubt, ask for help

# IVDMIA's

- Novelty and risk profile different than other home brew devices
- Locked cabinet analogy – if combination not needed, regulation not applied
- Regulation – risk based with opportunity for class I, II, or III depending on intended use

# Impact of FDA Regulation

- Independent assessment of data and labeling
- 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

# FDA Mission

- Promote public health
- Protect public health
- Good science