Why HIV Tests are Regulated as They are and Understanding the Package Insert

HIV Diagnostics Conference
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To Be Covered

- Why are HIV tests regulated as PMAs?
- Requirements for a 510(k) vs. a PMA
- Criteria used to evaluate a test
- How to (and why you should) read package inserts
- How test performance is evaluated
- Off-label use vs. CLIA requirements
- Why are “outdated” tests still on the market?
Why are HIV tests regulated as PMAs?

- Basis for regulatory authority
  - Laws/Acts
  - Regulations
  - Guidance documents

- Risk-based regulatory approach

- Data-driven marketing approvals
  - To provide EVIDENCE that the device is SAFE and EFFECTIVE for its INTENDED USE
The Tools: Regulatory Framework

- **Laws/Acts** = MUST
  - Federal Food, Drug, and Cosmetic Act of 1938
  - Medical Device Amendments of 1976
  - FDA Modernization Act of 1997
  - Medical Device User Fee and Modernization Act of 2002
  - FDA Amendments Act of 2007
  - FDA Safety Improvement Act of 2012

- **Regulations:** Code of Federal Regulations, Title 21 = MUST
  - Subchapter H, Part 800: Medical Devices
  - Part 50: Protection of Human Subjects
  - Part 56: Institutional Review Boards

- **Guidance documents** = RECOMMENDED
Bringing an IVD to Market in the US: Device Classification

- Risk-based regulatory approach
  - Class I (low risk)
  - Class II (moderate risk) [premarket notification, or 510(k)]
  - Class III (high risk) (premarket approval application, or PMA)

- Device regulatory controls include:
  - Quality Management System, including design controls
  - Premarket submission review
  - Labeling
  - Registration of manufacturer and listing of marketed devices
  - Vigilance - passive surveillance for all; active for a subset of devices
FDA Approval of HIV Diagnostics

• IVDs used for the detection of HIV infection are Class III devices

• Require submission of a premarket approval application (PMA)
  - Filed by a sponsor to obtain FDA approval to market a device
  - 21 CFR 814
## Requirements for a 510(k) vs. a PMA

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Criteria Used to Evaluate an HIV Diagnostic Test
PMA: Required Elements (814.20)

- Name and address of the applicant
- Table of contents
- Summary section
- Technical sections containing data and information in sufficient detail to permit FDA to determine whether to approve the application
PMA: Required Elements, cont.

- A complete description of:
  - The device, including pictorial representations
  - Each of the functional components
  - The properties of the device relevant to the diagnosis, treatment, prevention, cure, or mitigation of a disease or condition
  - The principles of operation of the device
  - The methods, facilities, and controls used in the manufacture, processing, packing, storage, and where appropriate, installation of the device.
- See also 21 CFR 820 - Quality System Regulations
  - Design controls
  - Manufacturing controls
PMA: Required Elements, cont.

- Bibliography of all published reports
- Copies of all proposed labeling for the device
- Environmental assessment
- Financial disclosure
- Additional information specified in 814.20
- Manufacturing site inspection
  - To meet requirements set out in Quality System Regulations (21 CFR 820)
  - Biennial post-approval inspections
Decision-Making Process

• Review committee consisting of product and clinical experts, statistician, reviewers for facility issues and bioresearch monitoring (to ensure quality of clinical data)

• 180-day review clock, communicating issues to sponsor throughout the review time
Guidance for Industry and FDA Staff

Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process

Document Issued on: December 11, 2008

This document supersedes “Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process” dated March 9, 2007.

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089274.htm
How to (and Why You Should) Read Package Inserts

• Critical legal role of the package insert
  - The package insert is used to make specific claims about the product.
  - If those claims are not met, then the product is considered to be “misbranded” under the Food, Drug, and Cosmetic Act and cannot be legally marketed

• Test performance established on the basis of following the product insert
  - Not doing so (e.g., altering the procedure, using expired reagents, using operating conditions outside of the acceptable range) may produce erroneous results
IVD Package Inserts: 21 CFR 809.10((b))

- The proprietary name and established name (common or usual name), if any
- The intended use or uses of the product
- Summary and explanation of the test
- The chemical, physical, physiological, or biological principles of the procedure
- Information on reagents
IVD Package Inserts: 21 CFR 809.10(((b), cont.

- A statement of warnings or precautions for users and a statement "For In Vitro Diagnostic Use" and any other limiting statements appropriate to the intended use of the product
- Instruments
- Specimen collection and preparation for analysis
IVD Package Inserts:
21 CFR 809.10((b), cont.

- Procedure: A step-by-step outline of recommended procedures from reception of the specimen to obtaining results
  - A list of all materials provided
  - A list of all materials required but not provided
  - Details of kinds of quality control procedures and materials required
  - Etc.

- Results: Explain the procedure for calculating the value of the unknown
IVD Package Inserts:
21 CFR 809.10((b), cont.

- Limitations of the procedure
- Expected values
- Specific performance characteristics such as accuracy, precision, specificity, and sensitivity
- Bibliography
- Name and place of business of manufacturer, packer, or distributor.
- Date of issuance of the last revision of the labeling identified as such
How HIV Diagnostic Test Performance is Evaluated

- Analytical studies (what are the capabilities of the device?)
  - Seroconversion panels, dilution panels, low titer panels
  - Interfering substances, unrelated medical conditions
  - Non-B subtypes
  - Reproducibility studies
  - Stability studies (shelf-life, shipping)
- Etc.
How HIV Diagnostic Test Performance is Evaluated, cont.

- Clinical studies (how will the device be expected to perform in real-world use?)
  - Known positives and prospective studies in low risk and high risk populations primarily in the U.S.
  - Studies for each matrix claimed
  - Multiple geographically distinct sites
  - Multiple independent kit lots

- Size of the clinical trials based on statistical considerations, to provide meaningful performance descriptions
Off-Label Use vs. CLIA Requirements

• The Clinical Laboratory Improvement Amendments of 1988 require that package insert instructions be followed when running tests.

• CLIA allows off-label use as long as that use has been validated through a study (remember: performance can vary with off-label use!)

• Consult with CLIA for details and specific requirements.

• Manufacturers may not market devices for off-label use.
Why are “outdated” tests still on the market?

• As long as the test meets its package insert claims (i.e., it is not misbranded), it may remain on the market
Additional questions?