



Overview of the FDA Approval Process for TB Diagnostics

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Definition: “In Vitro Diagnostic Device”

“Reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. ... for use in the collection, preparation, and examination of specimens from the human body.”
[21 CFR 809.3]



Typical IVD Device Development Pathway

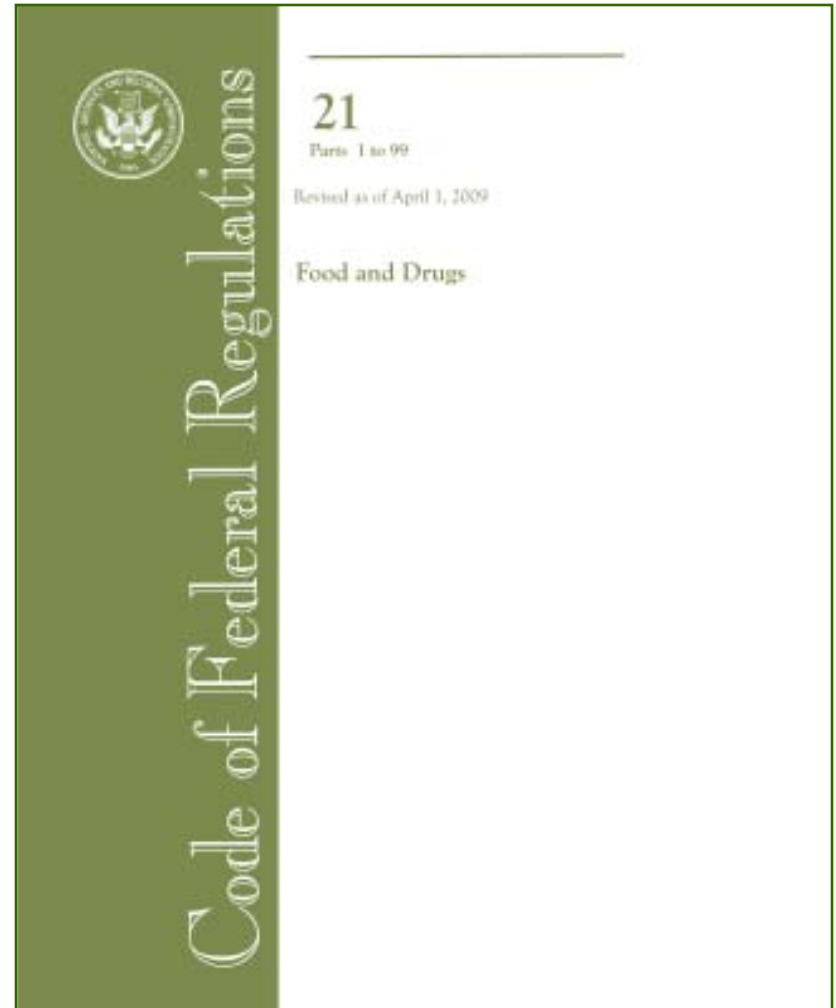
FDA Interaction →





FDA Regulatory Authority over IVDs

- **Federal Food, Drug and Cosmetic Act**
 - Established Regulatory Controls for Medical Devices (May 28, 1976)
- **Code of Federal Regulations, Title 21, Part 800**
 - Quality System, Part 820
 - Human Subject Protection, Parts 50 & 56, and Part 812






Basis of Device Review: “Safety and Effectiveness”

- **Safety**

- *Are there reasonable assurances, based on valid **scientific evidence** that probable benefits to health from use of the device outweigh any probable risks?*
[860.7(d)(1)]

- **Effectiveness**

- *Is there reasonable assurance based on valid **scientific evidence** that the use of the device in the target population will provide clinically significant results?* *[860.7(e)(1)]*



How Much Information Needed to Demonstrate “Safety & Effectiveness”?

“**Intended Use**”- risk/consequences of a false result drives device classification, amount of information needed and type of submission. Also important are intended specimen type and targeted population claimed



Risk-Based Classification based on 513(a) FD&C Act

- **Class I and II:** low/moderate risk devices
- General (I and II) and Special Controls (II) in place to mitigate risk
 - “Safe and Effective”
 - Substantial equivalence- **510(k) submission**
 - “Cleared” **90 day review**



Risk-Based Classification based on 513(a) FD&C Act cont.

- **Class III:** higher risk devices “of importance in preventing impairment of human health or if device presents a potential unreasonable risk of illness or injury”
 - General Controls and Premarket Approval to mitigate risks = increased stringency
 - Well controlled performance evaluations
Device stands on own
 - **PMA submission**
 - “Approved” **180 day review**



Similarities in 510(k) and PMA Scientific Review Requirements: IVD Performance Validation

For both 510(k) and PMA device submissions FDA makes available study design consultation, specific analyte guidances, interactive reviews and requires:

- **Analytical Performance Data:** Internal Site reliability and accuracy of analyte measurement
- **Clinical Performance Data:** External/Internal Sites Clinical sensitivity and specificity (PMA) and/or % agreement [PMA/510 (k)], etc.
- **Labeling Review:** Intended use, device design, directions for use, warnings/limitations, result interpretation, analytical & clinical performance characteristics

■ ■ ■ Similarities in Scientific Review Requirements: IVD *CLIA Waiver* Performance Validation

- For **all IVD device** CLIA Waiver applications FDA requires:
 - Evidence of simplicity of device
 - Performance data to demonstrate equivalent performance (accurate use and data interpretation) between untrained personnel in low complexity settings and trained medical technologists in high/moderate laboratory settings
 - Risk /hazard assessment of all steps of device
 - Guidance doc:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm079632.htm>



Differences Between a 510(k) and a PMA Submission Review

- **Manufacturing:**
 - PMA manuf.information submitted for review and manuf. site subject to inspection for quality system regulation compliance
 - 510(k) manuf.information kept on file by sponsor- open for inspection if a product issue
- **Clinical Trial:**
 - PMA pivotal sites undergo BIMO inspections for integrity and assessment of sponsor quality/GCP over site
 - 510(k) integrity inspection only if FDA finds a “due cause”. Information kept on file by sponsor- open for inspection if product issue



Differences Between a 510(k) and a PMA Review (2).

- **Post-Market Oversight:**
 - PMA requires submission of annual reports describing any minor changes made to labeling, manufacturing, review of published reports etc.
 - 510(k) no annual reports required, change documentation held by sponsor
- **Summary- FDA has more control over a Class III device**

Regulation of *M. Tuberculosis* IVDs

- **Class I Devices:** ID of *M. tuberculosis* from cultured isolates (866.2660) or acid-fast staining reagents for use on direct specimen smears (864.1850 & 866.3370). Designated Class I reserved in 1998 FR Notice
 - Risk: Incorrect result could lead to misdiagnosis, mistreatment, progression of disease and transmission
 - Mitigated by General Controls- registration and listing, record keeping, labeling & guidance requirements
- **Class II Devices:** Antimycobacterial susceptibility testing of cultured isolates of *M. tuberculosis* (866.1640)
 - Risk: Incorrect result could lead to all of above.
 - Mitigated by General and Special Controls including AST guidance

■■■ Regulation of *M. Tuberculosis* IVDs cont.

- **Class III Devices-** Devices for detection of *M. tuberculosis* directly from respiratory samples as well as interferon gamma release assays from whole blood (9/1994 CDRH Policy)
 - **Risk:** Higher risk of a false negative from NAT tests than from culture. Rapid result more likely to lead to erroneous result with additional risk not only for patient but for community at large. Timing (1994) coincided with large US resurgence of TB cases, especially in NY
 - Other concerns included testing performed on asymptomatic patients/AFB smear negative patients and lack of availability of data to support appropriate specimen types
 - **Mitigated** by General and Special Controls and Premarket Approval



Regulation of *M. Tuberculosis* IVDs Future ?

- Class III designation/PMA regulatory route often cited as factor in lack of rapid device pre-market submissions
- In 2010, has the performance of new devices to diagnose MTB infection improved since 1994? Have the risks of spread of infection to the general population been lowered?
- Could Special Controls be written for these devices in order to mitigate the risks and allow downclassification from Class III to Class II?
- Would the availability of a well characterized MTB clinical specimen repository enable more accurate assessments of new device performance? What proportion of freshly collected vs repository specimens would be appropriate?

■ ■ ■ Thanks.....

- Sally Hojvat
- Freddie Poole
- Yvonne Shea
- Janice Washington