Update on FDA Reclassification - Understanding the FDA Approval Process

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What I Will Try to Accomplish…

- Keep everyone awake
  - Not an easy task; this is dry stuff….
- Background of regulatory classification of devices….
- Reclassification….
- Where TB devices were in 2011….
- Where TB devices/reclassification is now in August, 2013….
- Answer any questions….

Background…..

- Unfortunately, appreciating the reclassification process requires some background on the classification process and the clearance/approval process for devices….

TB Diagnostics are In Vitro Diagnostic Device (IVDs)

In Vitro Diagnostic Devices are….

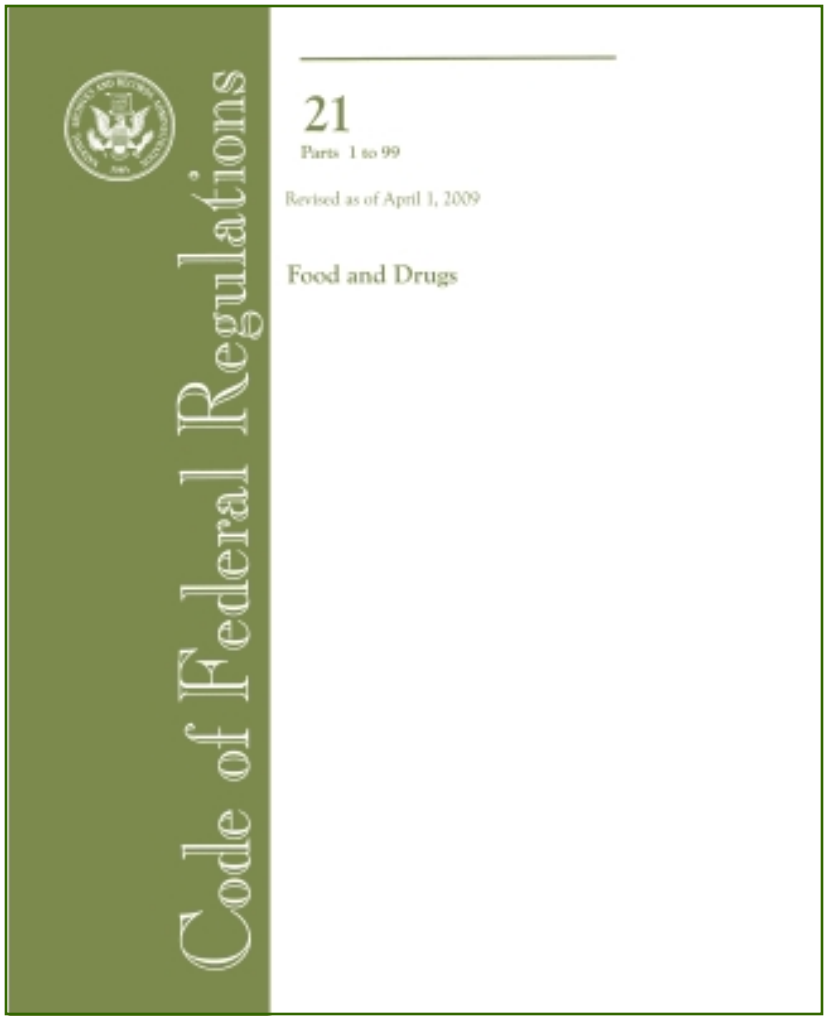
"Reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. [These devices are] … for use in the collection, preparation, and examination of specimens from the human body."

[21 CFR 809.3]

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
- CFR available at:

  http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm



Device Classification

A device should be placed in the lowest class whose level of control will provide reasonable assurance of safety and effectiveness

- Class I - General Controls
- Class II – General and Special Controls
- Class III - Premarket Approval

Regulatory Classes

Class I

Primarily devices for which any combination of general controls are sufficient to provide reasonable assurance of the safety and effectiveness of devices

General controls include (for example):

- Prohibition against adulterated or misbranding
- GMPs
- Registration of manufacturing facilities
- Listing of device types
- Record keeping
- Repair, replacement, refund

Regulatory Classes (Class II)

Class II

- Devices which cannot be classified into Class I because general controls by themselves are insufficient to provide reasonable assurance of the safety and effectiveness of such device, and
- For which there is sufficient information to establish Special Controls to provide such assurance

Regulatory Classes (Class II)

Examples of Special Controls

- Performance standards
- Postmarket surveillance
- Patient registries
- Tracking requirements
- Recommendations and other appropriate actions
- Special labeling requirements
- Note: as of recently, Special Controls will now be part of a published regulations. Guidances will not be published.

Regulatory Classes (Class III)

Class III

- Devices for which insufficient information exists to determine that general and Specials Controls are sufficient to provide reasonable assurance of safety and effectiveness
- Such devices:
  - Are life sustaining and/or life supporting
  - Are of substantial importance in preventing impairment of human health; or
  - Present potential or unreasonable risk of illness or injury (Sometimes a matter of perspective….)

Why is Classification Important

- **Class II devices are 'cleared' by the 510(k) process**
  - Devices are determined to be 'substantially equivalent' to a preexisting device, i.e., there are no new issues of safety or effectiveness
  - Different timelines (shorter)
  - Different submission requirements for sponsors (fewer)
  - Different user fees (cheaper)
  - Inspection not mandatory (Class III both manufacturing facility and clinical trial site inspections)

Why is Classification Important

- **Class III devices are 'approved' by the PMA (Premarket Approval application process)**
  - Different timelines (longer)
  - Different submission requirements for sponsors (i.e., more complete, primary data, more expensive)
  - Different user fees (higher)
  - Mandatory Inspections
  - Postmarketing changes all require FDA review
  - Labeling oversight
  - Annual reports required
  - Other significant differences…..

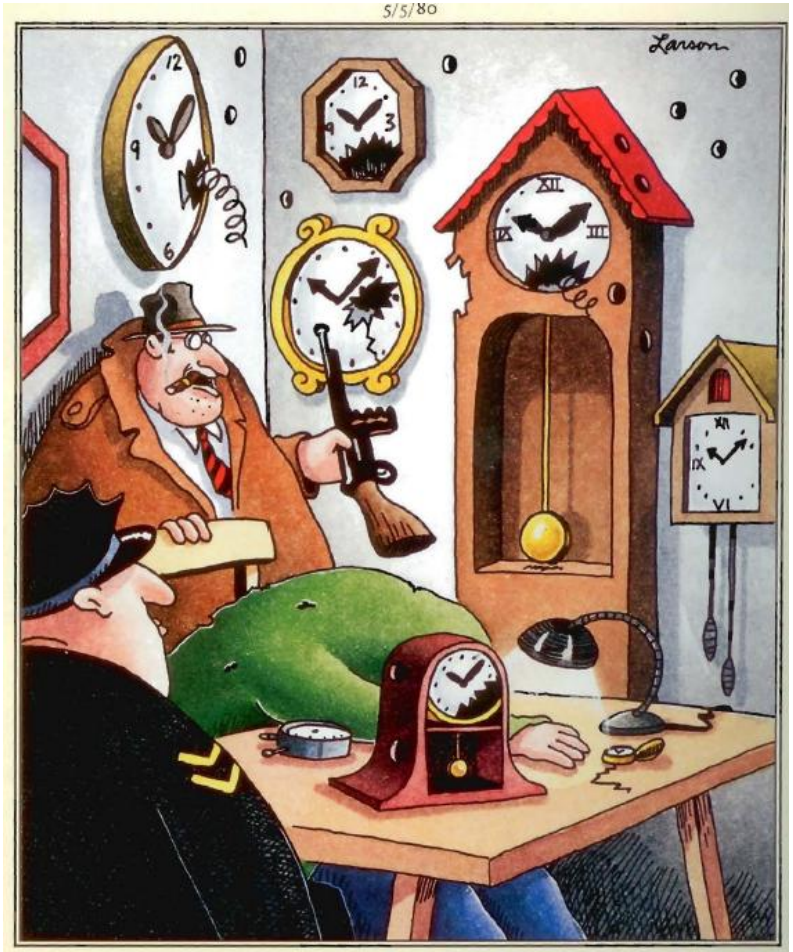
Classification of New Devices

- 'New' devices that are not 'substantially equivalent' to existing devices are automatically considered Class III
- Devices remain in Class III and require premarket approval, unless:
  - The device is reclassified into Class I or II
  - If submitted as a 510(k), after FDA review a recommendation is for resubmission via the de novo pathway (pre-2012)

  or (new under FDASIA)

  - A sponsor can apply directly for Class II designation under the de novo pathway (no fee and shorter review time [120 days])

How's Everyone Doing So Far….



2011 Status

Classification based on intended use and risk/mitigation– *not* technology:

- Staining (direct specimens): Class I (exempt)
- Mycobacterial growth:
  - Traditional culture media (e.g., Lowenstein-Jensen, 7H9 Broth): Class I
  - Automated systems and associated media (e.g. Bactec 460, MGIT 960): Class I
- Identification from cultured isolates: Class I
- Drug susceptibility from cultured isolates: Class II (FDA approved drugs only)
- Detection of *M. tuberculosis* complex (direct specimens): Class III
- Detection of drug resistance genetic mutations of *M. tuberculosis* complex (direct specimens): no products submitted; therefore not classified

Which leads to…..Reclassification

- May be initiated by either FDA or Industry
- FDA may, for good cause shown, refer a petition to a device classification panel
  - The Panel shall make a recommendation to FDA respecting approval or denial of the petition
- In this instance, initiated by FDA
- Why?
  - Technology now mature, benefit/risks different from early 1990's
  - Class III status was felt to be unnecessarily burdensome to industry and hindering applications in US
  - Public health concerns

Issues Considered in the Reclassification of *M. tuberculosis* complex IVDs

- Has the performance of new devices for the detection of *M. tuberculosis* complex directly from respiratory specimens 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?
- Essentially, through use of Special Controls, could the safety and effectiveness of devices for the detection of *M. tuberculosis* complex directly from respiratory specimens be assured.

Reclassification History

- FDA pursued reclassification with a public meeting of the Microbiology Medical Devices Panel on June 29, 2011
- Three issues discussed:
  - Classification of nucleic acid-based devices for the detection of *M. tuberculosis* directly from respiratory specimens
  - Classification of devices for the direct detection of mutations associated with antibiotic resistance to *M. tuberculosis*
  - Classification of devices for detection of latent TB

Discussion

- Panel members expressed unanimous support for Class II designation of nucleic acid-based devices for the detection of TB directly from respiratory specimens.
- Majority of the panel members (15/16) supported Class II designation of nucleic acid-based devices for the detection of drug resistance genetic mutations.
- Panel members felt reclassification of devices for the detection of latent TB infection was premature at this time
- Note:
  - Not a formal 'reclassification meeting' no vote was anticipated
  - Detection of drug resistance genetic mutations was not an issue for reclassification since this would be initial classification; i.e., de novo

Draft Guidance for Industry and Food and Drug Administration Staff

Class II Special Controls Guidance Document: Nucleic Acid-Based *In Vitro* Diagnostic Devices for the Detection of *Mycobacterium tuberculosis* Complex in Respiratory Specimens

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.
Document issued on: March 19, 2012

You should submit comments and suggestions regarding this draft document within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.regulations.gov. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this document contact Janice Washington at 301-796-6207 or by email at janice.washington@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Office of *In Vitro* Diagnostic Device Evaluation and Safety

Straightforward at this Point….

- Well, not really…..
- As pointed out, the guidance was published on March 19, 2012, with a 90-day comment period…..
- Not too many comments (valuable comments from CDC), nothing contentious…..
- But…
  - The Food and Drug Administration Safety and Innovation Act (FDASIA) signed into law on July 9, 2012, with the third authorization of the Medical Device User Fee Act (MDUFA)

FDASIA (Public Law 112-144)

'Based on new information respecting a device, the Secretary may, upon the initiative of the Secretary or upon petition of an interested person, change the classification of such device, and revoke, on account of the change in classification, any regulation or requirement in effect under section 514 or 515 with respect to such device, by administrative order published in the Federal Register following publication of a proposed reclassification order in the Federal Register, a meeting of a device classification panel described in subsection (b), and consideration of comments to a public docket, notwithstanding subchapter II of chapter 5 of title 5, United States Code. The proposed reclassification order published in the Federal Register shall set forth the proposed reclassification, and a substantive summary of the valid scientific evidence concerning the proposed reclassification, including……'

Ramifications…..

- Initially believed this would now preclude reclassification since prior panel meeting was not designated as a formal ‘reclassification’ meeting….
- However….. no (but this did introduce a delay…)
- What did occur, however, was reconsideration of the mechanism for release of Special Controls Guidances…. (remember back 3 slides: Class II Special Controls Guidance….), and it was determined going forward that Special Controls Guidances could not be issued, and thus reclassification delayed…

So Where Did That Leave Us…..

- Uncertain process….
- No reclassification ….
- By now you're thinking this may not be the optimal way of doing business (or a less kind euphemism)….
- However….
  - to serve the public good, congruent with other efforts, an opinion was rendered that a device *that simultaneously detected both M. tuberculosis complex and genetic mutations associated with antibiotic resistance* was a new device, thereby allowing such device to qualify for a *de novo* action. (Coincidence…?)

So Where Does This Leave Us Now…

- Guideline published for comment (next slide); *there is still time to comment .* The guideline is restricted to the reclassification of devices solely for the detection of *M. tuberculosis* complex directly from respiratory specimens.
- Accordingly, reclassification of devices of this type is still pending.

However….

- The Cepheid Xpert® MTB/RIF Assay was ~~cleared~~ approved ~~approved~~ authorized for marketing on July 25, 2013, via the *de novo* 510k regulatory pathway as a Class II device.
- The regulation includes Special Controls and refers to other controls in the guideline (next slide)
- Overall, the result is beneficial to all….

Draft Guideline for Industry and Food and Drug Administration Staff

Class II Special Controls Guideline: Nucleic Acid-Based *In Vitro* Diagnostic Devices for the Detection of *Mycobacterium tuberculosis* Complex in Respiratory Specimens

Draft Guideline

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Ask 8 Ball
Should my test be reclassified?
Ask
AdChoices
► Ask a Psychic
► Ask Lawyer
► Ask an Attorney
► Network Test
Most likely
Share this prediction on Facebook!
Tweet this prediction!

New Approach to Regulations…

The following items, which address the mitigation of risks specific to the detection of the genetic mutations associated with antibiotic resistance of *Mycobacterium tuberculosis* complex:

i) The device must include an external positive assay control as appropriate. Acceptable positive assay controls include *Mycobacterium tuberculosis* complex isolates containing one or more antibiotic-resistance associated target sequences detected by the device.

ii) The device must include internal controls as appropriate. An acceptable internal control may include human nucleic acid co-extracted with *Mycobacterium tuberculosis* complex containing nucleic acid sequences associated with antibiotic resistance and primers amplifying human housekeeping genes (e.g., RNaseP, β-actin).

iii) The device's intended use must include a description of the scope of antibiotic resistance targeted by the assay, i.e., the specific drugs and/or drug classes.

- Many more, including analytical, clinical studies, etc……
- Less detailed than guidances/guidelines…..

Thanks….

- Sally Hojvat
- Scott McFarland
- Yvonne Shea
- Janice Washington

Questions….

- Please only ask questions that I may have a reasonable chance of answering correctly. Thanks.