QC and Reference Material for Genetic Testing – US Regulatory Aspects

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Outline

- Brief Overview - FDA regulations for IVDs
- Control and reference material:
  - Regulatory Strategies / Requirements
  - Technical Issues
  - Current Initiatives
- Information Sources and Contacts

FDA Regulations

- Federal Food, Drug and Cosmetic Act as amended by:
  - Medical Device Amendments 1976
  - Safe Medical Devices Act (SMDA) -1990
  - FDA Modernization Act (FDAMA) -1997
  - Medical Device User Fee and Modernization Act (MDUFMA) - Oct 2002
- Office Of In Vitro Diagnostic Device Evaluation and Safety – Nov 2002

Medical devices:
In vitro diagnostic (IVD) products

"*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]

Distribution (where used)

- clinical laboratories
- other settings: point-of- care (e.g., ER, out-patient clinics), over-the-counter, prescription home use

Risk-Based Device Classification

- Class I: common, low risk devices
  - ✓ General control requirements
  - ✓ Most exempt from premarket submission
- Class II: more complex, higher risk
  - ✓ Special controls and general controls
  - ✓ Premarket Notification [510(k)]
- Class III: most complex, highest risk
  - ✓ Supported by valid scientific evidence
  - ✓ No established predicate, or new types safety and effectiveness questions
  - ✓ Premarket Application [PMA]

Genetic / Genomic / Molecular Tests

FDA – ensure that:

- commercially distributed genetic tests are reliable (safe & effective)
- patients and health care professionals understand both the value and the limitations of such testing (education; appropriate use)

QC material – means of ensuring consistency and reliability of genetic testing

Regulatory oversight of Quality Control Material (US)

- Premarket (Class I, exempt, Class II)
- Compliance
- Clinical laboratory use
- QC requirements

Regulatory Requirements for Quality Control Material

- General Controls
  - Register (21 CFR 807.20) and List
  - Good Manufacturing Practices (GMP)
    http://www.fda.gov/cdrh/dsma/gmp_man.html
  - Report device failures
  - Labeling (regulations 21 CFR 801 or 809)
  - Inventory of tests on the market
  - System for remedying device failures

Clinical laboratories – QC requirements

CMS [42 CFR §493.1256(d)(3)(iii)]48

- **positive** control material
- **negative** control material
- 2 different concentrations (if quantitative assay)
- control for **extraction**
- amplification (inhibition) control

- **external, internal** controls

Regulatory Strategies for Quality Control Material

- Regulated / Submitted:
  - with the assay
  - separately
- Reviewed the same in either case
- Class I or II (both have general control requirements)

QC material - review

- Unassayed controls
  - no value assigned
  - not linked to specific device/assay
- Assayed controls
  - assigned value
  - device link

(guidance: http://www.fda.gov/cdrh/ode/99.html)

Submission Content

- Intended use/indications for use
- Performance characteristics
  - Analytical
  - Clinical
- Labeling (package insert)

Intended Use

- assayed or unassayed
- for quantitative, semi-quantitative or qualitative testing
- matrix, analyte(s) to monitor
- analytical procedure, portion of the assay to monitor

concentration should challenge the medical decision point of the assay;

alternatively, monitor for gross systematic errors.

Reagent Information

- nucleic acid segment, sequence
- sources of components:
  - human, animal, synthetic, purified chemicals
  - recombinant, microorganism (ATCC strain)
- human donor characterization
- media, cell line used for culture
- matrix, stabilizers, preservatives, etc in control mixture
- volumes, concentrations, particle sizes
- inactivation methods

Performance Characteristics

Stability studies:

- real time (shelf life)
- ambient temperature (shelf life)
- stress testing (shipment)

Clinical laboratory evaluations – independent evaluation of consistency and performance of QC material by the intended user in the situations where most likely will be used

- validation (methods, i.e. sequencing mutations)
- reproducibility

Stress testing

Evaluate control reagent using corresponding assay after exposure to stress conditions:

- Elevated temperature studies (evaluate reactivity of several lots, unopened bottles)
- Freeze/thaw studies – multiple cycles – effect on reactivity
- Open vial stability – at various time intervals after bottles of reagent are opened

Labeling

- Procedures / instructions for use
  - handling, storage and stability for both opened and closed conditions
  - precautions (i.e., sodium azide warning)
- Performance characteristics
  - any matrix bias
  - ability or sensitivity to detect known analytical problems

Labeling (cont.)

- Performance characteristics / Expected values
  - range, SD, CV, CI
  - each constituent, level
  - protocols used to establish the acceptable value/range (e.g., low, mid or high level)
  - analytical methods, number of testing replications, test runs and instruments, statistical analyses
- Limitations

Current reference use

- Reference methods
- Reference materials/standards
  - Limited
  - Source – WHO, NIST, CDC, NIH, CBER etc.
  - Calibrators and controls – FDA regulated
    - Traceability
    - Assign values
    - Standardize and control assay performance

Synthetic nucleic acid based controls

- Unique sequences (can be customized)
- Can be highly useful for multiplex assays
- Internal control
- Can be e.g. controls for reverse transcription, labeling, hybridization, instrumentation
- Stable

Current Initiatives

- QC material for genetic testing (CDC)
  - Huntington QC material
  - Fragile X QC material
- Microarray controls
  - ERCC (External RNA Controls Consortium)
  - MAQC (Microarray Quality Control)

Sources of Information

- General information
  - http://www.fda.gov/cdrh/index.html
- OIVD website
  - http://www.fda.gov/cdrh/oivd/

OIVD Publications

Tezak Z, Ranamukhaarachi D, Russek-Cohen E, Gutman SI.
FDA Perspectives on Potential Microarray-based Clinical Diagnostics.
Human Genomics. In press.

Harper CC, Philip R, Robinowitz M and Gutman SI.
FDA Perspectives on Pharmacogenetics Testing.
Expert Rev Mol Diagn. 2005 Sep;5(5):643-8.

Mansfield E, O'Leary TJ and Gutman SI.
Food and Drug Administration Regulation of In Vitro Diagnostic Devices.
Journal of Molecular Diagnostics 7:1 p 2-7, Feb 2005.

Ardekani AM, Petricoin III EF and Hackett JL.
Molecular Diagnostics: an FDA perspective.
Expert Rev Mol Diagn. 2003 March; 3(2): 129-140.

OIVD Contacts for Molecular Diagnostic Submissions

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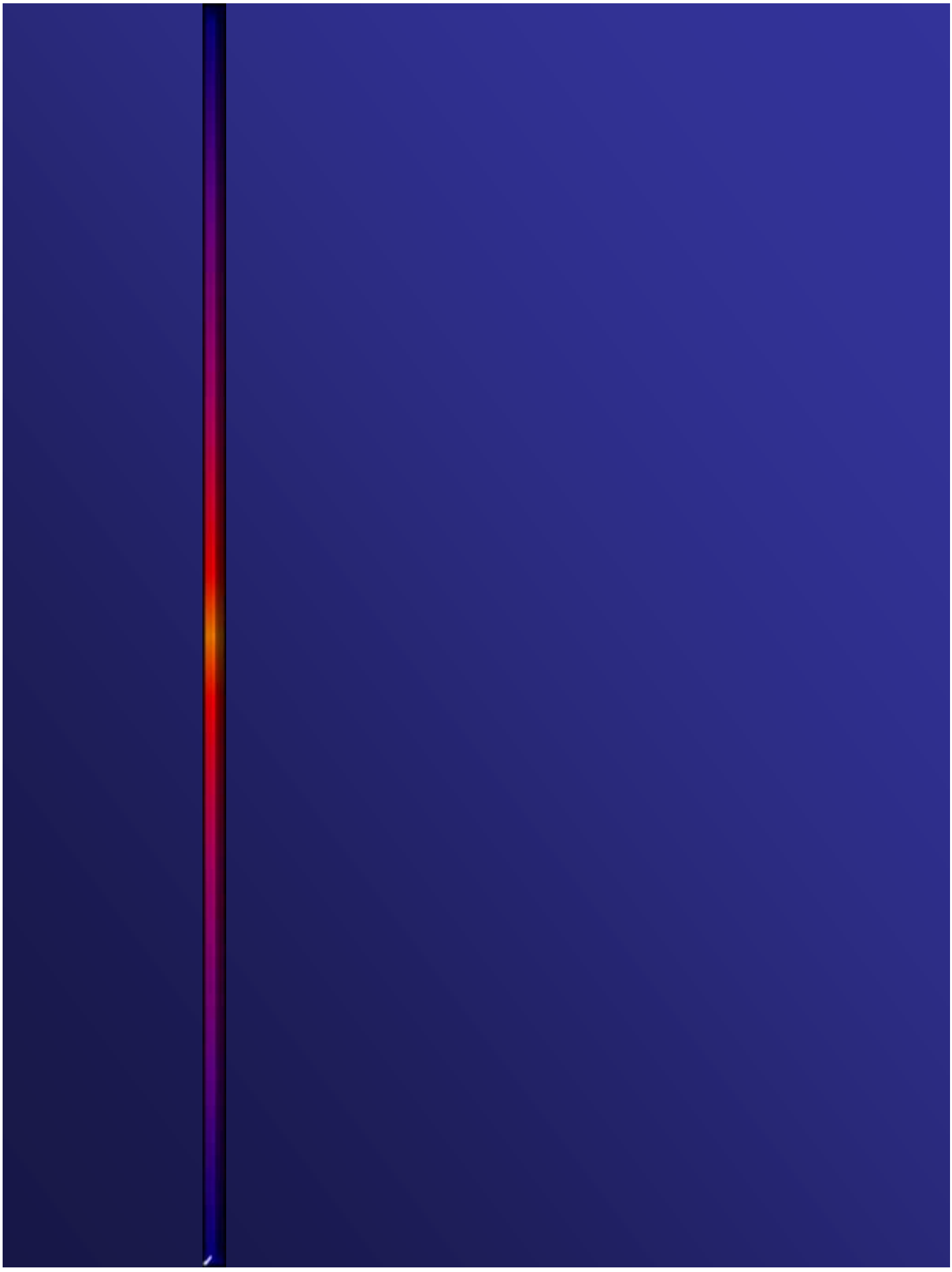
Follow Good Science

- Standardization
- Transparency of data
- Sharing of data



Pre-IDE Process for IVDs

- Not an IDE (misnomer)
- Protocol review and regulatory guidance
- No charge to the sponsor
- Non-binding on either party
- Recommended for novel devices/uses:
  - Familiarize FDA with new products
  - Learn about latest FDA thinking
- Understand and clarify questions up-front
- Decrease uncertainty

http://www.fda.gov/cdrh/oivd/presentations/042203-Altaie.html

De novo 510(k)

- Process for regulating new unclassified devices
- Six in past year with two under review
- Broad but not over-reaching view of risk
- Turnaround ranges from 9 days to four months for good submissions