FDA Perspective on CMV Viral Load Assay Reclassification

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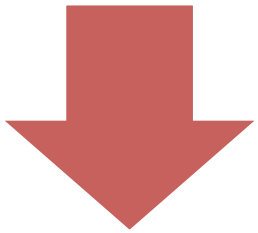
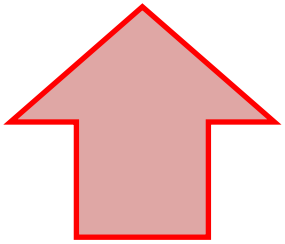
Risk Based Regulation of IVDs

Class I most 510(k) exempt



Knowledge

Risk



Class III - PMA

Class I - Low likelihood of harm register & list (21CFR §807)
General Controls

Class II - Moderate likelihood of harm or risk can be mitigated
Special Controls

Class III - High or unknown likelihood of harm Significant Risk
Pre-market Approval

Regulatory Classification

- **Class I** (low to moderate risk): general controls
  - Prohibition against adulterated or misbranded devices (labeling medical devices in accordance with the labeling regulations, 21 CFR 801 or 21 CFR 809),
  - Good Manufacturing Practices (GMPs)/Quality Systems,
  - Registration of manufacturing facilities,
  - Medical Device Listing with FDA of devices to be marketed,
  - Manufacturing the devices in accordance with Good Manufacturing Practices,
  - Medical Device Reporting of adverse events as identified by the user, manufacturer and/or distributor of the medial device.
- **Class II** (moderate to high risk): general controls and Special Controls
- **Class III** (high risk): general controls and Premarket Approval (PMA)

What Are Class I Devices?

- Devices for which general controls are sufficient to provide reasonable assurance of the safety and effectiveness.
- Class I devices typically do not require FDA premarket review.

What Are Class II Devices?

- Cannot be classified into Class I:
  - because general controls 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.
- Class II devices typically require premarket notification (i.e., a 510(k)) and review prior to being marketed.

When is a Device Class III

- it is purported or represented to be for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health,

  or

- presents a potential unreasonable risk of illness or injury.

Section 513(a)(1)(C) (21 U.S.C. 360c(a)(1)(C))

- In essence, a device that cannot be classified into Class II because:
  - insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of the safety and effectiveness

Basis of Pre-Market Device Approval: Safety and Effectiveness

- **Safety**
  - *There is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks. The valid scientific evidence used to determine the safety of a device shall adequately demonstrate the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions of use. [860.7(d)(1)]*
- **Effectiveness**
  - *There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.*

    [860.7(e)(1)]

What Does FDA Usually Require for PMA and 510(k) Applications

Pre-Market Data Requirements

- Analytical performance measures
  - Precision (repeatability, reproducibility)
  - Accuracy
  - Reactivity (inclusivity)
  - Sensitivity, Limit of Detection
  - Specificity (interference, cross-reactivity)
  - Sample type / matrix
  - Sample preparation / conditions
  - Performance around the LLoQ and ULoQ, ‘cutoffs’
  - Linearity
  - Potential for carryover, cross-hybridization
  - Stability
- Studies and specifications may vary depending on technology or other unique device characteristics
- These do not change with reclassification.

What Is Different About the Class III and Class II

- Manufacturing section: Complete study reports and documentation are required for Class III submissions. Similar studies are conducted but are not included in a Class II submission.
- Pre-approval inspection (GMP compliance) only for Class III submissions (standard manufacturer inspections are unchanged) .
- BIMO (bioresearch monitoring visit to clinical and/or sponsor sites) for Class III submissions only.
- Post-approval: Requirements for annual reports for Class III approval, not for Class II clearance.
- Validation studies should test multiple lots in performance studies in Class III submissions.

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm

When is Downclassification Appropriate?

- Class III devices can be downclassified to Class II when sufficient information becomes available to establish **Special Controls** that reasonably assure safety and effectiveness.

Safety/Risks to Health

- **An inaccurately low test result or false negative result:**
  - May lead to inappropriate patient management decisions such as premature discontinuation of antiviral therapy or withholding of therapy (e.g., preemptive management).
- **An inaccurately high or false positive result:**
  - May contribute to unnecessary initiation of treatment, additional diagnostic studies, a change in therapy, or prolonged duration of therapy.
- With increasing decentralization of follow-up and restrictions on test selection, increased risk of patients being exposed to measurements of CMV viral load by tests from different sources. Variability across different devices may lead to increased risks if patients are measured by different devices, even if each device is performing correctly.

Potential Class II Special Controls

- **Examples of Potential Special Controls for CMV Viral Load Assays**:
  - Device labeling
  - Manufacturing information
  - Method comparison studies
  - Analytical studies
  - Clinical performance studies
  - Postmarket controls
- Each of these will be described subsequently; however, these do not represent all possible special controls

Potential Special Controls Applicable to CMV Viral Load Assays

- **Limitations on device labeling:**
  - e.g., a warning that a patient must (or should) be followed using the same assay prior to and post-transplant
  - recommendations to follow published guidelines
- **Manufacturing information:**
  - e.g., how traceability to a standard is maintained
  - how manufacturing specifications will ensure that the product will consistently meet design specifications (specific to the device and above existing FDA guidance)
- **Method Comparison Study**
  - e.g., confirming acceptable performance using patient samples relative to an FDA accepted assay

Potential Special Controls Applicable to CMV Viral Load Assays (2)

- **Analytical Studies**
  - e.g., require comparison to a recognized standard and to an FDA accepted comparator method. These studies could include predefined maximum allowable total difference (ATD) zones between the new assay and comparator test material, as well as a maximum deviation from linearity. (Similar to tolerance in current PMAs.)
  - **Existing standards:**
    - NIST Standard Reference Material 2366 for Measurement of Human Cytomegalovirus DNA (Towne-BAC)
    - 1st WHO International Standard for Human Cytomegalovirus for Nucleic Acid Amplification Techniques (Merlin-whole virus)

Potential Special Controls Applicable to CMV Viral Load Assays (3)

- **Clinical Performance**
  - Populations studied
  - Prospective and/or retrospective specimens
  - Distribution of samples
  - Comparisons methods
  - ‘Contrived samples’
  - Inclusion of patients studied longitudinally for response to treatment

Potential Postmarket Special Controls

- Possible Postmarket Controls
  - e.g., periodic postmarket studies to demonstrate an absence of drift in assay performance and to confirm inclusivity
  - Manufacturers describe (in their submission) the use of an accepted method of risk assessment for managing risks when modifying the device.

Panel Question

- Do committee members believe that **special controls**, in addition to general controls, are necessary and sufficient to **mitigate the risks** to health presented by quantitative CMV viral load assays?
  - In addressing this question, please discuss the proposed special controls and any additional special controls that would be recommended if reclassification could be considered for quantitative CMV viral load assays

CMV Reference Standards

- As a follow-up to this question, in the discussion of special controls by panel members, the following should be addressed:
  - Commutability of FDA-approved assays calibrated to standard reference materials
  - Challenges of commutability at concentrations near the limit of quantitation
  - Benefit of BAC or whole virus standard reference material
  - Effect of sample matrix

Thanks

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