EBV and BK Viruses

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What Is the Purpose of This Second Session?

- Take a deep breath
- Not to address a specific regulatory decision but to provide insight and expert opinion on the classification of viral load assays for *other* transplant associated viruses, focusing on EBV and BK Viruses

FDA Classification

- As you heard this morning, FDA has three classifications for all devices, including *in vitro* diagnostics: Class I, Class II, and Class III
- Devices can be reclassified either up or down from the initial classification as additional information regarding safety and efficacy accumulates. This is uncommon, but over the past few years DMD has been involved in reclassification of molecular diagnostics for Tuberculosis (Class III ⟶ Class II) and Rapid Influenza tests (Class I ⟶ Class II)

De novo Requests for Classification

- If no predicate is available (e.g., a test for a wholly new analyte, i.e., one for which an FDA approved (PMA) or cleared (510k) device does not exist ~~(~~and for which there is no prior classification~~)~~, the test is automatically classified in Class III and subject to premarket approval by operation of law.
- However, if the risks associated with the test are low to moderate and can be sufficiently mitigated by general controls or a combination of general and special controls, the test may be a candidate for the *de novo* process.

De Novo Requests - Eligibility

- If a submitter believes a test is eligible for the *de novo* process, the submitter may submit a *de novo* request for classification as the premarket submission in which the submitter provides information to demonstrate that general controls or general controls and special controls are sufficient to provide a reasonable assurance of safety and effectiveness of the test.
- If a sponsor has questions regarding the eligibility of the test for the *de novo* process, a "Pre-submission" may be sent to FDA to obtain feedback on the premarket review pathway for the test.

This Afternoon's Discussion

- There are no cleared or approved assays for EBV or BK virus; hence, FDA should provide recommendations to individual sponsors regarding the correct approach for a later regulatory submissions since there is no precedent. As discussed previously, this may be viewed as a challenge to market entry.

Discussion

- The literature for EBV and BK virus is complex for both analytes, particularly EBV:
  - Recall that FDA's regulations require adequate directions for use, e.g clinicians need to know who to test (population), what to test (matrix), when to test (performance under different conditions), and how to interpret a test
  - Clinical effectiveness is far less certain than for CMV; establishing this for EBV may be particularly challenging
  - Interassay variability poses even greater challenges in the setting of unclear clinical use
  - Treatment may pose greater risks than for CMV

Recall from the Morning Discussion

- PMA status offers greater FDA oversight
- It may be challenging to identify special controls (when in combination with general controls) that are sufficient to provide reasonable assurance of the safety and effectiveness of such devices.
  - Once special controls are established, difficult to change as these are included in regulation
- Specific instructions for use requirements may be challenging to develop.

The Remainder of the Day…

- We again much appreciate presentations by Dr. Limaye and Dr. Cook
- We recognize that time is limited and that detailed discussion of questions for each virus will be difficult at best
- Accordingly , the question to the committee is likely one that can’t be fully answered, today, but where insight and expert recommendations can strongly aid our further discussions.

Questions for Discussion…

1. Do the risks and information known regarding EBV and BK infection in the transplant patient warrant Class III status for either

2. Regardless of your response, what unique considerations exist regarding EBV and BK virus that must be addressed during FDA premarket review and/or as special controls


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