Inmazeb Case Study: FDA Perspective

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AGENDA

INMAZEB BLA Case Study

• Review Issues

• FDA’s Ongoing Efforts to Enhance the Quality of the Integrated Review

• Respecting and Documenting Scientific Differences of Opinion

Information sourced from FDA summary basis of approval for INMAZEB accessible at: Drugs@FDA: FDA-Approved Drugs
Review Issues

- Review issues are key issues pertinent to the decision-making process (usually approvability, Benefit/Risk, or labeling).

- The Integrated Review process is designed to enable early identification of review issues and interdisciplinary collaboration to address those issues.

- The Integrated Review process complements the 21st Century review process by facilitating the mid-cycle and late cycle communication process.

- Review issues can be identified by the review team throughout the review process:
  - Before the application is filed
  - At the Benefit-Risk Scoping Meeting around the time of filing
  - By the Mid-Cycle and sometimes later
Articulation of key review issues in the Review Issues Section of the Interdisciplinary Assessment

<table>
<thead>
<tr>
<th>Issue</th>
<th>Background</th>
<th>Assessment</th>
<th>Conclusion</th>
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| • Identification of key issue with a specific description of the issue | • Explanation regarding relevance of review issue | • Succinct review of essential data and analyses, including relevant tables and figures, Assessment of key issue in relation to recommended outcome measures  
• Rationale for outcome measure taken to address issue (indication change, PMR/PMC issued, labeling)  
• Summary of differences in reviewer conclusions (if applicable) | • Review team conclusion regarding the issue, including action taken |
## A Look Back at INMAZEB Review Issues

### Review Issues Relevant to Evaluation of Benefit

<table>
<thead>
<tr>
<th>Issue</th>
<th>Communication with Applicant</th>
</tr>
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<tbody>
<tr>
<td>Investigational drug as active comparator</td>
<td>Internal Only- Scoping Meeting</td>
</tr>
<tr>
<td>Lower efficacy in subjects with higher viral load</td>
<td>IR post filing, Mid-Cycle Comm, PMC for future trial discussion post Mid-Cycle</td>
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<tr>
<td>Contribution of each component of the combination</td>
<td>Pre-BLA discussion re non-clinical data to support</td>
</tr>
<tr>
<td>Pediatric clinical experience and labeling for low birth weight neonates born to EBOV-infected mothers</td>
<td>Internal Only – post Mid-Cycle</td>
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<tr>
<td>Indication for treatment of EBOV infection acquired by routes other than natural transmission</td>
<td>Internal Only– post Mid-Cycle</td>
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</tbody>
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### Review Issues Relevant to Evaluation of Risk

<table>
<thead>
<tr>
<th>Issue</th>
<th>Communication with Applicant</th>
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</thead>
<tbody>
<tr>
<td>Characterization of resistance against Inmazeb</td>
<td>PMR discussion post Mid-Cycle</td>
</tr>
<tr>
<td>Immunogenicity</td>
<td>PMR discussion post Mid-Cycle</td>
</tr>
<tr>
<td>Infusion volume and times for neonates</td>
<td>Mid-Cycle Comm</td>
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Enhancing Quality of the Integrated Review

- **Internal Training and Support**
  - Live and self-paced training, peer ambassadors, support and coaching, quick start Guides, Trackers, and Planners, How-to-Guides and Templates, FAQs

- **External Engagement**
  - Federal Register Notices requesting feedback
  - Public meeting held October 30, 2020 with public docket

- **Internal Feedback**
  - FDA reviewers and team leaders - systematic qualitative data collection
  - Critical formal quality assessment of completed review documents by senior CDER staff
Enhancing Quality of the Integrated Review

• Tools to facilitate the review process (ongoing)
  • Sponsors are often requested to provide a protocol synopsis in Word for some of the more important clinical trials.
  • Question based review tools for efficacy and safety
Scientific Differences of Opinion

The Integrated Assessment (process and documentation) embraces and respects scientific differences of viewpoints.

The process allows for the capture of and opportunity for early, frequent, and intensive meetings around differences of opinion.

Differences of opinion that remain at the time of the marketing application decision must be documented as a review of the issue in a separate document that resides in the Appendices.
Integrated Assessment Respects Scientific Differences of Opinion and Equal Voice

Avenues for expression of scientific disagreement & Equal Voice:

**Process**

- **Interdisciplinary meetings** provide a forum for early, frequent, & thorough discussions of key issues & sharing, addressing, & discussing differences in viewpoints

**Documentation**

- **Executive Summary** includes high-level description of key scientific differences of opinion & final decision by the signatory authority; summarizes any major differences of opinion & documentation for each reviewer/discipline and the rationale for the resultant regulatory action

- **Interdisciplinary Assessment** includes discussions of differences in opinion regarding key review issues on the review team and how scientific disagreement was addressed

- **Appendices** includes separate reviews written by reviewers who disagree with significant elements of the Executive Summary and Interdisciplinary Assessment sections or the marketing application decision of the signatory authority
Examples of Documentation Outline of Scientific Differences of Opinions

Review Issues Section

I. Issue
II. Background
III. Assessment
IV. Conclusion

If a difference of opinion is related to a significant element of the planned action (e.g. labeling, post marketing actions, overall decision on marketing application), a separate, detailed review should additionally accompany the review document in the Appendices.

A. Clinical Review Team Perspective
B. Non-Clinical Review Team Perspective
C. Signatory Perspective (identifies which perspective the signatory aligns with & why)

Should also be addressed in the Executive Summary.
INMAZEB Review: Disagreement between disciplines re the Indication: “naturally acquired infection” only?

• Clinical review team perspective: “…restricting to “naturally acquired” infection could result in delay or deferral of use despite evidence that there may be some benefit in the context of needlestick exposure or other healthcare-associated exposures.”

• Clinical Virology perspective: “…indication should state “naturally acquired” given that a needlestick exposure, which may occur at higher concentrations of EBOV, was not studied and the disease course is likely to be significantly different in the event of an intentional release…”

• Signatory perspective: “Depending on level of exposure, INMAZEB may mitigate disease and offer benefit…labeling that would delay or limit this off label use does not seem appropriate.”
Thank You

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