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

Issue	• **Identification of key issue with a specific description of the issue**
Background	• **Explanation regarding relevance of review issue**
Assessment	• **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)**
Conclusion	• **Review team conclusion regarding the issue, including action taken**

A Look Back at INMAZEB Review Issues

Review Issues Relevant to Evaluation of Benefit	Communication with Applicant
Investigational drug as active comparator	Internal Only- Scoping Meeting
Lower efficacy in subjects with higher viral load	IR post filing, Mid-Cycle Comm, PMC for future trial discussion post Mid-Cycle
Contribution of each component of the combination	Pre-BLA discussion re non-clinical data to support
Pediatric clinical experience and labeling for low birth weight neonates born to EBOV-infected mothers	Internal Only – post Mid-Cycle
Indication for treatment of EBOV infection acquired by routes other than natural transmission	Internal Only– post Mid-Cycle
Review Issues Relevant to Evaluation of Risk	Communication with Applicant
Characterization of resistance against Inmazeb	PMR discussion post Mid-Cycle
Immunogenicity	PMR discussion post Mid-Cycle
Infusion volume and times for neonates	Mid-Cycle Comm

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**

Should also be addressed in the Executive Summary

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)

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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