Selected Quality Issues for Clinical Trial Drugs

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Context for Review

- What is the intended use, patient population, size of trial?
- What is the phase of trial and stage of development of the drug?
- What is already known about the product?
  - Previous trials
  - Drug development
- Is product type/class known to have specific quality concerns (e.g. problematic impurities, previous safety issues)
- What is the level of experience of the manufacturer and the degree of their involvement in drug development?
- Is there enough data present to assess the safety of the drug from a Quality (CMC) standpoint and is the data supportive?
Issue: Indirect Access to data

- In some cases the Clinical Trial Sponsor has limited access to detailed manufacturing information. Approaches include:
  - Parallel data filing by fabricator and sponsor
  - Reference to an existing approved submission
  - Reference to a Drug Master file
  - Necessary to treat proprietary data appropriately

Plenary Discussion

- Concerns?
- Unresolved issues?
- Additional Clarification?
- Experiences to Share
Issue: Limited Stability Data

- Is there data in place to support the continued acceptability of the product for the duration of the trial?
- If full data isn’t available is there a commitment to monitor actual clinical batches (or representative batches) throughout the duration of the trial and a summary of the testing to be performed and the test stations?
- Is accelerated stability data provided?
- For drug products that are reconstituted or diluted, is there data to support the proposed in-use period?
- Should be using principles in ICH QIA-E (Pharmaceuticals) and Q5C (Biologics)

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Issue: Limited Stability Data

Expectation: Data to support that product will remain in specification for the duration of the trial.

- Data often limited in terms of # of lots and real-time data
- From data available is there evidence for changes to key parameters on storage?
  - Do these changes have implications for Safety? Efficacy?
- Is there a commitment to conducting ongoing real-time stability studies and lots enrolled? For Biologics: may need an amendment to extend expiry dating
Case Study # 1

Plenary Discussion

- Concerns?
- Unresolved issues?
- Additional Clarification?
- Experiences to Share
Issue: Pharmaceutical Development

- As development of formulation and manufacturing process proceeds expect some changes in formulation and process optimization. Is there a comparison of the current formulation (or process) with earlier iterations? Do these changes impact the relevance of earlier studies (e.g. stability)?

- Is there an assessment of the potential impact of changes on extrapolation of results from pre-clinical earlier clinical trials to the proposed trial?

- The scientific rationale for the approach taken should be provided.

Issue: Pharmaceutical Development

- Whenever the manufacturing or purification process is adjusted (e.g. to address an undesirable impurity) the potential exists for introduction of new impurities or product variants.

- If the product attributes have changed, is the necessary data in place to link current and previous materials? Is it still possible to use results from pre-clinical or earlier clinical trials to support the proposed trial?

- There should be a continuous “storyline” leading from early studies to the product intended for market.
Case Study # 2

Plenary Discussion

- Concerns?
- Unresolved issues?
- Additional Clarification?
- Experiences to Share
Issues: Analytical Methods/Specifications

- It is fairly common for analytical method development and validation to proceed along with the development of the product and manufacturing process.
- The amount of data in place required to support the suitability of analytical methods is dependent on several factors:
  - Stage of clinical development
  - Criticality of parameter measured
  - Specification limits for parameter measured
  - Type of measurement being made

Case Study # 3
Plenary Discussion

- Concerns?
- Unresolved issues?
- Additional Clarification?
- Experiences to Share

Thank You!

Questions?