Early Development Best Practices for Stability- Regulatory Perspective

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Outline

• Purpose of an IND
• Regulatory requirements for stability information
• Stability expectations at early IND stage
  – Guidance recommendations
  – General observations from submitted INDs
  – Some examples
• Points for discussion during breakout sessions
Purpose of an IND

- IND required when an investigator intends to conduct a clinical investigation with an investigational product
- FDA conducts a review of the IND contents and has 30-days to determine if the study is safe to proceed
- Information that needs to be submitted depends upon;
  - Novelty of the drug
  - Previous human experience
  - Known or suspected risks
  - Developmental phase
Purpose of an IND

• The FDA’s review focus is:
  – To assure the safety and rights of the subjects in phase 1
  – To help assure that the quality of the scientific evaluation is adequate to permit an evaluation of the drugs effectiveness and safety during phase 2/3

• The information submitted in the IND should be enough for the FDA to meet these objectives.
Stability requirements for INDs

• CFR 312.23 (a)(7)(iv)(a): ….and information sufficient to support stability of the drug substance during the toxicological studies and the planned clinical studies

• CFR 312.23 (a)(7)(iv)(b): …and information sufficient to assure the product’s stability during the planned clinical studies
Data recommended

• 21 CFR 312.23(a)(7)(ii): …stability data are required in all phases of the IND to demonstrate that the drug substance and drug product are within acceptable chemical and physical limits for the planned duration of the proposed clinical investigation

• The amount of data will depend upon the duration of the proposed clinical study
What does it mean

• Stability information to support stability of DS during toxicological studies
• Stability information to assure the product’s stability during planned clinical studies
• All phases of INDs need to contain DS and DP stability data that assures products acceptable quality during the proposed clinical studies
Purpose of stability studies

- During early investigational studies
  - DS stability data from toxicological batches provide impurity profile of the batches qualified during non-clinical toxicological studies
  - Provides information about the inherent stability of DS and its suitability for use in making DP
Purpose of stability studies

• The DP stability data should provide information about the stability behavior of the clinical batches
• The stability information should provide assurance that the quality, purity and safety of the investigational product is acceptable throughout the clinical trial period
Expiration dating period

• Investigational products are exempt from having an expiration dating period (CFR 211.137 (g))
  – “new drug products for investigational use are exempt from the requirements of this section provided that they meet appropriate standards or specifications as demonstrated by stability studies during their use in clinical investigations”

• Expiration information needed for the reconstituted drug products
  – “where new drug product for investigational use are to be reconstituted at the time of dispensing, their labeling shall bear expiration information for the reconstituted drug product”
Data recommended

• FDA guidance on phase 1 studies states
  – A brief description of the stability study and test methods used to monitor the stability of the product packaged in the proposed container/closure system and storage conditions
  – Preliminary tabular data based on representative material
Data recommended contd.

- FDA recommendations for phase 2 studies
  - Provide a list of tests, analytical procedures, acceptance criteria, time points for each test, storage conditions, and duration of study that covers the trial duration
  - Available stability data from phase 1 study that were not reported previously (amendment)
  - Data from phase 2 clinical material as data become available (annual report)
  - Encourages early performance of DS stress studies
General observations from submitted INDs

• For early phase studies
  – Appropriate stability attributes are monitored on storage (e.g., assay, impurities, sterility, in vitro drug release)
  – Typically contains long-term and accelerated storage stability data for DS and DP clinical batches
  – Often have 1-3 month of data on clinical DP and DS batches
  – At times may have additional data on developmental batches
  – Sometimes data for closely related developmental DP batch with commitment to pursue concurrent stability studies on DP clinical batch
  – Data from DS batches for stable molecules with commitment to follow DP stability concurrent to the clinical studies for simple drug products (powder in bottle or powder in capsule) with proper justification
General observations from submitted INDs

• For early phase studies
  – Data to support in-use period for the DP that involve extemporaneous reconstitution or dilution of DS alone or DP, mixing of DP with foods prior to clinical use.
  – Appropriate stability data when the FDA approved drug product is manipulated prior to its use in clinical studies
  – Appropriate stability data when an approved drug is used as comparator after manipulation by the sponsor
  – Stability information for placebo if changes in physical characteristics or degradation is suspected (appearance, hardness, microbial purity of meter-dose container)
  – No stability data can be a cause of concern
Potential stability concerns

• Scenario 1: Non formulated API-in-bottle or API-in-capsule drug product
  – No DS stability data, clinical or representative batch
  – No DP stability data, clinical or representative batch
  – Proposal to monitor stability of clinical DP batch
Potential stability concerns

• Scenario 2: Formulated product
  – Acceptable DS stability data
  – No clinical or representative DP stability data
  – No API-excipient compatibility data
  – Proposal to monitor stability of clinical supplies
Reviewer’s concerns

• Is the provided stability data sufficient to ensure stability and quality of drug substance and drug product during the clinical evaluation period?

• If data is from representative batches, are the representative batches really representative of clinical batches?

• What is the plan for monitoring the stability of GMP clinical batches?

• Is there a rationale to support the proposed plan for monitoring stability of clinical supplies when needed?
Points to be discussed in the breakout sessions

• What are the considerations for leveraging accelerated stability data from drug substance and drug product developmental batches to support an initial IND?

• What are the considerations for leveraging real-time stability data from developmental drug substance and drug product batches to support an initial IND?

• What are the considerations to ensure the stability and safety of clinical batches during the proposed clinical study duration?
Available resources

• FDA Guidance for industry: Content and format of investigational new drug applications (INDs) for phase 1 studies of drugs, including well characterized, therapeutic, biotechnology-derived products (1995)

Thank You!!

• Questions?

• NewDrugCMC@fda.hhs.gov