Current FDA Thinking on Stability Practices for New Drug Products

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Outline

- Why is stability information needed
- Stability expectations at IND stage
    - Available resources
    - General observations from submitted INDs
- Stability expectations at NDA stage
  Available resources
  Design stability studies
  Recommended data at the time of submission
  Case studies

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 DS and DP 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

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)

- FDA Guidance for industry: INDs for phase 2 and phase 3 studies. Chemistry, Manufacturing and Controls information (2002)

Purpose of stability studies

- During investigational studies
  - To obtain impurity profile of the batches used during non-clinical toxicological studies
  - To ensure that the quality and safety of the investigational product is acceptable throughout the clinical trial period

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

Data recommended contd.

- FDA recommendations for phase 3 studies
  - Provide changes in the stability program from phase 2 studies
  - Available stability data from phase 2 not reported previously and data from phase 3 clinical material as data become available
  - Stress studies to assess potential changes in physical and chemical characteristics, if not performed earlier
  - Develop protocol for formal stability studies to support filing of NDA

General observations from submitted INDs

- For phase 1 studies
  - Typically contains long-term and accelerated storage stability data
  - Have 1-3 month of data on clinical DP and DS batches
  - May have additional data on developmental batches
  - Sometimes data for closely related developmental DP batch with commitment to pursue stability studies on DP clinical batch
  - Data to support in-use period for the DP that involve extemporaneous reconstitution or dilution of DS alone or DP prior to clinical use.
  - Appropriate stability data when a comparator has been manipulated by the sponsor otherwise no comparator data
  - 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 cause of concern

Stability considerations in support of new drug applications

Purpose of stability studies at the NDA stage

- To establish appropriate retest or expiration dating period applicable to all future drug substance and drug product batches manufactured, packaged and stored under similar circumstances

- To establish the long-term storage conditions

- To provide evidence of the effect of various environmental conditions on the quality of the drug substance and drug product

Why assign retest date/expiration date

- CFR211.137(a): To assure that a drug product meets applicable standards of identity, strength, quality, and purity at the time of use, it shall bear an expiration date determined by appropriate stability testing described in 211.166

- CFR 211.166(a): There shall be a written testing program designed to assess the stability characteristics of the drug products

- 314.50(d)(1)(i): A full description of the drug substance including its physical and chemical characteristics and stability…

- 314.50(d)(1)(ii)(a): -----stability data with proposed expiration dating

Available guidances

- Guidance for Industry: ICH Q1A(R2)-Stability testing of new drug substances and products
- Guidance for Industry: ICH Q1B-Photostability testing of new drug substances and products
- Guidance for Industry: ICH Q1C-Stability testing for new dosage forms
- Guidance for Industry: ICH Q1D-Bracketing and matrixing designs for stability testing of new drug substances and drug products
- Guidance for Industry: ICHQ1E-Evaluation of stability data

Basic requirements for assigning expiration/retest dating period

- Assigned based on submitted primary stability data generated using primary batches of drug product/drug substance packaged in the to-be-marketed container/closure system and stored under proposed storage, accelerated storage, and intermediate conditions, if needed

- Additional supportive stability data helpful in assigning expiration/retest dating period beyond the primary data

Batch selection for NDAs

	Drug substance	Drug product
# and size of batches	3 batches, at least pilot scale	3 batches, 2 at least pilot, one can be smaller with justification
Manufacturing and Container/ closure (CC)	•Representative of proposed commercial material (same synthetic route) •Stored in CC same as, or simulates, that proposed for commercial storage	•Manufactured using different DS batches •Formulation, CC and manufacturing representative of commercial product •Represent each strength and CC unless bracketing/matrixing applied
Additional	Any supportive batches	Any supportive batches

Testing frequency

- Establish stability profile for long-term studies
- Long-term: every 3 month 1st year, every 6 month second year and annually, thereafter
- Accelerated: a minimum of 3 time points including initial and final (0, 3, and 6 month)
- Intermediate storage if needed: minimum 4 time points including initial and final (0, 6, 9 and 12 months)
- In-use studies for reconstituted/diluted solutions done at initial and final time point for primary batches

DP storage conditions

Proposed Storage	Study Type	Storage Condition	Time (mos)
Controlled room temp.	Long term	25° C / 60% RH 30° C / 65% RH	12
	Intermediate	30° C / 65% RH	6
	Accelerated	40° C / 75% RH	6
Refrigerator	Long term	5° C	12
	Accelerated	25° C / 60% RH	6
Freezer	Long term	-20° C	12

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Bracketing and matrixing (Q1D)

- A reduced design can be a suitable alternative to a full design, if justified

- Full design: Samples for every combination of all design factors are tested at all time points

- Reduced design: Samples for every factor combination are not tested at all time points

Bracketing and matrixing (Q1D)

- Bracketing: The design of a stability schedule such that only samples on the extreme of certain design factors (e.g., strength, package size) are tested at all time points as in full design
    - A bracketing design assumes that the stability of the intermediate levels is represented by the stability of the extremes tested
- Matrixing: The design of a stability schedule such that a selected subset of the total number of possible samples for all factor combinations is tested at a specified time point
    - That the stability of each subset of samples tested represents the stability of all samples at a given time point

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Stability information expected (Q1AR(2))

- Generally a minimum of 12 month long-term and 6 month accelerated for three primary batches (6M long-term and 6M acc. data for new dosage forms Q1C)
- Any available supportive stability data
- Appropriate statistical analysis, if needed, to support proposed extrapolated expiration/retest date
- Stability data on reconstitution/dilution/admixing at initial and final time point to qualify the in-use period on primary batches (not needed for commitment batches)
- Data from forced degradation and photostability studies
- Appropriate post approval stability commitments

Case study 1

- Sublingual tablets
- Provided 15 month of long-term and 6 month of accelerated data for three batches of drug product packaged in bottles and blisters
- The quantitative attributes include assay, impurities, pH, disintegration time, and water content
- 24 month expiration period proposed

Stability data

- Stability data showed no significant change under accelerated conditions

- Long-term data showed some variability and trending for the quantitative attributes (assay, moisture, pH, total impurities)

- Used one-sided or two sided 95% confidence intervals in calculating the projected shelf life

- Statistical analysis confirmed that the product will meet the specification at 24 months

- 24-month expiration date was assigned

Case study 2

- Injection dosage form
- Company initially submitted three month long-term and accelerated data for three batches
- Product goes out of proposed impurity specification in three months under accelerated conditions
- Increasing the impurity limit was not possible due to safety reasons
- No intermediate conditions stability data
- 24 month proposed shelf-life

Initial comments to company

- Submit additional long-term stability data to support your proposed expiration period
- Provide stability data under intermediate storage conditions as significant change under accelerated conditions is observed

Company response

- Company submitted 12-month long-term stability data for one batch and 9-month long-term stability data for 2 batches

- No intermediate storage data was provided

- The statistical analysis of long-term data supported >12-month expiration period

Final outcome

- Lack of intermediate storage data considered as significant change at intermediate conditions

- No extrapolation was allowed based on significant change under accelerated and intermediate storage conditions

- Nine month expiration period was assigned based on satisfactory long-term stability data

Conclusion

- There are statutory and scientific reasons for the inclusion of appropriate stability data during IND and NDA stages.

- Stability data submitted to supports an IND is commensurate with the stage and length of the clinical trial

- The proposed retest/expiration period for DS and DP is based on well designed stability studies, evaluation of the data and appropriate extrapolation based on statistical analysis and supporting stability data

- The granted retest/expiration period at the time of NDA review is later confirmed through confirmatory studies using commercial production batches, if needed

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