Driving Quality Innovation & Culture

Checklists for Stability Programs to Meet FDA and ICH Expectations

1. Before Clinical Development: Understanding stability profile, characteristics of drug substances

- ❑ Appoint a detail-oriented person to oversee program administration
- ❑ Be sure to never lose a stability sample
- ❑ Be sure to never test into compliance (handle OOS results properly)
- ❑ Track and trend: stability results, method performance/non-performance, lab investigations, OOS results, OOT results
- ❑ Analyze results of tracking and trending. Leverage them to drive change in your stability program
- ❑ Characterize DS, DP, analytical methods
- ❑ Study FDA 483s and Warning Letters to keep knowledge up to date
- ❑ Develop stability-indicating methods early (especially biological potency assay, if needed)
- ❑ Make API/DS stability part of molecular characterization
- ❑ Do short-term real temperature and accelerated stability of API/DS and experimental DP
- ❑ Make stability part of feasibility and "Checkpoint Zero"
- ❑ Assess stability/degradation state of material used in model systems
- ❑ Generate a degradants profile
- ❑ Start qualifying/re-qualifying stability chambers/rooms, etc.
- ❑ Assess stability of test article and test article in carrier during pivotal pre-clinical trials, as required by regulations
- ❑ Write reports for Phase 1 IND
    - ❑ Include stability characterization of the drug substance
    - ❑ Include stability characterization of experimental drug product
    - ❑ Include stability assessment of material used in pivotal toxicology study/studies
    - ❑ Include rationale for each stability-indicating method (seen in stress, accelerated, real time/temp studies), as well as stability-indicating data (Qualification or Validation)
- ❑ Develop working reference standard (should be material used in pivotal toxicology trials)
- ❑ Determine stability of any materials where using vendor's expiration date is not appropriated
- ❑ Start developing a sampling plan and identifying where stability samples will come from

Checklists for Stability Programs to Meet FDA and ICH Expectations

2. During Clinical Development: Doing the "Homework"

- ❑ Continue all non-completed items from pre-clinical lists
- ❑ Assess stability of all clinical trial material
- ❑ Optimize assays
- ❑ Finalize assessment of degradation pathways, kinetics, and products of API/DS & DP
- ❑ Validate/Qualify stability chambers, rooms, etc. (actual conditions of use; mapping)
- ❑ Determine need for hold time stability studies of process intermediates
- ❑ Develop primary and working reference materials
- ❑ Fully characterize any degradants seen in real-time/temperature studies and primary accelerated studies (studies used to establish/justify expiration date/shelf life)
- ❑ Begin to evaluate container/closure systems
- ❑ Develop stability specifications (finalize before manufacture of Phase 3 material)
- ❑ Write stability protocol and include:
    - ❑ Manufacturer of DS, DP, and excipients
    - ❑ Proposed retest or expiration dating period
    - ❑ Type, size, number of batches
    - ❑ Type, size, source of containers and closures
    - ❑ Test parameters
    - ❑ Validated stability-indicating test methodology for each parameter assessed
    - ❑ Storage conditions
    - ❑ Storage conditions
    - ❑ Container orientations
    - ❑ Sampling plan
    - ❑ Test time points
    - ❑ Acceptance criteria
    - ❑ How data will be presented
    - ❑ Statistical approaches and methods for evaluation of results and determining retest or expiration dates
    - ❑ Stability Commitment
    - ❑ Pre-determined acceptance criteria
    - ❑ Section on how to modify protocol
- ❑ Validate stability-indicating methods specifically for ability to assess stability before pivotal clinical efficacy trials (Phase 3)

2. During Clinical Development: Doing the "Homework" (Cont.)

- ❑ Write Stability report with the following sections:
  - ❑ General Information
    - ❑ Product Name
    - ❑ Study Number
    - ❑ Reporting Period
    - ❑ Length of Study
    - ❑ Storage Conditions
    - ❑ Sampling Plan
    - ❑ Formulation Code/#
    - ❑ Composition & Supplier
    - ❑ Container
    - ❑ Closure
    - ❑ Seal
    - ❑ Drug Substance (Manufacturing Site/Date, Batch Type & Size, Batch Number)
    - ❑ Drug Product (Manufacturing Site/Date, Batch Number, Dosage and Strength, Packager Site and Date)
    - ❑ Statement assuring that long-term testing will continue for duration of expected retest period and shelf life
    - ❑ Information about contract firms used
  - ❑ Summary information
    - ❑ Physical, chemical, microbiological attributes
    - ❑ Stability-indicating profile
    - ❑ Regulatory release specs
    - ❑ Regulatory stability Specs
    - ❑ Stability-indicating Test Methods
    - ❑ Description of the biological assay used for potency determination (if applicable)
    - ❑ Location of validation information
    - ❑ Statement of changes likely to occur upon storage
    - ❑ Rationale for selection of parameters monitored
    - ❑ Description of sampling plan
    - ❑ Expected duration of study
    - ❑ Conditions for storage
    - ❑ Location of Data
    - ❑ Summary of Data
    - ❑ Specification Failures
    - ❑ Summary of information on previous formulations and container/closures during product development
    - ❑ Conclusions

2. During Clinical Development: Doing the "Homework" (Cont.)

- ❑ Specifications and test methodology
  - ❑ Individual and total limits (Impurities/degradation products)
  - ❑ Justification, levels seen in preclinical and clinical materials
- ❑ Study design and conditions
  - ❑ Batches selected
  - ❑ Different containers and closure systems and number of each
  - ❑ Number of units selected
  - ❑ Statistical method used to select units
  - ❑ Whether tests conducted on individual units or composites
  - ❑ Sampling time points
  - ❑ Reconstitution studies
- ❑ Stability data
  - ❑ Individual data (source of each data point, batch type (research, pilot, production); batch number; manufacturing date
  - ❑ Data tabulated by storage condition
- ❑ Data analysis
  - ❑ Data tables, plots, graphs and evaluations
  - ❑ Documentation for statistical methods used
  - ❑ Estimated dating periods
- ❑ Degradation product information
  - ❑ Procedure for isolation and purification
  - ❑ Test methods and validation data
  - ❑ Identity and structure
  - ❑ Physical and chemical properties
  - ❑ Degradation pathways
  - ❑ Levels detectable and quantifiable
  - ❑ Individual and total acceptance criteria
  - ❑ Biological and pharmacological relevance
  - ❑ Analysis of potential hazards
- ❑ Conclusions
  - ❑ Proposed dating periods and justifications
  - ❑ Regulatory specifications

3. After Approval/Licensure

- ❑ Do formal studies per ICH using: a GMP-compliant protocol, validated methods, full change control, and QA review and approval before work begins under the protocol
- ❑ Write Stability report, including all deviations, discrepancies, OOS, and their thorough investigations
- ❑ Get ready for FDA inspection of your Stability program
- ❑ Achieve full GMP compliance in your Stability program, including rigorous change control and discrepancy and failure investigations
- ❑ Keep your Stability commitments. Do an annual stability batch, special Stability studies
- ❑ Track, trend, audit, investigate, CAPA