Stability Studies to Support PET Drug Applications

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Objective

My objective is to provide information to help you decide the best stability study practices for your submission. We will discuss the following:

- Review the purpose for stability studies
- Review what to include in stability studies
- Process development/control relationship to stability studies
- Vial size and orientation considerations
- Expiration time
- Elevated temperatures and other considerations

What are Stability Studies?

Stability studies are used to confirm the drug product is:

- stable under the defined storage conditions
- stable at the highest radioactive concentration
- stable at expiration time

The entire batch volume is stored in the intended container/closure for the duration of the study.

Stability Studies

Stability studies address concerns due to:

- Radiation-related radiolysis
- Chemical changes
  - Interaction between drug product components and vial/stopper
  - Ability of container/closure to protect against contamination (container/closure integrity)

Analytical methods must distinguish degradation products and impurities

- Process development and process controls – impurity profile
  - Analytical method development/validation

Stability Studies – New Submission

Three stability batches (qualification batches) are provided in the initial submission

- Should be performed on three consecutive business days – adequate planning
- Why not all in one day?
  - ALARA concerns
  - Logistics – difficult to perform 3 stability batches in one day (especially for F-18 products)
  - You are not involving parts of the quality system that may impact the chemical profile. For example:
    - Daily reagent/diluent preparation
    - Daily chemistry module set-up/cleaning
    - Formulation dilution
    - Daily mobile phase preparation
    - Cleaning

Stability Studies – New Submission

Stability program is described in your submission

- Includes a summary paragraph
- Table summarizing QC tests and stability indicating tests for the product
  - Summary of the stability batch data.
- Post-approval commitment
  - Single stability study performed annually

How do I develop the program?

- What are your goals?
  - Derived from process development
- Once these are defined then the protocol can be written.

What do I need to include in stability studies?

The stability protocol typically consists of the following:

1. Summary/purpose, Schedule, Procedure
2. Full QC at T_0 (as defined in your submission)
3. Perform stability indicating tests at defined time points:
   - Radiochemical identity and purity
   - Radionuclidic purity
   - Appearance
   - pH
   - Stabilizer/preservative effectiveness
   - Chemical purity
   - Specific activity (if necessary)
4. Summary report
   - Includes complete and legible batch records

Best Practices

Best Practices

- Appearance
- pH
- Radiochemical purity and identity
- Stabilizer/preservative effectiveness
- Chemical purity
- Specific activity (if necessary)
- Radionuclidic purity
- Endotoxin testing
- Sterility testing

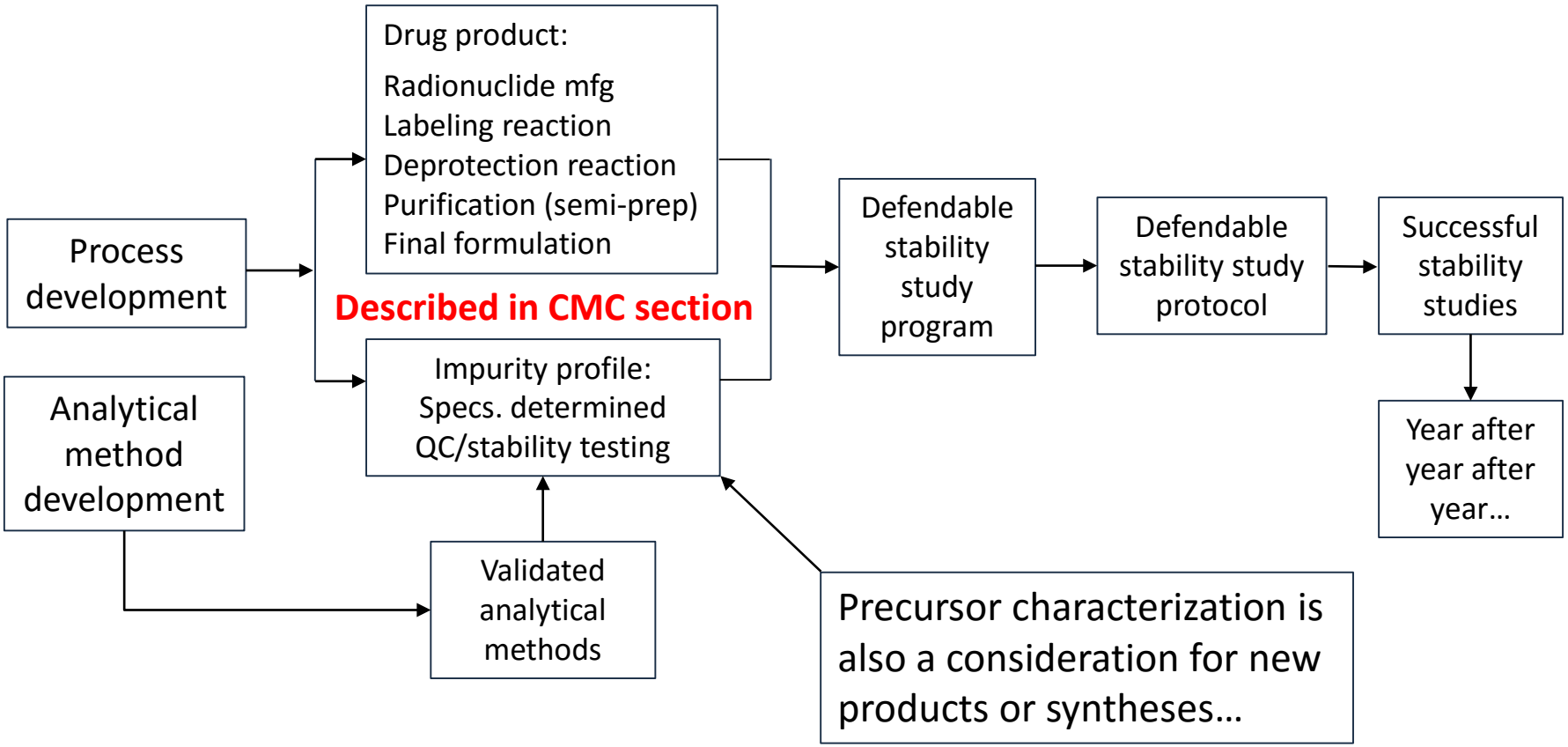
Best practices for stability study QC testing begins with process development.

- Establishes which QC and stability indicating tests to perform (or not perform)

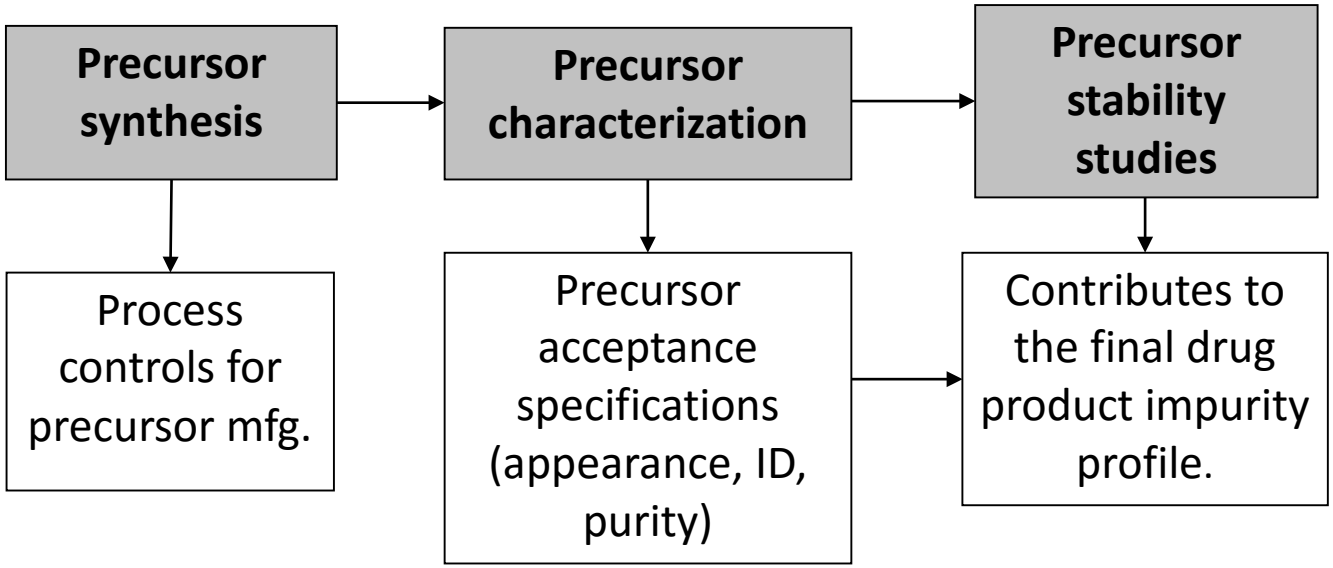
If you claim it then prove it.

- Most CMC review questions answered with process development data…

Best Practices



Best Practices – Precursor Stability



Best Practices – Process Development

Take the time to ensure process development is adequate:

- There is value in "justifying the ruggedness" of a process with a certain number of batches before finalizing your CMC section.
  - Especially for complex syntheses
  - Finalize process controls/stability program
  - The stability batches must be performed using the process submitted in the application
  - Do not want to be in the position of amending the CMC section of an application during review
    - This will require the stability study/qualification batches to be repeated
- Provides support for expiration time and time points.

Best Practices – Expiration

What about expiration time?

- Decision is based on stability goals - process development
  - A good starting point for new products is 6 half-lives

Which time points should I use for stability testing?

- Well studied products (for example FDG, NaF, ammonia) have used two points: EOS (t_0) and t_{expiry}
  - Two points have been used successfully for IND drug products
- An additional time point may be needed
  - For example: t_0, t_6, t_{12}
  - Decision is based on process development/process controls

What About Vial Orientation?

Should vials be stored upside down or right side up?

Stability studies should be performed with inverted configuration

- Formulation is in contact with all surfaces of the container/closure
  - Interaction between drug product components and vial/stopper
  - Container/closure integrity
  - Specified in the PET drug application guidance “Sample Formats – Chemistry, Manufacturing, and Controls (CMC) Section” for FDG, NaF, ammonia.

Upright configuration may be acceptable.

- Justify in the application

What About Vial Size?

Do you need to perform stability studies on each vial size used in PET drug manufacturing?

The PET Q&A Guidance for PET Drugs (Dec 2012) addresses this (Q68):

- Recommends that the largest vial size be used
- If you manufacture in 30 mL and 50 mL vials, then use 50 mL vials
  - May need to test the 30 mL vial if the headspace oxygen-to-surface ratio differs significantly
  - If you manufacture into 30 mL vials and want to use 50 mL vials, then new stability studies will be required (in triplicate)
    - Will require a prior-approval supplement for a change in the container closure.

Other Considerations

Elevated temperature study – necessary?

- Likely not needed
  - PET Q&A Guidance for PET Drugs (Dec 2012) Q69: not required for commonly used PET drugs (e.g. FDG, NaF, ammonia)
  - New drug products: may need to consider elevated temperatures.
    - Especially if shipped long distances
    - Use process development data to justify your position.

- Other stability considerations
  - Product is photosensitive

Discuss with FDA review division – For example, end of Phase 2

Other Considerations

Stability studies to be performed in triplicate for:

- Change in strength
- Change in stabilizer/preservative content
- Change in final product container/closure
- Change in storage conditions
- Change in expiration time
- Addition of a precursor manufacturer
- Addition of a target material manufacturer (for example, [^{18}O]water)

Submitted as an annual report, CBE or prior approval supplement as appropriate.

Documentation

Lack of good documentation practices is a frequent cause of stability study issues during internal reviews

Some errors have resulted in the rejection of a stability batch.

- A thorough review at T_0 and T_{expiry} will save time correcting mistakes
  - or starting over
- Second person review critical

Risk during FDA review…

Documentation

Consider the following good documentation practices:

1. Clear – Must be legible
2. Traceable – (who, what, when, where, why)
3. Accurate – Avoid transcription errors
4. Complete – The record must be complete with all attachments
5. Reviewed – Timely and detailed review of the batch record is critical
   - Errors detected can be immediately corrected
     - Procrastination can lead to exasperation
   - Annotated properly – Single line through/date/initial and explanation

Summary

Best practices are derived from process development and can be used to support/justify these stability study goals:

- Impurity profile - analytical methods must distinguish degradation products/impurities
- Vial orientation
- Expiration time
- Elevated temperatures/photosensitivity/other

Stability program - defines t_0 and t_{expiry} stability testing to perform, or not to perform

- Consistent with goals
- Stability protocol derived from the stability program
- If you claim it, prove it

Good documentation practices are important

- Don’t jeopardize your study (or submission) with errors
- A 30 minute detailed review can save hours of time

Thank You!