Table 6 and Table 24: Best Practices to Design Forced Degradation Studies / Design of Stability Studies for Accelerated Product Development

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Key Words:

Stability, Forced Degradation

Scope:

Per the ICH Q5C guidance Stability Testing of Biotechnological/Biological Products: "Primary data to support a requested storage period for either drug substance or drug product should be based on long-term, real-time, real-condition stability studies." With accelerated clinical development compressing timelines to only a few years from product concept to licensure, the time to generate sufficient long-term real-time stability data to support a reasonable commercial shelf-life becomes the critical path. This time crunch is compounded by the fact that the commercial manufacturing process is often finalized late in the overall development cycle, to minimize investment costs prior to clinical proof of concept.

Similar to accelerated stability conditions, forced degradation studies aim to degrade drug substance or drug product using conditions beyond those typically found under accelerated stability studies. To accelerate product development, can shorter term studies under accelerated or forced degradation conditions be leveraged to overcome this data gap?

Questions for Discussion:

1. Can data from accelerated stability studies be used to extend shelf-life at real-conditions for a biological product? How would such studies be designed and analyzed?
2. Should the conditions of accelerated stability / forced degradation studies be chosen to ensure that trends in product degradation are seen and can be measure or is the lack of change more supportive for the extension of shelf-life?
3. Are there certain types of assays that should always be included in a forced degradation / accelerated stability study or is it permissible to eliminate any assay based on data showing no change over time?
4. When is the best time during product development to perform forced degradation studies?
5. Is there an opportunity to leverage data that may come from forced degradation studies as they apply to comparability to extend shelf-life?

Discussion Notes:

Roundtable Session 1

Self-intro of attendees: various interest in best practice, impact of process automation on forced deg study design, phase-appropriate, extension of expiration, when and how, leverage early-phase results, using existing forced-deg data to extrapolate real stability, study design, etc.

Facilitator emphasizes the distinction between forced deg and accelerated stability

1. How to do accelerate stability and use the data to forecast real time stability?
    a. Early phase, use -20C, 2-8C for -70C as accelerated conditions for DS, 25C (~1 yr) and 40C (~3 month) for 2-8C DP storage; based on non-GMP lot (e.g. 6 month data) and ongoing GMP stability (at least 1 month) to convince agency to have at least 1 year of shelf life;
    b. For non-mAb modalities, 25C and 30/35C as accelerated temp for less stable molecules
    c. What is the criteria to set the expiration based on accelerated data?
        i. Meet specs under accelerated conditions should predict the stability under real-time stability
    d. In-use stability (a separate topic)
    e. Use accelerated stability to investigate Mfg temp excursions etc.
    f. Freeze-thaw studies
    g. Accelerated stability has been used in post-approval process change (DP example with Health Canada), because accelerated is more informative than real-time stability, indicative of product quality. Data package include pre- and post-change showing the same trending has used in comparability.
    h. Some companies proposed to use platform knowledge and historical data, combined with modeling to predict stability. However, others argued that this strategy may be challenging, as different molecules may behave differently and not necessarily fit into the model.
    i. Leveraging historical knowledge using statistical analysis to predict stability? Have used in post-approval changes; literature available.
    j. -20C can be worse than 5C for -70C DS, depending on formulation used (intermittent freeze-thaws)

2. Forced deg: what can you learn? When is the best time to do it?
    a. A paper from Biophorum detailing this topic
    b. Might have to repeat forced deg when formulation etc. changes
    c. Used in method validation/suitability/formulation dev/process
    d. Identify lability of molecule after formulation established
    e. Detailed study design guidelines available in the aforementioned paper, conditions may vary based on molecule, might need to refine the conditions to achieve 30-60% degradation; however, having more platform conditions will allow comparison between molecules
    f. Used in candidate molecule selection (conditions may be less stringent)
    g. Which section does forced deg data go in the filing for late-phase? Maybe in formulation dev. Methods have to be final and qualified at this stage.
    h. Used in CQA assessment, early phase before process dev

3. What is the phase-appropriate forced deg?
    a. Later phase requires forced deg to be done in appropriate formulation/container; may also include DP if significant formulation difference from DS. (e.g. photo-stress, which is out of scope)

b. Some do a comprehensive forced deg early in development right after developability; some do a reduced panel of forced deg (many early-stage programs) and repeat in later stage.
c. Early stage has limited conditions; later stage add more conditions for BLA; depending on the speed of program
d. Some repeat forced deg after formulation change
e. Keep retains of forced deg material in case methods are not ready
f. Side-by-side forced deg for comparability, but not side-by-side for accelerated stability
g. UV forced deg? Follow ICH guidelines? (papers suggest conditions in ICH guidelines are too extreme, ambient condition is more appropriate)
h. Consideration of correlation with in-vivo behavior (e.g., drugs get deamidated in vivo anyway)

4. Logistics
    a. Is there a protocol of forced deg? Some have internal guidance, later stage may have protocols
    b. Which department is leading? Typically AD, some involves both formulation and AD
    c. If resource limited, prioritize the conditions with highest criticality based on product understanding
    d. Potency assay can be difficult to tell the trending due to assay variability etc.; But potency assay tells the impact of the change; can use several data points to plot the trend.

Roundtable Session 2

Facilitator emphasized the distinction between accelerated stability and forced deg.

1. Can data from accelerated stability studies be used to extend shelf-life at real-conditions for a biological product?

- One opinion is yes. Temperature has to be selected right, otherwise it will trigger different degradation pathways.
- Another opinion is that heat stress conditions may not predict real time situation. ICH Q5 does not allow to do that.
- FDA did not require stability prior to the 80s. Later based on papers on small molecules, degradation prediction using the Arrhenius equation (temperature dependent reaction rate) could be used to predict long term stability. Real time stability could be extrapolated based on the temperature difference based on the equation. However, this kind of reaction may not hold true for proteins.
- There is a paper on forced deg study design. The conditions must be selected to obtain 5-30% degradation.
- FDA might allow up to 18-month stability based on accelerated data of 6 months. But this may not be true for more complexed biologics.
- There is a desire to initiate a cross-company study for accelerated stability of mAbs for publication.
- Standard approach is to call ICH Q5C. However, using a representative batch to help set up shelf life seems to be open for FDA. mAbs are more complexed than small molecules and should require more real time stability.

- How many times do we see the prediction is correct when using accelerated to predict real time stability?
    - One company has started automated data mining on this
    - Experience with multiple products will be helpful; Cross-company study on this might be needed.

How would such studies be designed and analyzed? What are the conditions to be included for accelerated stability?

- The selection of accelerated temperature could use the Tm information based on DSC, though many molecules' Tm is very high.
- One company carries out accelerated stability under multiple temperatures to find at which temp the Arrhenius reaction applies. For 5C storage, maybe explore 5C, 25C, 30C, 40C, 45C, etc. This is also to consider countries having high room temperatures.
- One company used real time stability and extrapolated data in BLA to extend shelf-life. Use the degradation behavior at different temp to extrapolate and justify the shelf life.
- Different consideration for DS and DP if present in different format

2. Should the conditions of accelerated stability / forced degradation studies be chosen to ensure that trends in product degradation are seen and can be measure or is the lack of change more supportive for the extension of shelf-life?

- Usually want to see degradation in forced deg.
- However, when used in the case of temperature excursions, you probably do not want to see change
- When there is no change in accelerated stability, there is limited information to be learned
- Sometimes when product is too stable and do not show change, must use forced deg to show changes.
- One case: For post-approval, annual stability protocol, agency argues that frozen condition is not enough to show changes, so company had to add 5C arm (this is case by case).

3. Are there certain types of assays that should always be included in a forced degradation / accelerated stability study or is it permissible to eliminate any assay based on data showing no change over time?

- Typically purity methods, reduced and non-reduced CE-SDS, SEC, icIEF, etc. as these assays are stability indicating

4. When is the best time during product development to perform forced degradation studies?

- Usually determined by analytical group
- One opinion is to be done if the product makes Phase II
- Many companies do it early during sequence selection, to ensure method is stability indicating
- May have to repeat forced deg if formulation/process changes
- Registration batches should be done according to ICH guideline, early batches could be done using a reduced panel of conditions/assays
- How to store forced deg materials and access them later?
    - One company uses MAM to monitor multiple attributes and review the data later
    - Freeze/thaw study is needed to ensure the frozen retains can be used

5. Is there an opportunity to leverage data that may come from forced degradation studies as they apply to comparability to extend shelf-life?

- Forced deg is to understand degradation pathway but not to extend shelf life
- What company intended is to demonstrate the degradation trends similarly for the comparability purpose (have used this strategy in clinical phases but not in commercial)
- Depending on what is the process change, and associated risks.
- Industry generally has more success with this approach than before. Usually requires further commitments afterwards.
- Usually have the first comparability batch goes to stability.
- EU and FDA have different requirement for labeling of shelf life.

Other comments:

- Based on small molecule experience, the regulatory requirement may change over time.
- Resource differs between big and smaller companies
- Machine learning used in stability prediction

  Last year, there was a WCBP presentation that a company used a sophisticated modeling data to predict stability. But FDA still requires real time stability and bracketing data. This approach is still under development and requires confirming the modeling results using real time data.