Roundtable Session 2 – Table 6 - Relevance of Accelerated and Forced Degradation Studies for a Frozen DS/DP

Facilitator: Elisabeth Krug, *Eli Lilly & Company*
Scribe: Kirby Martinez-Fonts, *Merck*

Abstract:
ICH Q5C (Stability Testing of Biotechnological/Biological Products) 5.3 states: "Wherever significant quantitative or qualitative changes indicative of degradation product formation are detected during long-term, accelerated and /or stress stability studies, consideration should be given to potential hazards and to the need for characterization and quantification of degradation products within the long-erm stability program..."
Accelerated temperature storage and forced degradation studies are conducted throughout development to ensure that the primary degradation pathways are identified and monitored with appropriate analytical methods to satisfy ICH Q5C requirements. However, what is the relevance of those studies for a frozen DS/DP when "nothing is happening"?

Discussion Questions:

1. *Does your company consider forced degradation and accelerated temperature studies relevant at all?*
2. *What approach does your company take to for elucidating degradation pathways for frozen DS and DP?*
3. *What duration of testing the non-frozen state does you company regard as meaningful?*
4. *How does your company handle comparability for frozen DS/DP?*

Notes:

1. Does anyone have frozen DP?
    a. Many do for clinical studies
    b. When you go to lyo it is necessary to do FD for comparability?
2. How do you define an FD study
    a. Conditions at which you can see a difference in activity - could be accelerated or stressed temperature
        i. Method feasibility
        ii. Safety and immunogenicity - can we see a change in safety or immunogenicity?
    b. GMP -only heat and light is accelerated or stressed stability.
    c. FD is in the development space with all the conditions. Heat light, pH, peroxide etc.
        i. Product understanding and CQA understanding and
        ii. Analytical method development to ensure methods are stability indicating methods
    d. Comparability
        i. Often only a high temp arm is used
3. Does your company consider forced degradation and accelerated temperature studies relevant at all?
    a. Mostly for the above reasons - assay performance and molecular understanding
    b. Mostly DS + intermediate if relevant
    c. Would you also do on DP?
        i. If significant difference may do on DP

    d. Photo stress - is in DP for BLA - may be more formal
    e. 2 types of photo stress in development according to ICH but formulation group does another study that is more real life to cover packaging criteria
    f. Early on like to do the FD study to understand the molecule better - some groups are more reticent to do it early/don't see the value
4. Would you select based on the sequence liability
    a. Some would some plan to in the future but currently do more modeling to determine if they are liable
5. For GMP stability study do you always do a stressed arm?
    a. Yes to support shipping excursion - (-20) on a molecule that is frozen
    b. For ph3 you for need to
6. Do you include FD studies in comparability (Temp and pH (assumed) for the Q)
    a. Some just stick with thermal
    b. If liabilities we may include more conditions
    c. If frozen do you need to? - maybe not
7. Do you do serum stability
    a. Most groups often don't do it
    b. In some situations the agency will require based on how complicated the molecule is or if there is a presumed or known sensitivity
8. Do you test a higher temp for frozen DS/DP
    a. Yes, to cover patient usage
        i. 48 hours - beyond that more microbial concerns
        ii. Depends on dosing scheme
9. pH effects from FT
    a. For biosimilars looked at Ox - compare to innovator
    b. Formulation DP - more concerned about particles - visible or sub vis - if FT is not controlled
        i. Is this more a concern for higher concentrations? Perhaps
10. ADC
    a. Intermediate - different formulation -no polysorbate
    b. ACD
    c. Payload - not all do this
11. What area does FD study?
    a. Research unit does it early and then again as a more comprehensive study.- support with MS - focus on CDR
    b. Temp alone, acid base, peroxide, refrigerated, 25, 40C, light - some will be in the right range - for BLA can tune more based on prior experience
        i. For BLA - formal study in GMP lab for data integrity - not all companies but some
12. Lyo product -how do you do accelerated and stressed temp? How do you design a comparability going from frozen to lyo?
    a. Do both lyo and reconstituted both on comparability - have the reconstitution there to bridge and the lyo you expect to see no change
    b. For stability just do accelerated more as a check mark because you may not get a change
        i. How do you manage the expectation that you should see changes?
13. What if your molecule is very stable?
    a. Challenge for showing method feasibility

    b. Can you justify that it isn't a CQA - may be challenging but could try
14. To learn more about method - do FD in water - buffer exchange into water from an unformulated TFF sample
    a. In case the formulation is masking a CQA - show the methods are still good
    b. Analytical focused
15. What if a non mAb or something weird
    a. May have to tune down conditions so you have a reasonable amount of degradation