**Table 11: Forced Degradation Studies - Best Practices. What, When, How, Where and Why?**

Facilitators –

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**Scope:**

Forced degradation studies (FDS) are a vital part of drug development and a regulatory expectation. The studies demonstrate an understanding of degradation and the appropriateness of the methods used to monitor it. In this roundtable we will share best practices that our industry uses to maximize the value of FDS – discussing what defines and justifies a stress condition, interpretation and use of the data, and connection to product quality and control.

**Questions for Discussion:**

1. When do you perform the experiments? What is your starting point? What is the role of prior knowledge? How do earlier studies inform later work?
2. What is it all for? Beyond simply product knowledge and registration - where do you specifically use FDS? Candidate selection, formulation development, method capability, CQA assessment, control system design justification, comparability, root cause investigations?
3. When have we gone too far? When do you shift from a focus on observed change to considering the magnitude of stress applied? How do you incorporate relevance into the study design? How do you select conditions beyond temperature, light, or pH, to examine important chemical and physical degradation pathways - without becoming too harsh or exotic?
4. How do you interpret, and do you connect results to manufacturing process, shipping, handling, use? What do you do with difficult to interpret results, such as complex degradation where the mechanism at the amino-acid level cannot be explained by Mass Spec characterization, or when results from various analytical methods do not correlate?
5. Where within the sections of the common technical document do you summarize forced degradation information? Both for ease of presentation and best impact?

**Discussion Notes:**

January 25 and 27, February 2 and 4, *combined* –

- What/when is an appropriate use of FDS?
    - Formulation screening
    - Understanding product degradation mechanisms/mode of degradation and stability
    - Structure activity relationship (SAR) studies
    - Demonstrating method capability/validation
    - Identifying critical quality attributes (CQA), protein regions susceptible to modification.
        - Good point made around the value that FDS studies bring towards understanding where analytical methods are stability-indicating based on the identified CQAs.
        - Once CQAs are identified, the FDS studies are useful for risk assessment.
        - Justification of specifications (some have been successful in using to argue against monitoring specific attributes)
    - Comparability
        - Terminology and practice differences among companies.
        - FDS vs stress stability, these can be intertwined but same design is not always a good idea
        - Some have been able to use FDS knowledge to negotiate with agency requests for comparability testing (and what conditions should be used)
    - As a basis to design other studies (comparability for example)
    - To validate a "platform" or family of molecules, to set criteria that support inclusion of a new molecule in the platform ("comparability across molecules"), or leverage

for use of the prior knowledge for shelf/life support

- When (in timeline) are FDS studies conducted?
    - Great range of philosophy and opinion: Replies among participants from those who do most FDS work early and through Ph1/2, to those that do very little FDS early with most in late Ph2/Ph3.
        - For the "late FDS" responders, why? 1) Resources: Forced deg studies are labor intensive – MS is the most labor-intensive analytical tool. Many CE, LC methods are also labor intensive, and the sample set is large. 2) Relevance: Better to do important biophysical characterization when you have vetted your molecule through the clinic. Process might change.
        - Other comment on timing: Some consider waiting until the analytical methods are well-qualified, so that the FDS results have less variability and there is higher confidence around interpreting results.
- What are most common FDS approaches?
    - Temperature stress & SEC testing for primary degradation pathways.
    - Freeze – Thaw and agitation stress to support shipping or handling excursions.
    - Full release panels.
    - MS (peptide mapping and intact), functional assays to determine impact to mechanism of action, including binding assays and cell-based assays
    - Focus on structure-function characterization at late stage
    - For vaccine, the characterization of the platform (previous FDS) can be leveraged, not everything needs to be redone, if only the nucleotides are different...
    - Frozen retains for FDS experiments can be very valuable (for method bridging, or when method is better developed, to have different levels of stress, etc.)

- Some input was that the approach (experimental design, type of stress, degree of stress) may/should differ throughout development… the idea of having an FDS "program" that changes over time with the product.

- How to select conditions / design FDS studies?
  - For some products, like adenovirus-based products that are extremely stable to thermal stress (melting temps 50-60C), heat treatment is not useful.
  - ICH photostability conditions may be too harsh and controls (such as at DP level) assumed. Perhaps better to use worst-case manufacturing facility conditions, that are more applicable.
  - For oxidation, AAPH chemical treatment may be better than hydrogen peroxide because it is easier to control and may also give information about free-radicals impact.
  - One panelist mentioned an EBE concept paper that discusses other types of stress conditions to consider based on your product / protein knowledge, such as trace-metal stress. (EBE Concept Paper: "Forced Degradation Studies for Therapeutic Proteins", March 24, 2015)
  - Conditions might be different depending on what question you are trying to answer.
  - Use QTPP and ATP to drive targets.

- When have we gone too far?
  - Understanding the degree of stress applied is essential.
  - Using conditions that are too harsh rarely results in product or process understanding.
  - If data are generated with harsh conditions, then need to put the data into perspective.

        - For example, “at this stress level, data that might otherwise support the identification of a product CQA do not.”
        - This is difficult, but important, to explain in response to regulatory questions or when summarizing conclusions around FDS data in regulatory filings.

- Where does forced deg info go in the filing? There was different experience between stability vs. development sections.
    - S.2.6 or P.2.3? S.3.1.?
    - S.7 and P.8 are sometimes used - depends on the company (typical for vaccine)
    - Seen in formulation sections for some products.
    - Also depends on what we are using the data for in the filing (justification of specs, stability, comparability, formulation development)?
    - Need to consider global dossier approach - may have to do with which sections are more routinely updated.