Roundtable Session 1 – Table 8 – Timing and Frequency of Forced Degradation and Variant Characterization Studies

Facilitator: Stephen Cypes, *Protein Metrics*

Scribe: David Bush, *Novartis*

Abstract:

Forced degradation and variant characterization studies are an important aspect of candidate lead selection and drug development activities, ensuring drug liabilities and associated impurities are identified and monitored during process and formulation development. From these studies, potential critical quality attributes (CQAs) can be understood and analytical strategies to monitor and control those CQAs can be put in-place during development. More recently, increasing complexity of modalities as well as increased capabilities of analytical technologies have impacted the timing and frequency in which organizations are performing these forced degradation and characterization studies. Automation, high-throughput analytical techniques and data science are enabling shifts in approaches companies can take for these experiments. This roundtable will discuss the historical approach to forced degradation and variant characterization studies, how new analytical and data science techniques are impacting the approach going forward, and how increased complexity of therapeutic modalities may have changed the timing and scope for forced degradation and variant characterization activities.

Discussion Questions:

- How is automation and high-throughput analytical technologies impacting strategies around forced degradation and variant characterization studies in terms of timing (i.e. earlier in development or candidate selection) and overall depth of analysis?
- How has data science such as AI and machine learning impacted the approach to forced degradation and variant characterization in terms of numbers of physical experiments needed?
- With increasing complexity of therapeutic modalities such as multispecifics, fusion proteins, oligonucleotides and conjugates, how has that impacted the approach to forced degradation and stress testing to ensure potential liabilities are understood at the appropriate phases of development?
- What approaches for each forced degradation and variant characterization studies are employed, in particular with an approach more on intact-level analyses (easier sample prep) versus peptide-level analyses (more comprehensive data)?

- How has externalization strategies (CROs, CDMOs) impacted the scope and timing for forced degradation and variant characterization studies?

Notes:

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- How is automation and high-throughput analytical technologies impacting strategies around forced degradation and variant characterization studies in terms of timing (i.e. earlier in development or candidate selection) and overall depth of analysis?

  Forced degradation assessment is happening earlier and with a higher variety of conditions, especially for BLA enabling conditions (required for submission). However, not all forced deg. samples require LC/MS assessment, some degradation can be assessed with charge-based or biophysical methods. E.g. freeze thaw does not need LC/MS at all. For a large formulation / long term stability study, you might generate 10's or 100's of samples but only a few need to be assessed by LC/MS to determine PTMs that can be mapped to features in other assays.

  It is ideal to have a platform method to improve throughput, but it might need adjustment for specific programs. Depending on the assay, this can be an inconvenience or require dedicated hardware ($$$)

  For biosimilars, early forced deg. is very critical, one participant stated that it was happening too late and required process optimization late in the program.

  What do you mean by automation? Robotic sample prep and digestion.

  Are you the first to do stress in Development? Consensus: there is developability assessment in Research before Development sees it:

- The developability assessment that happens in research includes Forced Deg. in order to assess how much effort will be required to develop methods
- Ideally it informs whether a platform method is suitable, whether it requires optimization or whether a new method needs to be created.
- FD is also required in research to support formulations, ideally you can rule out sources of stress in research (light, heat, etc).
- A CRO participant stated: we encourage people to get stressed material early (limited FD) to check methods for development downstream. ICHQ14 should encourage this.
- Ideally Research can tie structure with bioactivity for early CQA assessment.
- Material limitations in early stages drive experiment design decisions (included forced deg.) to carry the project to the next stage.

  When you have a second site for manufacture, you need to do forced deg for comparability, this is defined by regulators.

  Rarely ever need to analyze old products, but frequently will use multiple recent production batches as comparators.

Most attendees at the roundtable do not use MS in QC yet. Although MAM and metabolite tracking is discussed heavily, they are still novel methods. Late development and PAT don't use MS as much, other methods are more established.

- How has data science such as AI and machine learning impacted the approach to forced degradation and variant characterization in terms of numbers of physical experiments needed?

  Although only for oxidation, in silico prediction can guide whether we put candidates on stress: if its not predicted to be liable, we don't stress it. Only for oxidation, in silico methods for other PTMs being assessed.

  Late stage, forced deg, do you use multiple cells or batches to get statistics? A: yes, but the analytical method depends on protocols, sometimes MS not needed.

  Formal comparability requires side-by-side stress. Need at least 3 or 4 samples from each process.

  Do you see proposal submitted to regulators with AI? Not yet.

- How has externalization strategies (CROs, CDMOs) impacted the scope and timing for forced degradation and variant characterization studies?

  Individual responses:

- "We're the early side still in research and we won't send anything out without IP protection."
- "We generally don't do our developability assessments externally."
- Training is difficult and time-consuming, so there is a long lag before cost savings is achieved and so forced deg. wouldn't really scale. We tried it some time ago, but we don't do it anymore. Insourcing would be more practical.