Roundtable Session 1, Table 17 – Best Practices to Design and Submit Forced Degradation Studies

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Abstract:

Regulatory guidance on how to design and perform forced degradation studies during product development focuses on the importance of understanding a product's degradation pathways and inherent stability. Selection of appropriate stress conditions, assessment of suitable validated stability indicating methods, and interpretation of generated data are routinely expected to completed and submitted within tight industry timelines across development through commercialization. Strategically, how can manufacturers best design their product's forced degradation studies and leverage that data to possibly reduce the amount of supportive long-term stability data to be filed?

Notes:

Question 1: What is the optimal time being to design or execute a products forced degredation study to ensure establishment of appropriate shelf life?

Forced degredation studies can be applied throughout a product’s lifecycle. Early studies are used to understand product liabilities, while late-stage studies are more extensive and continue to build understanding of the molecule or used for comparability studies. For some attendees, early FD studies use heat and photo degredation only for liability assessment. Some attendees perform early FD studies in water or PBS, while others perform stress in intended formulation to better assess real degredation profile. In some cases plasma/serum stability studies are used in early development for candidate selection.

Common early-stage FD assays are SEC, peptide mapping, and potency/binding assessments.

There was a discussion of the use of AAPH vs Peroxide as oxidizers in FD studies. The table was divided on their preference.

Question 2: How can the reliability and accuracy of validated analytical methods be ensured throughout the duration of forced degradation study?

Forced degredation samples should be tested with a combination of release/stability and characterization assays. In early development these samples can be used to help select or further develop platform assays. During later stages (II-III) FD samples should be tested with qualified/validated release and stability methods in addition to any characterization testing. Testing of forced degradation samples with release/stability assay can be a key factor in demonstrating the specificity/utility of those assays. Most attendees are selective about which samples are tested with potency assays, for some only the first and last timepoints are tested. Others feel 3 samples is the minimum to show a potency trend. Some attendees execute qualified/validated assay’s in a development lab, while others test FD samples in the GMP QC lab. All agree that QC testing of FD samples can be a very important part of method transfer, and some attendees have received regulatory feedback that stress samples should be tested in both sending and receiving labs as part of stability method transfers.

Question 3: For ongoing process development, changes in formulation, and other related manufacturing changes, can forced degradation studies be leveraged to lessen the length of long term stability data generation required for submission?
This question received minimal discussion. There was a clear consensus that FD data is not a substitute for long-term stability data.

Question 4: In context of regulatory compliance, what documentation and reporting requirements should be considered when designing and submitting forced degredation studies and what can be negotiated with health authorities?

FD studies conducted during preclinical and clinical development are non-GMP, but should be documented properly so that information can be relied on in regulatory submissions. For early phase studies being used for molecule engineering or candidate selection many attendees rely on a predesigned study format which is applied, and results are documented in a report (no study protocol). For later stage studies with a molecule specific approach most attendees issue a protocol and report. For FD studies conducted after BLA and used for comparability full GMP is generally applied.