A Regulatory Perspective on Forced Degradation Studies

Ruth Cordoba-Rodriguez, Ph.D.
Division of Monoclonal Antibodies
Office of Biotechnology Products
FDA/CDER/OPS

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Presentation Overview

• Guidance
• When to perform Forced Degradation Studies (FDS):
  - drug stage of development
• What should be forced degraded?
  - DS, DP, final packaged DP, final formulation?
• What type of FDS should be used?
  - e.g., oxidation, pH, temperature, light
• When to submit data
• Where to submit data
• Conclusions
Guidance on forced degradation studies for biotechnology products

Little guidance on strategies and principles

ICH Q1A: Stability Testing of New DS and Products

- Stress Testing (2.1.2) Stress testing of the DS can help identify the likely degradation products, which can in turn help establish the degradation pathways and the intrinsic stability of the molecule and validate the stability indicating power of the analytical procedures used. The nature of the stress testing will depend on the individual drug substance and the type of drug product involved.

- Stress testing is likely to be carried out on a single batch of the DS. It should include the effects of temperature, humidity, oxidation and photolysis on the DS…susceptibility of hydrolysis across a wide range of pH…Photostability testing should be an integral part of stability testing.

- However, it may not be necessary to examine specifically for certain degradation products if it has been demonstrated that they are not formed under accelerated or long-term storage conditions.
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Additional guidance is provided in ICH Q1b:

ICH Q1b: Photostability Testing of new DS and products

- For drug substances photostability testing should consist of two parts: forced degradation testing (FDT) and confirmatory testing. To (FDT) evaluate the overall photosensitivity of the material for method development purposes and/or degradation pathway elucidation.

- A systematic approach to photostability testing is recommended covering, as appropriate, studies such as tests on the exposed drug product outside of the immediate pack, in the immediate pack, and if necessary, in the marketing pack.
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Additional guidance is provided in ICH Q2 (R1):

ICH Q2 (R1): Validation of Analytical Procedures: Methodology

- For determination of assay specificity, degradation products can be used during method validation.
- The quantitation limit is a parameter of quantitative assays for low levels of compounds in sample matrices, and is used particularly for the determination of impurities and/or degradation products.
- …specificity may be demonstrated by comparing the test results of samples containing impurities or degradation products to a second well-characterized procedure. As appropriate, this should include samples stored under relevant stress conditions: light, heat, humidity, acid/base hydrolysis and oxidation.
When to perform Forced Degradation Studies

**During Pre-IND**
- During formulation Studies: stability indicating quality attributes, degradation routes
- For pre-clinical studies: degradants, identification of toxic components (e.g., Antibody-Drug Conjugates).

**During clinical development**
- Comparing pre-clinical to clinical quality
- Comparing pre- to post- manufacturing changes
- In-use stability (e.g., central i.v. bag distribution)

**Post-marketing** - normally studies not performed but,
- Identified new stresses (e.g. new pump design)
- Manufacturing changes (e.g., vial to PFS)
- Additional indications (Different in use stability conditions)
What should be Forced Degraded?

Drug Substance – rates and modes

Drug Product – deviations on intended storage conditions

Final Drug Product

In final package
Final formulation
Reconstituted material
IV bag material

Is a single forced degradation study representative of the stresses of Intermediates and final drug product all the way thru administration?
What type of Forced Degradation Study should be performed?

- Thermal
- Humidity-Dehydration
- Acid-Base Hydrolysis
- Oxidation
- Photolysis
- Freeze-Thaw
- Shear (e.g., shaking, pump filling)

Does the list represent the minimal set of stresses indicated for biotechnology products?

Type of Forced degradation study should be focused on the quality of the QTPP
FDS should be driven by the stability profile of the product

**Chemical stability**
- Hydrolysis
- Deamidation
- Isomerization
- Oxidation
- Disulfide exchange
- Beta elimination

**Physical stability**
- Conformational stability (1°, 2°, 3° structures)
- Denaturation
- Absorption
- Aggregation
- Self-association
FDS should be driven by the stresses experienced by the product through lifecycle

• During manufacture
• During storage
• During shipping
• In-use stability
How to perform Forced Degradation Studies

*It depends on how much degradation levels will be allowed 10%-20%? When to stop?*

**What does that mean?**

Generally forced-degradation studies tie degradation pathways with analytical method validation (ICH Q1a)

When considering the comparability of products, the manufacturer should evaluate, for example the need for stability data, including those generated from accelerated or stress conditions, to provide insight into potential product differences in the degradation pathways of the product….. (ICH Q5E)

*What about inter-dependence among quality attributes?*
After change, alteration in the pathway and rate of degradation were observed in the accelerated and stressed studies. Real-time data (6 months) did not show a pronounced change in rate or pathway, however by 9 months potency was decreased and was predicted to fail by 12 months. Sponsor withdrew change from IND.
Use of Arrhenius Modeling to predict ‘shelf-life’/product stability

- It is unclear that Arrhenius modeling is appropriate to apply to the stability of complex protein products.

- Pathways of degradation may not have linear rates and may interact/impact one another (e.g., protein aggregation).

- For comparability, there isn’t a presumption of comparability to begin with, data need to be provided that demonstrate comparability so the actual rates and pathways of degradation need to determined. Extent of data needed is dependent on phase of development/extent of change.
Excipients should also be evaluated for degradation

polysorbate 80 can exhibit peroxide formation over time which can lead to protein degradation through oxidation. Please describe how you plan to control for this possibility. You may wish to include an assay capable of measuring peroxide formation into the lot release and stability testing of the IV Bag Diluent used during XXXX administration.

We note that the formulation includes histidine and polysorbate 80. Polysorbate 80 may contain impurities that interact with histidine resulting in a yellow coloration of drug product. This yellow coloration may cause product lots to fail the visual inspection assay. We recommend that (1) you establish raw material acceptance criteria and appropriate storage conditions and shelf-life for the polysorbate 80 to control oxidant formation and (2) you determine if product quality is impacted should yellow coloration occur. Provide comment.
When to Submit Forced Degradation Studies Data

As per ICH guidance, data from forced degradation studies are expected by license application. But……

Data from forced degradation studies may be critical to help assessing comparability during IND.
Submitted Forced Degradation Studies Data

- **Pre-IND**
  - Rarely
  - Comparable pre-clinical and clinical degradation

- **Early IND Phase**
  - Not common

- **Late IND Phase**
  - Common
  - Comparability pre- and post-change
  - Degradation routes
  - Method validation

- **Post-Marketing**
  - Less common
  - Comparability pre- and post-change
  - Degradation routes
  - Method validation

*FDS data during IND may help support comparability evaluations when stability data are limited or stability data analyses are inconclusive*
Where to submit Forced Degradation Study Data?

- 3.2.S.7 Drug Substance Stability
- 3.2.P.8 Drug Product Stability
- 3.2.S.2.6 DS Manufacturing Process Development
- 3.2.S.3 Characterization
- 3.2.S.4.3 Validation of analytical procedures
- 3.2.P.2 Pharmaceutical Development

Information should be provided in a manner that is easily retrievable if it applies to multiple sections (e.g., hyperlinks) and, rationale should be clearly understood.
Conclusions

- Forced degradation studies cover an undefined set of evaluations of the API and intermediates when subjected to a variety of stresses. The use of a science-based and risk-based approach is critical to determine the design of the forced degradation study.

- The use of a panel of methodologies to address the quality and stability profile of a product should be comprehensive but guided by sound rationale.

- Current biotechnology products development are more aggressive in timelines which lead to limited stability data being presented to the Agency. Well designed FDS can help support a given claim of stability profile of the product.
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Division of Monoclonal Antibodies

Patrick Swann, DMA DDD
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