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An industry perspective on the use of forced degradation studies to assess comparability of biopharmaceuticals.

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“An industry perspective on the use of forced degradation studies to assess comparability of biopharmaceuticals.”

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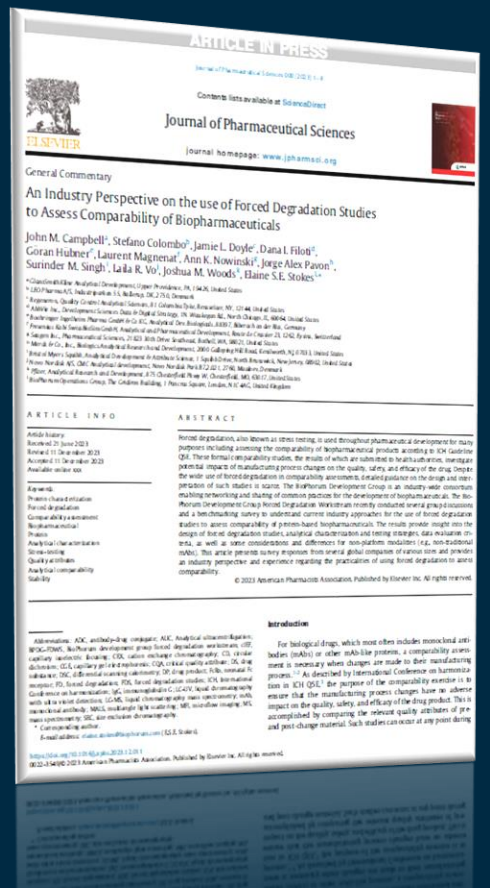

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BioPhorum: a co-ordinated program of industry change

BioPhorum creates an environment where the global biopharmaceutical and device industry can collaborate and accelerate their rate of progress, for the benefit of all. We do this by:

Bringing leaders together to create future visions that focus the industry's energy on the key emerging opportunities

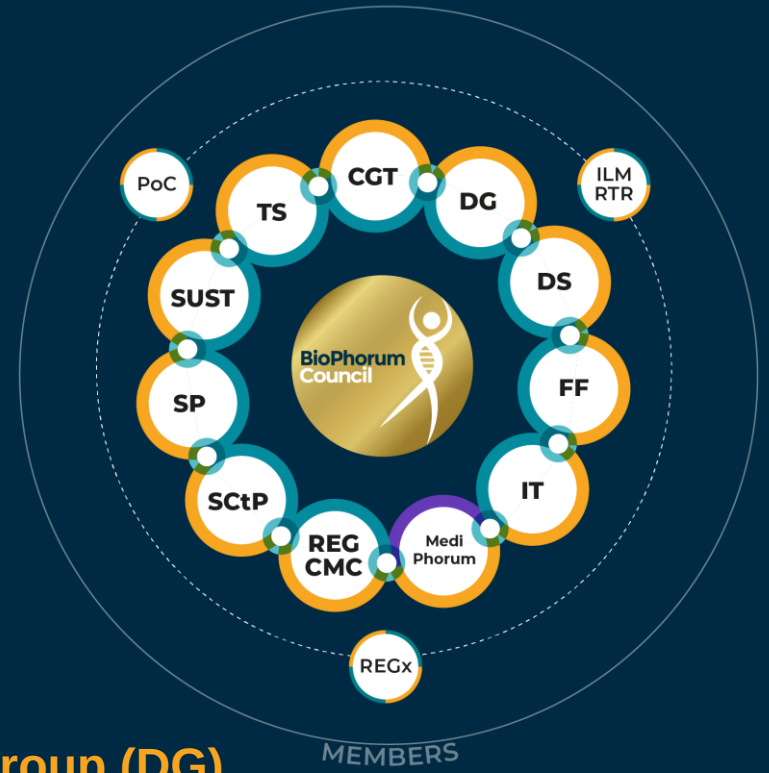
Mobilizing communities of the top experts around these opportunities, up and down the biopharma value chain

Creating partnerships that enable change and provide the quickest route to implementation and results

Replacing isolation with collaboration so that the industry shares, learns and builds the best solutions together

…making the journey better, faster and cheaper than it would be for individual companies to do it on their own.

There are currently 10 Phorums providing a wealth of opportunities for companies to align their interests with similarly committed organizations.



Development Group (DG)

37
member companies

14
Collaborative workstreams

+900
Active participants

50+
External publications and presentations

Forced Degradation workstream began in 2015

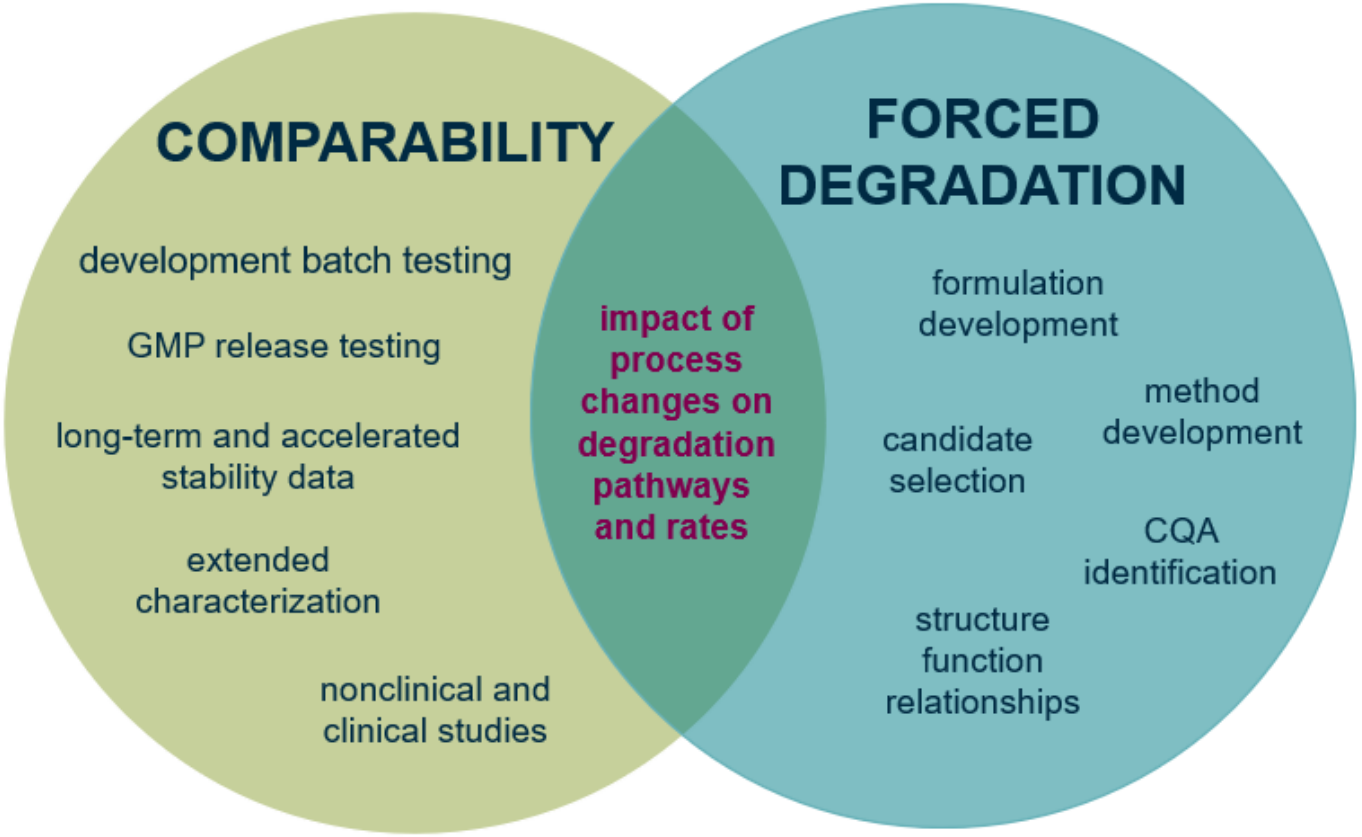
Presentation summary

- Introduction
- Factors that influence use of Forced Degradation Studies (FDS)
- FDS Design
  - Stress conditions
  - Stress duration and sampling
  - Selection of batches
- Analytical characterization and testing
  - Overall drivers for analytical characterization strategy
  - Analytical characterization used for forced degradation testing
- Evaluation criteria
- Challenges with non-platform biologic modalities
- Discussion / Conclusions

Introduction

Forced degradation studies may be included in comparability assessments

Comparability assessments are necessary when changes are made to the biological drug manufacturing process to ensure there is no adverse impact on the quality, safety, and efficacy of the drug product



Forced degradation studies (FDS) apply stress conditions to drug substance or drug product which may exceed those used for stability studies performed according to ICH Q5C*

* ICH Expert Working Group. Quality of biotechnological: stability testing of biotechnological/biological products Q5c. ICH Harmonized Tripartite Guideline. 1995

Details regarding the design and interpretation of forced degradation studies within the context of comparability are limited

- ICH Q5E* explicitly avoids the prescription of a particular comparability strategy
  - Recommends that “to identify the impact of a manufacturing process change, a careful evaluation of all foreseeable consequences for the product should be performed” to inform the extent of the comparability study
  - Many companies conduct risk assessments which help guide comparability strategy and scope

- The use of forced degradation studies are cited in ICHQ5E: “Accelerated and ***stress stability studies*** are often useful tools to establish degradation profiles and provide a further direct comparison of pre-change and post-change product.”

* ICH Expert Working Group. Comparability of biotechnological/biological products subject to changes in their manufacturing process Q5e. ICH Harmonized Tripartite Guideline. 2004.

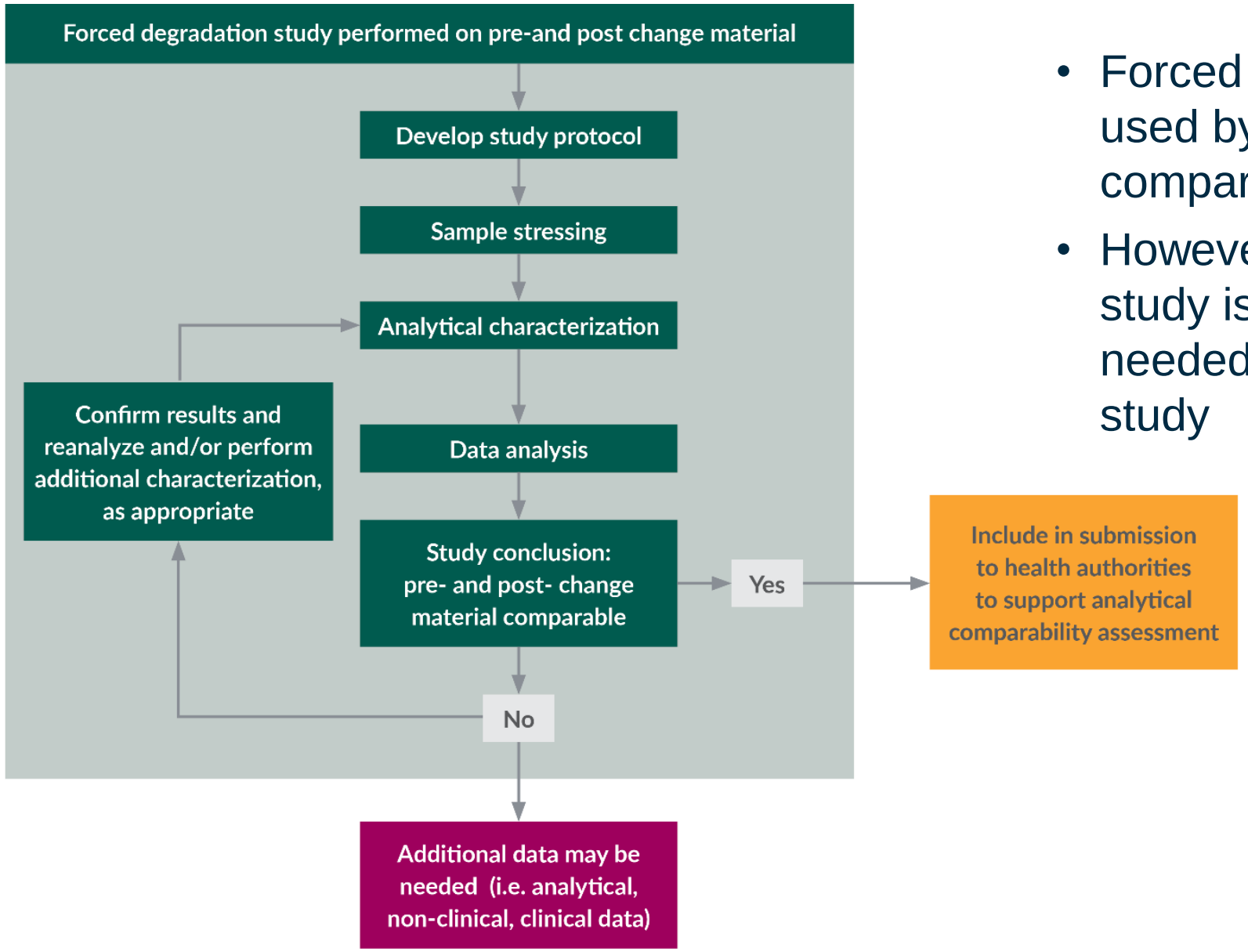
A representative summary of overall industry practices

- BioPhorum Development Group Forced Degradation Workstream (BPDG-FDWS) conducted a benchmarking survey in 2022 on the use of forced degradation studies in comparability assessments
- This presentation is a composite view of opinions shared by the whole of the BioPhorum Forced Degradation workstream and should not be attributed to the individual positions of the participating companies.
- Each survey question received responses from at least 14 global pharmaceutical companies of various sizes with diverse product portfolios and a wide range of business models. All participating companies were members of the BPDG-FDWS, and each company was limited to a single response for each question.

Survey focused on

- Factors that influence the decision to use forced degradation for comparability
- Forced degradation study designs
- Analytical characterization and testing strategies
- Data evaluation criteria
- Application of forced degradation for non-mAb modalities

Process flow for the use of forced degradation studies in comparability assessments



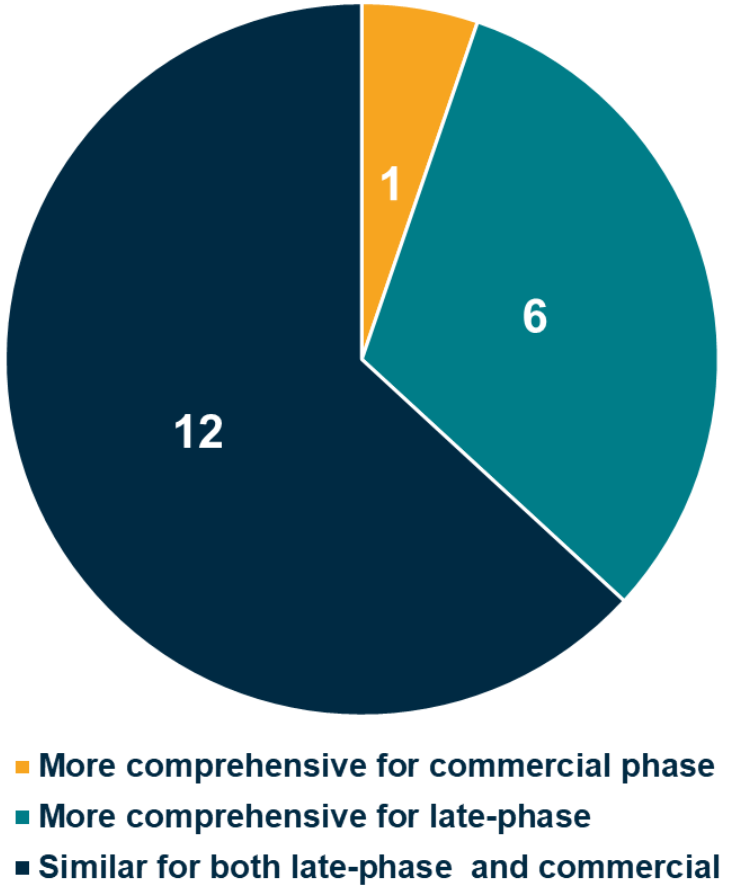
- Forced degradation studies are used by all companies to support comparability
- However, a forced degradation study is not always appropriate or needed for every comparability study

Factors that influence use of FDS

Considerations for using FDS to support comparability

- Extent of process changes
  - Majority of companies use risk-based assessments
  - Ranking of risk determines if FDS is needed
- Process step where changes occur
  - Product may require FDS on drug product when changes are made to drug substance
- Amount of product knowledge
  - Typically, there is less data accumulated for early-phase projects
  - More product understanding for commercial programs requiring more comprehensive comparability

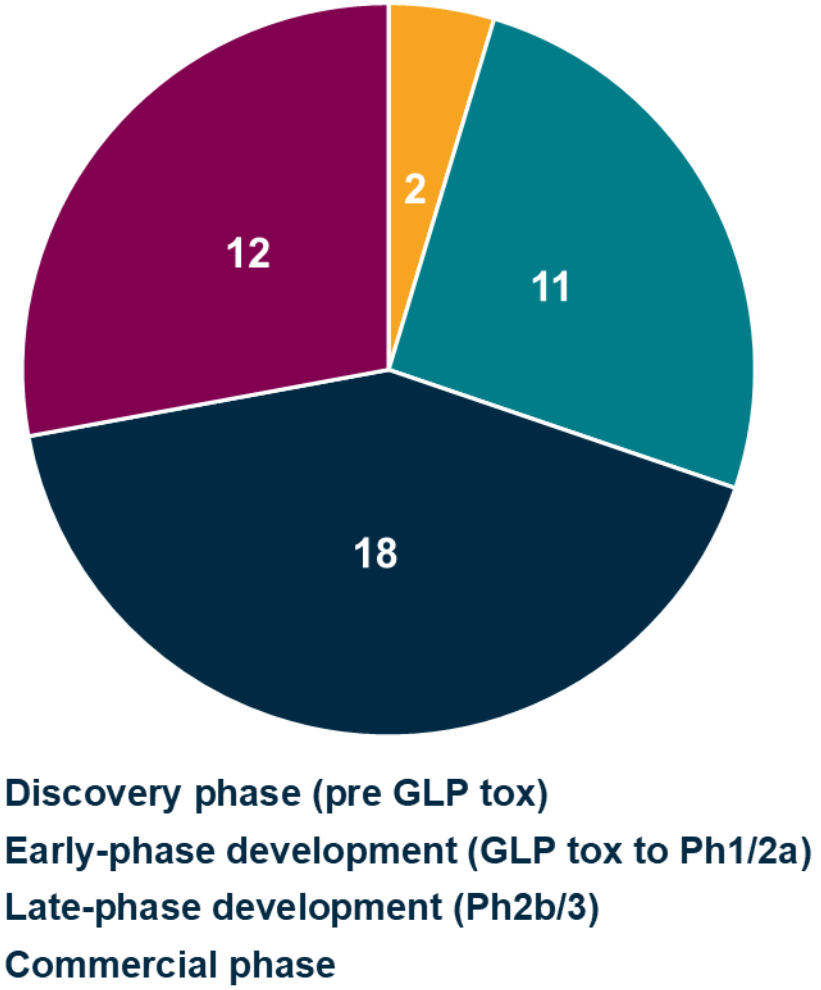
How comprehensive are your FDS studies used for comparability assessments in late stage compared to commercial phase? (19 respondents)



When are companies using FDS to support comparability

- All companies are using FDS during late-phase comparability
- Less need observed for earlier stage programs as there is less opportunity for process development
- Early-stage comparability assessed on a case-by-case basis
- Process changes are common in later phases and often require FDS to support comparability

Which phases of development has your company applied FDS in formal comparability studies? (20 respondents)



Forced degradation study design

Forced degradation study design

FDS Study Assigned

- Need for FDS determined based off risk assessment or other factors

Assess Impact to CQAs

- What changes may be expected?
- What conditions may prompt that change?

Review Prior Knowledge

- Is there data that can be leveraged to remove or modify a condition?
- Are there any apparent gaps or data that needs robustness?

Stress Conditions Establish Strategy

- What conditions will be most appropriate to induce the stress targeted?

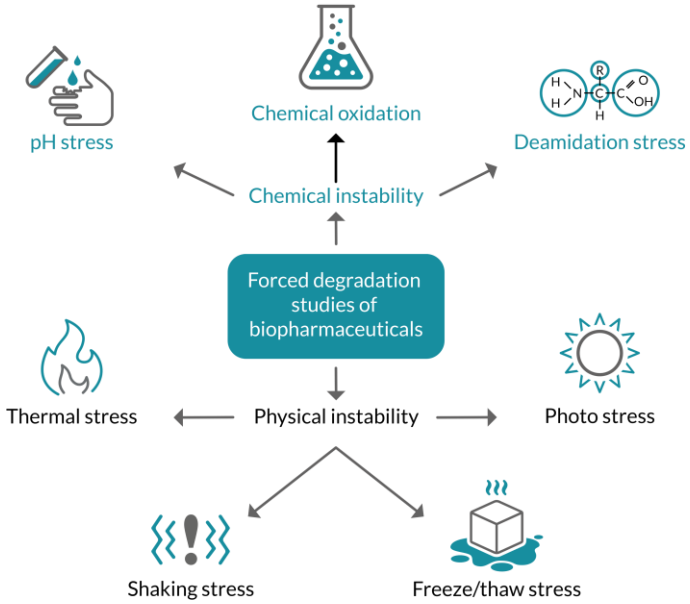
Time points Batches Phase

- How long should the study be performed to optimize comparability?
- How many batches are available?
- What phase is the material in?

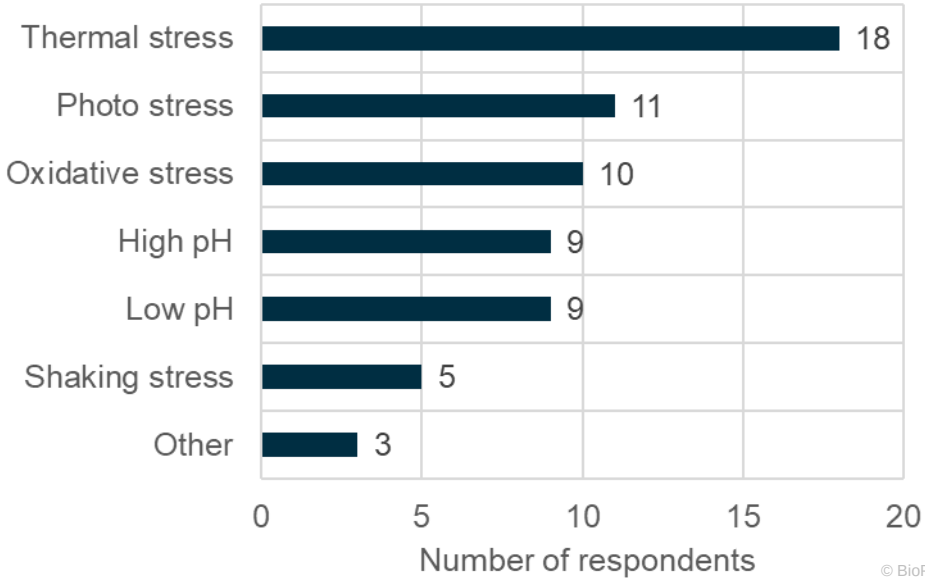
Stress conditions

- Common considerations when selecting FDS stress conditions for DS or DP studies:
  - Most common condition: temperature stress (*J Pharm Sci*. 2020; 109(1):6-21).
    - Temperatures between 40°C and 55°C mostly used to induce degradation

- Temperature stress alone may not be sufficient to induce changes to all targeted CQAs and may not provide a complete model of degradation
  - Depending on the molecule, additional stress conditions are considered such as: light exposure, pH stress, oxidative stress, shaking stress



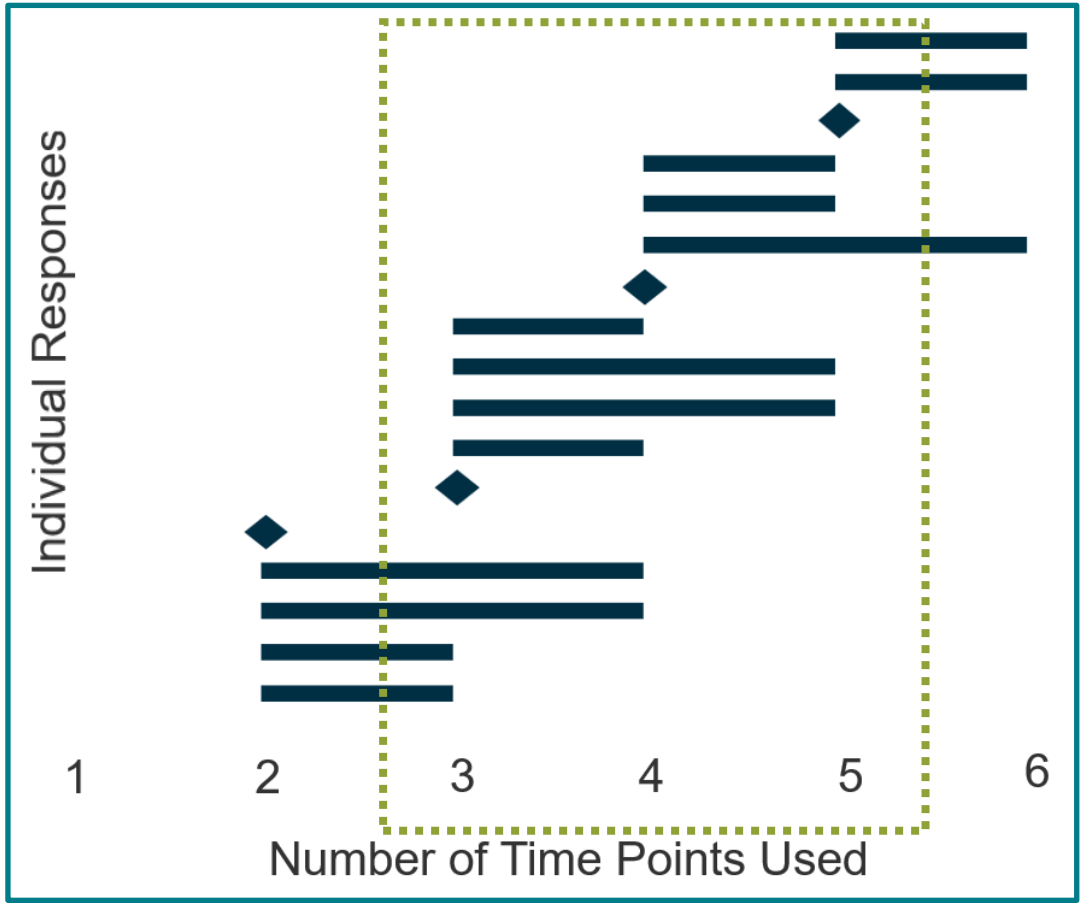
For a typical forced degradation formal comparability study, what forced degradation conditions are utilized? (18 respondents)



Survey results for stress duration and sampling

- Stress duration varies with choice of stress
  - Most common stress (thermal) duration is typically ≤1 month
  - Other stresses (e.g., pH, photo and oxidative stress) duration is typically shorter ≤ 1 week
- Number of timepoints also varies with choice of stress
  - Majority of respondents favor use of between 3 to 5 time points

How many time points do you include in your study? (17 respondents)



Selection of batches

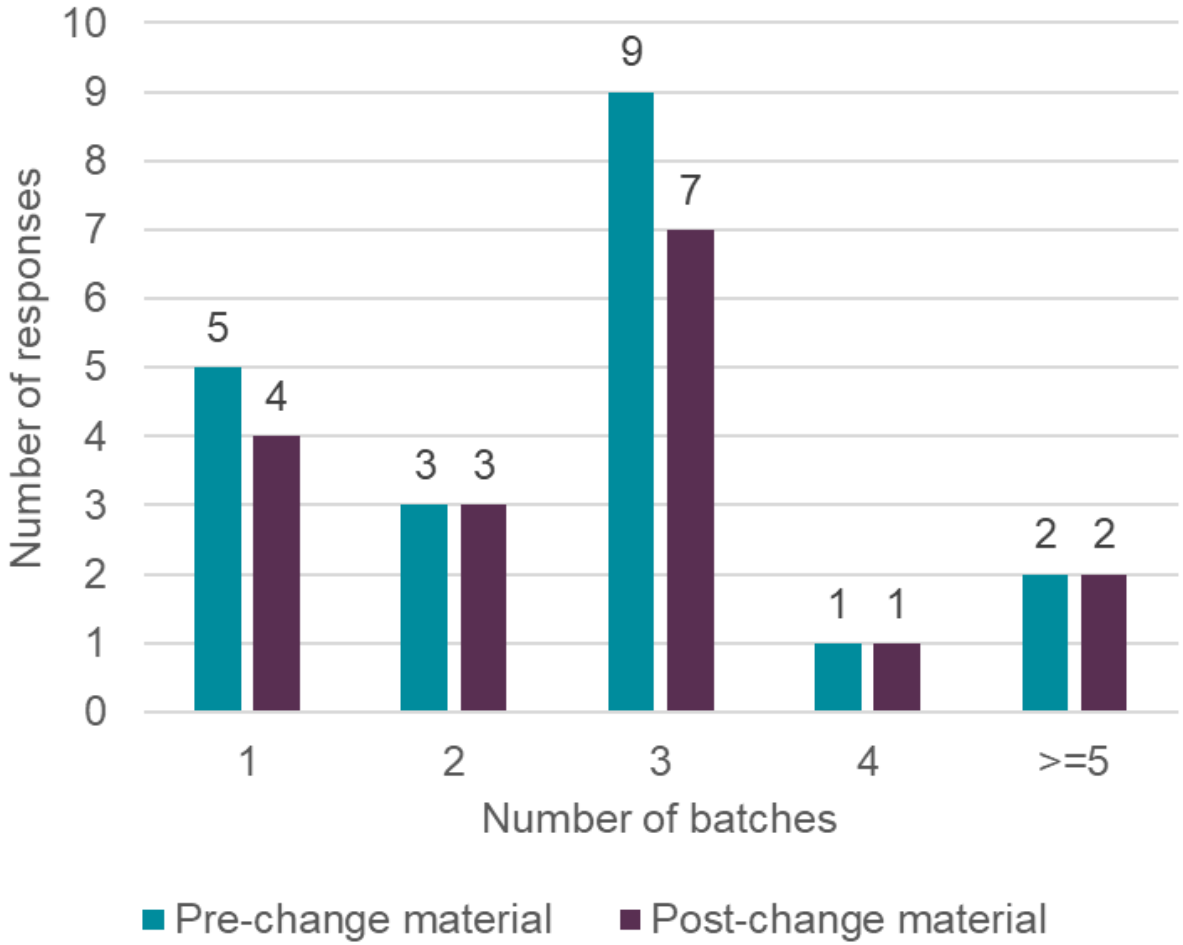
Comparability must be established between the pre- and post- change material

- 3 batches are most common but not always achievable

Selection of batches is often impacted by:

1. Material availability
2. Phase of development

In a forced degradation study intended to support manufacturing process comparability, how many batches of pre- and post-change material would typically be used in the forced degradation study? Check all that apply (14 respondents)



Analytical characterization and testing

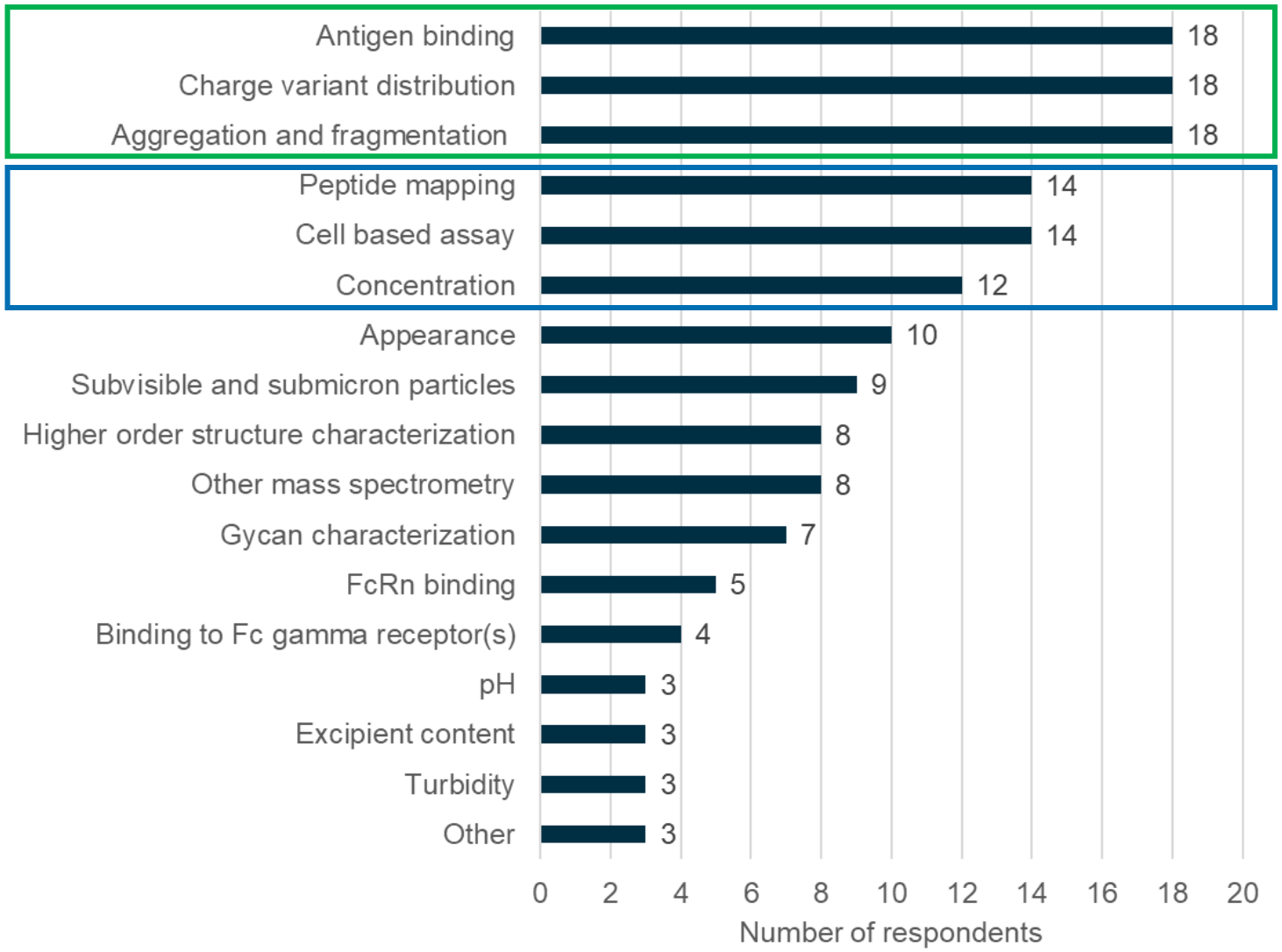
Overall drivers for analytical characterization strategy

- The degradation pathways drive the selection of assays included in the analytical characterization strategy for use of FDS in comparability studies

- Other factors that may influence the analytical characterization strategy mentioned by respondents to the survey include:
  - The stage of the project
  - The nature of the process change
  - Whether it impacts DS or DP
  - The results of a CQA risk assessment on the potential impact of the change on product quality, safety and efficacy

- Other considerations
  - Analytical variability
  - Testing efficiency

Analytical characterization used for forced degradation testing



For a typical forced degradation formal comparability study, what analytical characterization is used to evaluate samples? (18 respondents)

These attributes were also frequently included

Depending on factors influencing the analytical characterization strategy other attributes may be applied

Evaluation criteria

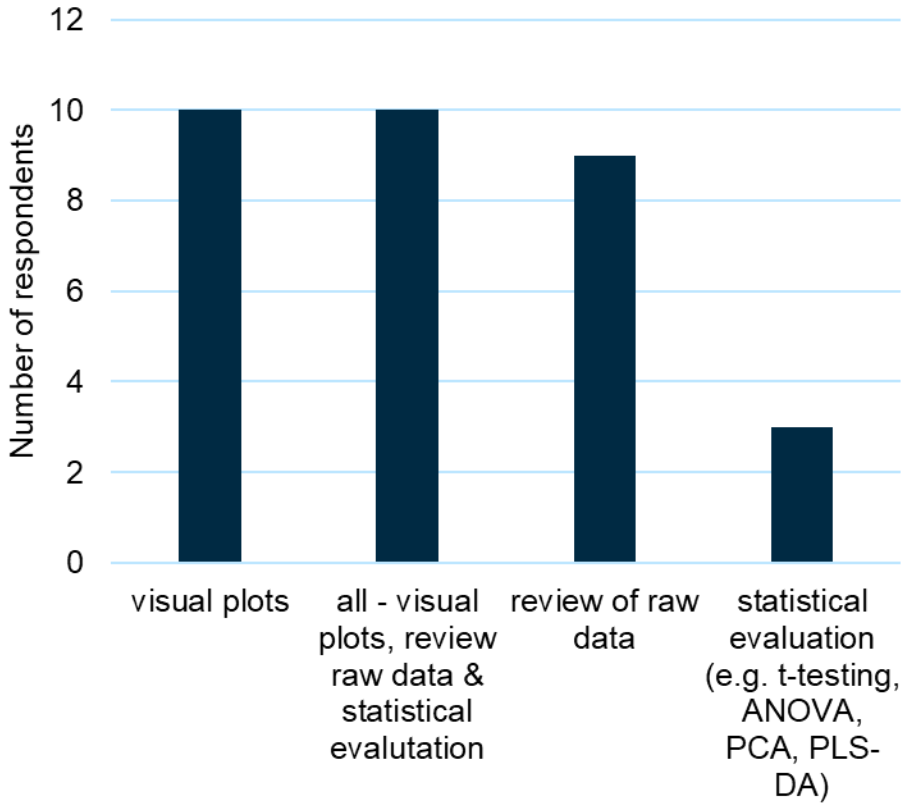
Evaluation of results

- ICH Q5E states*:

  "Generally, quality data on the pre- and post-change product are generated, and a comparison is performed… The comparison of the results to the **predefined criteria** should allow an objective assessment of whether or not the pre- and post-change product are comparable."

- The vast majority of survey respondents did not pre-define any quantitative pass/fail acceptance criteria to forced degradation comparability results
- Most survey respondents pre-define **"evaluation criteria"**, which includes a comparison of degradation pathways and degradation rates

How are forced degradation formal comparability studies evaluated? (18 survey respondents)



* ICH Expert Working Group. Comparability of biotechnological/biological products subject to changes in their manufacturing process Q5e. ICH Harmonized Tripartite Guideline. 2004.

Evaluation and reporting of results

- A statistical evaluation of analytical data sets can be a tool to establish similarity, however many comparability studies will not allow for this type of assessment due to the limited quantity of data
  - When data sets allow, **t-testing** is one common strategy as reported by respondents

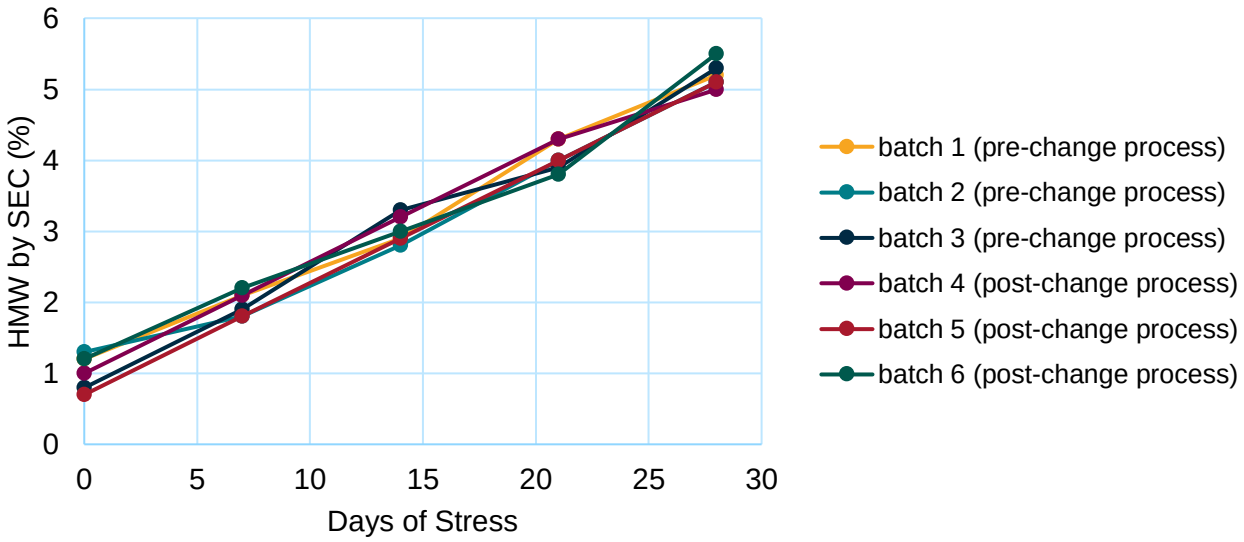
$$t = \frac{\bar{x}_1 - \bar{x}_2}{\sqrt{(s^2(\frac{1}{n_1} + \frac{1}{n_2}))}}$$

- When a numerical, statistical evaluation cannot be completed, as is often the case, general approaches include:
  - Rate comparison (alternative numerical approach)
  - Visual comparisons or plots
  - Combination of alternative qualitative and quantitative assessments

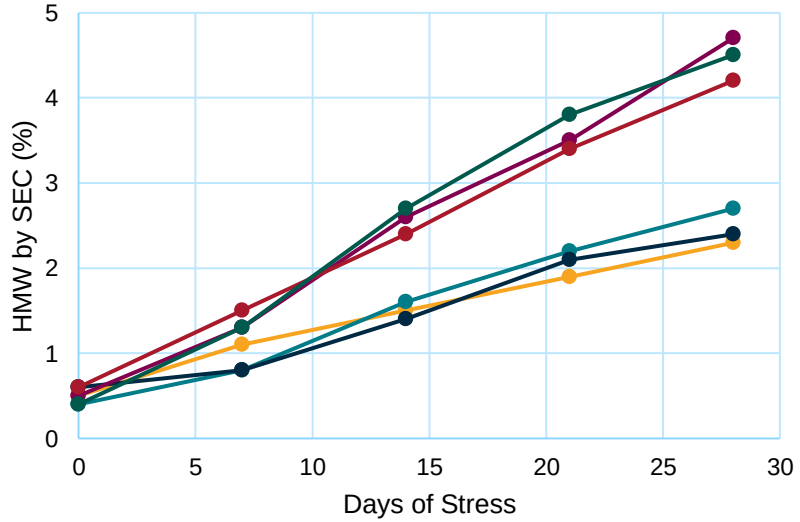
Example of visual plots and possible conclusions

- Hypothetical SEC data is shown in the visual plots below
- Results shown in **plot 1** would be considered supportive of comparability
  - When the results do not reveal any meaningful differences between the pre- and post-change material, the study may be considered supportive of comparability
- Results shown in **plot 2** reveal differences between the pre- and post-change material and may not be supportive of comparability.
  - An additional evaluation should be performed to understand the differences, determine whether the differences can be justified, and assess their potential impact on comparability.

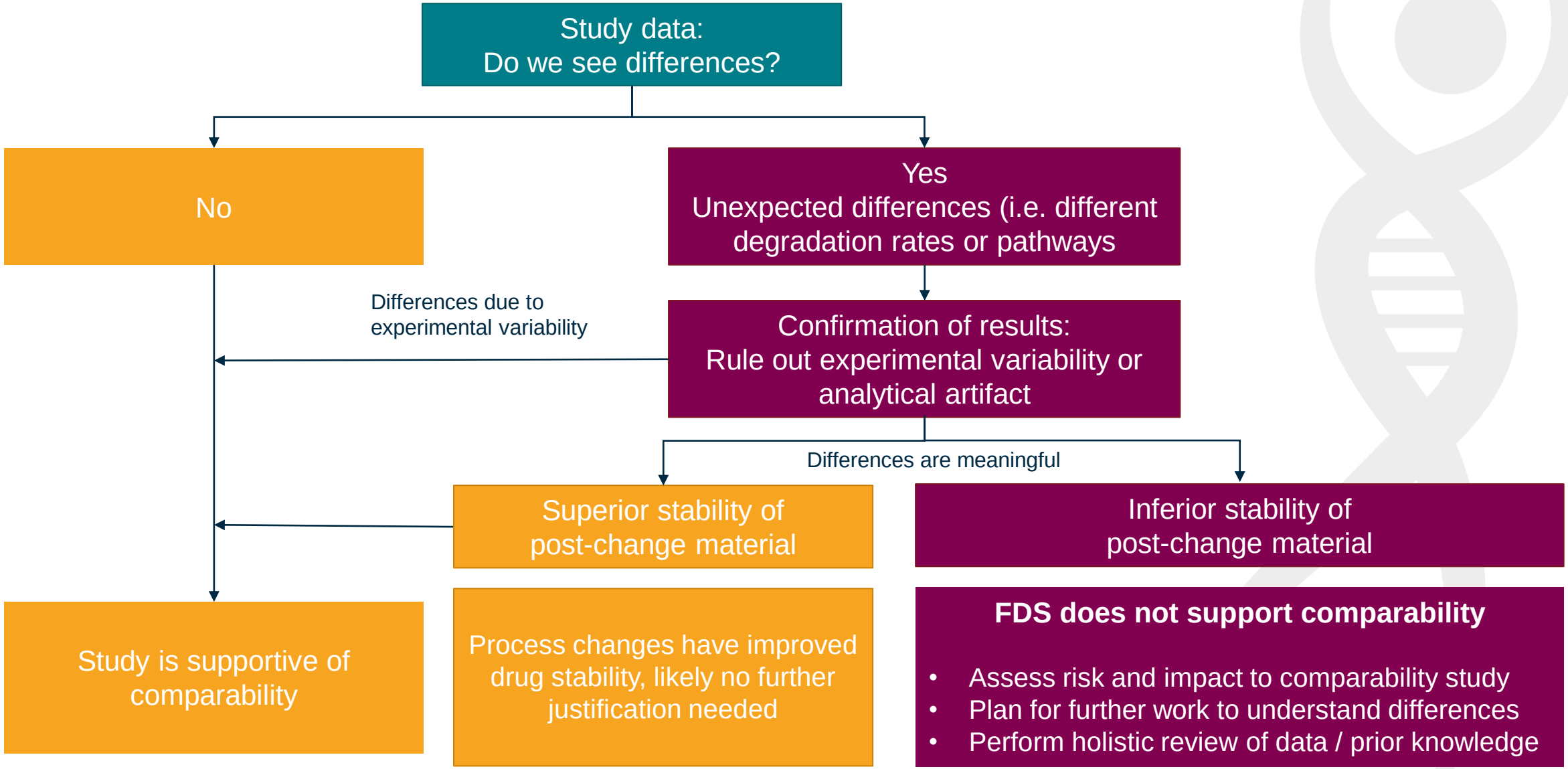
Plot 1



Plot 2



Possible conclusions (when differences are observed in FDS)



Overall comparability conclusions when differences are observed in FDS

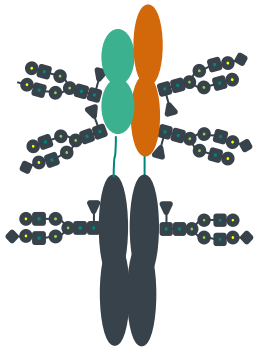
- When determining comparability, the results of forced degradation should be taken in context with results of other components of the comparability study (such as GMP release testing and extended characterization)

- **Remember (from Q5E*):**
  - **"Comparable" doesn't mean identical, but "highly similar"**
  - **Differences may be acceptable if it can be ensured there is no adverse impact to safety or efficacy**

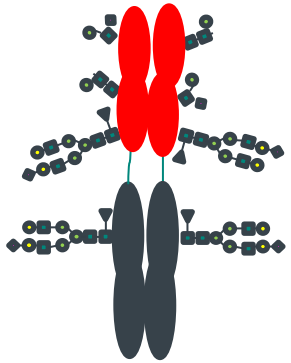
* ICH Expert Working Group. Comparability of biotechnological/biological products subject to changes in their manufacturing process Q5e. ICH Harmonized Tripartite Guideline. 2004.

Challenges with non-platform biologic modalities

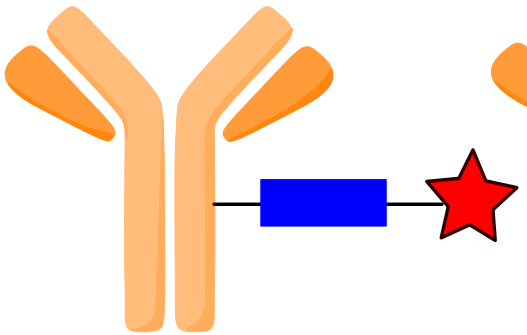
Challenges with non-platform biologic modalities



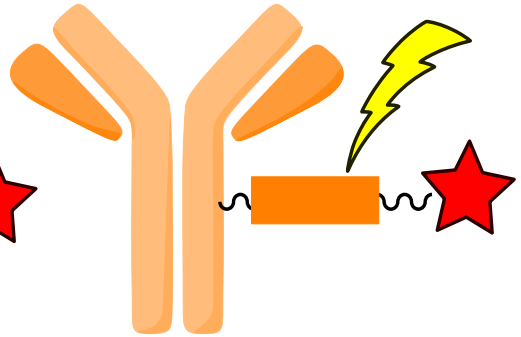
N-glycosylated heterodimer fusion protein



O- and N-glycosylated homodimer fusion protein



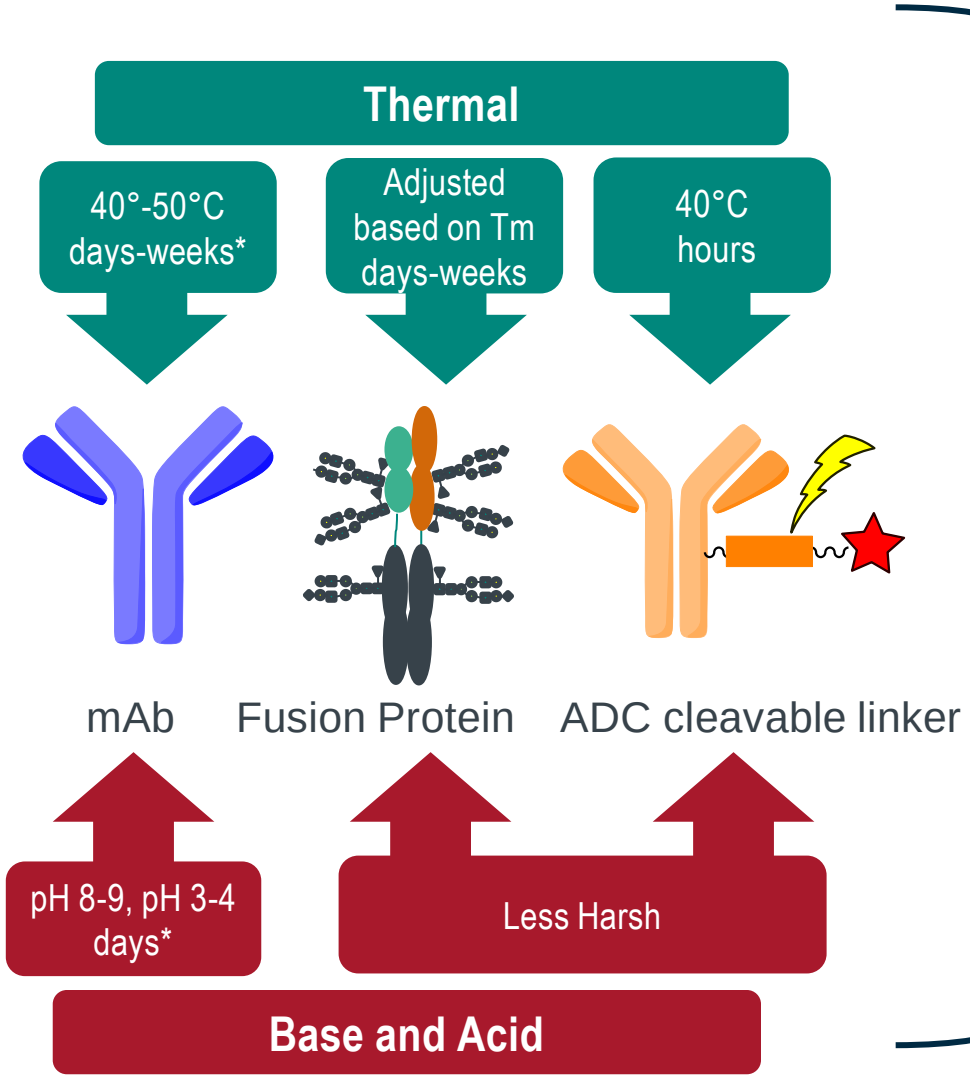
ADC with non-cleavable linker



ADC with cleavable linker

- Platform biologics typically refer to mAbs (IgG1, IgG2 and IgG4).
- Examples of Non-platform biologics
- General principles are broadly applicable to most biologics with modality specific FD modifications and complex analytics (e.g., testing for free drug content, DAR and complex charge variants analysis for fusion proteins)

Challenges with non-platform biologic modalities



- Scouting studies are typically executed to identify suitable stress conditions
- Examples of modifications to stress conditions
- In general survey respondents acknowledged that the lack of prior knowledge poses a challenge for non-platform biologics

*An Industry Perspective on Forced Degradation Studies of Biopharmaceuticals: Survey Outcome and Recommendations. *J Pharm Sci*. 2020; 109(1):6-21.

Conclusions

- Forced Degradation Studies (FDS) are utilized by all companies that responded to the survey as a component of comparability studies.
    - Most companies utilize FDS when major changes are made to the manufacturing process
    - Most companies utilize FDS in later phases of development
- The industry survey results are intended to assist pharmaceutical companies and regulatory authorities in designing and interpreting forced degradation comparability studies
- FDS for non-platform biologics remains a challenging process due to the diversity of molecules coupled with the lack of industry experience and guidelines on best practices

Acknowledgments

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Answers to questions at this meeting represent personal views and are not necessarily the views of other authors and their institutions listed on the presentation

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Q&A Session Disclaimer

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