Providing the Right Data at the Right Time: Stability Strategies to Support Analytical Comparability

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AMGEN PRODUCT QUALITY
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PRESENTATION OUTLINE

- Analytical Comparability Overview
- Key factors in analytical comparability stability studies
  - Method selection
  - Study conditions
  - Comparison to pre-change
  - Assessment criteria
  - Drug product data to support a drug substance change
- Conclusions

ANALYTICAL COMPARABILITY CORE CONCEPTS

- Manufacturers make process changes throughout the product lifecycle in order to ensure continued quality, compliance, and supply
- Common changes include site transfer, scale-up, manufacturing process change, primary container, new drug product presentation
- Demonstration of product comparability supports the extension of safety and efficacy data generated with the pre-change product to the post-change product
- **ICH Q5E**: The goal of the comparability exercise is to ensure the quality, safety, and efficacy of the drug product following manufacturing process changes
  - Pre-change and post-change product must be highly similar
  - Must address whether any differences in quality attributes will have an adverse impact on safety and efficacy
  - Nonclinical and/or clinical studies may be necessary if impact of differences cannot be explained through existing knowledge

ANALYTICAL COMPARABILITY COMPONENTS

- Analytical comparability studies generally include some combination of the following, as determined by the nature of the changes and the associated risk:
  - Batch analysis (typically lot release testing, but may include in-process control testing)
  - Characterization testing (biochemical, biophysical, biological methods not routinely used)
  - **Degradation Studies (i.e., Stability)**
    - **Accelerated storage condition (ASC)**
    - **Stressed storage condition (SSC)**
    - **Forced degradation (FD)**
      - Not discussed in ICH Q5E but often used across industry to assess product stability differences in comparability studies
- Real time/real temperature (i.e., recommended storage condition (RSC)) studies must be initiated per ICH Q5C and Q1A(R2)

METHOD SELECTION: WHAT ARE THE KEY ATTRIBUTES?

- The methods to be included in the degradation component of the analytical comparability evaluation should be informed by:
  - The nature of the proposed change(s) and the impacted unit operations
  - Stability-indicating CQAs that are potentially impacted by the change
- The methods should be capable of detecting meaningful change in the CQAs over the intended study duration
- The purity methods or more specific characterization methods are often the most relevant for detecting differences that could impact product quality or patient safety
  - Other methods may be relevant depending on the change that the studies are intended to support
  - Bioassay is typically expected by regulators though bioassays are less capable of detecting small but significant changes in product quality
    - The study design can be adjusted for attributes that do not change at the study conditions, such as testing only the beginning and end time points

CASE STUDY 1: APPROPRIATE SELECTION OF METHODS FOR COMPARABILITY DEGRADATION STUDY

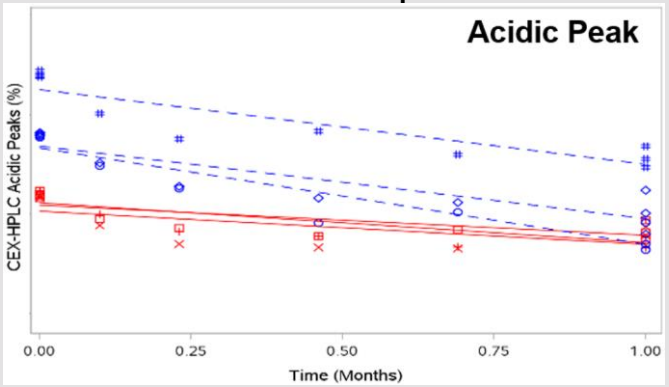
- Protein product
- Change: Major changes to the upstream and downstream drug substance process; same final formulation
- Differences in non-critical attributes were expected

Methods Included in Degradation Assessment to Support Drug Substance Process Changes

Analytical Method	Attribute	Critical Quality Attributes
SE-HPLC	High molecular weight species	Aggregation
CEX-HPLC	Charge variants	Deamidation, Methionine Oxidation
Reduced CE-SDS	Fragmentation	Fragments
Bioassay	Potency	Efficacy

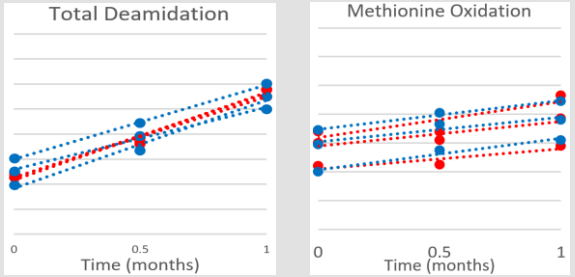
CASE STUDY 1: APPROPRIATE SELECTION OF METHODS FOR COMPARABILITY DEGRADATION STUDY

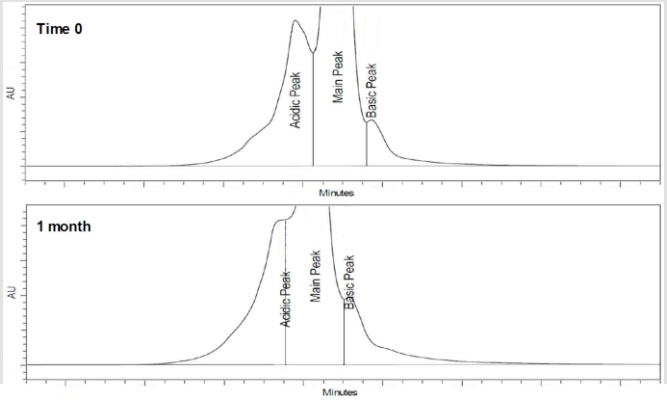
- Degradation study showed apparent difference in CEX acidic and main peak rates
  - Evaluation of specific attribute rates did not demonstrate a difference
  - Difference attributed to offset of initial acidic peak level and method performance at stressed condition



Loss of peak resolution at stressed condition resulting in increased variability

LC-MS results demonstrated comparable rates for critical and non-critical attributes





Pre-change Post-change

CASE STUDY 1: APPROPRIATE SELECTION OF METHODS FOR COMPARABILITY DEGRADATION STUDY

- Change: Drug substance site transfer with minimal process changes to achieve facility fit
- CEX excluded from degradation study based on prior experience at stressed condition
  - Peptide map characterization method included to evaluate CQAs monitored routinely by CEX

Methods Included in Degradation Assessment to Support Drug Substance Process Site Transfer

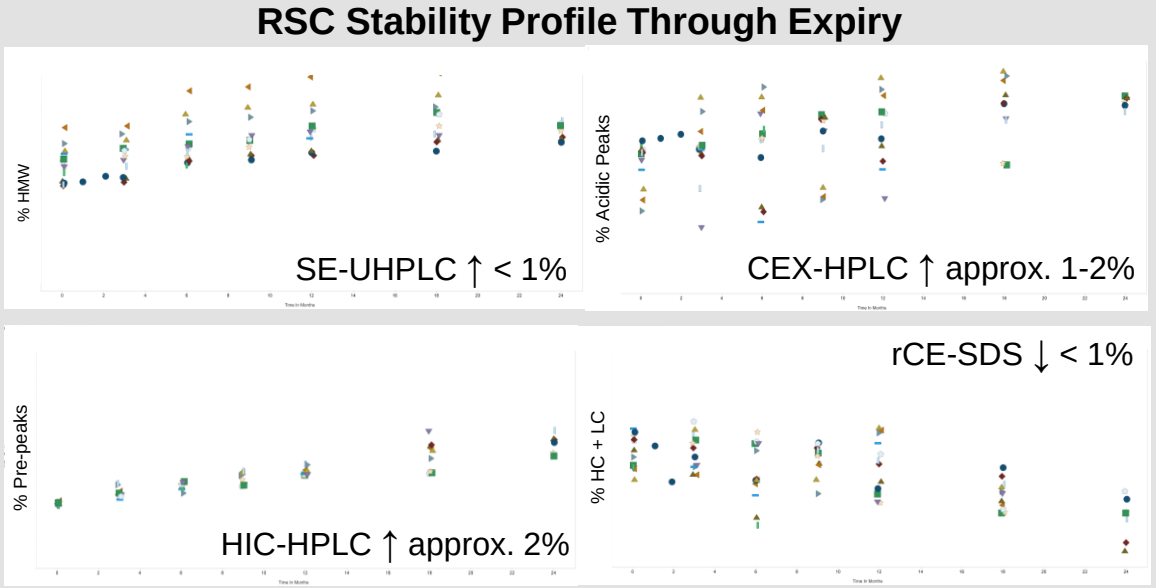
Analytical Method	Attribute	Critical Quality Attributes
SE-HPLC	High molecular weight species	Aggregation
Peptide Map	Deamidation, Oxidation	Deamidation, Methionine Oxidation
Reduced CE-SDS	Fragmentation	Fragments
Bioassay	Potency	Efficacy

DEGRADATION STUDY CONDITIONS: HOW MUCH CHANGE IS ENOUGH?

- Comparability degradation studies are intended to evaluate meaningful changes in product-specific degradation pathways and attribute degradation rates that are not readily detected at release or under short term storage at the RSC (e.g., 6 months)
  - Supports the application of pre-change expiry to post-change product
  - Often the rate limiting step in an analytical comparability study because the purpose is to evaluate change over time
- The degradation induced in the study should match or exceed the expected attribute change over the product shelf life, including any allowed room temperature storage
- Method performance must also be considered – need enough degradation to be outside the expected method variability
- Extensive degradation through overly harsh conditions may not be meaningful to the product – the study conditions should be relevant to the product whenever possible

CASE STUDY 2: IDENTIFYING THE STABILITY STUDY CONDITIONS NECESSARY TO ELICIT SUFFICIENT DEGRADATION

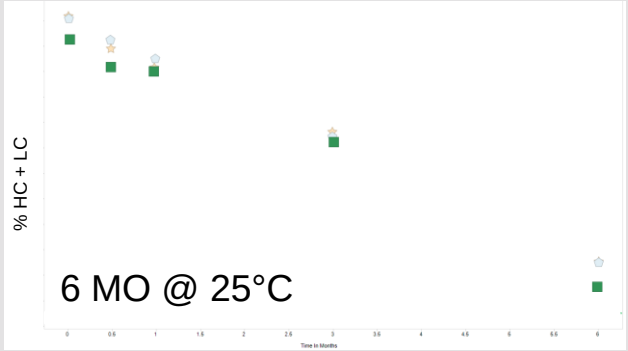
- Product: Protein sensitive to thermal stress
- Shelf-life: 24 months at 5°C
- Primary degradation pathways:
  - HMW by SE-UHPLC
  - Charge variants by CEX-HPLC
  - Asp isomerization by HIC-HPLC
  - Fragmentation by rCE-SDS

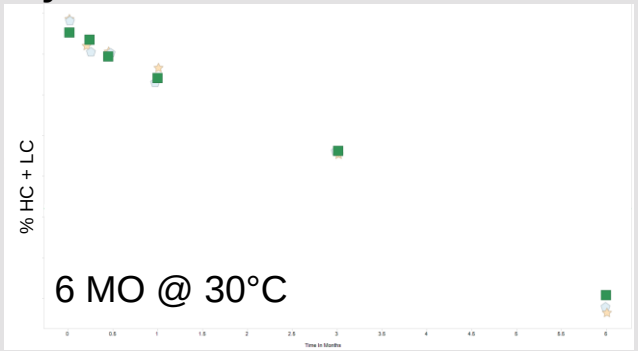


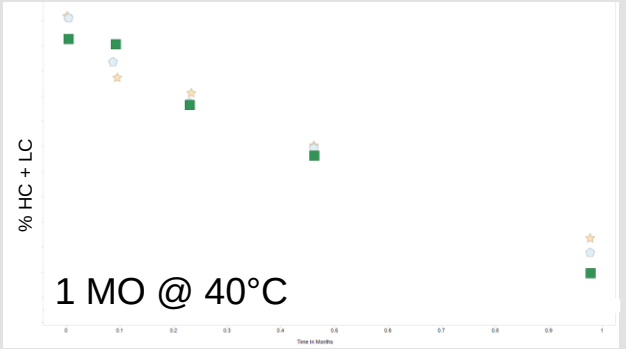
CASE STUDY 2: IDENTIFYING THE STABILITY STUDY CONDITIONS NECESSARY TO ELICIT SUFFICIENT DEGRADATION

- Target temperature and study duration identified using available stability data
- Product fragmentation by rCE-SDS exceeds expected shelf life degradation in 1 month at 40°C
- Other CQAs also exceed expected shelf life degradation under the same conditions
- Supports the use of a single stability condition as part of the comparability study

rCE-SDS Stability Profile at Accelerated and Stressed Conditions







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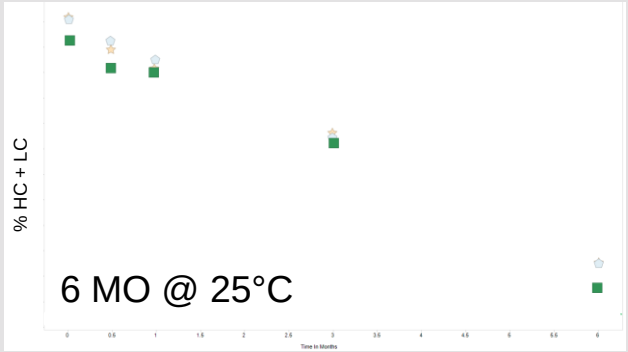
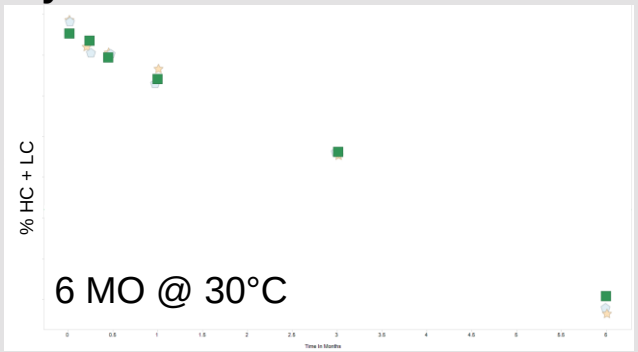
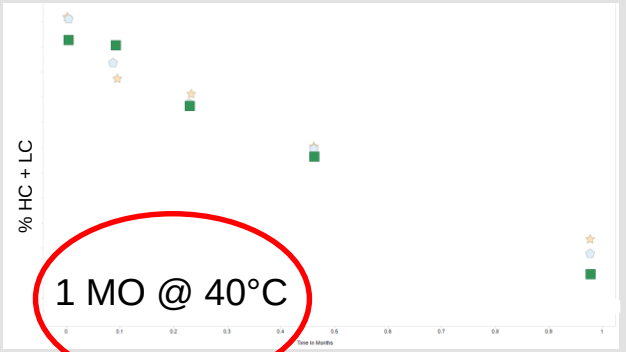
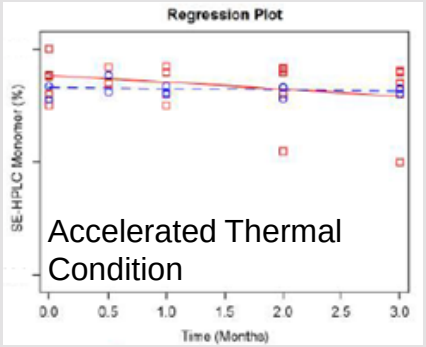


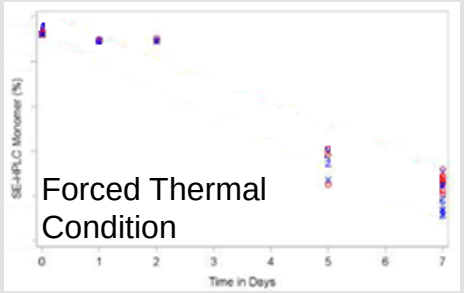


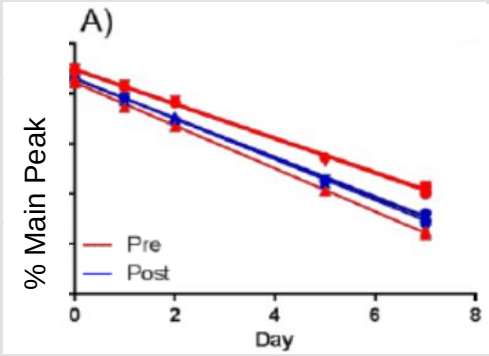


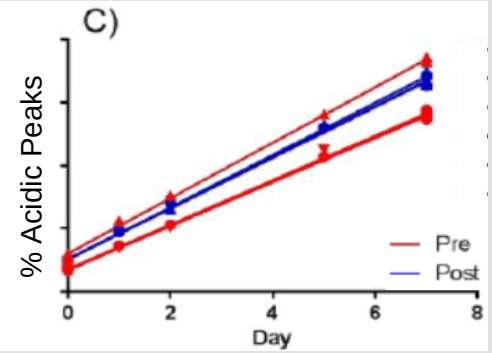
CASE STUDY 3: IDENTIFYING THE APPROPRIATE STRESS CONDITION TO ELICIT SUFFICIENT DEGRADATION

- Product: Protein stable under thermal stress
- No degradation at the accelerated thermal condition
- Highly sensitive and unpredictable degradation observed under forced thermal conditions
- Reconstituted samples exposed to cool, white light for 7 days
  - Predictable, meaningful degradation observed by CEX-HPLC









COMPARISON TO PRE-CHANGE: SIDE-BY-SIDE OR COMPARISON TO HISTORICAL?

- Comparability degradation studies, whether at the ASC, SSC, or forced degradation condition, are commonly performed side-by-side
- Side-by-side studies are intended to minimize sources of variability in order to evaluate potential differences between pre- and post-change material based on the correlation of the study condition to the quality attribute
- Side-by-side studies can be challenging because they are logistically complex
  - Sample handling and testing to minimize variability; age of pre-change material
- An effective evaluation of the pre- and post-change degradation profile can be obtained by comparing post-change stability data to historical pre-change data if the historical data reflects expected analytical variability and was analyzed under similar controlled conditions

COMPARISON TO PRE-CHANGE: SIDE-BY-SIDE OR COMPARISON TO HISTORICAL?

Factors to Consider in Comparability Degradation Study Design

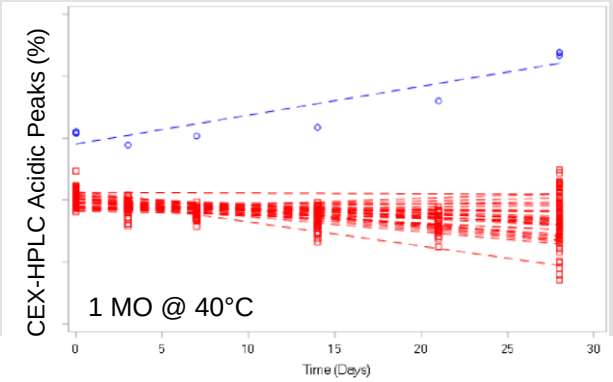
Factor	Side-By-Side	Comparison to Historical
Availability of pre-change material	Available	Limited or not available
Changes to analytical methods between manufacturing of pre- and post-change	Shift in method performance	Consistent method performance
Quantity and variability of historical pre-change data set	Limited data set or variability that is less than expected intermediate precision	Fully representative
Product sensitivity to chosen stress condition (thermal, light, etc.)	Unpredictable, highly sensitive to stress condition	Predictable, consistent response

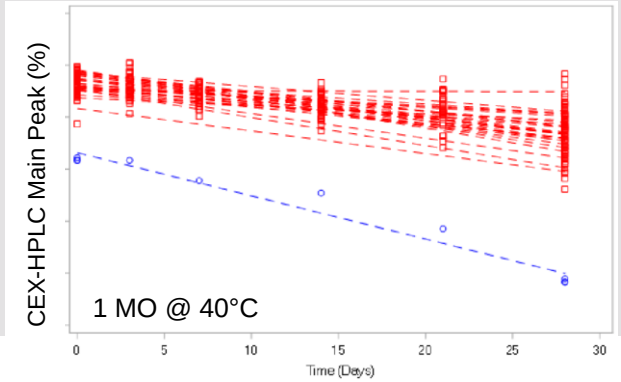
CASE STUDY 4: EVALUATION OF DRUG PRODUCT TO SUPPORT MAJOR DRUG SUBSTANCE CHANGE

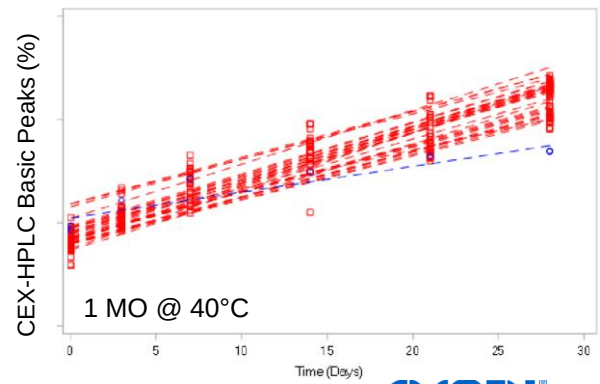
- Product: Protein sensitive to thermal stress
- Drug substance manufacturing process changes made to increase yield, increase final protein concentration, and formulation change
- Process changes expected to result in minor increase in oligomers and deamidation variants due to the protein concentration and formulation changes
- Analytical comparability study performed to evaluate differences in pre-change DP to post-change DP manufactured with post-change DS
- DP evaluated at SSC of 40°C for 1 month with comparison to stability data from 31 historical pre-change DS and DP lots
- Fitted regression lines for pre- and post-change were visually assessed for differences

CASE STUDY 4: EVALUATION OF DRUG PRODUCT TO SUPPORT MAJOR DRUG SUBSTANCE CHANGE

- CEX-HPLC post-change results demonstrated higher rate of acidic peak species formation, with inversely correlated degradation rate in main peak
- Change in CEX-HPLC stability profile due to increase in deamidated species caused by formulation change
- Pre- and post-change chromatograms similar with no new peaks identified
- Product characterization data used to support no impact until acidic peak species are well beyond the observed levels







Pre-change Post-change

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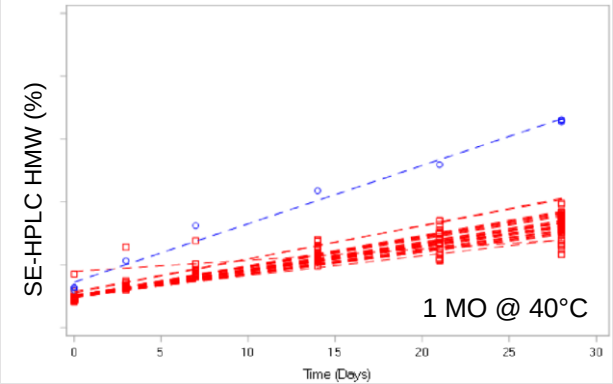
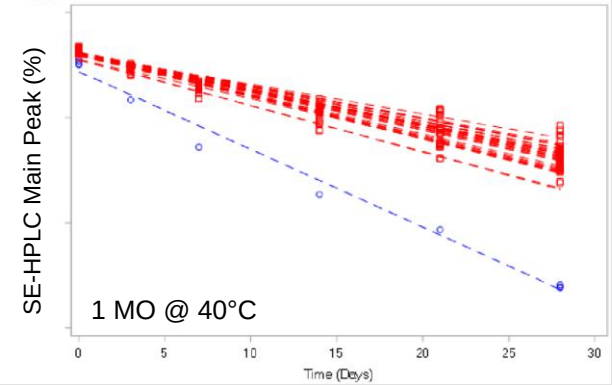
CASE STUDY 4: EVALUATION OF DRUG PRODUCT TO SUPPORT MAJOR DRUG SUBSTANCE CHANGE

- SE-HPLC results demonstrated higher rate of HMW formation, with inversely correlated degradation rate in main peak
- Change in SE-HPLC stability profile due to increase in protein concentration
- Pre- and post-change chromatograms similar with no new peaks identified
- Existing stability data used to justify no impact to safety/efficacy when product is stored at the RSC

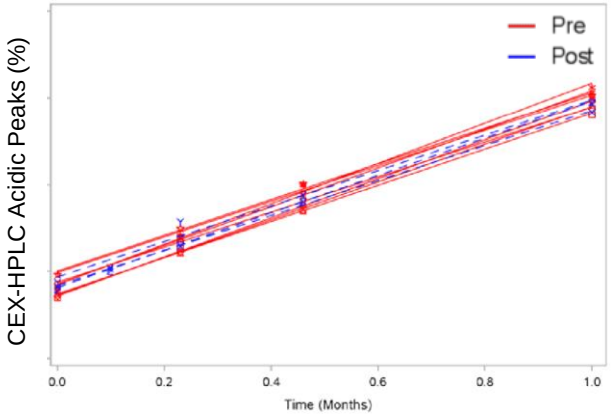


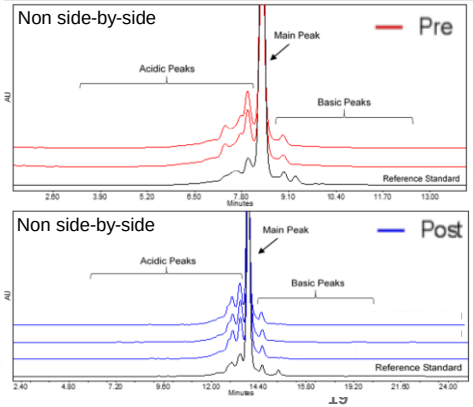


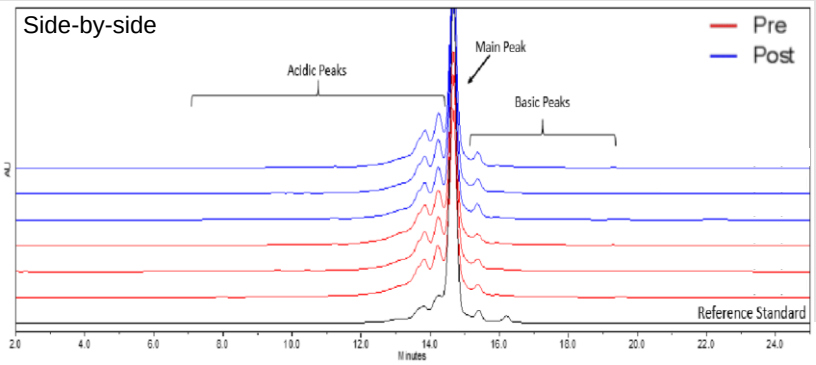
Pre-change Post-change

CASE STUDY 5: METHOD DIFFERENCES IN STRESSED STABILITY STUDY FOR A DP SITE TRANSFER

- Product: Protein sensitive to thermal stress
- Stressed stability study (40°C for 1 MO) with comparison to historical stability data for DP site transfer
- Visually similar rate of degradation observed by CEX-HPLC acidic peaks
- HPLC chromatograms showed differences in acidic peak shape and retention time between pre- and post
- Overlay differences attributed to method optimization after pre-change material was tested
- Side-by-side testing of 40°C 1 MO sample retains show no overlay differences





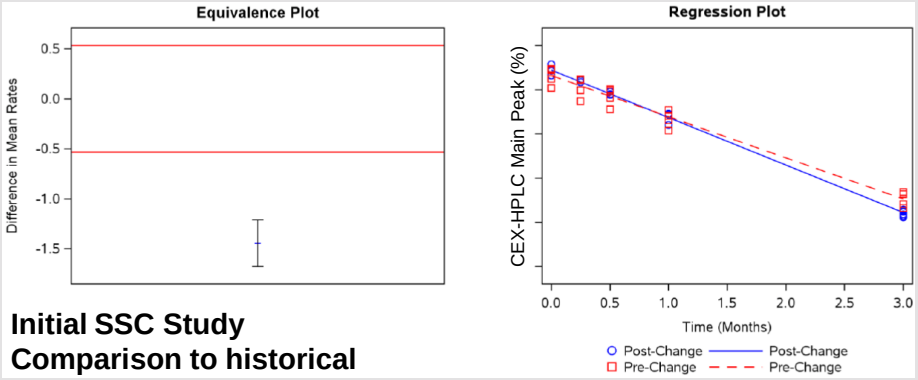


ASSESSMENT CRITERIA: STATISTICAL EVALUATION VS. VISUAL EVALUATION?

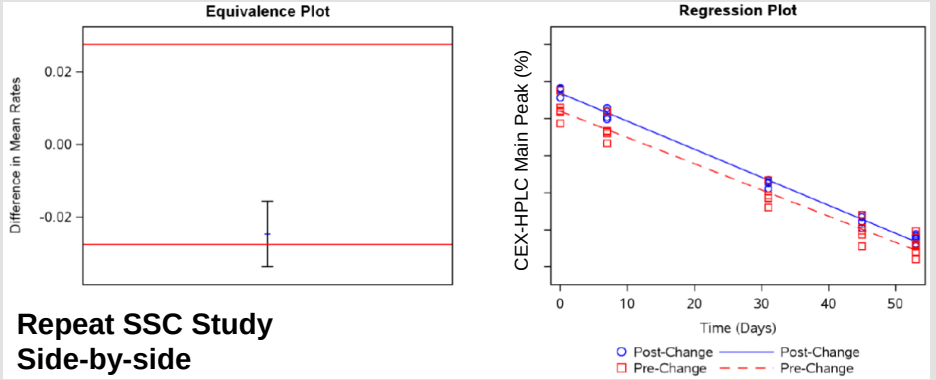
- Statistical evaluation of ASC/SSC/FD studies provides objective criteria for the demonstration of a similar stability profile in pre- and post-change product
- The statistical test of equivalence was previously used by Amgen to evaluate the difference in the degradation rate in comparability stability studies
- Inconclusive or failed equivalence acceptance criteria (EAC) were frequently observed despite minimal difference in the degradation rate
  - The statistical approach often yields criteria that are too stringent for very precise methods, or too wide for methods with greater variability
- Statistical evaluation is also challenging for attributes that exhibit a non-linear degradation profile
- A visual assessment is preferred because it encourages a science and risk-based approach to product differences based on process and product knowledge

CASE STUDY 6: REPEATED EQUIVALENCE ISSUES IN COMPARABILITY STRESSED STABILITY STUDIES

- Product: Protein sensitive to thermal stress
- Stressed stability study (40°C) with comparison to historical stability data for DS site transfer
- Study repeated side-by-side due to SE-HPLC and CEX-HPLC results that were not statistically equivalent or were inconclusive
- CEX-HPLC main peak and acidic peaks statistically inconclusive in repeat study
- Product knowledge used to justify no impact to product safety or efficacy due to minor stability differences



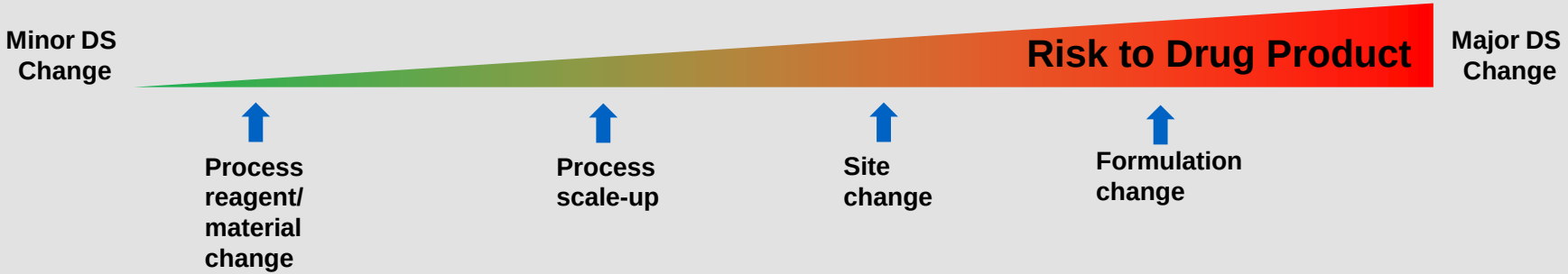
Initial SSC Study
Comparison to historical



Repeat SSC Study
Side-by-side

DRUG PRODUCT DATA FOR A DRUG SUBSTANCE CHANGE: HOW MUCH DATA IS ENOUGH?

- ICH Q5E guidance: *. . . even though all process changes occurred in the manufacture of the drug substance, in cases where the drug product could be impacted by the change, it might be appropriate to collect data on both the drug substance and the drug product to support the determination of comparability.*
- The potential risk posed to drug product quality will depend on the nature of each intended drug substance change



Note: Examples are intended to illustrate DS changes that may present risk to drug product quality.
Actual risk will vary depending on the process and product details.

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DRUG PRODUCT DATA FOR A DRUG SUBSTANCE CHANGE: HOW MUCH DATA IS ENOUGH?

- ICH Q5E provides guidance on the factors that will determine the extent of the studies necessary to demonstrate comparability:
  - Production step where the changes are introduced
  - Potential impact of the changes on the purity, physicochemical, biological properties of the product
  - Availability of suitable analytical techniques (i.e., the product control strategy)
  - Relationship between quality attributes and safety and efficacy
- The above considerations can be summarized and evaluated in a risk assessment, the complexity of which should be commensurate with the complexity of the proposed change

CASE STUDY 7: DETERMINATION OF COMPARABILITY APPROACH THROUGH A PRODUCT RISK ASSESSMENT

- Protein product
- Proposed change: scale-up of select drug substance purification process steps to enable a higher run rate
  - Cell culture and harvest processes unchanged
  - No new process reagents or product contacting materials introduced
  - Minor modifications required for the column 2 chromatography, column 3 chromatography, viral filtration, and ultrafiltration/diafiltration (UF/DF) steps
- No changes to the drug product manufacturing process

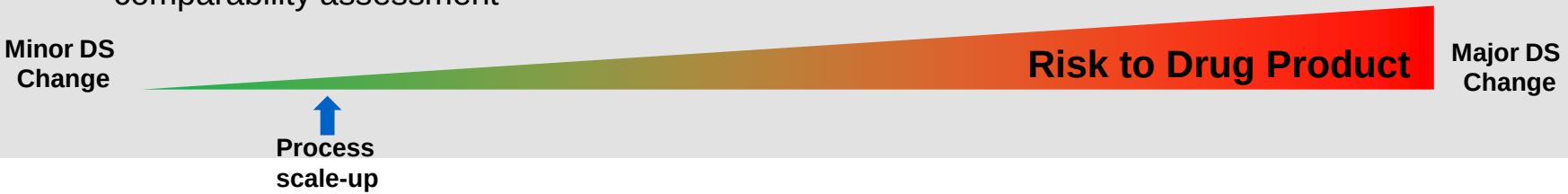
CASE STUDY 7: DETERMINATION OF COMPARABILITY APPROACH THROUGH A PRODUCT RISK ASSESSMENT

Summary of Process Scale-Up Changes and Associated Risks

Unit Operation	Process Change	Supporting Process Information	Risk Level
Column 2 Chromatography	• Column diameter ↑ • Number of cycles ↓	• No change in resin type • Scale independent process parameters unchanged	Low
Column 3 Chromatography	• Minor changes to process parameters within acceptable range • Number of cycles ↓	• Load range supported by viral clearance study • Scale independent process parameters unchanged	Low
Viral Filtration	• Filter surface area ↑ • Number of cycles ↓	• Scale independent process parameters unchanged	Low
UF/DF	• Membrane area ↑ • Number of cycles ↓	• No change in membrane type • Scale independent process parameters unchanged	Low

CASE STUDY 7: DETERMINATION OF COMPARABILITY APPROACH THROUGH A PRODUCT RISK ASSESSMENT

- Minimal comparability degradation studies were performed as supported by an assessment of the risks associated with the process scale-up
- Drug substance
  - Validation lots placed on stability at RSC, ASC, SSC as part of formal stability program
  - Stability results not presented as part of comparability package since this was assessed as minor change
  - Evaluation of stability data performed as part of routine product monitoring
- Drug product
  - No drug product lots were manufactured with post-change drug substance to support the comparability assessment



CONCLUSIONS

- Ever increasing process and product knowledge can be leveraged to identify and justify an efficient comparability degradation strategy (i.e., right data) to reduce time to filing and implementation (i.e., right time)
- The data available in the product stability program is a powerful tool that can be used to support the assessment criteria (visual) and the comparison type (side-by-side vs. historical)
- It is generally acceptable to exclude a comparability degradation study for minor changes, but ICH stability guidance must still be followed
- Resist the urge to simply do what was done before - the comparability degradation strategy should never be identified in isolation from the proposed changes
- The condition, target level of degradation, and methods should be relevant to the process, product, and expected degradation over the shelf life
- The comparability degradation strategy should be designed with the analytical method capabilities and history in mind

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