GILEAD
Creating Possible

Side-by-side Stress Studies Designed to Support Post-Change Shelf-Life

Tawnya Flick

Sr Director, Biologics Pivotal and Commercial Analytical Development

January 29, 2026.

Comparability is used to demonstrate consistent product quality after product lifecycle changes

A determination that a product is **"Comparable"** indicates that products are highly similar before and after a process change and that no adverse impact on the quality, safety or efficacy of the drug product occurred (**ICH Q5E**).

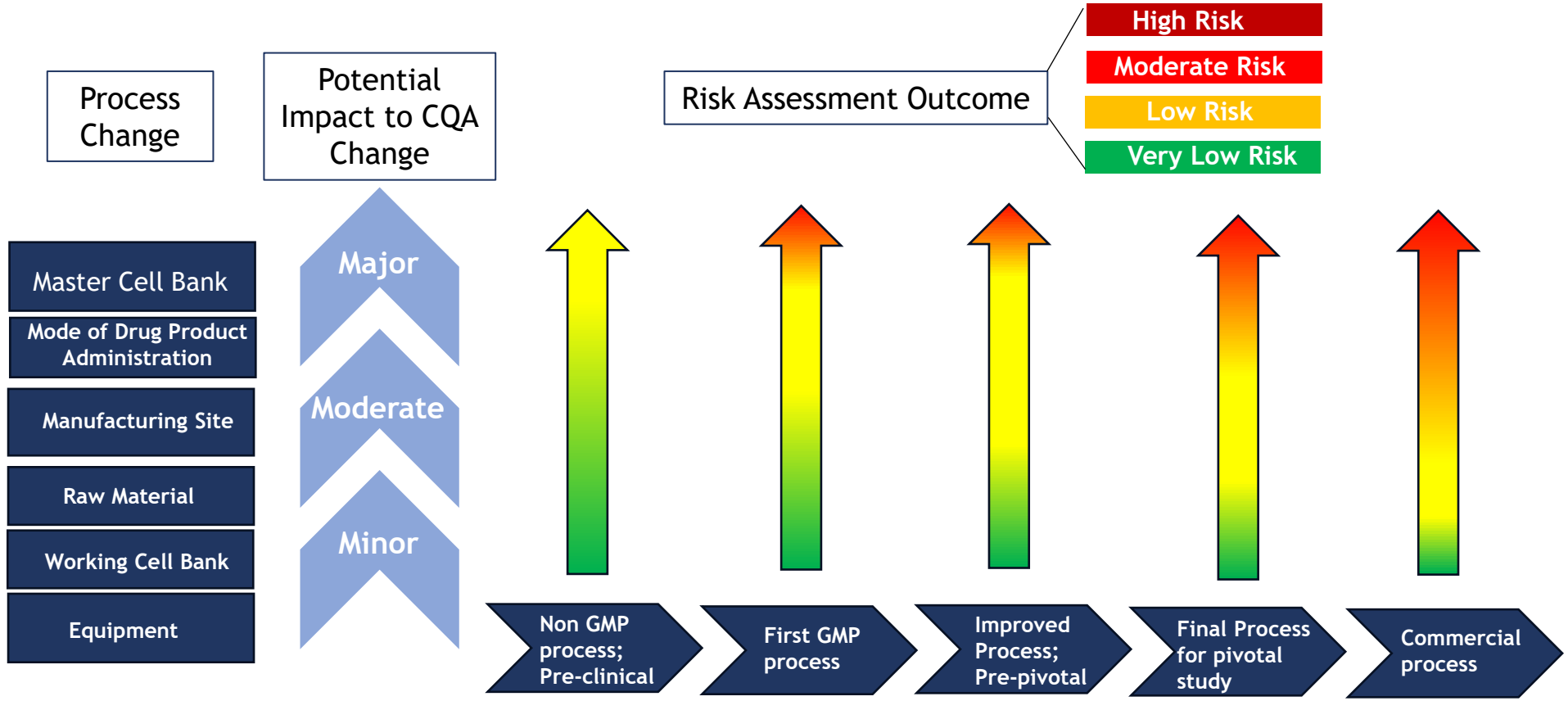
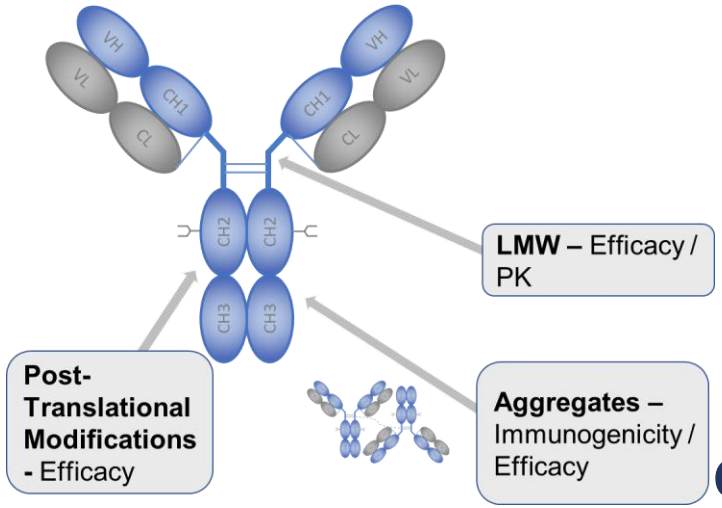


Figure courtesy: Journal of Pharmaceutical Sciences 113 (2024) 1415–1425

Process Change Risk Assessment drives the Analytical Comparability Testing Plan

Product Knowledge:
- CQA Impacts
- Clinical Product Quality Ranges
- Degradation Behavior

Process Understanding:
- Process parameters / CQA Linkage
- Post-Change differences in process, and facility.



Process Change Risk Assessment to Critical Quality Attributes

Comparability Testing Plan defined to assess impacts of a process change to drug safety and efficacy

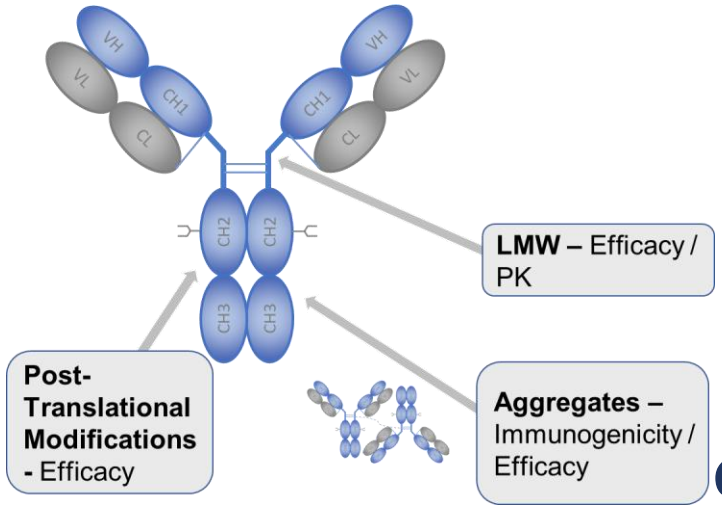
- Release
- Extended Characterization (structural & functional)
- Side-by-side stressed stability

3

Process Change Risk Assessment drives the Analytical Comparability Testing Plan

Product Knowledge:
- CQA Impacts
- Clinical Product Quality Ranges
- Degradation Behavior

Process Understanding:
- Process parameters / CQA Linkage
- Post-Change differences in process, and facility.



Process Change Risk Assessment to Critical Quality Attributes

Comparability Testing Plan defined to assess impacts of a process change to drug safety and efficacy

Release

Extended Characterization (structural & functional)

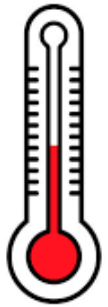
Side-by-side stressed stability

Can similarity in degradation pathway / rates be used to justify post-change shelf life?

4

Thermal Stress Condition is most relevant to modulate stability-indicating attributes of long-term condition

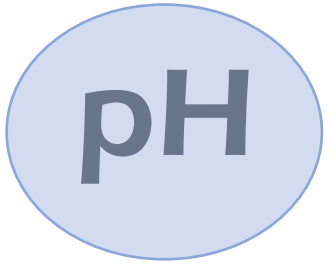
Thermal



- Accelerates degradation pathways representative of shelf-life storage conditions

Common

pH



- Buffering capacity of formulation results in pH being well maintained during long term storage

Photostress

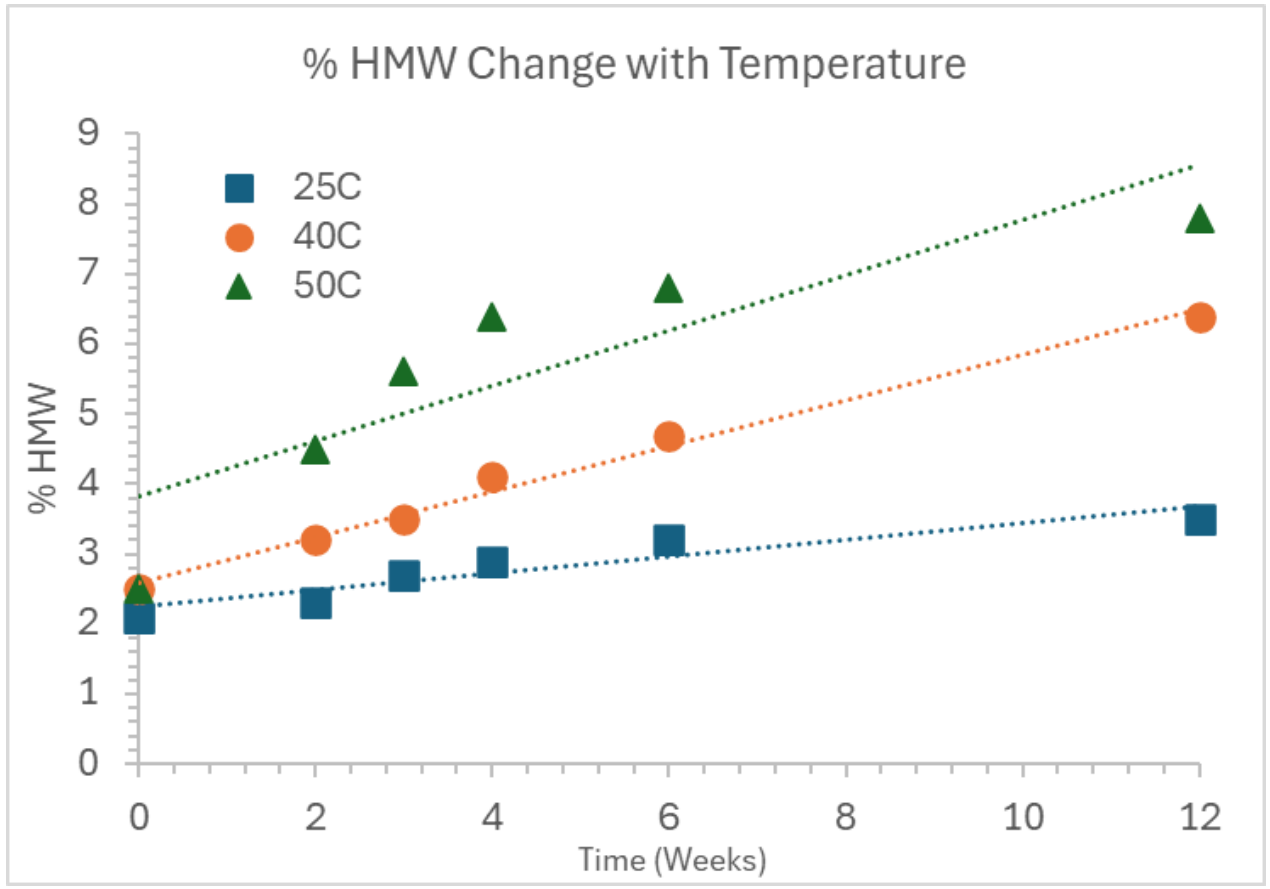
- Light-Sensitive biotherapeutics products are often protected from light during storage

Oxidation

- Not relevant if long-term stability studies indicate oxidation is not a degradation pathway on long-term stability

Less common - extreme conditions require sample manipulation and form irrelevant degradation products

Thermal stress study is designed to accelerate degradation of shelf-life limiting attributes



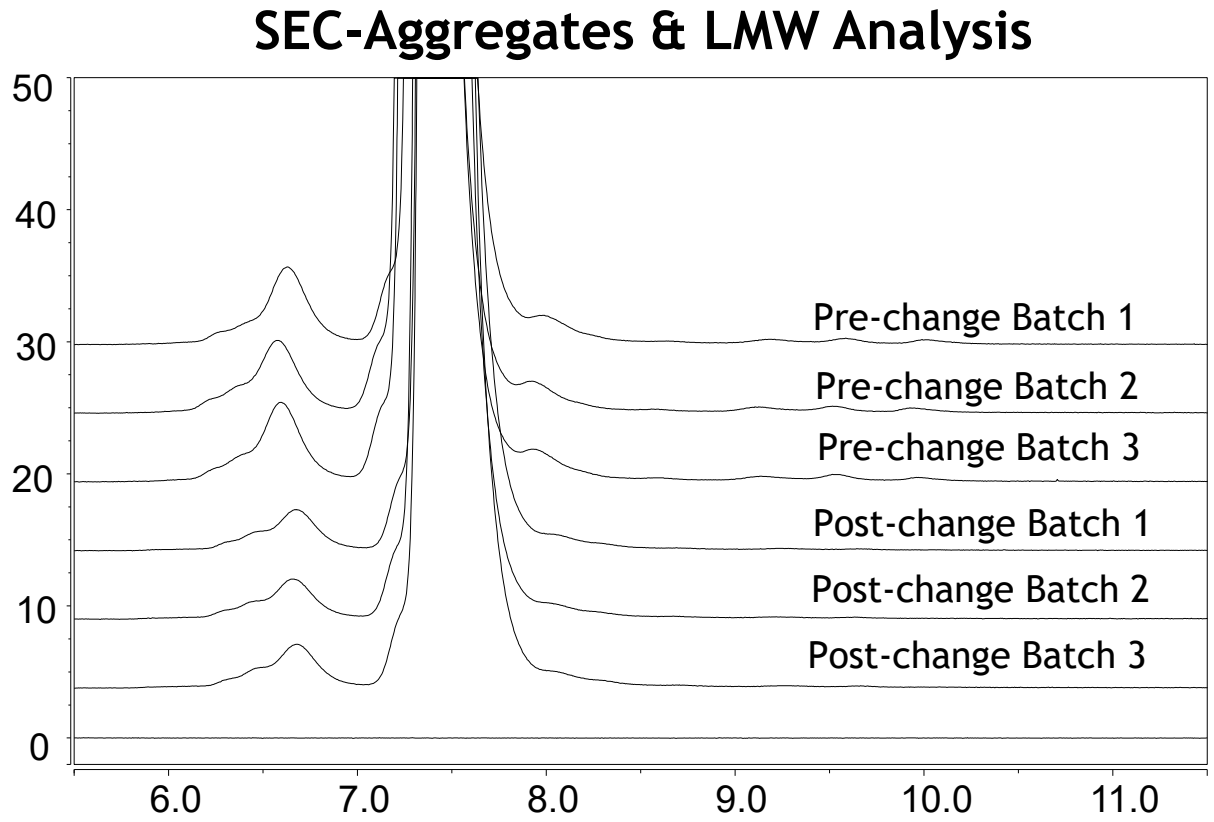
Key Lessons:

- ✓ A pre-assessment of degradation rates at different temperatures / timepoints to ensure meaningful degradation and linearity
- ✓ Stress and test pre- and post-change lots side by side
- ✓ Pre-change batches should have minimal degradation to reduce age dependency degradation rate differences
- ✓ Obtain at least 4 data points across the degradation trend is important for a good linear regression fit

6

Criteria #1: Visual Assessment of profiles to ensure similarity in degradation pathways

- ✓ Criteria #1: Visual assessment of chromatograms / electropherograms to evaluate no new peaks, peak shapes, and rank orders.



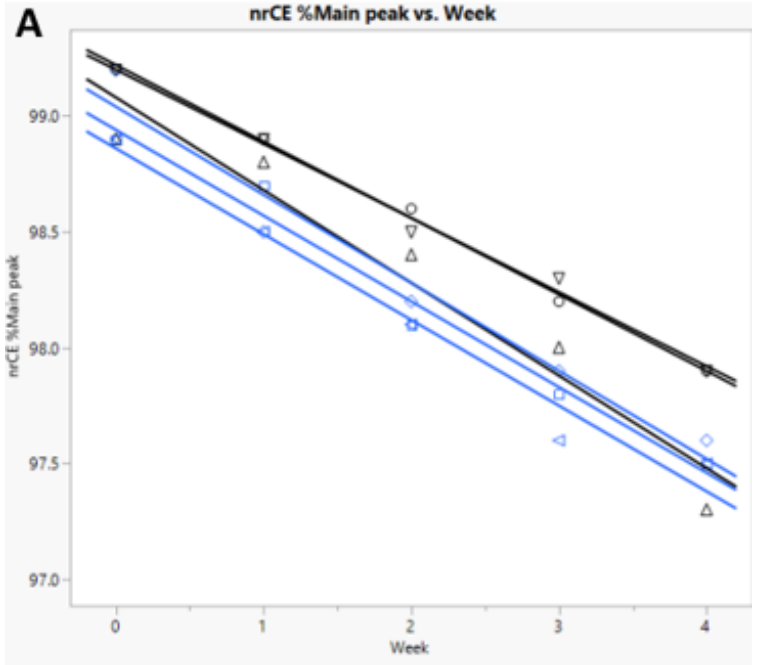
Not similar but aggregate / LMW improvement in post-change batches results in potential improvement in the efficacy / safety profile for patients

7

Criteria #2: Assessment Criteria approach evaluates similarity in degradation rates

- ✓ **Criteria #2: Comparison of similarity of degradation for pre- and post-change batches**
  - ✓ **Slope comparison for linear trends**
  - ✓ Results reported where a non-linear trend is observed or no significant change

Linear: % main peak by nrCE



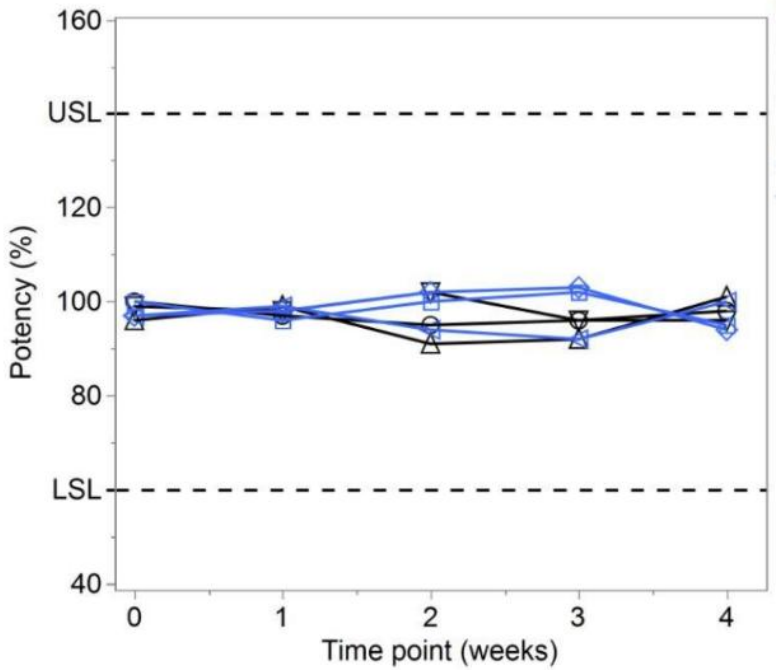
Process	Slope Min-Max
Pre-Change	-0.38 to -0.37
Post- Change	-0.40 to -0.32

8

Criteria #2: Assessment Criteria approach evaluates similarity in degradation rates

- ✓ Criteria #2: Comparison of similarity of degradation for pre- and post-change batches
  - ✓ Slope comparison for linear trends
  - ✓ **Results reported where a non-linear trend is observed or no significant change**

Non-Linear: % Relative Potency

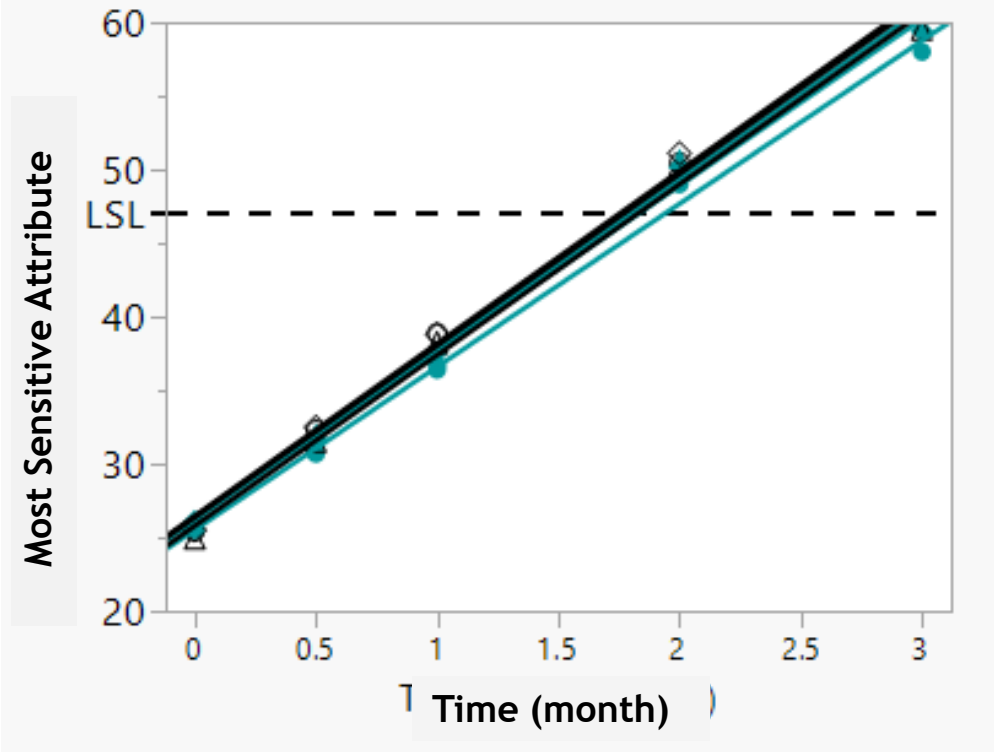


Process	Reported Values Min-Max
Pre-Change	92-103
Post-Change	91 -102

9

Criteria #3: Assessment Criteria requires statistical similarity for most stability-indicating attribute

- ✓ Criteria #3: Statistical analysis criteria are applied (such as poolability test or t-test) for most stability-indicating attribute.



Examples of Statistical Analysis

Poolability of Slope	p ≥ 0.25

10

Case Study: DP Manufacturing Site & SKU change for Launch

- **No DS process changes**
- **DP Process Changes:**
  - SKU: 120 mg /8R from 120 mg / 6R vial
  - Manufacturing site – including process fit changes (i.e. pooling, mixing)

+

11

Case Study: DP Manufacturing Site & SKU change for Launch

- No DS process changes
- DP Process Changes:
  - SKU: 120 mg /8R from 120 mg / 6R vial
  - Manufacturing site – including process fit changes (i.e. pooling, mixing)

+

Multiple stability indicating attributes are modulated at 40°C, 4 weeks

Test Methods	Attributes	Approximate Change after T=4 weeks at 40°C
CEX	Acidics	+12%
	Basics	-1%
SEC	HMW	+1.2%
nrCE	LMW	+1.0%

12

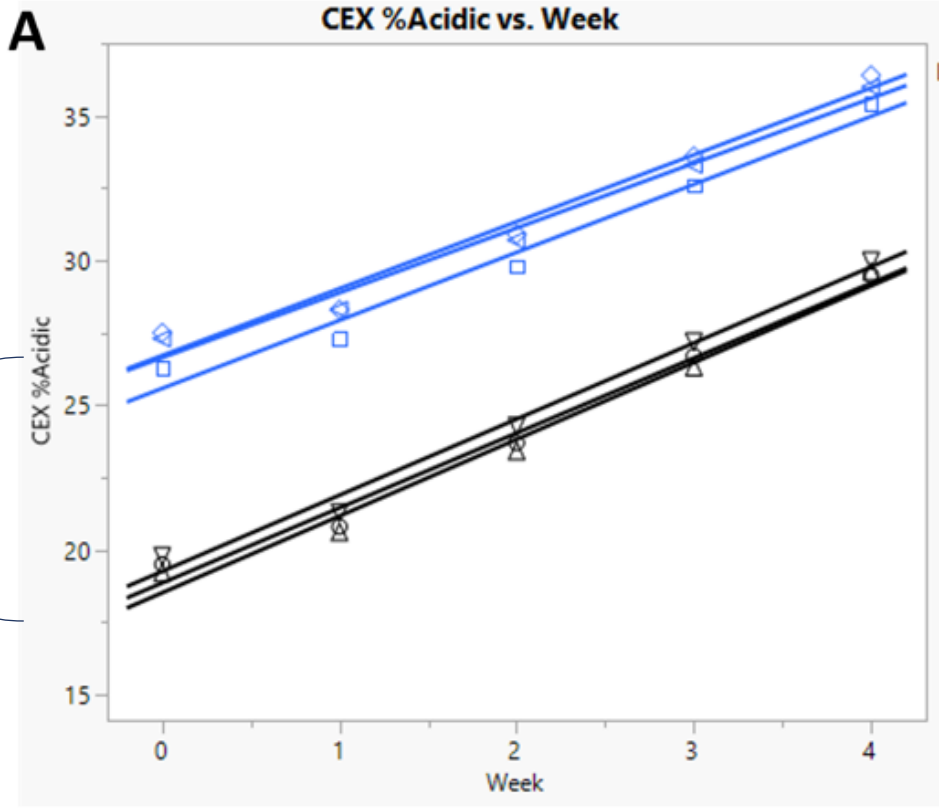
Case Study: DP Manufacturing Site & SKU change for Launch

- No DS process changes
- DP Process Changes:
  - SKU: 120 mg /8R from 120 mg / 6R vial
  - Manufacturing site – including process fit changes (i.e. pooling, mixing)

+

Starting Point difference linked to age of Pre-Change comparator lots

Shelf-life Limiting Attribute



Linear Regression analysis performed

Slope Pre-Change: 2.2 to 2.4

Slope Post-Change: 2.6 to 2.7

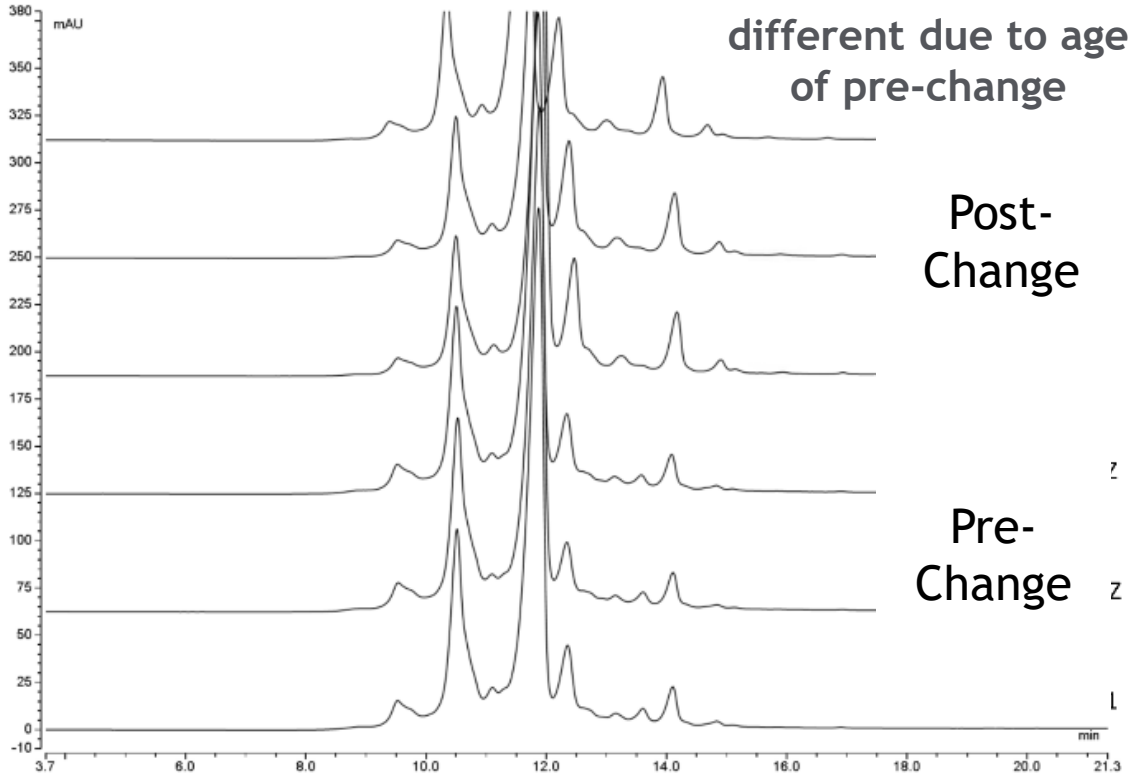
Poolable according to ICH Q1E (α ≥ 0.25)

13

Chromatogram Assessment ensures same degradation pathways between pre- and post-change batches

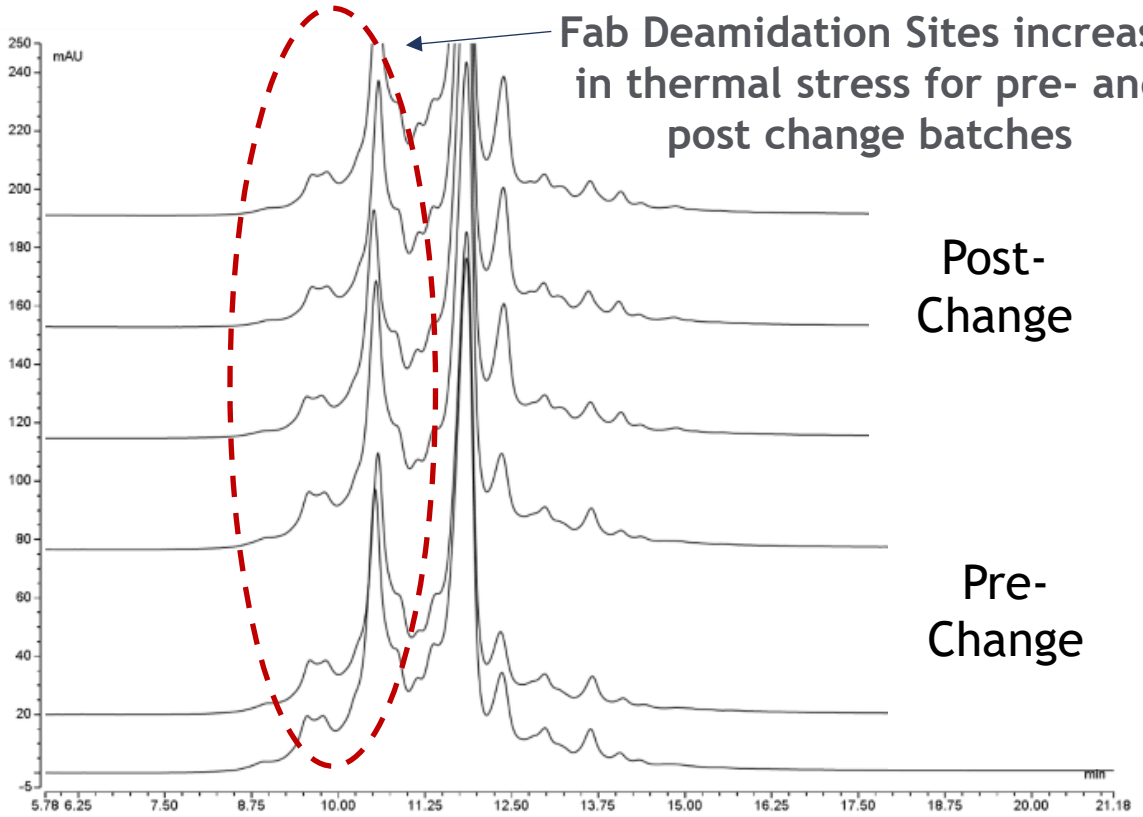
T=0

Starting Levels of Acidics /Basics are different due to age of pre-change



T=4w (40°C ± 2°C / 75% ± 5% RH)

Fab Deamidation Sites increase in thermal stress for pre- and post change batches



Due to similarity of degradation trends / pathways, positive feedback received from FDA that pre-change stability could be used to justify post-change shelf life.

Closing Thoughts

- Stress condition and timepoints are critical for a successful side-by-side stress study design. Thermal is most common but should consider justification why other forced degradation conditions are not used.

- Purity profiles are crucial to ensure the same degradation pathway between pre- and post-change batches.

- It is critical to evaluate at all stability-indicating attributes even though similarity criteria is on most sensitive stability-indicating attribute.

- Positive outcome can be achieved in using comparability to justify application of pre-change shelf-life to post-change processes. However, challenges in applying pre-change shelf life can occur when magnitude and risk of changes is high.

Thank You