Assessing Comparability: It's More Than Just Numbers

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CGTP Summit

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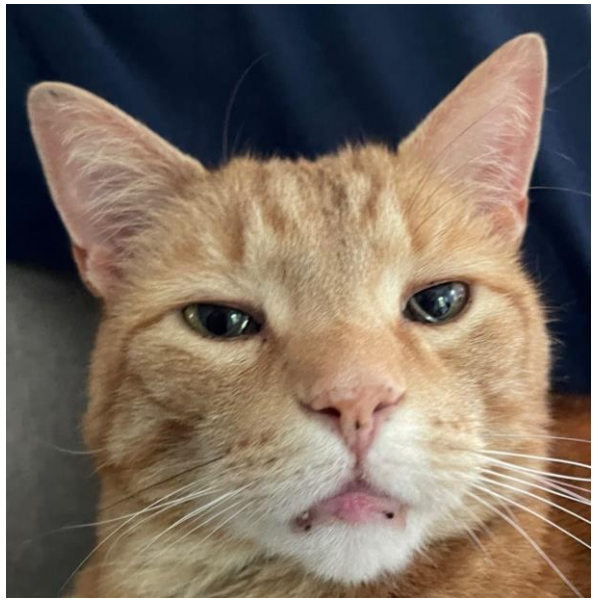
Comparable ≠ Identical: Are These Comparable?



Key Messages

Frame the Question

Consider All the Data

Employ Statistics Thoughtfully

Comparability Defined

comparability … does **not necessarily** mean that the quality attributes of the pre-change and post-change product are **identical**, but that they are **highly similar** and that the existing knowledge is sufficiently **predictive** to ensure that any differences in quality attributes have **no adverse impact** upon safety or efficacy of the drug product. – ICH Q5E

Pre- and Post-Change

"The goal of the comparability exercise is to ascertain that **pre- and post-change** drug product is comparable in terms of quality, safety, and efficacy." – ICH Q5E

Clearly define pre-change and post-change

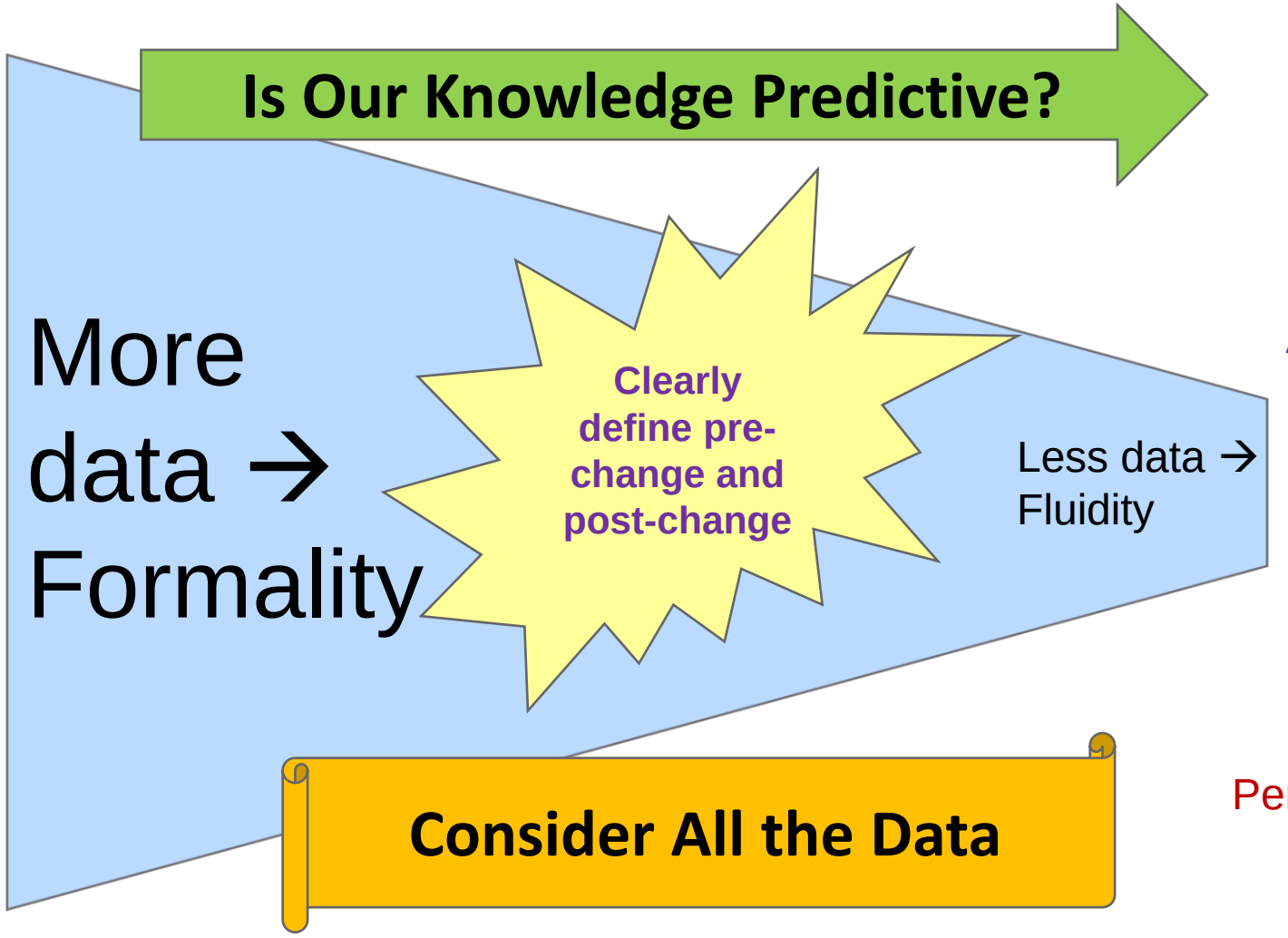
Data Drivers: Rarity, Ability to Characterize, and Urgency

Product = Process

Traditional development

Replacement products

Pandemic



Precision medicine

Accelerated reviews

Unmet needs

Emergency use

Rare disease

Personalized therapies

Match the Method to the Question

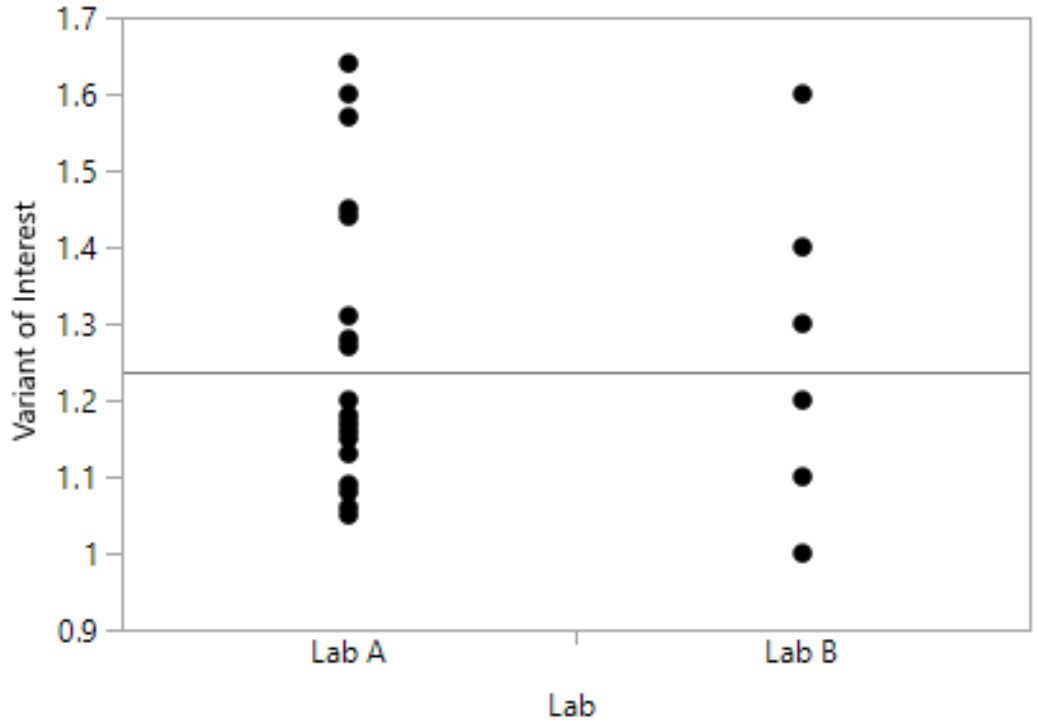
Question	Method
Do the post-change results demonstrate no adverse impact on safety or efficacy?	Compare to meaningful ranges (Patient Centric Specifications if available)
Are the post-change results highly similar to the pre-change results?	Graph the results and LOOK Descriptive summary statistics ** Descriptive Quality Ranges **
Is knowledge predictive of post-change results?	Prospective criteria

** Descriptive Quality Ranges may be applied to selected quality attributes of high or moderate risk. **

Example: Test Method Transfer Do-It-Yourself (DIY) Statistics

Mutation rate for a variant of interest – tested at 2 different labs

Initial conclusion: difference between labs is “not significantly different”

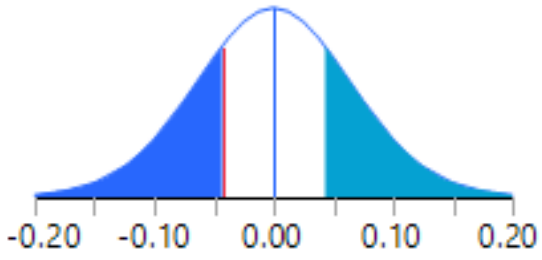


Pooled t Test

Lab B-Lab A

Assuming equal variances

Difference	-0.04316	t Ratio	-0.66413
Std Err Dif	0.06498	DF	36
Upper CL Dif	0.08864	Prob > |t|	0.5108
Lower CL Dif	-0.17495	Prob > t	0.7446
Confidence	0.95	Prob < t	0.2554

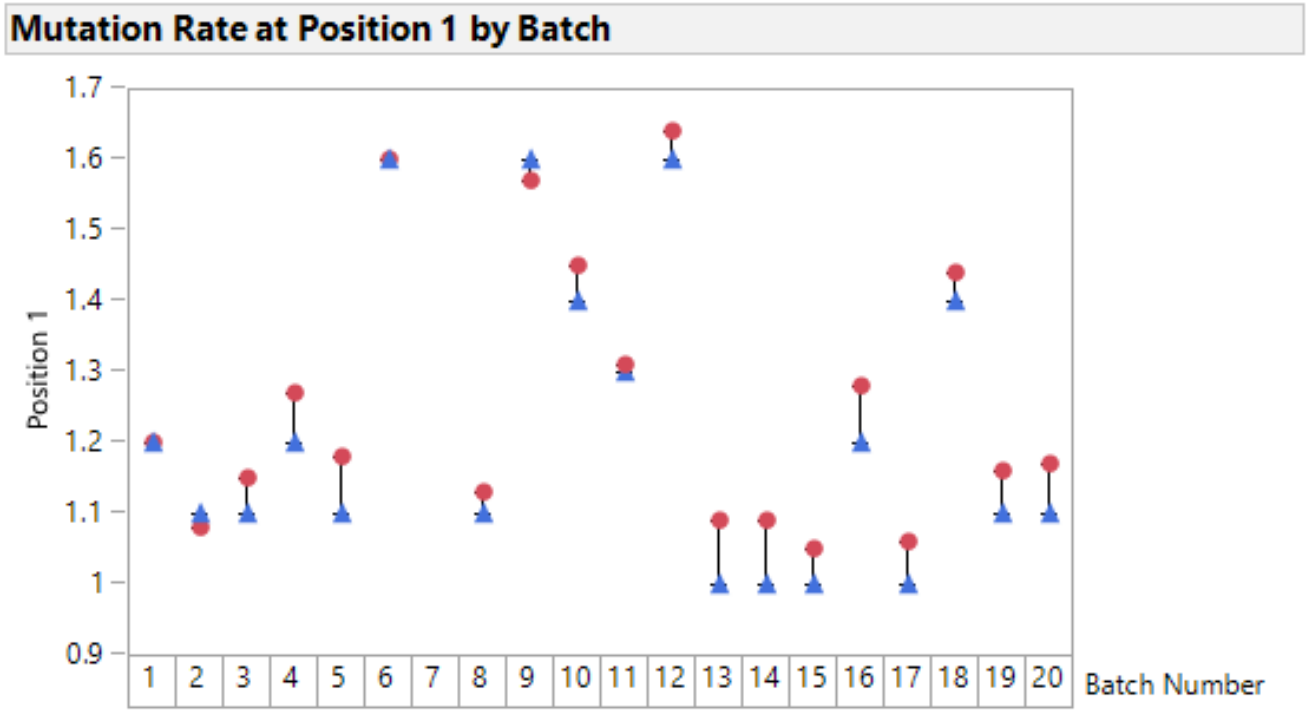


Same Example – Recognizing Study Design

Mutation rate for a variant of interest – tested at 2 different labs (red & blue) – for 20 Batches

Do we still think these are highly similar?

Is this difference meaningful?



Compare to Meaningful Ranges

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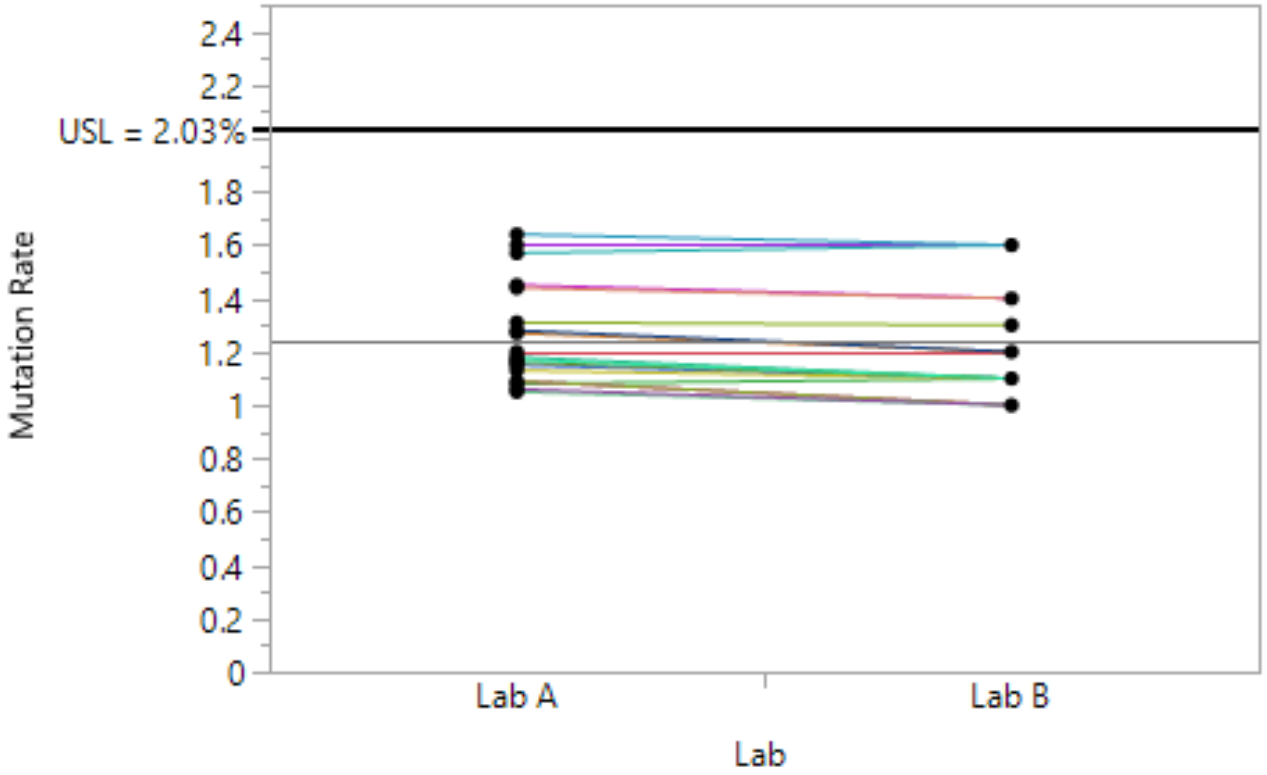


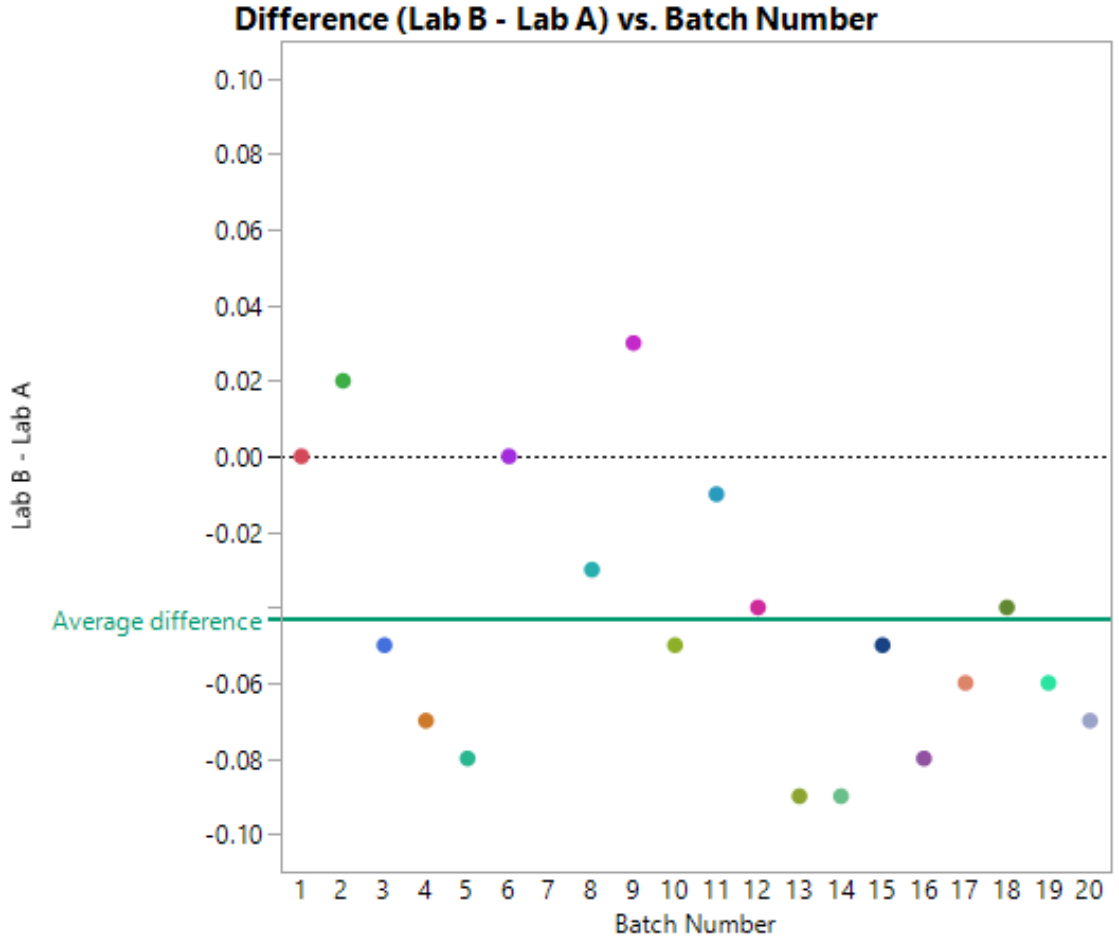
Look at the Differences (Lab B – Lab A)

There is a statistically significant bias between Lab A and Lab B for this variant of interest.

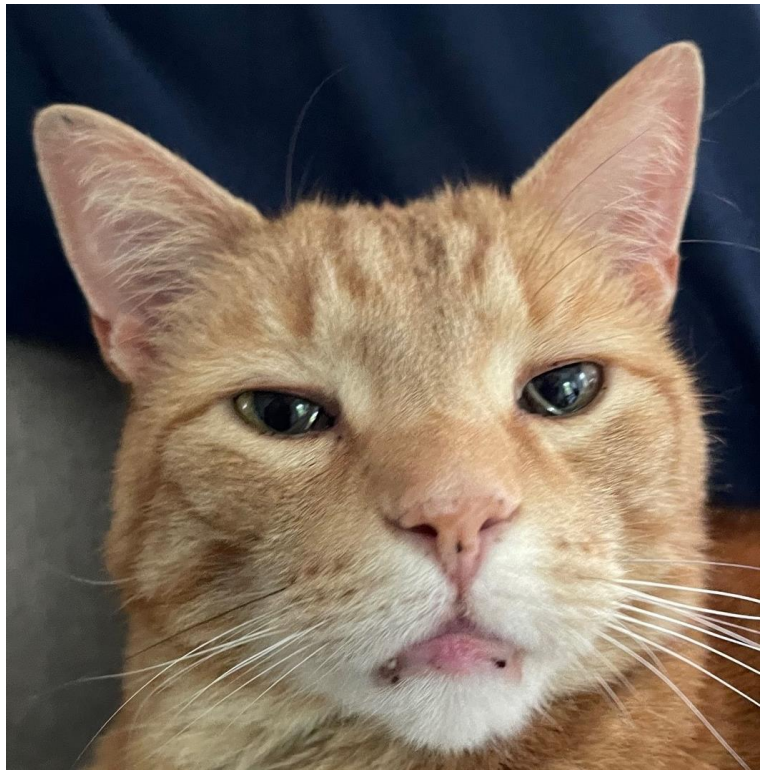
Confidence Intervals				
Parameter	Estimate	Lower CI	Upper CI	1-Alpha
Mean	-0.04316	-0.06061	-0.0257	0.950
Std Dev	0.036217	0.027366	0.053559	0.950

This is an opportunity to improve method agreement.

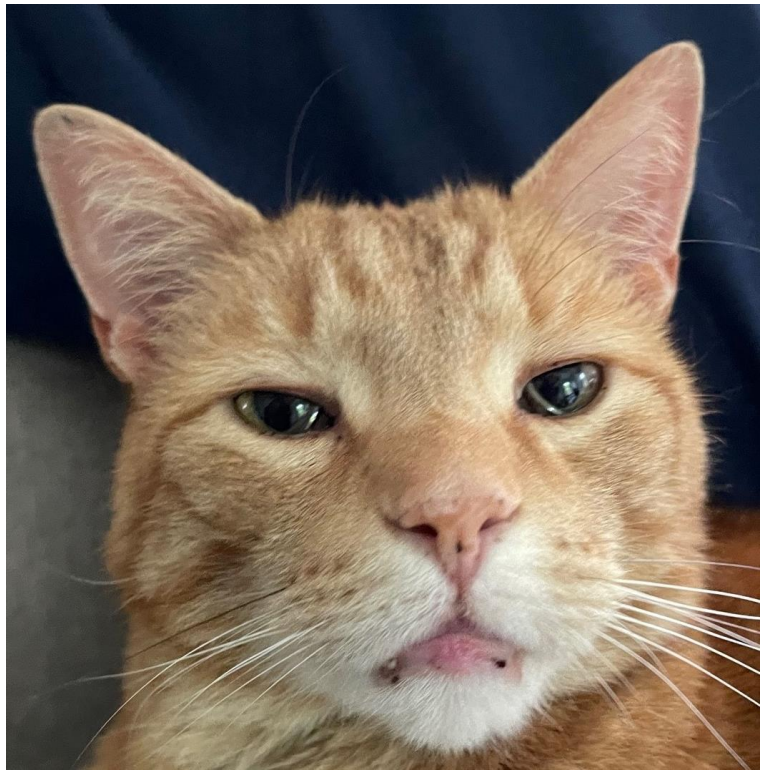
But is a difference of -0.043% (95% CI -0.061 to -0.026%) meaningful to safety or efficacy?

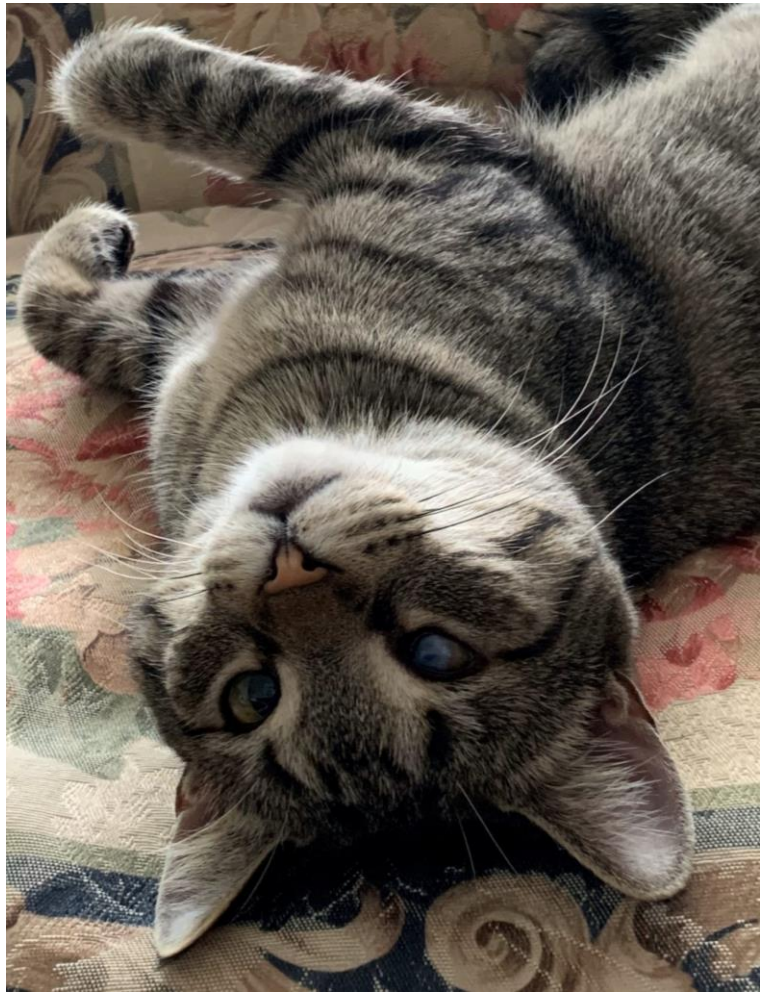


Are These Highly Similar?



THIS is the Value of n = 3





Recommended References & Resources

Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process (ICH Q5E)

Burdick, Richard K. (2020): Statistical Considerations for Comparative Assessment of Quality Attributes, Statistics in Biopharmaceutical Research, DOI:10.1080/19466315.2020.1767194

Start here – DIY?

Burdick, Richard K. et al., Springer (2017) *Statistical Applications for Chemistry, Manufacturing and Controls (CMC) in the Pharmaceutical Industry*, Chapter 9: Analytical Comparability and Similarity"

EMA (2019) Questions and answers: Comparability considerations for Advanced Therapy Medicinal Products (ATMP), Q11

FDA (2019) Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations

Training available through JMP and certain vendors and conferences – contact me for more information

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Recall the Key Messages

Frame the Question

- Clearly define pre-change and post-change
- Formality vs Fluidity
- Predictive → Prospective vs Retrospective

Consider All the Data

- Visibility to reviewers

Employ Some Statistics

- Graph. LOOK.
- DIY statistics is risky, especially with small data sets
- Resources

For More Information

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