ANALYTICAL SIMILARITY ASSESSMENT FOR BIOSIMILAR INITIAL APPROVAL, LIFECYCLE MANAGEMENT, AND EXTRAPOLATION OF INDICATIONS

JENNIFER LIU

CASSS CMC STRATEGY FORUM CHINA 2021, APRIL 23-24

AMGEN BIOSIMILARS

BIOSIMILAR DEVELOPMENT BEGINS WITH THOROUGH CHARACTERIZATION OF THE REFERENCE PRODUCT

Reference product knowledge

- Known mechanism of actions, safety and efficacy profiles
- Knowledge for the same class of molecules

Define critical quality attributes

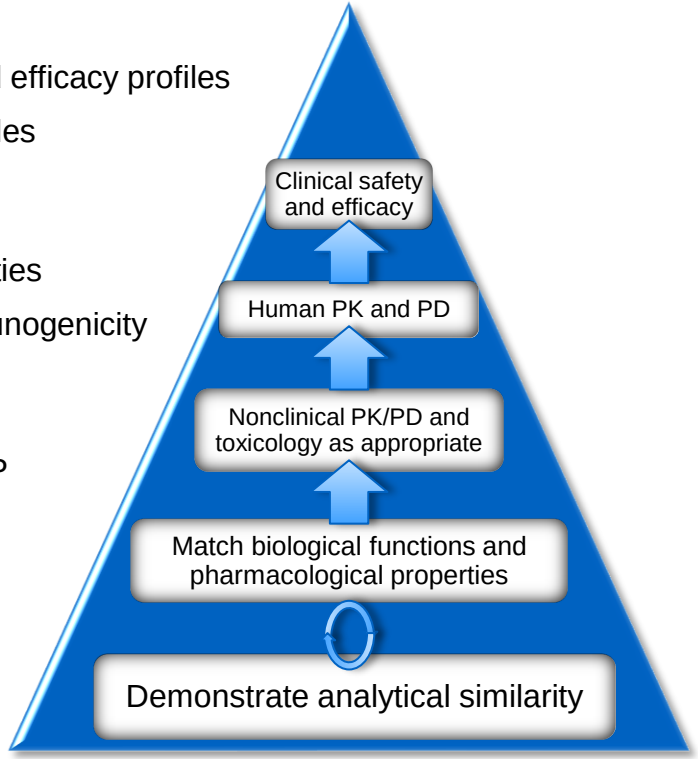
- Demonstrated impact to biological activities
- Potential impact to PK, safety, and immunogenicity

Establish Biosimilar's QTPP ranges

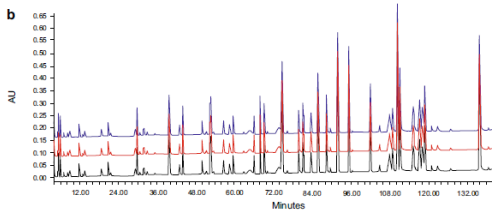
- Biosimilar QTPP should be based on RP
- QTPP based on multiple lots of RP

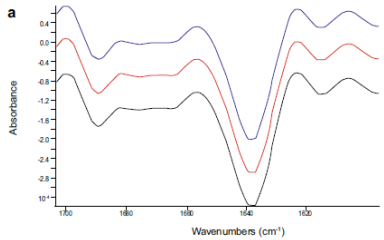
Refine QTPP as knowledge increases

- Increased RP data to refine QTPP
- Risk ranking of similarity CQA



COMPREHENSIVE ANALYTICAL SIMILARITY ASSESSMENT IS THE FOUNDATION FOR DEMONSTRATING BIOSIMILARITY



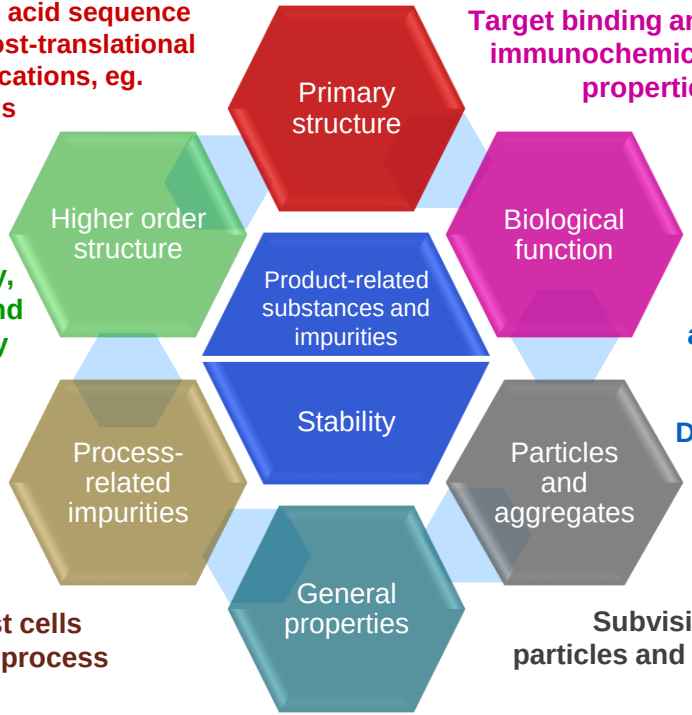


Amino acid sequence and post-translational modifications, eg. glycans

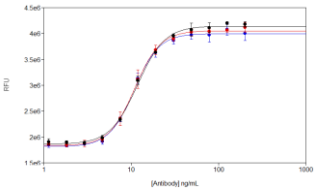
Secondary, tertiary, and quaternary structure

Impurities from host cells and manufacturing process

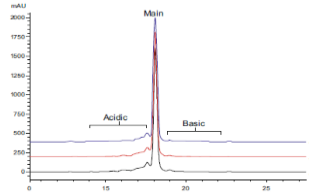
Properties of the finished drug product including strength



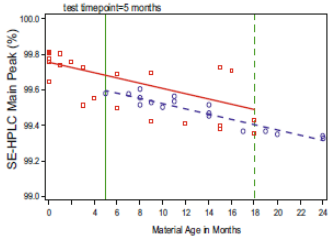
Target binding and immunochemical properties



product variants and their identities



Degradation profiles denoting stability



Subvisible, submicron particles and characteristics

Liu, BioDrugs (2016)

HOW TO ASSESS COMPLEX DATASET WITH OBJECTIVITY

Analytical testing/attributes	ABP 501 [range (*n*)]	Adalimumab (US) [range (*n*)]	Adalimumab (EU) [range (*n*)]
Protein concentration (mg/mL)	47.9–52.6 (10)	48.1–52.3 (23)	49.6–53.7 (18)
Volume (mL)	0.79–0.81 (12)	0.80–0.81 (14)	0.79–0.81 (10)
Intact molecular weight (Da)			
A: Glycosylation—G0F:G0F	148,083–148,084 (4)	148,083–148,083 (4)	148,083–148,084 (4)
B: Glycosylation—G0F:G0F (+K)	148,208–148,212 (4)	148,212–148,212 (4)	148,211–148,212 (4)
C: Glycosylation—G0F:G1F	148,244–148,245 (4)	148,244–148,245 (4)	148,244–148,245 (4)
D: Glycosylation—G1F:G1F or G0F:G2F	148,407–148,407 (4)	148,406–148,407 (4)	148,405–148,407 (4)
Reduced and deglycosylated heavy chain (Da)	49,200.4–49,200.7 (4)	49,200.4–49,200.6 (4)	49,200.4–49,200.5 (4)
Reduced and deglycosylated light chain (Da)	23,412.2–23,412.4 (4)	23,412.2–23,412.4 (4)	23,412.2–23,412.4 (4)
Glycosylation at Asn 301 (%)	99.0–99.4 (10)	97.5–98.3 (24)	97.7–98.8 (18)
Glycan map (%)			
Galactosylation	19.9–26.5 (7)	17.6–21.6 (24)	17.7–21.5 (18)
High mannose	5.0–8.5 (7)	7.0–9.7 (24)	6.8–8.6 (18)
Afucosylation	1.6–2.2 (7)	1.1–1.7 (24)	1.2–1.7 (18)
Total afucosylation	6.6–10.8 (7)	8.9–12.4 (24)	9.0–10.9 (18)
Sialylation	0.5–0.8 (7)	0.1–0.3 (24)	0.2–0.3 (18)
FTIR/spectral similarity (%)			
US RP	99.3–99.9 (6)	99.0–99.9 (6)	99.2–99.8 (6)
EU RP	99.4–99.9 (6)	98.9–99.8 (6)	99.2–99.9 (6)
Near UV-CD/spectral similarity (%)			
US RP	97.4–99.3 (6)	98.8–99.4 (6)	98.8–99.4 (6)
EU RP	97.4–99.2 (6)	98.8–99.3 (6)	98.2–99.5 (6)
DSC (°C)			
T_{m1}	71.7–72.1 (6)	71.7–72.1 (6)	71.7–72.1 (6)
T_{m2}	82.2–82.7 (6)	82.5–83.0 (6)	82.4–82.9 (6)
AUC-SV/monomer (%)	98.4–99.9 (6)	97.4–99.8 (6)	97.5–99.5 (6)
SE-HPLC-LS MW (kDa)			
Monomer	145–145 (3)	145–146 (3)	145–146 (3)
Dimer	318–322 (3)	307–320 (3)	310–318 (3)
LO/particles-size (particles/mL)			
≥2 μm	5140–23,748 (10)	4560–31,000 (7)	9447–15,820 (7)
≥5 μm	1000–7630 (10)	1057–13,600 (7)	3577–7587 (7)
≥10 μm	93–1525 (10)	107–3727 (7)	570–2284 (7)
≥25 μm	0–14 (10)	4–97 (7)	3–60 (7)
MFI/non-spherical particles-size ≥5 μm (particles/mL)	24–172 (10)	18–139 (7)	7–183 (7)
CHO cell protein by ELISA (ppm)	0–46 (10)	129–168 (3)	87–171 (3)

Objective assessment is based on criteria that can be measured against

Subjective assessment requires interpretation by a subject matter expert

Liu, BioDrugs (2016)

AMGEN BIOSIMILARS

INCLUSION OF STATISTICAL COMPARISON MAY INCREASE OBJECTIVITY IN SIMILARITY ASSESSMENT

Consideration for assessment approaches

- Reference product data
- Reference product knowledge
- Stability-indicating properties
- Manufacturing process controls

Approaches to establish acceptance criteria

- **Statistical comparison**
- **Non-statistical comparison (Scientifically justified criteria)**
- **Qualitative comparison (Visual)**

COMPARISON OF EMA AND FDA EXPECTATIONS FOR USE OF STATISTICS IN ANALYTICAL SIMILARITY ASSESSMENT

EU

Ranges should be based primarily on the measured quality attribute ranges of the reference medicinal product and should not be wider than the range of variability of the representative reference medicinal product batches, unless otherwise justified.

A descriptive statistical approach to establish ranges for quality attributes could be used, if appropriately justified.

EMA/CHMP/BWP/247713/2012
Committee for Medicinal Products for Human Use (CHMP) Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1)

US

Data analysis should consider Risk Assessment and method(s) for Quantitative/Qualitative Data Analysis

Recommendations for Quantitative Data Analysis:

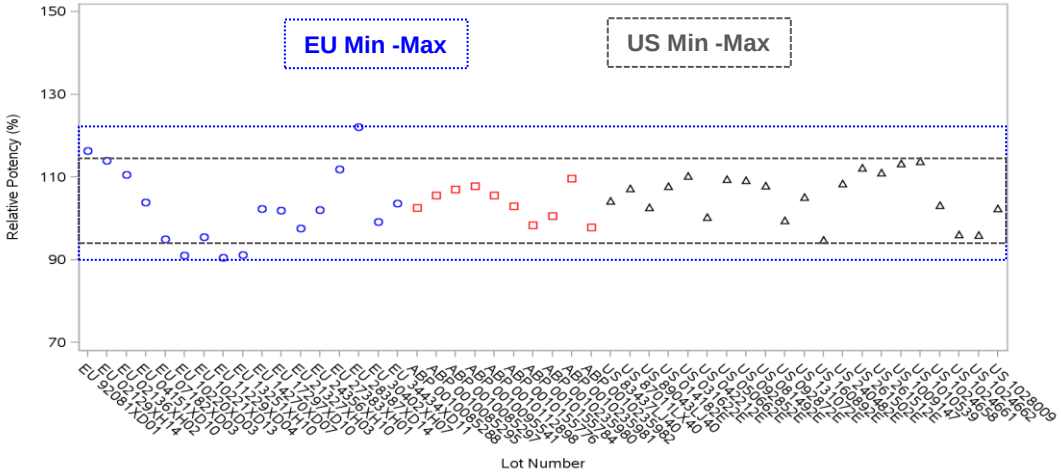
- Quality ranges for assessing quantitative quality attributes of high and moderate risk
- Tolerance intervals are not recommended for establishing the similarity acceptance criteria
- The sponsor can propose other methods of data analysis, including equivalence testing

FDA May 2019 Biosimilars Guidance for Industry
Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations

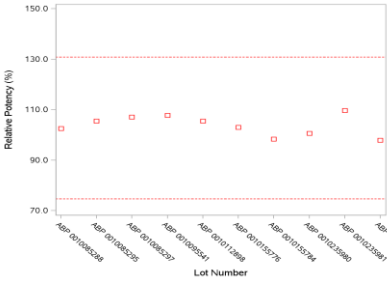
AMGEN BIOSIMILARS

SIMILARITY ACCEPTANCE CRITERIA USING QUALITY RANGE

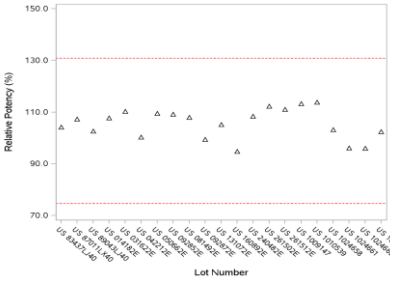
Quality range confirms visual (Min-max) test



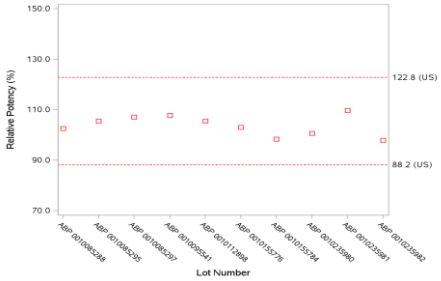
ABP vs EU



EU vs US



ABP vs US



Quality Range = mean ± 3 times standard deviation of the reference product lots

QR may underestimate RP variability

- **DP lots from same DS lot**
- **Impossible to sample all lots to cover RP clinical experience**

Expect 90% lots fall within the quality range

NON-STATISTICAL ACCEPTANCE CRITERIA CAN ALSO BE SCIENTIFICALLY JUSTIFIED FOR BIOSIMILAR COMPARISON

Some analytical results are not amenable to statistical analysis

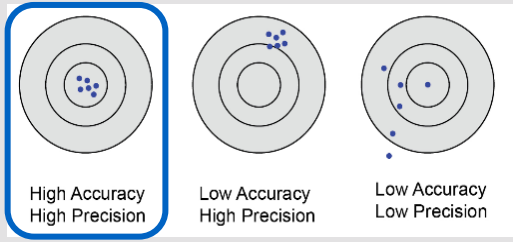
- Data close to or below limit of quantification (LOQ)
- Side-by-side (visual) comparison of chromatograms and spectrum
- Include objective criteria, e.g. similar profile with no new peaks above detection limits

Acceptance criteria should consider method and instrument capability

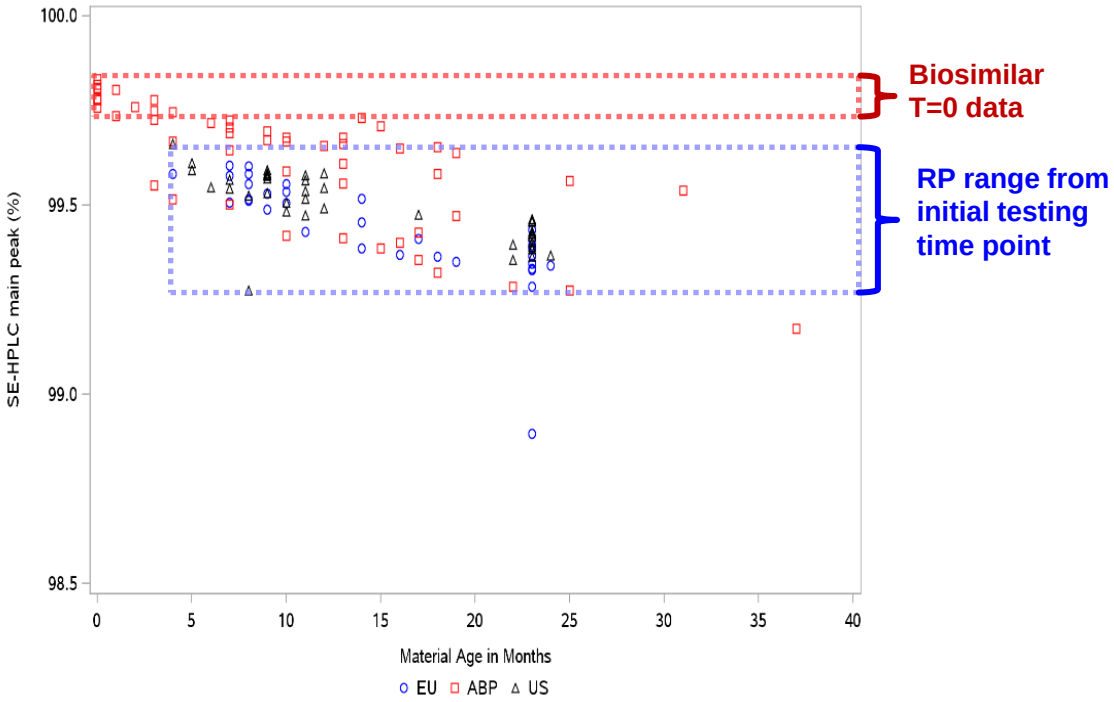
- Intermediate precision expected based on method qualification
- Consider both precision and accuracy relative to theoretical values based on RP

Some PQA are unique to biosimilar manufacturing process and should be controlled by in-process and lot release specifications

- Process-related impurities
- Formulation-dependents attributes
- Device-specific properties



SIMILARITY ACCEPTANCE FOR STABILITY-INDICATING PROPERTIES SHOULD CONSIDER MATERIAL AGE



Challenges:

It is impossible to obtain reference products at T=0

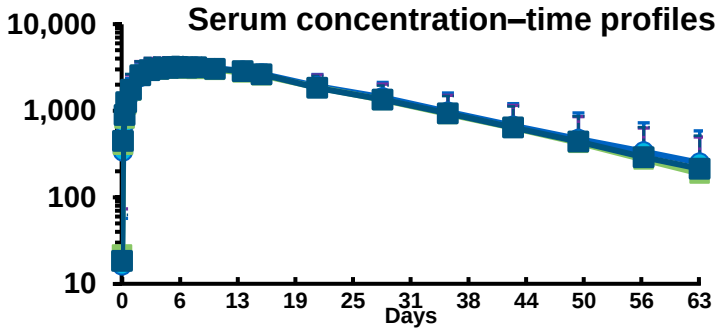
Observed differences maybe due to shelf life differences between tested biosimilar lots and reference product lots

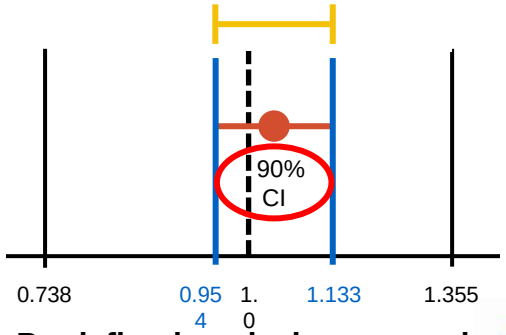
EXAMPLE OF AN APPROVED BIOSIMILAR MAB

Minor Differences in Product Variants

Attribute	Similarity outcome
SE-HPLC	✓
rCE-SDS	Minor differences
nrCE-SDS	Minor differences
CEX-HPLC	Minor differences
Glycan map	Minor differences
Potency	✓
ADCC	✓
CDC	✓

Equivalent PK and Clinical Efficacy

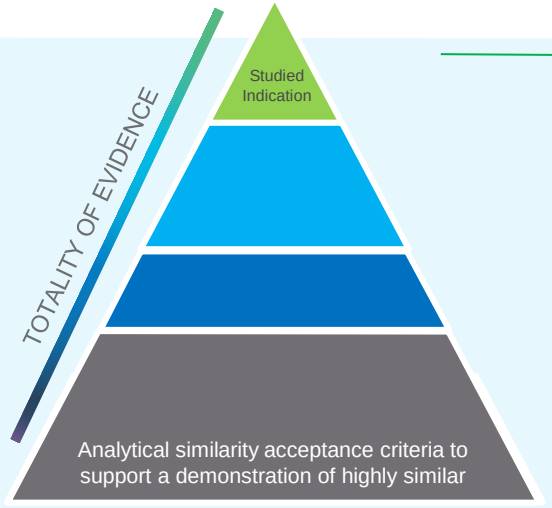




Predefined equivalence margin

EXTRAPOLATION IS BASED UPON KNOWLEDGE OF THE REFERENCE PRODUCT, TOTALITY OF EVIDENCE, AND SCIENTIFIC JUSTIFICATION[1]

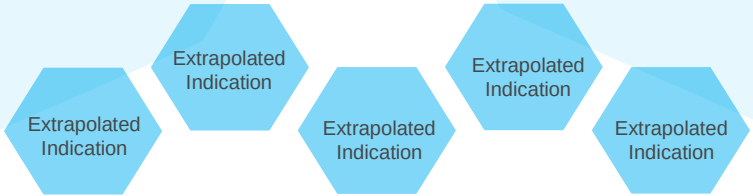
EXTRAPOLATION



BIOSIMILAR DEVELOPMENT[2]

Demonstrate biosimilarity to the reference product

NRAs previous finding of safety and efficacy for the reference product



SCIENTIFIC JUSTIFICATION

1. FDA. Considerations in Demonstrating Biosimilarity to a Reference Product. Guidance for Industry. Published April 2015 https://www.fda.gov/regulatory-information/search-fda-guidance-documents/scientific-considerations-demonstrating-biosimilarity-reference-product
2. Mysler T, et al. *Rheumatol Int.* 2016;36:613-615. 3. Declerck P, et al. *Pharm Res.* 2016;33:261-268

ARE PRODUCT-SPECIFIC MONOGRAPHS OBJECTIVE STANDARDS FOR ANALYTICAL SIMILARITY?

- **Biologic product complexity is not well suited for product-specific monographs**
- **Versions of biologic products can differ in relative amounts of product variants (size, charge, glycosylation, etc.)**
  - **Applies to all biologic products, including biosimilars or post-approval changes**
  - **Monographs based on one product at a point in time may not fit another product**
- **Health authorities should assess totality of evidence justifying quality, safety and efficacy**
  - **Compliance with product monographs is not necessary to ensure product quality or safety and efficacy and may also restrict innovation**
  - **There is the possibility for a monograph to be inappropriately linked to regulatory approval in lieu of a biosimilarity or comparability exercise**

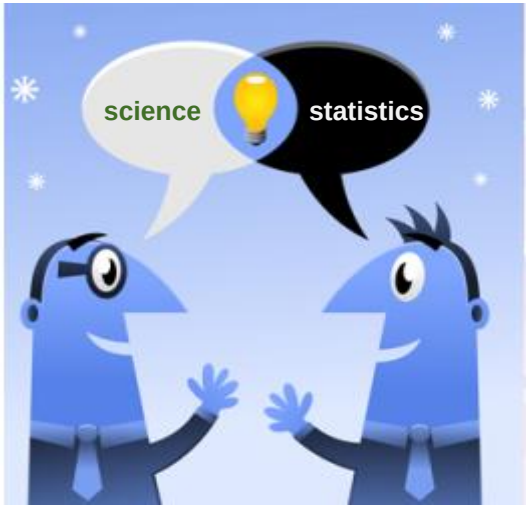
AMGEN BIOSIMILARS

CONSIDERATIONS FOR BIOSIMILAR PRODUCT LIFE CYCLE MANAGEMENT

- **After approval, biosimilar sponsors may file CMC variations**
  - **Improve manufacturing processes and optimize supply chains**
  - **Introduce new product presentations**
- **Sponsors should meet regulatory requirements for CMC changes**
  - **Data package and filing based on change level (minor, moderate, major)**
  - **Comparability should be demonstrated to pre-change product (ICH Q5E) and *analytical comparability acceptance criteria* are expected to be applied**
  - **Comparisons to reference product not generally required; therefore, *analytical similarity acceptance criteria* is not relevant**
- **For some changes, regulatory authorities may require targeted comparisons to reference product**
  - **E.g., new product strengths should match reference product strengths if available**
  - **Data necessary to support proposed change should be discussed with regulatory authority**

SUMMARY

- **Analytical similarity acceptance criteria should be scientifically justified based on attribute knowledge**
- **Statistics increase objectivity and confidence for the overall analytical similarity assessment conclusion**
- **Stability-indicating product attributes need to consider material age for meaningful comparisons**
- **Product-specific monographs are not well-suited as objective standards for analytical similarity assessment**
- ***Analytical similarity* acceptance criteria do not influence extrapolation or product lifecycle management beyond the initial required demonstration of biosimilarity**



ACKNOWLEDGEMENT

Leah Christl

Gino Grampp

Patrick Swann