FDA U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION & RESEARCH
OFFICE OF CLINICAL PHARMACOLOGY

Biosimilars: Bioanalysis Perspective

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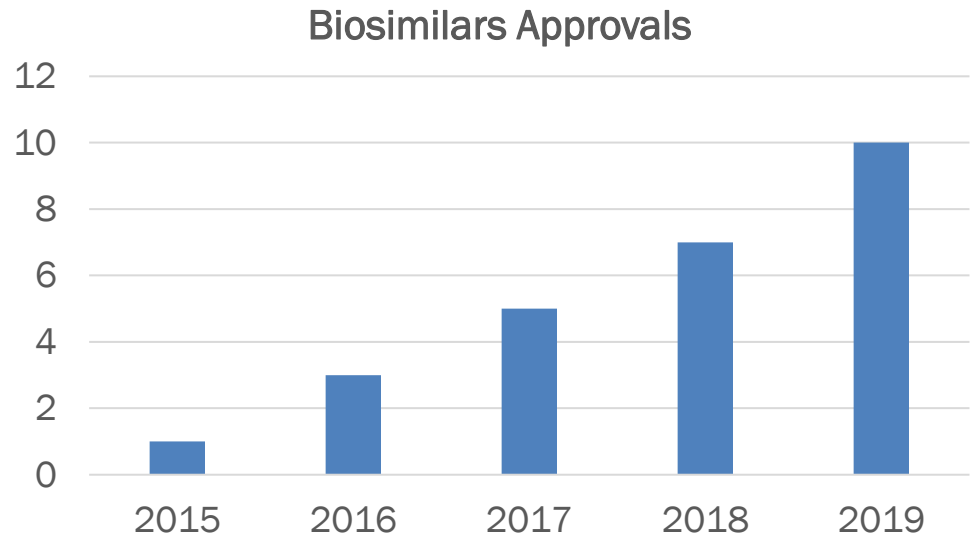
Learning Objectives

- Introduction to Biosimilars
  - Definitions
  - Submission components
  - Bioanalysis
- Case Examples
  - Bioanalysis Platform
  - Validation: QC, SC, and Long-term stability
  - Validation: SC
- Recommendations

Regulatory Pathway

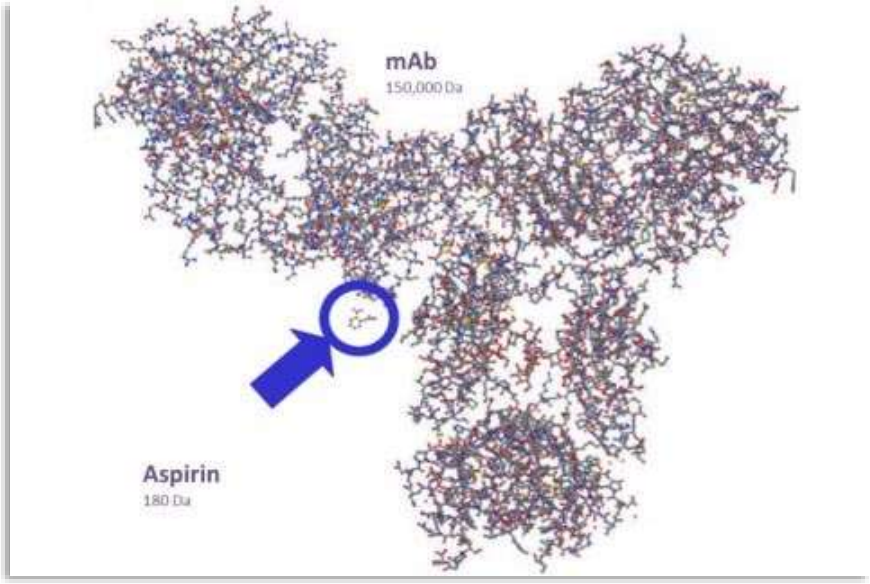
- Biologic Price Competition and Innovation Act of 2009 (BPCI act)
  - Part of the Affordable care Act of 2008
- Abbreviated licensure pathway 351 (k)
- Steady increase in biosimilars approvals
- Biosimilars are not generics



Complexity

- Complexity of biologics
  - Primary sequence
  - Higher order structures
  - Post-translational modifications
  - Higher variability

- Biosimilar: minor differences in clinically inactive components



https://www.linkedin.com/pulse/biosimilars-next-money-makers-pharma-industry-macarena-fritz

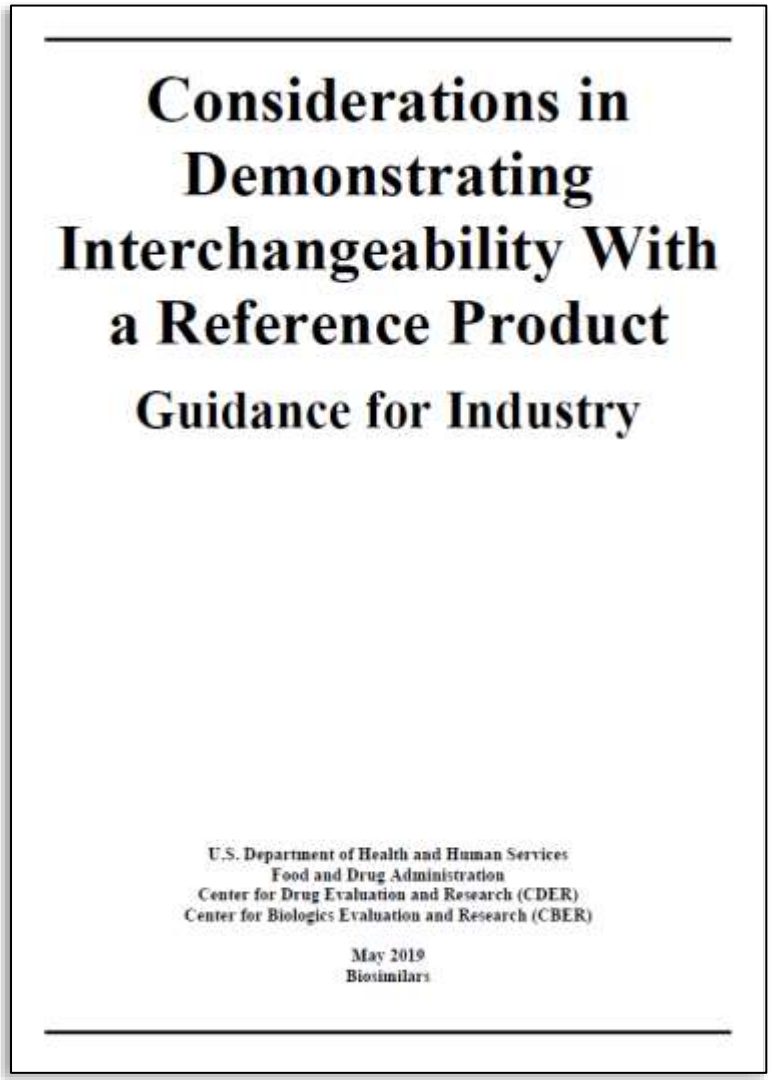
Establishing Biosimilarity

- Step-wise approach
- Analytical similarity
  - Structural
  - Functional
- PK assessment is essential
- Comparative clinical studies
  - Address residual uncertainties

https://www.fda.gov/drugs/biosimilars/biosimilar-development-review-and-approval

Interchangeability

- The same clinical result in any given patient
- Clinical risk of switching is not higher than using reference
- Substituted for the reference without HCP intervention
- Interchangeability studies:
  - Compares switching versus non-switching
  - **PK endpoints**


Considerations in Demonstrating Interchangeability With a Reference Product

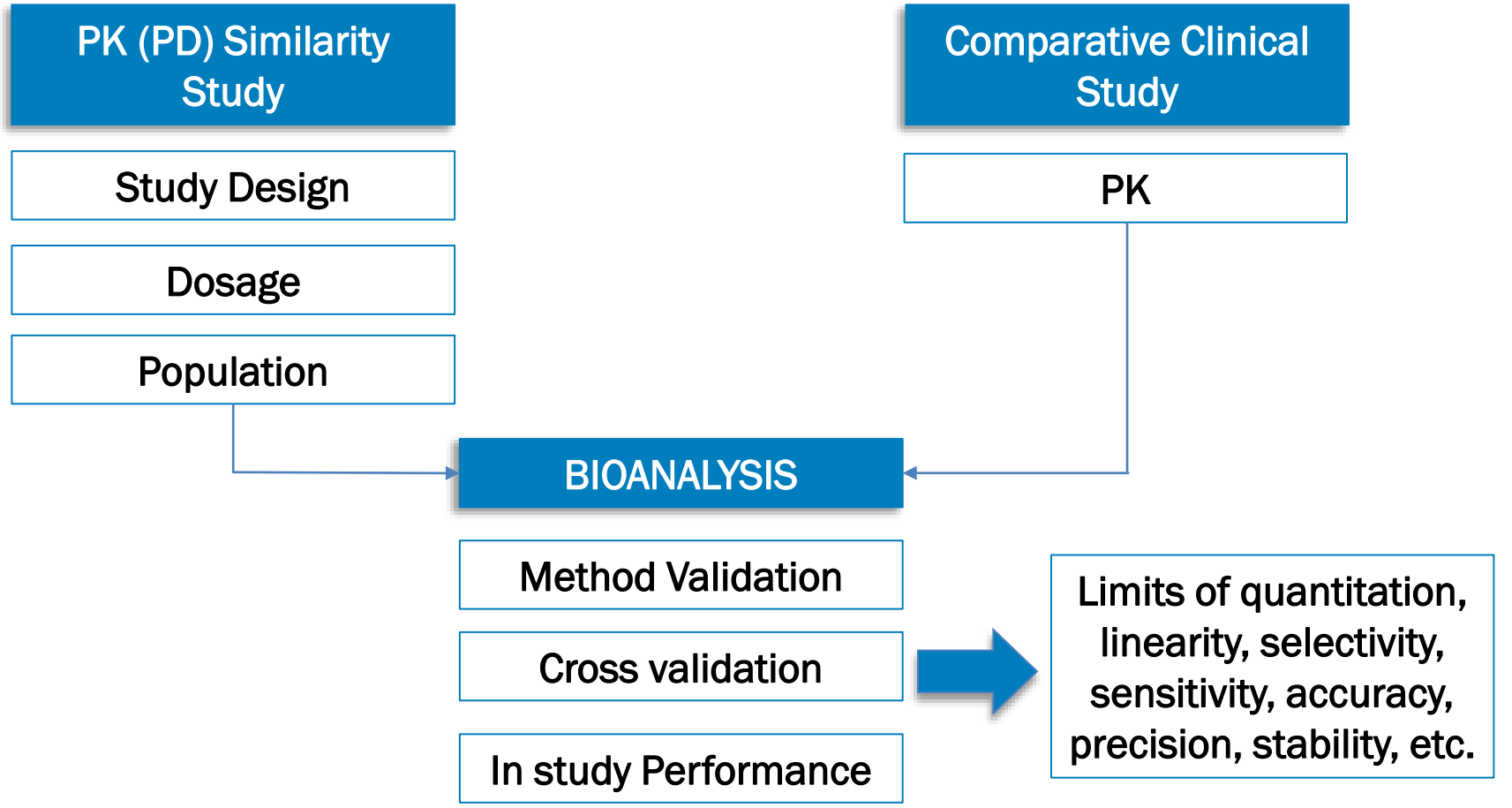
Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2019
Biosimilars

https://www.fda.gov/media/124907/download

Scope of Clinical Pharmacology Review



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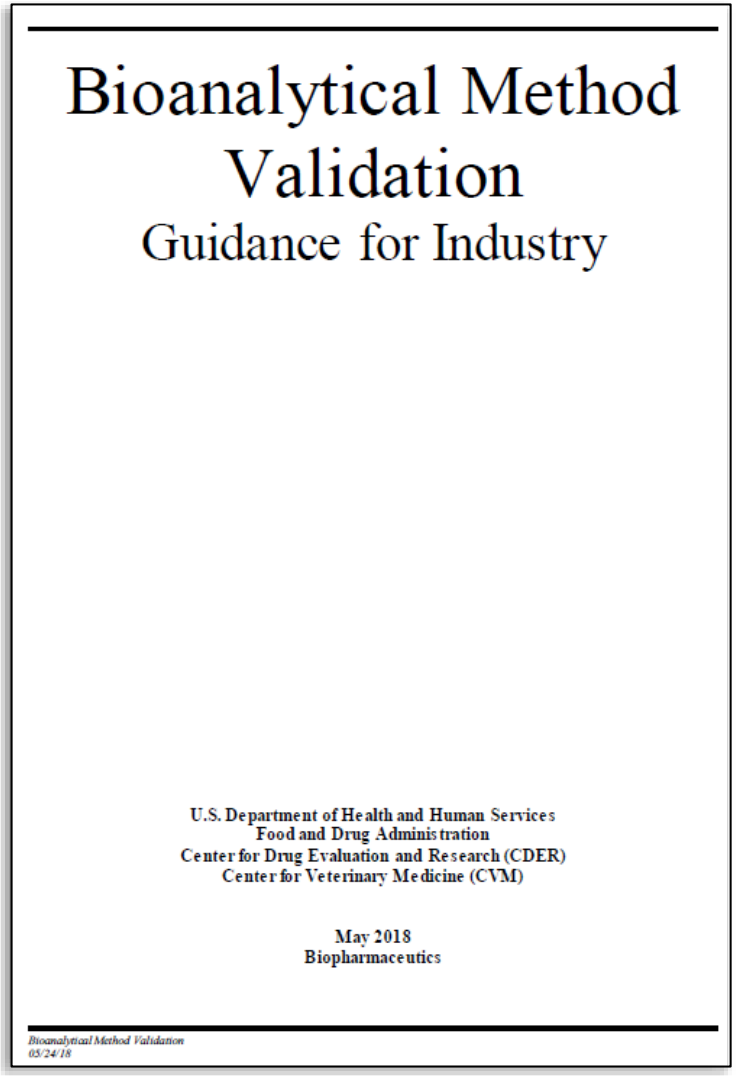

Bioanalytical Method Validation

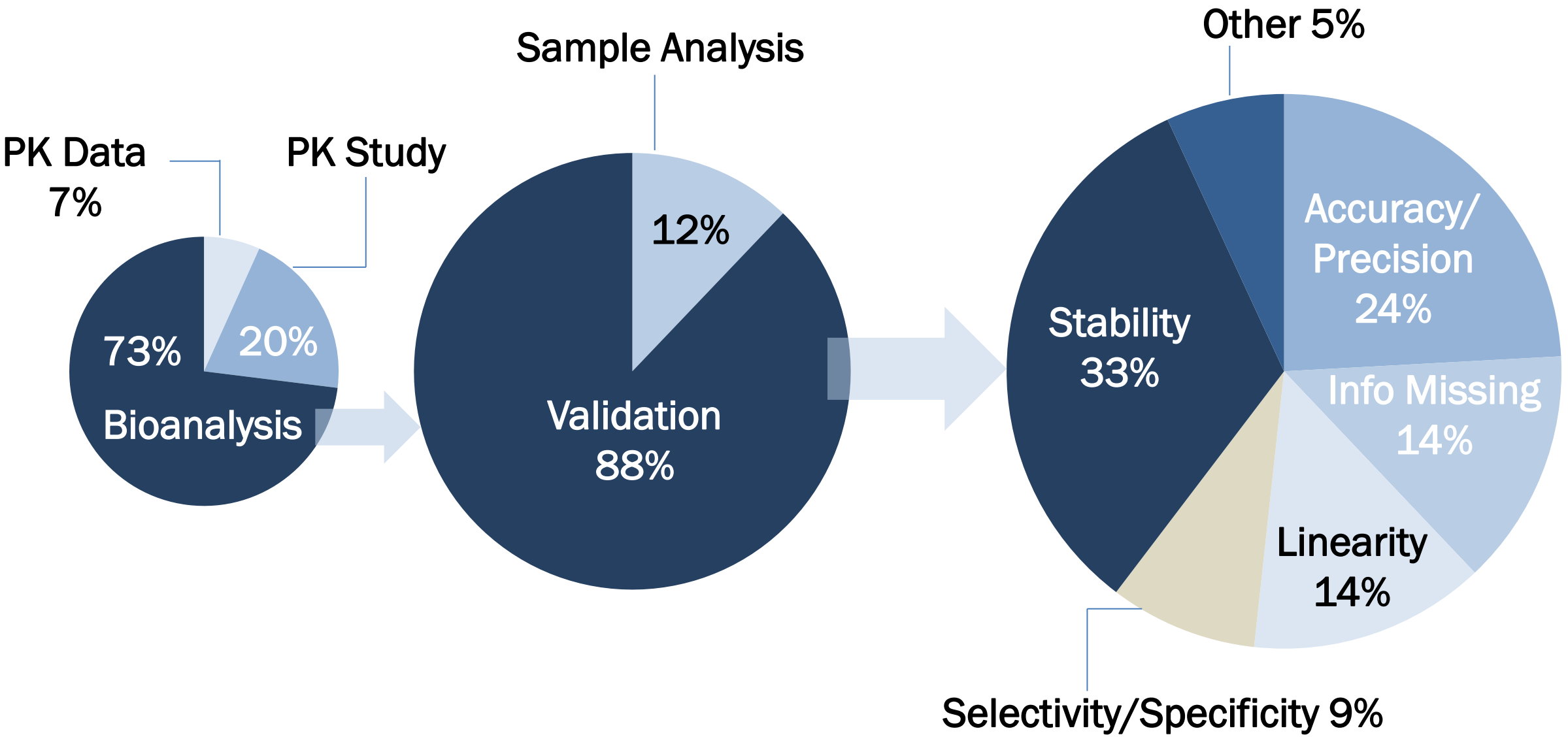
Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Veterinary Medicine (CVM)

May 2018
Biopharmaceutics

Bioanalytical Method Validation
05/24/18

Information Requests



CASE 1

BIOANALYSIS PLATFORM

Background

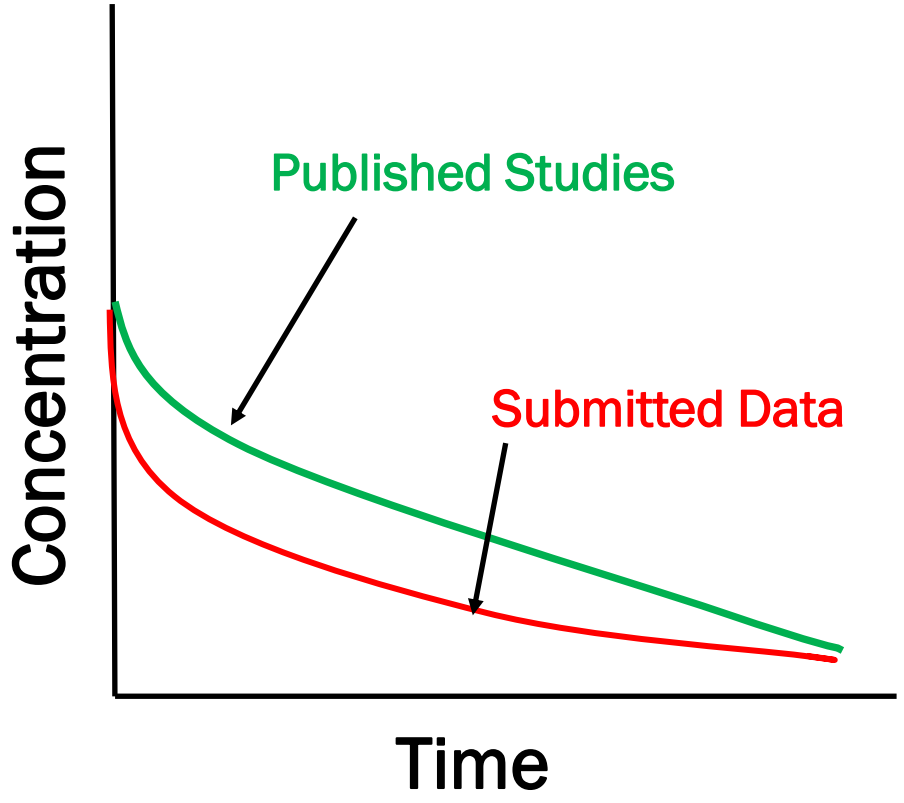
- Monoclonal Antibody
- Multiple applications submitted
- Pharmacokinetics are well-characterized and consistent
- Design of PK similarity study is acceptable

Review Issue

- PK similarity study: low observed concentrations in both test and reference
  - $AUC_{0\text{-inf}}$ of US-reference product is 55% of published data

- No difference in patient demographics

Parameter	PK Similarity Study	Published Information
Age (years)	34 (11.2)	35.3 (9.2)
Weight (kg)	81.4 (11.0)	77.3 (10)
RACE		
Asian	34%	NK
Black	17%	49%
White	49%	25%



Review Issue

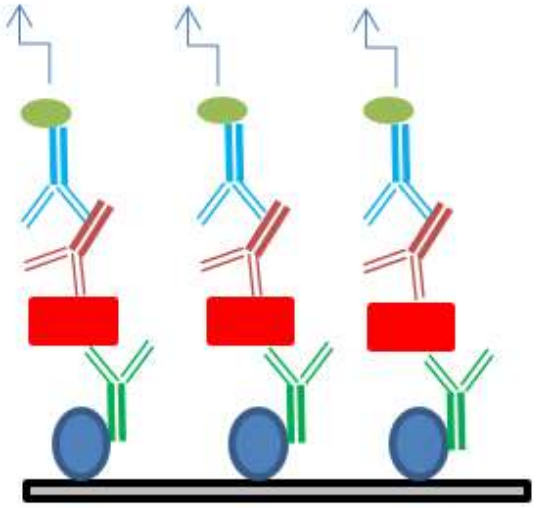
- Information request issued to the Applicant

- Applicant stated:
  - No notable differences in study design
  - No notable differences in patient demographics
  - **The observed difference is likely due to assay platform:**

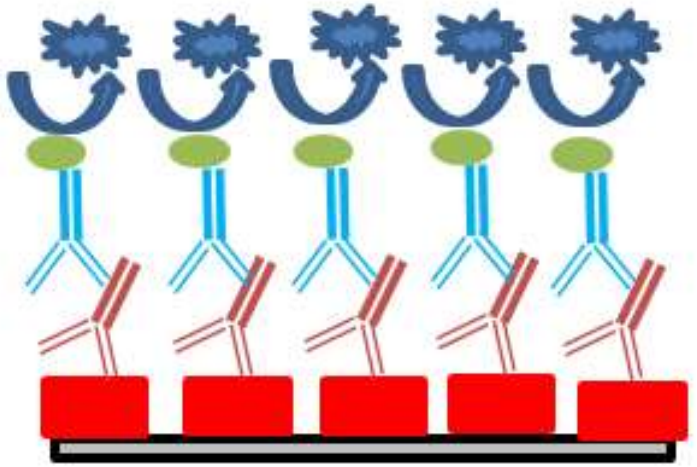
    Method 1 *versus* **Method 2**

Assay Platform

Method 1



Method 2

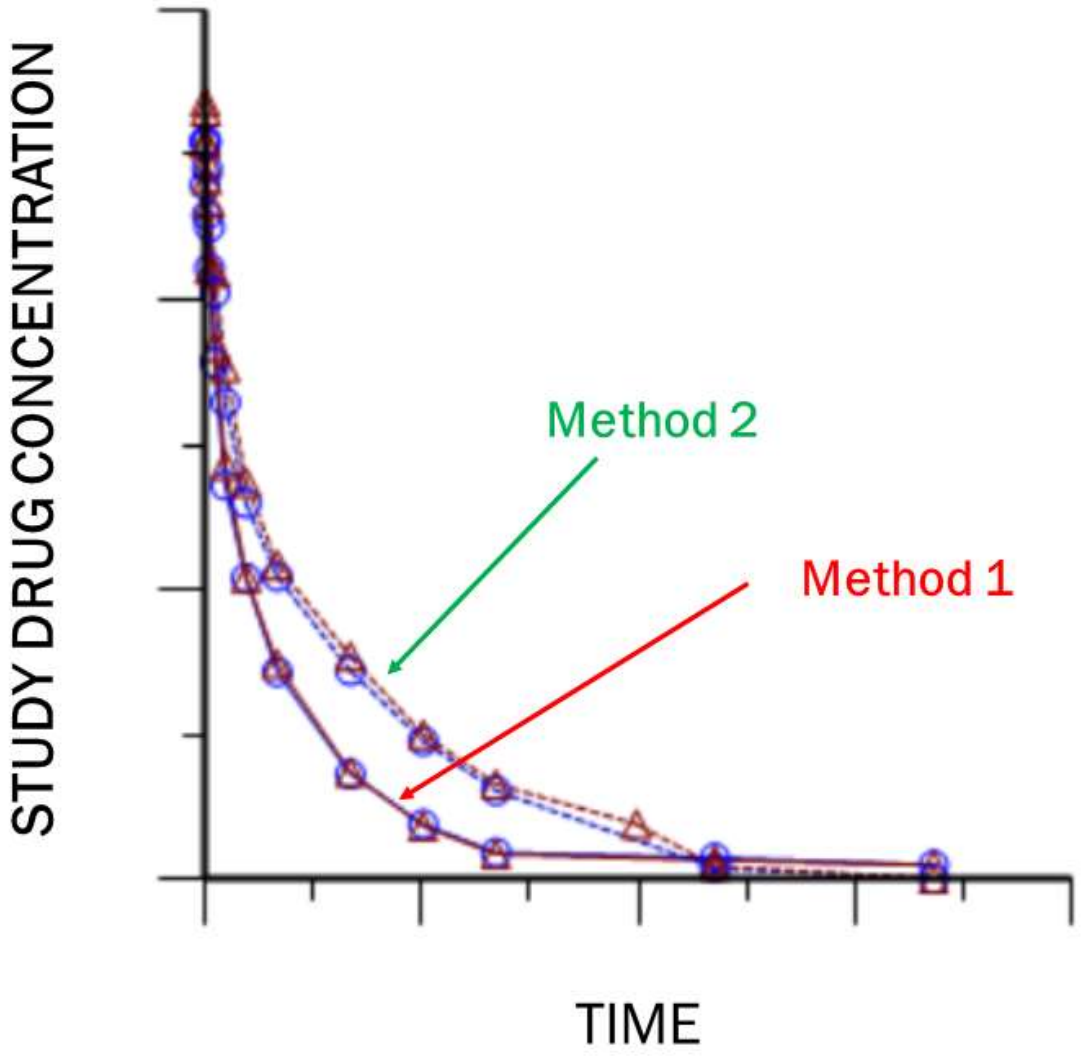


Differences:

- Required binding and wash steps
- Required dilutions
- Reagents
- Dynamic Range

Reanalysis with Method 2

- Reanalysis of study samples with Method 2
- Higher concentrations observed
- PK very similar to published data



Potential Issues

- Accuracy may be an issue
  - Suboptimal capturing (incubation, reagents, methodology)
  - Underreporting of actual concentrations
  - Insensitive to detecting potential differences in PK
  - Communicated with the applicant to resolve the issue

- Method 2 assay results were used for regulatory review and approval
  - Samples were reanalyzed with method 2 during the course of the review

CASE 2

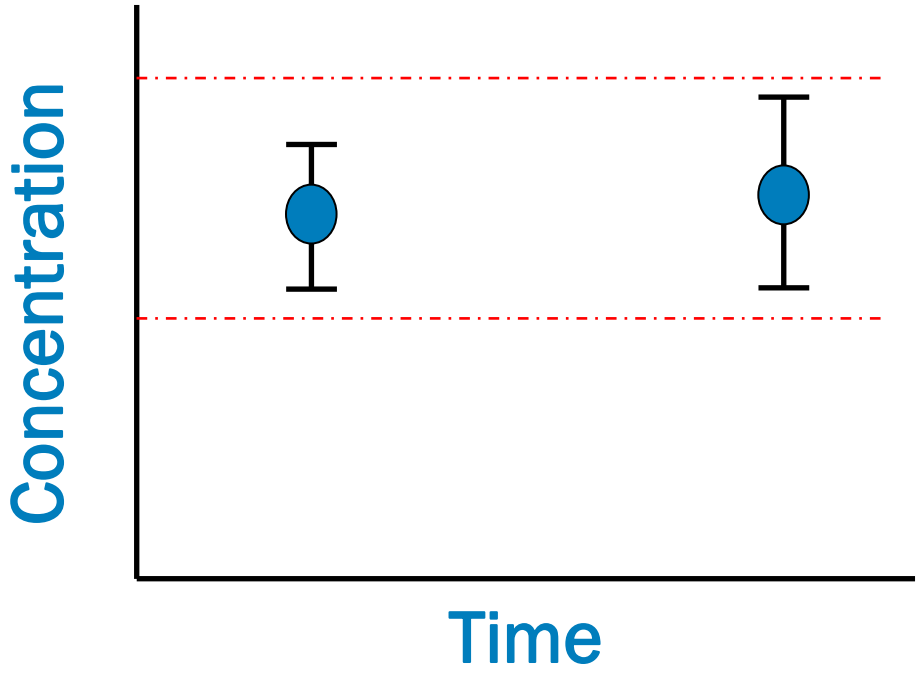
VALIDATION: QC, SC, LONG-TERM STABILITY

Background

- Monoclonal Antibody
- Design of PK similarity study is acceptable
- Pharmacokinetic data appear generally adequate and similar to other products
  - US-licensed product
  - EU-approved product
  - Proposed biosimilar

Validation Runs

- One validated method with a chosen set of SC and QC should be used for method validation and sample analysis



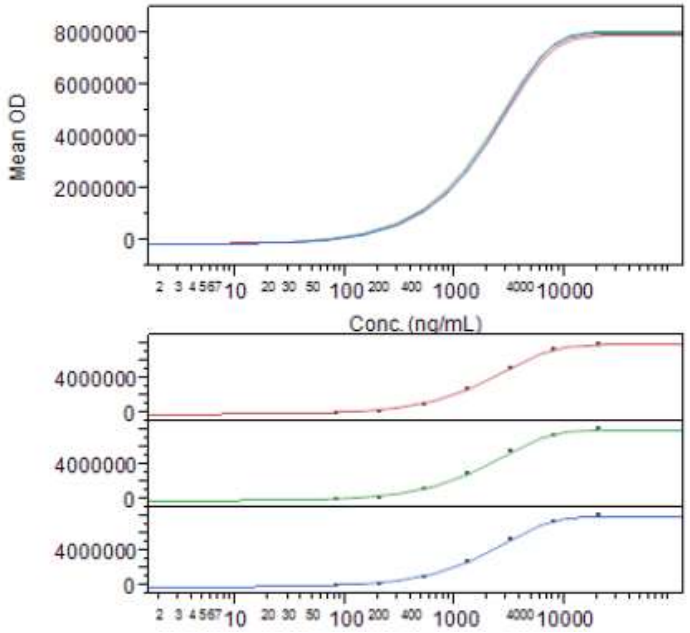
- CS and QC were prepared using different products during validation:
  - CS with US-licensed product up to Day 29
  - CS with EU-approved product at later time points

Review Issue

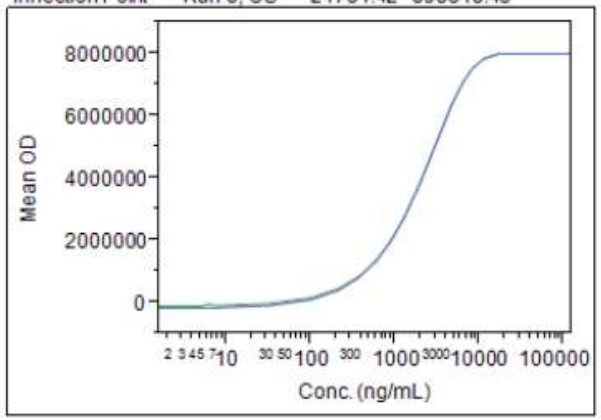
- Reject runs after switching SC to EU-approved product?
  - No LTS stability data
  - Bioanalytical similarity between SC and QC?
- No acceptable LTS EU-approved product (at any time point)
- No freeze/thaw or bench-top stability for EU-approved product
- Dilutional linearity
  - Validated range supported 500 to 2500 dilution factors
  - Dilution factors used in sample analysis were 5 to 500

Bioanalytical Similarity of CS

- Nominal CS value vs instrument readout (3 products)
- Overlaid CS show similar profile but not within the validated range
- QC bias between products is not established
- The applicant provided stability data for US-product and proposed product with the CS and QC samples using US-product



Parameter	Group	Estimate	Std Error
Growth Rate		0.0003456	3.8369e-5
Lower Asymptote		-1.52e+10	4.403e+12
Upper Asymptote		8025619.3	80765.602
Inflection Point	Run 8, BSI	-21787.05	838818.24
Inflection Point	Run 8, EU	-21808.67	838817.44
Inflection Point	Run 8, US	-21781.42	838818.45



Validation Data

- Long-term stability for EU-product was using US-licensed CS during the review cycle
- Freeze/thaw stability and bench-top stability for EU-approved product using US-licensed CS
- Dilutional linearity in sample analysis range was validated

Summary

- Stability should be established for each product individually
  - Long-term storage, bench top, and freeze-thaw

- Calibrators and QC samples should be consistently prepared with one product during validation and analysis runs

CASE 3

VALIDATION: CALIBRATION STANDARDS

Background

- Monoclonal antibody
- PK study design is acceptable
- Pharmacokinetic data appear generally adequate and similar to other products

QC and Calibrators

- Calibrators:
  - 5*, 10, 15, 25, 45, 75, 125, 225, 300, and 500* concentration units
- QC:
  - 10, 30, 70, 210, and 300 concentration units

- Study samples are analyzed with calibration range of 10-300 conc. units

Review Issue

- Selectivity failed at 10 but was established at 30
- LLOQ is 30
- Calibrators:
  - 5*, 10*, 15*, 25*, 45, 75, 125, 225, 300, and 500* conc units
- QC:
  - ~~10~~, ~~30~~, 70, 210, and 300 concentration units

Review Issues

- Inadequate assay validation
  - 5 calibrators only
  - Low QC below the revised calibration range
  - Stability not reliable

- Additional issue: dilution linearity validated up to 100-fold
  - Analyzed samples diluted up to 150-fold
  - High dilution QCs were 2- to 4-fold lower than C_{max}

Information Request

- Demonstrate selectivity at 25 conc units (calibrator available at 25 conc units)
- Re-estimate calibration curves for all runs
  - New range: 25-300 conc units
  - 10 and 500 as anchor points
- Generate new PK profiles and reassess PK similarity
- Provide dilution linearity data

Recommendations

- Follow the FDA bioanalytical method validation guidance
- Method validation, like other applications, should cover conditions encountered in study
- Single bioanalytical method to support PK similarity assessment
- Good Practice: Method assessment-Thway et al AAPS J (2020) 22: 15
  - Calibrators and QC samples should be consistently prepared with one product during validation and analysis runs

Recommendations

The AAPS Journal (2020) 22: 15
DOI: 10.1208/s12248-019-0397-8

Regulatory Note

Current Perspectives on Ligand-Binding Assay Practices in the Quantification of Circulating Therapeutic Proteins for Biosimilar Biological Product Development

T. M. Thway,[1,2] Y. M. Wang,[1] B. P. Booth,[1] K. Maxfield,[1] S. M. Huang,[1] and I. Zineh[1]

Acknowledgments

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Challenge Question #1

A biosimilar product is an exact copy of the reference (innovator) product

a. True

b. False

ANSWER

Minor differences that do not affect the clinical performance of the biosimilar product are allowed

Challenge Question #2

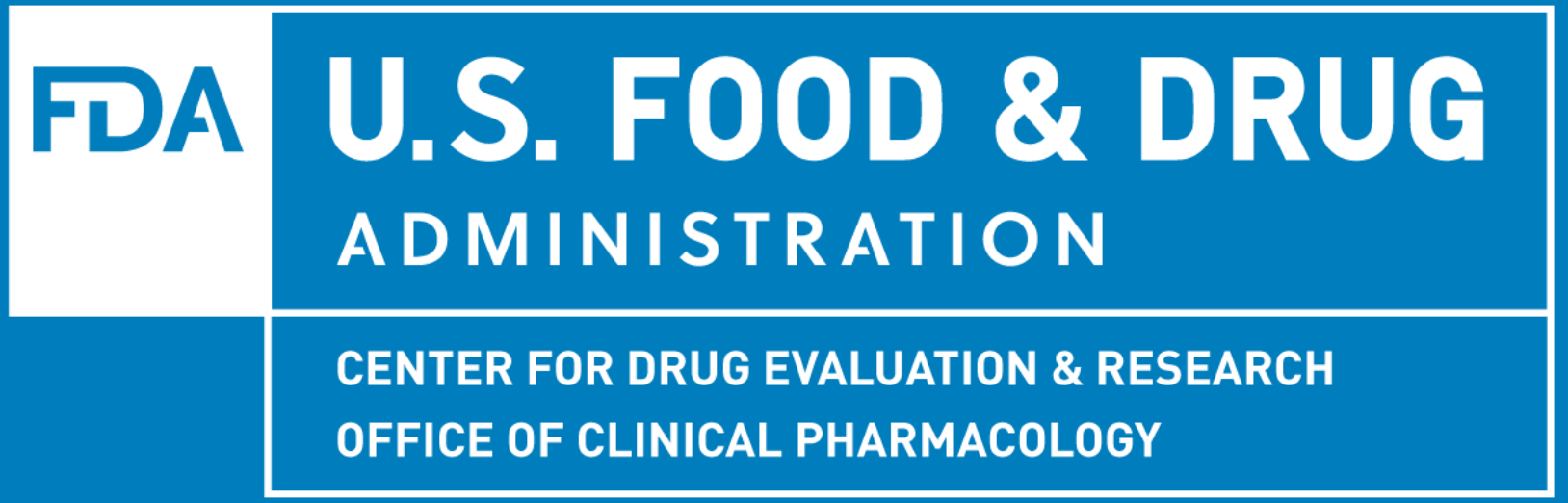
An interchangeable product can possibly have higher clinical safety-efficacy risk compared to reference product, yet can be substituted without HCP intervention

a. True

b. False

ANSWER

An interchangeable product is not expected to have higher clinical safety-efficacy risk compared to reference product



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Review Questions

- How many bioanalytical methods used in the application?
- Are there changes to the method? Is there cross-validation?
- Does the method validation report meet regulatory guidance?
  - Specificity
  - Selectivity
  - Accuracy and precision
  - Linearity
  - Stability
- Is the sample analysis report acceptable?
  - Performance/inclusion of calibration standards and QC samples
  - Run acceptance criteria
  - Incurred sample reanalysis