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Biosimilars

January, 19th
2017

AAPS **Biosimilar Focus Group** Committee

Chair: Shefali Kakar (Novartis)

Past Chair: Carol Kirchhoff (Pfizer)

Secretary: Safa Alvandkouhi (BioAgilytix Labs)

Student Representative: Robert Dingman (University of Buffalo)

Communications: Susan Hurst (Pfizer)

"Recommendations from the AAPS Biosimilars Focus Group Committee on the Development and Validation of Neutralization Antibody Assays for Biosimilar Drug Development"

Steering Committee

Biosimilar Focus Area	Individual	Organization
Clinical PK/PD/Immunogenicity	Penny Zhu	Sandoz
Non-clinical/Clinical Assay (subcommittee co-leads)	**Dominique Gouty**	**BioAgilytix**
	Tina Satterwhite	Charles River
CMC-Analytical/DS/DP	Henriette Kuehne	Coherus

Contact: Shefali (shefali.kakar@novartis.com)

AAPS LBABFG Biosimilars Action Program Committee (APC)

THE APC MANDATE:

To identify unique bioanalytical (PK, Immunogenicity, Biomarker assay) challenges related to Biosimilars development and to provide guidance/recommendations to address them.

THE APC OUTPUT:

White Paper(s) to provide recommendations to the bioanalytical community, which in turn may help provide recommendations to any regulatory authority guidance initiative.

Lead:
- Joseph C. Marini (Janssen R&D/J&J)

Ad hoc:
- Lakshmi Amaravadi (Chair, LBABFG)

Working Members:
- Mike Anderson (ICON)
- Ron Bowsher (B2S Consulting/AITB)
- Xiao-Yan Cai (Merck)
- John Chappell (CPR Pharma Services)
- Todd Coffey (CMC Biostatistics)

Consultants:
- Robert Bell (Drug & Biotechnology Development)
- Marian Kelley (MKelley Consulting)
- Wendell Smith (B2S Consulting)
- Dominique Gouty (BioAgilytix)
- Aparna Kasinath (Clinigene)
- Vera Koppenburg (Sandoz)
- Philip Oldfield (Bioanalytical Consulting)
- Shannon Rebarchak (Janssen R&D/J&J)

Biosimilars

The final goal of this exercise is to provide:

Meaningful interpretation of comparability study data for biosimilar drug development not only to ensure safety and efficacy but also allow for drug **substitution** and **exchangeability.**

It is critical to demonstrate the comparability of the Biosimilar to the Originator product.

The Future of Biosimilars

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Biosimilars

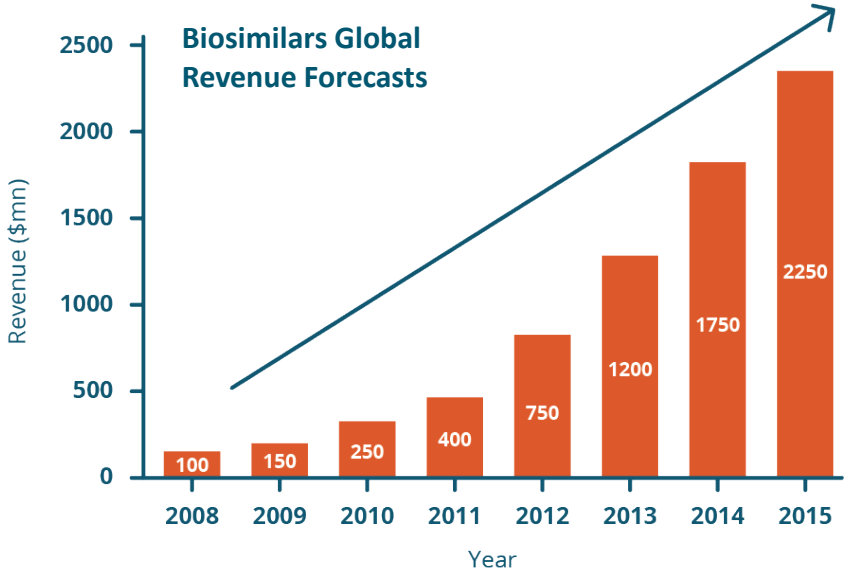
A biosimilar is a biological product that is **highly similar to a reference biological product notwithstanding minor differences in clinically inactive components,** and for which there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product."

From FDA DRAFT Guidance: *"Quality Considerations in Demonstrating Biosimilarity to a Reference Product."* Feb 2012.

Future of Biosimilars

Biosimilars Global Forecast

Forces **driving the rapid expansion of the biosimilar industry** are an ever-increasing pressure to reduce healthcare costs, expectations for booming market growth due to patent expiry of high-value innovator biologics, and better-defined regulatory pathways.



Future of Biosimilars

Risks and Requirements

Biosimilar Development

Strategies must adapt to evolving regulatory requirements

Clinical Development

Strategies must focus on patient selection and appropriate clinical endpoints

Commercial Strategies

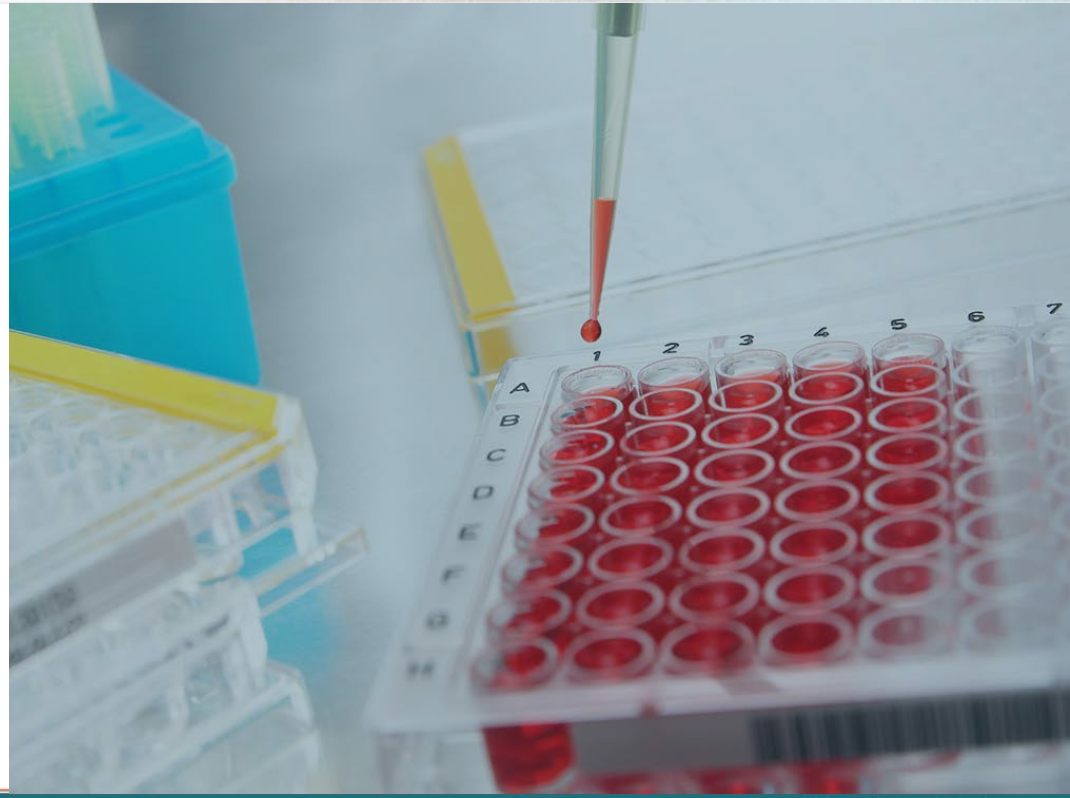
Must optimize market uptake of biosimilars market

Future of Biosimilars

Development Requirements

Structural Characterization for Biosimilar Products

- ✓ Amino acid sequence
- ✓ Amino acid composition
- ✓ Terminal amino acid sequence
- ✓ Peptide map
- ✓ Sulfhydryl group(s) and disulfide bridges
- ✓ Carbohydrate structure



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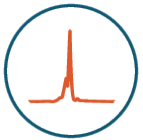
Development Requirements

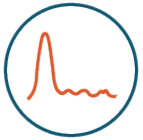
Physcio-Chemical Properties of Biosimilar Products

Molecular Weight or Size



Isoform Pattern

Extinction Coefficient



Electrophoretic Pattern

Liquid Chromatographic Pattern

Spectroscopic Profiles

Future of Biosimilars

Manufacture and Formulation Requirements

Structural and Functional Characterization

Primary Structures	→	Identical Amino Acid Sequence
Higher Order Structures	→	Secondary, Tertiary, Quarternary and Aggregation
Enzymatic PTM	→	Glycosylation, Phosphorylation, g-Carboxylation, b-Hyroxylation
Other Protein Variants	→	Amidation/Deamidation, Oxidation, Disulfide Bonds

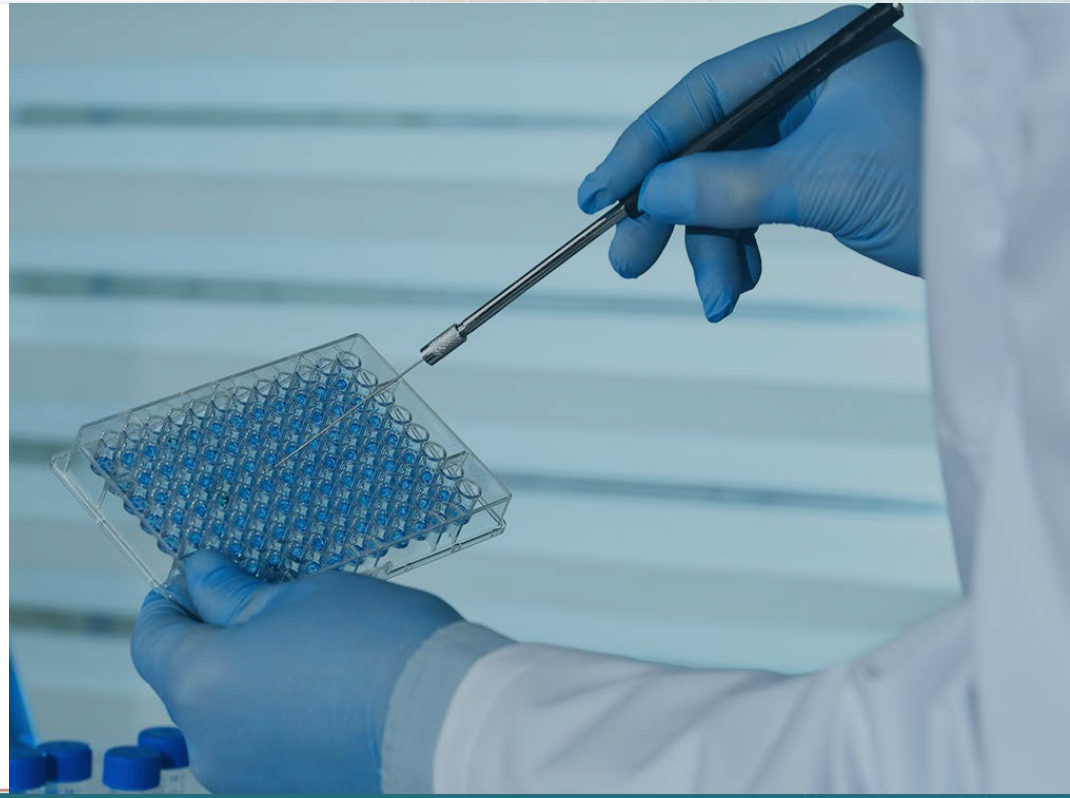
Identify Post-Translational Modifications (PTM) and Assess Impact

Future of Biosimilars

Manufacture and Formulation Requirements

Purity & Comparability

- ✓ In vitro receptor-binding or cell-based assays
- ✓ Biosimilarity testing
- ✓ Levels of product related impurities (aggregates, oxidized forms, deamidated forms)
- ✓ Process related impurities and contaminants (host cell proteins, residual genomic DNA, reagents, downstream impurities)



Future of Biosimilars

Preclinical and Clinical Studies

- ✓ **Non-Clinical Studies**
  - Comparative studies, single dose
  - Assess toxicity, additional support for biosimilarity, and contribute to the immunogenicity assessment
- ✓ **Comparative Clinical PK and PD**
  - Including immunogenicity
- ✓ **Comparative Clinical Safety and Effectiveness Data**

PRECLINICAL → PHASE I → PHASE II

Introduction

No regulatory guidance clearly describes the requirements for the bioanalytical testing of Biosimilars.

- ✓ An increasing number of patents for Innovator biological products are due to expire
- ✓ Opportunity for the development of Biosimilars within the Biotech industry
- ✓ Critical to demonstrate the “similarity” of the Biosimilar products to its Innovator (reference) product
- ✓ Pharmacokinetic and Immunogenicity assays to support the non-clinical and clinical similarity

Pharmacokinetics

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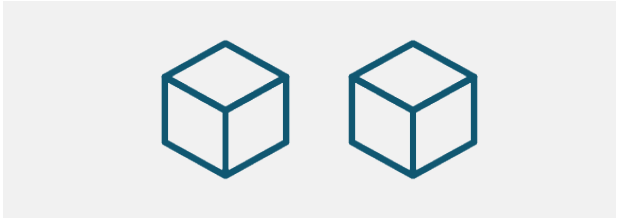
Biosimilar **Pharmacokinetics**

> The goal is to confirm **'bioanalytical similarity'** of Biosimilar and Reference drugs (Originator)"

Biosimilar **Pharmacokinetics**

Are we comparing Biosimilar to Originator U.S. only or to U.S. and Europe?



Biosimilar | Originator U.S.

Validation Approximately 12-15 Runs

Biosimilar | Originator U.S. | Originator E.U.

Validation Approximately 18-22 Runs

Correction factor accepted in Europe – Not acceptable in U.S.

Future of Biosimilars

Bioanalytical PK

A single LBA should be used to support PK assessments

Development Phase

Standard curve generated using Biosimilar drug should be demonstrated to be parallel to a Originator drug standard curve

Validation Phase

Biosimilar drug QC samples should be demonstrated to be bioanalytically similar to Originator drug QC samples

Successful completion enables a laboratory to use one assay to support Biosimilar drug development program

Biosimilar **Pharmacokinetics**

- ✓ Confirms “Similarity” of standard curves
- ✓ Ensures Innovator biotherapeutic and Biosimilar curves are parallel
- ✓ Recommended a statistically based approach for comparing curves
- ✓ Software availability (ALLFIT)

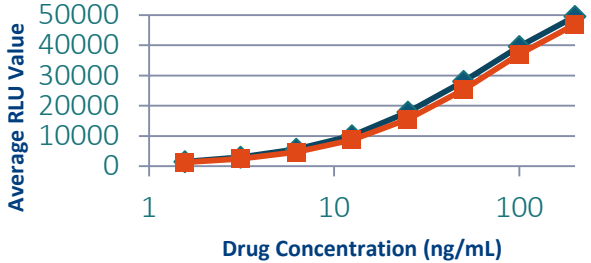
- ✓ Confirmatory evaluation of parameters established in Development prior to Validation

- ✓ Confirms comparable reactivity of Biosimilar & Innovator in common LBA
- ✓ Systematic comparison of QC results
- ✓ Phase 1: Intra-batch evaluation
- ✓ Phase 2: Inter-batch evaluation
- ✓ Direct comparison of Biosimilar against innovator

Calibration Curve – Example

Biosimilar Originator

	1 2	3 4	5 6	7 8	9 10	11 12
A	100 ng/mL	100 ng/mL	100 ng/mL	100 ng/mL	100 ng/mL	100 ng/mL
B	50 ng/mL	50 ng/mL	50 ng/mL	50 ng/mL	50 ng/mL	50 ng/mL
C	25 ng/mL	25 ng/mL	25 ng/mL	25 ng/mL	25 ng/mL	25 ng/mL
D	12.5 ng/mL	12.5 ng/mL	12.5 ng/mL	12.5 ng/mL	12.5 ng/mL	12.5 ng/mL
E	6.25 ng/mL	6.25 ng/mL	6.25 ng/mL	6.25 ng/mL	6.25 ng/mL	6.25 ng/mL
F	3.13 ng/mL	3.13 ng/mL	3.13 ng/mL	3.13 ng/mL	3.13 ng/mL	3.13 ng/mL
G	1.56 ng/mL	1.56 ng/mL	1.56 ng/mL	1.56 ng/mL	1.56 ng/mL	1.56 ng/mL
H	NSB	NSB	NSB	NSB	NSB	NSB



- ✓ Three independently prepared Biosimilar and Innovator standard curves in duplicate
- ✓ Average response for each calibrator across three preps
- ✓ Two plates, two analysts

Calibration Curve – Example

ALLFIT Software

Fit calibrator curve models independently to Biosimilar and Innovator (Unrestricted Model)

Fit calibrator curve models for Biosimilar and Innovator assuming each curve has the same parameters except EC50 (Restricted Model)

Assess parallelism using F-test (assume parallel if p-value>0.05)

If parallel, calculate ratio of EC50 values for Biosimilar and Innovator

- ✓ **At least 1 of the 2 comparisons of standard curves must be judged to be parallel**
- ✓ **All EC50 ratios must be between 0.8 and 1.25**

GEN 5 and JMP can also do this data interpretation

Parameters: Typical PK + Specific QC - Selectivity

Standard Curve Selected : Preferable Biosimilar

Quality Control for biosimilar & originator(s)

- ✓ Intra-batch evaluation for each QC concentration (%CV)
- ✓ Inter-batch evaluation, Biosimilar and Innovator
- ✓ Inter-batch mean bias (%RE) ±20% (25% ULOQ, LLOQ)
- ✓ Check for variability

Selectivity for biosimilar & originator(s) at least 3 individuals

- ✓ (%RE) ±20% (25% ULOQ, LLOQ)

Validation Plan

	Runs	Comments	STD wells	QC wells
Run 1	Accuracy -Precision		1 set x 2 wells x 8 STD	3 sets x 2 wells x 5 QC
Run 2	Accuracy -Precision		1 set x 2 wells x 8 STD	3 sets x 2 wells x 5 QC
Run 3	Accuracy -Precision		1 set x 2 wells x 8 STD	3 sets x 2 wells x 5 QC
Run 4	Accuracy -Precision		1 set x 2 wells x 8 STD	3 sets x 2 wells x 5 QC
Run 5	Accuracy -Precision		1 set x 2 wells x 8 STD	3 sets x 2 wells x 5 QC
Run 6	Accuracy -Precision		1 set x 2 wells x 8 STD	3 sets x 2 wells x 5 QC
Run 7	2 sets QC (biosimilar)	Selectivity (Biosim)	1 set x 2 wells x 8 STD	2 sets x 2 wells x 3 QC
Run 8	2 sets QC (biosimilar)	Selectivity (Biosim)	1 set x 2 wells x 8 STD	2 sets x 2 wells x 3 QC
Run 9	2 sets QC (biosimilar)	Selectivity (originator)	1 set x 2 wells x 8 STD	2 sets x 2 wells x 3 QC
Run 10	2 sets QC (biosimilar)	Selectivity (originator)	1 set x 2 wells x 8 STD	2 sets x 2 wells x 3 QC
Run 11	2 sets QC (biosimilar)	Short Term Stab. (all)	1 set x 2 wells x 8 STD	2 sets x 2 wells x 3 QC
Run 12-13	2 sets QC (biosimilar)	FTS (all)	1 set x 2 wells x 8 STD	2 sets x 2 wells x 3 QC
Run 14-15	2 sets QC (biosimilar)	Linearity (all)	1 set x 2 wells x 8 STD	2 sets x 2 wells x 3 QC

Validation **Acceptance Criteria**

	Acceptance Criteria
Accuracy -Precision	✓ For a minimum of six runs, the mean calculated result of each VS must be ±20% of the nominal value, except for the LLOQ and ULOQ, which may be ±25% of nominal. ✓ For a minimum of six runs, the CV for each VS must be ≤20%, except at the LLOQ and ULOQ, where the CV can be ≤25%.
STD Curve	✓ 75% of non-zero standards must be within ±20% of the nominal concentration, except for the highest and lowest standards which may be within ±25% of nominal. ✓ CVs must be ≤20%, except for the highest and lowest standards, for which the CVs must be ≤25%.

Validation **Acceptance Criteria**

	Acceptance Criteria
Selectivity	✓ The mean calculated result must be within ±25% of the nominal value for 80% of samples tested at the LLOQ, or within ±20% of the nominal value for samples tested at a higher concentration.
Short Term Stab.	✓ Mean calculated result of each sample must be ±20% of the expected value and have CVs ≤20%
Freeze Thaw Stab.	✓ Mean calculated result of each sample must be ±20% of the expected value and have CVs ≤20%
Linearity	✓ Mean calculated result of dilutions when corrected for dilution must be ±20% of the nominal value and have CVs ≤20% ✓ Confirmed if the observed response is within the quantifiable range of the assay for a sample whose nominal concentration is above the ULOQ.

QC Special **Acceptance Criteria**

Bioanalytical PK 1 Assay

Phase 1

- Intra-batch evaluation for each QC concentration
- Lab system suitability requirements for pre-validation

Phase 2

- Inter-batch evaluation, Biosimilar and Innovator
- Inter-batch mean bias (%RE) ±20% (25% ULOQ, LLOQ)
- Inter-batch %CV ≤20% (25% ULOQ, LLOQ)
- Inter-batch %TE ≤30% (37.5% ULOQ, LLOQ)

Phase 3

- Inter-batch comparison between Biosimilar and Innovator
- Absolute value of Biosimilar and Innovator inter-batch %RE ≤20% (25% ULOQ, LLOQ)
- 90% confidence interval for this difference ±30% (±37.5% ULOQ, LLOQ)

QC **Acceptance Criteria**

Five Biosimilar and Innovator QC samples independently prepared 3 times

↓

All samples placed in the duplicate on one plate

↓

6 independently prepared assay plates, preferably in balanced design of 3 operators running 2 assay plates over 3 days

Originator (Case Study 1)				
Conc	Mean %RE	Intrabatch %RE	Interbatch %CV	Total Error
LLOQ	2.78	7.12	7.12	9.89
Low	4.78	12.47	12.47	17.25
Mid	1.99	8.1	8.54	10.53
High	4.46	4.33	4.38	8.84
ULOQ	5.99	2.71	4.05	10.04

Biosimilar (Case Study 1)				
Conc	Mean %RE	Intrabatch %RE	Interbatch %CV	Total Error
LLOQ	9.44	8.34	8.34	17.78
Low	2.94	12.74	14.16	17.1
Mid	0.17	2.54	3.5	3.68
High	7.18	5.76	6.06	13.24
ULOQ	2.04	3.26	3.26	5.29

Difference (Originator and Biosimilar)				
Conc	Mean %RE	Intrabatch %RE	Interbatch %CV	Total Error
LLOQ	-3.33	-6.49	-0.17	**3.16**
Low	-0.56	-7.02	5.91	**6.46**
Mid	0.91	-1.56	3.38	**2.47**
High	-1.36	-4.88	2.16	**3.52**
ULOQ	1.98	-0.1	4.05	**2.07**

Immunogenicity

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Immunogenicity Objectives

The final goal of this exercise is to provide:

Meaningful interpretation of comparability study data for biosimilar drug development not only to ensure safety and efficacy but also allow for drug **substitution** and **exchangeability**

To achieve this goal, the agencies' recommendations are:

- ✓ The biosimilar is **less or equally immunogenic** than the originator
- ✓ Challenges related: Immunogenicity assays are **qualitative assays**

One or Two Assays?

Scenario 1:

1

One assay can quantify both Reference and Biosimilar

Validate One Assay

Scenario 2:

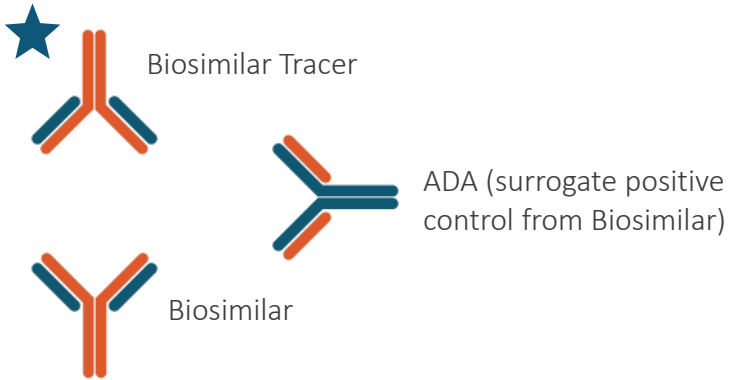
2

One assay for Reference, One assay for Biosimilar

Validate Two Assays

Recommendation: Validate One Assay

One Assay



Using the biosimilar for coating and detection is the conservative approach for detection of ADAs, which ensures that antibodies that are generated against the biosimilar are reliably detected.

Comparability testing during assay validation (specificity / confirmatory assay) would have already demonstrated the assay's ability to detect ADAs against biosimilar and innovator drug equally.

One Assay

Advantages:

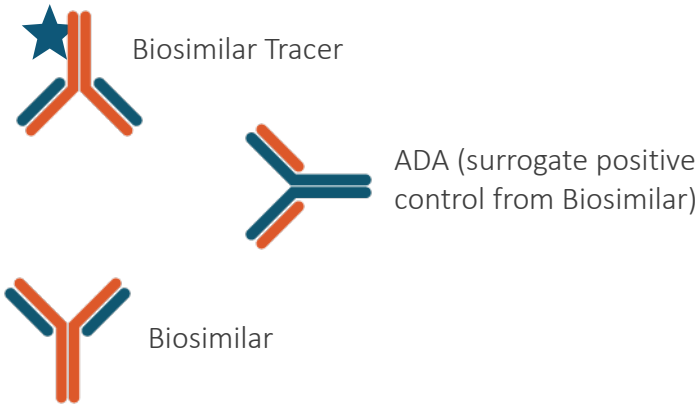
- ✓ Less inter-assay variation as only one set of reagents are used
- ✓ Only need to analyze the study sample once
- ✓ In a comparative blinded trial all samples can be easily analyzed in one assay format
- ✓ Confirmation of putative positives from the screening step can be obtained either by incubating all the samples with the innovator or biosimilar if the study is un-blinded; or with Innovator and biosimilar if the study is blinded
- ✓ Sensitivity will be based on performance of one surrogate positive control
- ✓ Natural progression of samples from binding assay to one neutralizing antibody assay

***Key assumption**: Biosimilar has been demonstrated to be comparable by the CMC team- therefore physicochemical properties of both proteins will be conserved upon capture and labeling for secondary reagent.*

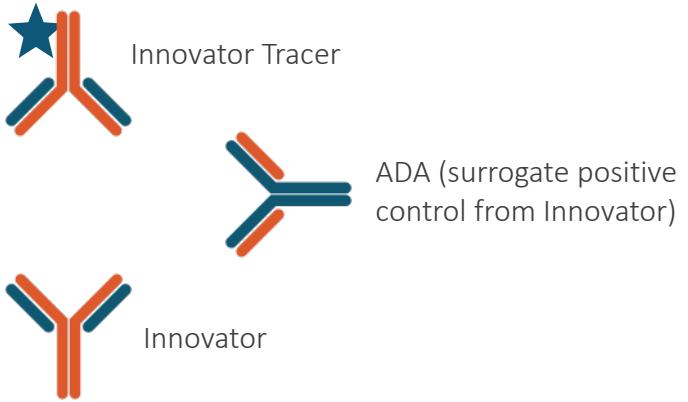
Disadvantages:

- ✓ ADA against unique structure of the innovator drug may not be detected
- ✓ Risks of missing out putative positive antibodies to either drug depending on the assay format

Two Assays



Microtitre Plate Well



Microtitre Plate Well

Essentially, two separate assays are validated: one for ADAs against the biosimilar, and the other for the innovator.
However, comparability between the methods would also have to be demonstrated.

Two Assays

Advantage:

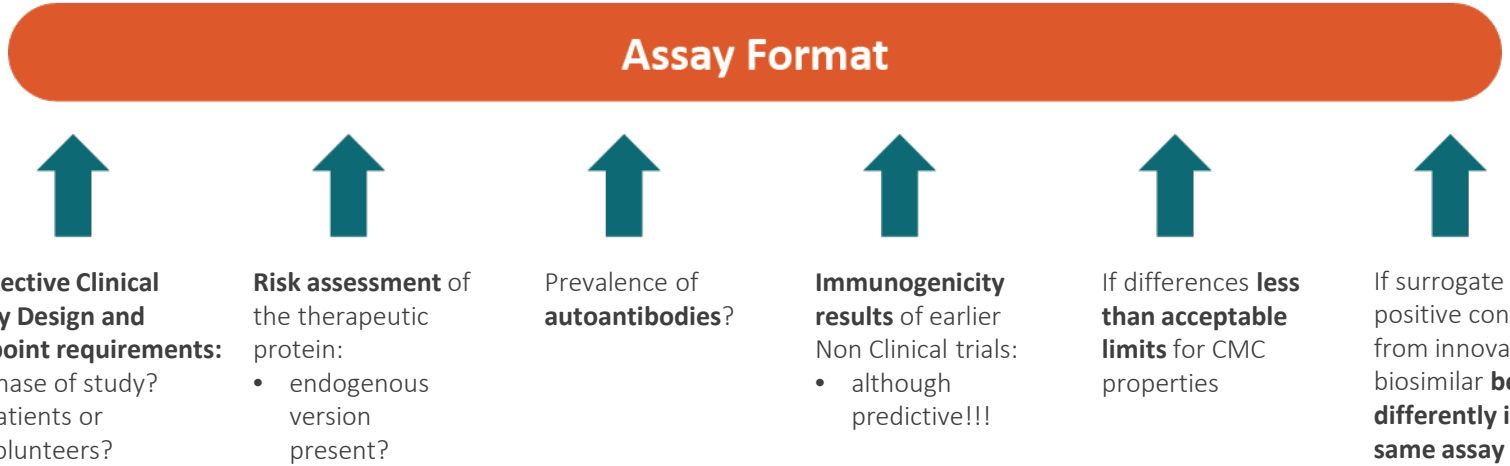
- ✓ Potential for determining the true immunogenicity differences between innovator and biosimilar using a statistically-powered study.

Disadvantages:

- ✓ Additional sample volume required since two assays are involved
- ✓ Validation criteria has to be very carefully examined for the 2 assays to be “comparable”
- ✓ If a blinded study– the study samples should be analyzed in both assays independently
- ✓ The clinical team must be able to analyze the data coming from both assays to arrive at Biosimilarity… may prove challenging

Other **Considerations**

When Deciding on an Assay Format

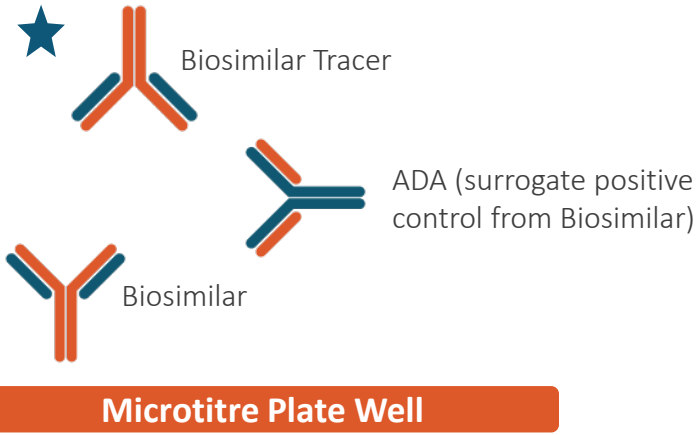


Our **Conclusion**

Go with one assay where possible.

The decision was based upon the logistics of having to develop and compare two different methods. More importantly, how to interpret the study sample results if two methods are used for what is essentially a non quantitative screening assay. **By using the biosimilar as the reagents, the bar is being set high as this would be the worst case scenario, since the one assay approach may give by definition false negative results for the innovator.**

For situations in which the biosimilar could be expected to potentially have a different or high rate of immunogenicity, a decision tree would be employed to represent the “pros/cons” on a case by case basis.



Validation Considerations for One Assay

1. Where and when possible, comparative study of surrogate positive controls from Innovator and Biosimilar **must demonstrate congruence in data**

2. Selectivity and stability to be **performed with both positive controls**

3. Of great importance is the confirmatory/ inhibition assay where **there should not be a palpable difference in the response of both positive controls** when incubated in a zig-zag manner with both innovator and biosimilar

Appendix – **Case Study** – Variability in Bioanalytical Method Immunogenicity

Anti-Originator ADA			
ADA (ng/mL)	Biosimilar Biotin/Tag (S/N)	Originator Biotin/Tag (S/N)	Absolute % Difference
100.00	3.62	3.86	6.5
50.00	2.26	2.63	16.2
25.00	1.58	1.56	1.3
12.50	1.22	1.26	3.3
6.30	1.12	1.16	3.7
3.13	1.05	0.97	7.1
1.56	0.95	0.84	11.0
0.78	0.98	0.98	0.3

Anti-Biosimilar ADA			
ADA (ng/mL)	Biosimilar Biotin/Tag (S/N)	Originator Biotin/Tag (S/N)	Absolute % Difference
100.00	3.84	4.38	14.0
50.00	2.51	2.69	7.4
25.00	1.57	1.65	4.7
12.50	1.24	1.28	3.4
6.30	1.09	1.16	6.4
3.13	1.02	1.04	1.1
1.56	0.96	0.98	1.9
0.78	0.94	0.96	1.6

Biosimilar Biotin and SulfoTAG			
PC (ng/mL)	Anti-Biosimilar ADA (S/N)	Anti-Originator ADA (S/N)	Absolute % Difference
100.00	3.84	3.62	5.7
50.00	2.51	2.26	9.8
25.00	1.57	1.58	0.4
12.50	1.24	1.22	1.1
6.30	1.09	1.12	2.6
3.13	1.02	1.05	2.1
1.56	0.96	0.95	1.5
0.78	0.94	0.98	4.5

NAb

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Immunogenicity Comparability

Meaningful interpretation of comparability study data shows that:

The biosimilar is ***less or equally immunogenic*** than the originator.

Meaningful comparability data:

- ✓ **Incidence** (% of the patients with a positive immune response)
- ✓ **Titer** (low, mid or high titer, quantify??)
- ✓ **Neutralization ADA %**
- ✓ **Clinical relevance of ADA**

Immunogenicity Flow Diagram

Test Specimen

Screening Assay
Titer Assay

Reactive

Confirmatory Assay

NEGATIVE

NEGATIVE

NAb Negative

Subject is Positive
for Binding Antibodies

NAb Positive

Subject is Positive
for Neutralizing Antibodies

POSITIVE

Incubate Incubate Read

Stimulation Step Detection Step

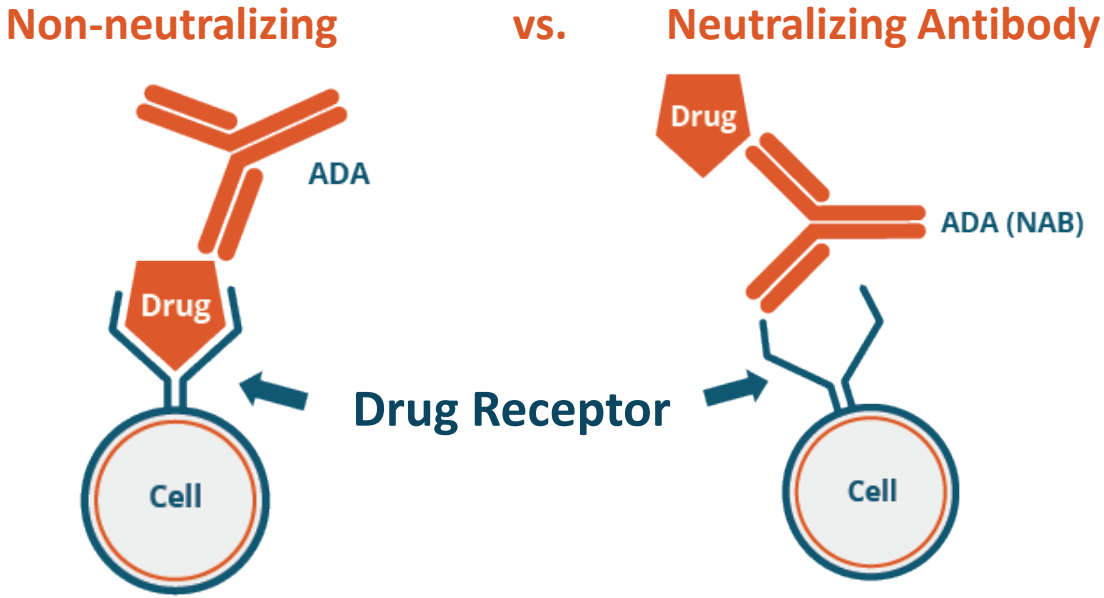
NAb Assay (Cell-Based & Non Cell-Based)

Immunogenicity Assays: NAb

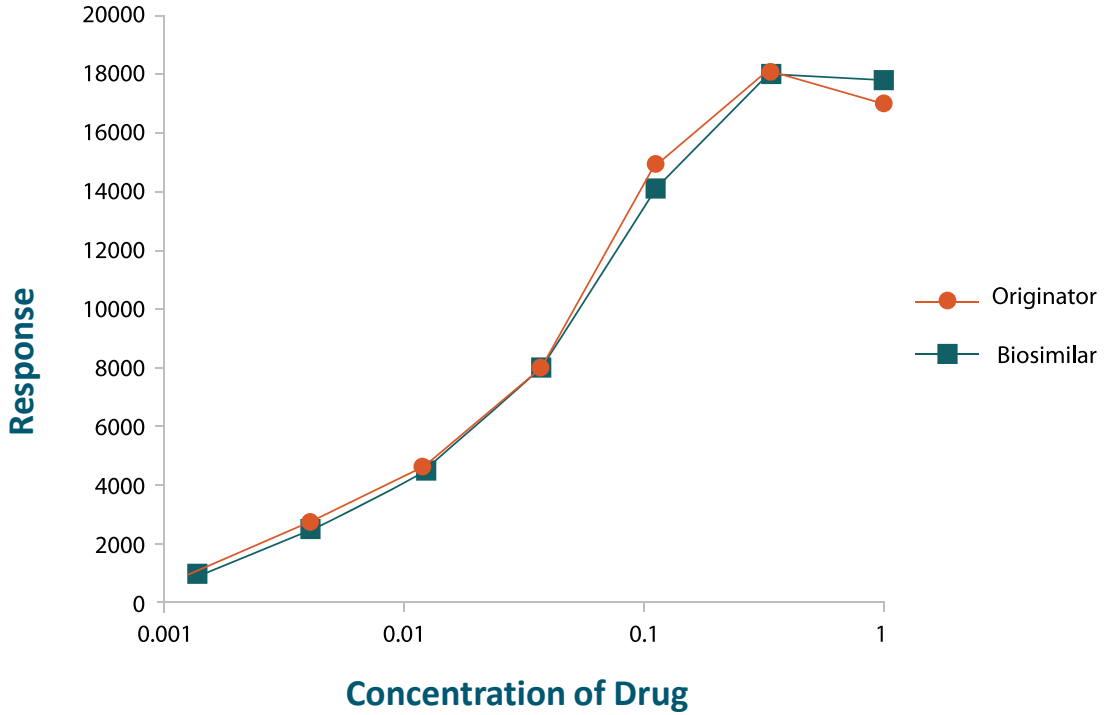
NAb assays are qualitative assays

How does one quantitatively compare two qualitative assays?

Neutralization Assay



Neutralization Assays

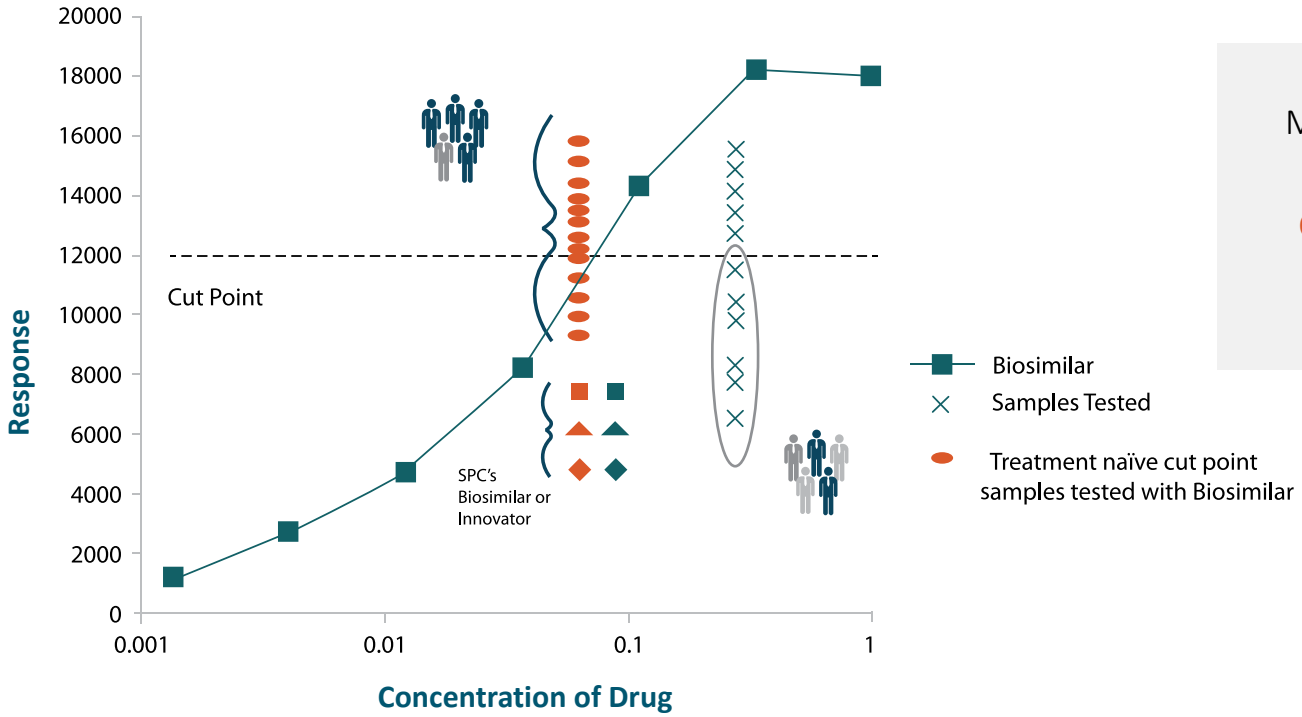


Potency assay **should give similar response** for Originator and Biosimilar

Neutralization Assays

Advantage 1 assay	Disadvantage 1 assay	Advantage 2 assays	Disadvantage 2 assays
✓ Cost ✓ Analysis of Blinded studies ✓ Less inter-assay variation, comparability easier to perform	✓ ADA against unique structure of the innovator drug may not be detected ✓ Biosimilars can artificially have higher immunogenicity NAb incidence	✓ Potential for determining the true immunogenicity differences between innovator and biosimilar using a statistically-powered study.	✓ Validation criteria has to be very carefully examined for the 2 assays to be "comparable" ✓ Difficulty to compare 2 qualitative assays results

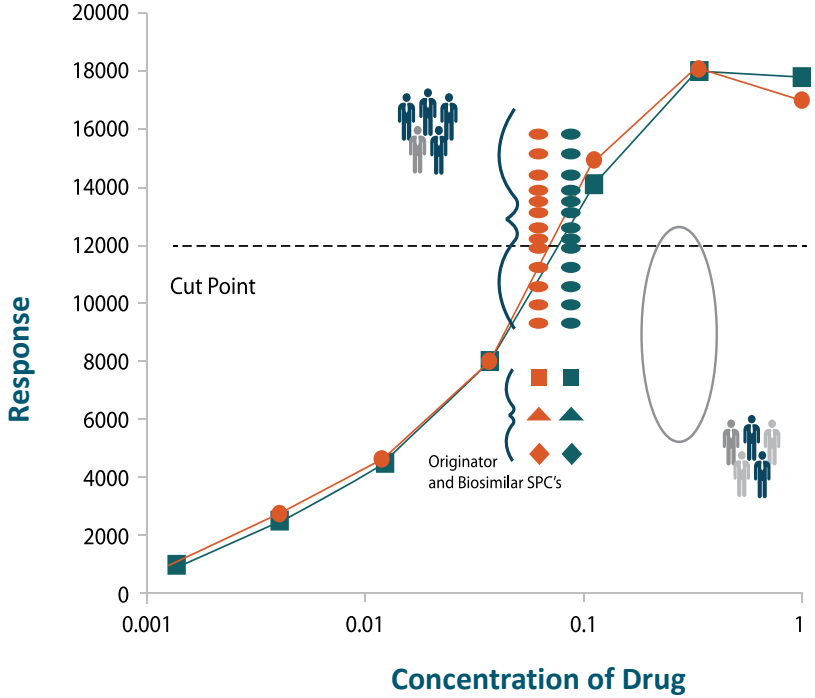
Neutralization Assay: 1 Assay



Meaningful interpretation of comparability study data:

Compare to response rate Innovator vs. Biosimilar

Neutralization Assay: 2 Assays



Originator

Biosimilar

Treatment naïve cut point samples tested with of Originator
2nd set tested with Biosimilar

Test samples tested with
2nd set tested with Biosimilar

Meaningful interpretation of comparability study data:

Challenges

- **Biosimilar and Originator are expected to have "same" NAb profile**
- **NAb assays are qualitative assays**

Neutralization Assay

Choice of the Neutralization Assay Platform:

Cell-based Bioassays:

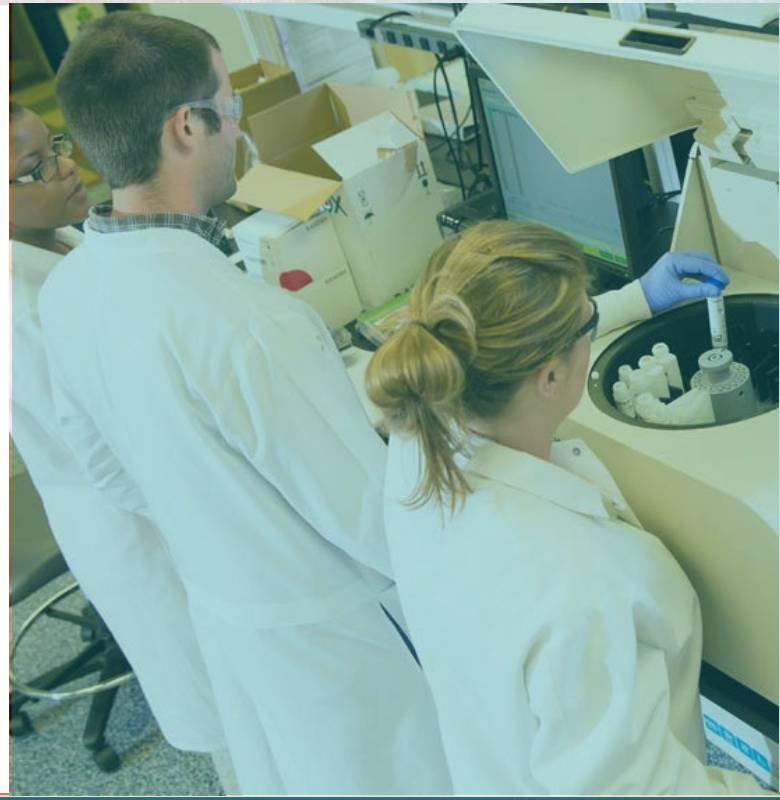
- ✓ FDA recommends assays that are more reflective of *in vivo* state
- ✓ Should be related to product mechanism of action
- ✓ Should be informative as to the effect of NAb on clinical results

Non Cell-based Bioassays:

- ✓ When cell-based assays are not feasible/available
- ✓ Appropriateness for use must be demonstrated
- ✓ Assays may use direct (inhibition of stimulation) or indirect (inhibition of inhibition = stimulation)

In **Summary**

- ✓ Agencies **require immunogenicity testing for Biosimilars** to compare to Originator molecule
- ✓ One of the **failures in application is related to bioanalysis** (ADA, PK and Cell-based assay)
- ✓ **Challenges exist in quantitatively comparing** inherently qualitative assays
- ✓ **1 assay will lead to more successful program:**
  - Limit variability when there is so many factors contributing
  - LBA favorable to reduce the complexity and variability



FDA Biosimilar Guidance

BioAgilytix | IPM Biotech
A Subsidiary of BioAgilytix

FDA Biosimilar Guidance

A stepwise approach with respect to:

- Structure
- Function
- Animal toxicity
- Human pharmacokinetics (PK) and pharmacodynamics (PD)
- Clinical immunogenicity
- Clinical safety and effectiveness

Structural analysis includes:

- Primary structures
- Higher order structures (3D,quaternary structure, aggregation)
- Enzymatic post-translational modifications (PTM)
- Other potential variants (deamidation, oxidation)
- Chemical modifications (e.g. PEGylation sites)

Functional analysis includes:

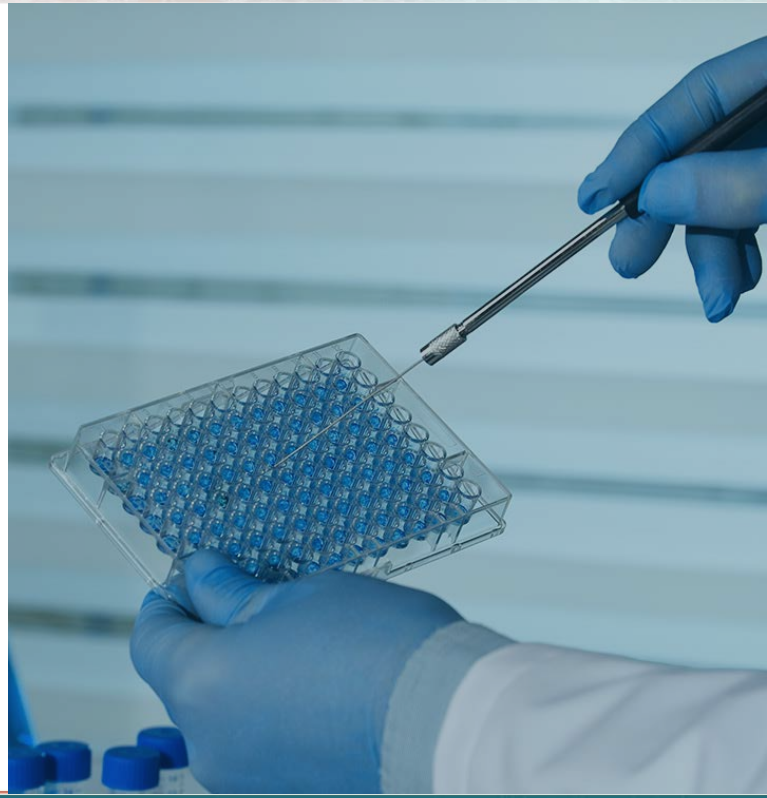
- Bioassays
- Biological assays
- Binding assays
- Enzyme kinetics

FDA Biosimilar Guidance

Animal Data:

- ✓ Toxicity Studies
- ✓ PK and PD Data
- ✓ Immunogenicity Studies

Poor reasons to perform animal studies since immunogenicity in animals cannot be transferred to humans. Only if unusual PK/PD results are expected are animal studies justified.



Clinical Data

PK / PD

- Not adequately predicted by functional assays
- Human data essential in supporting comparability

Immunogenicity

- Altered PK
- Anaphylaxis induction
- Neutralizing Ab
- Pre-market data essential
- Comparative studies in nature

Study Design

- Two-side test by design
- Equivalent safety / immunogenicity at the therapeutic dose; one-side test
- Powdered to detect:
  - ✓ Relevant safety signals
  - ✓ Clinical meaningful differences
  - ✓ Study population (e.g. Concomitant medications)

Safety and Immunogenicity

Safety and immunogenicity data from the clinical pharmacology studies should be collected and evaluated including relevant **patient populations** that are not immunocompromised.

Clinical Pharmacology Assessment

Clinical pharmacology studies may lead to **clinically meaningful differences** between the test and the reference product which may lead to additional investigations and/or clinical studies conducted to investigate these potential differences.

Clinical Pharmacology Assessment

Publicly available information of the reference product should be considered.

If the reference product is known to have the potential for immune-mediated toxicity, immunogenicity assays should be developed in advance, so that immunogenicity can be evaluated in real time . Otherwise, **samples can be stored** for future analysis.

Thank You

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