BioAgilytix | BioAgilytix Europe

Recommendations from the [forthcoming] AAPS White Paper: Development and Validation of Immunogenicity Assays in Support of Biosimilar Programs

Todd Lester

Associate Director, BioAgilytix

November 22nd, 2019

12th EBF Open Symposium – Breakout Session: Biosimilars

AAPS **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:

Authoritative, state-of-the-art White Paper(s) to provide consensus recommendations to the bioanalytical community supporting biosimilar development, which in turn may help provide recommendations to any regulatory authority guidance initiative.

Historical Context – AAPS Focus Groups (now AAPS Communities)

- AAPS Ligand Binding Assay Bioanalytical Focus Group – Biosimilars APC
- AAPS Biosimilars Focus Group

Companion White Papers

Biosimilar PK Assays
Marini, et al. AAPS J. (2014); 16: 6.
https://dx.doi.org/10.1208%2Fs12248-014-9669-5

Biosimilar NAb Assays
Gouty, et al. AAPS J. (2018); 20: 25.
https://doi.org/10.1208/s12248-017-0181-6

Co-Authors **Diverse, Global Representation**

Stakeholders across industry, consultant organizations, and government with expertise in the biosimilar bioanalytical arena.

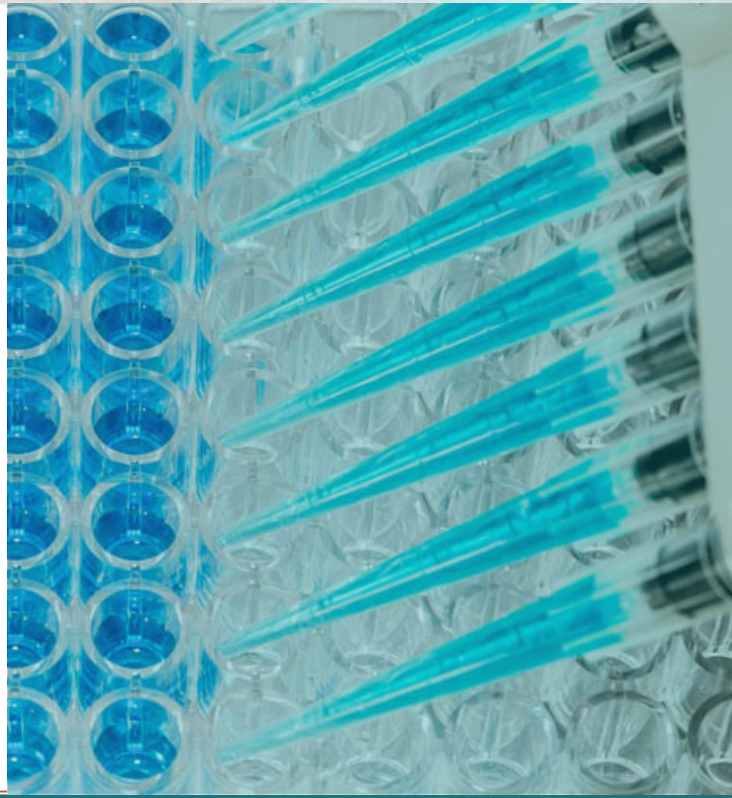
Guidance on **Immunogenicity**

FDA: "The goal of the immunogenicity assessment is to evaluate potential differences between the proposed product and the reference product in the incidence and severity of human immune responses…**Thus, establishing that there are no clinically meaningful differences in immune response between a proposed product and the reference product is a key element** in the demonstration of biosimilarity.

EMA: "Immunogenicity testing of the biosimilar and the reference products should be conducted within the comparability exercise by using the same assay format and sampling schedule. **Assays should be performed with both the reference and biosimilar molecule in parallel** (in a blinded fashion) to measure the immune response against the product that was received by each patient."

No regulatory guidance clearly and comprehensively describes the requirements for the bioanalytical testing of biosimilars.

Overall **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 **equally or less immunogenic** than the originator
- ✓ Historical challenge: Immunogenicity assays are **qualitative assays**

Immunogenicity **Comparability**

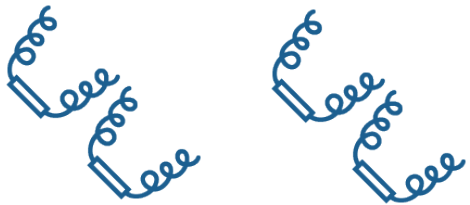
Goal: Evaluate potential differences between the biosimilar and the originator

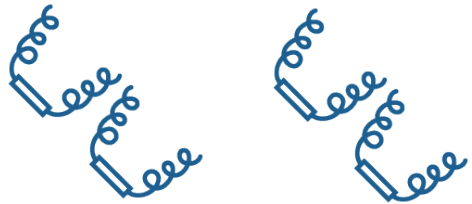
Meaningful interpretation of comparability study data shows that:

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

Meaningful comparability data:

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





An Evolution in Thought and Practice

Historical challenges rooted in the nature of ADA assays, which are inherently qualitative…

- ✓ One vs two assays?
- ✓ How does one quantitatively compare two qualitative assays?
- ✓ Which parameters? How much data?
- ✓ How similar is similar?
- ✓ Development vs validation?
- ✓ Meaningful acceptance criteria to demonstrate bioanalytical similarity?

A decade's worth of progress

- ✓ Both industry and regulators shaping the landscape
- ✓ Ever-increasing experience with biosimilars, case studies, approvals
- ✓ Growing body of knowledge and increased familiarity with data

Need to balance the perception that more data is better, and the need to meaningfully assimilate and interpret immunogenicity data.

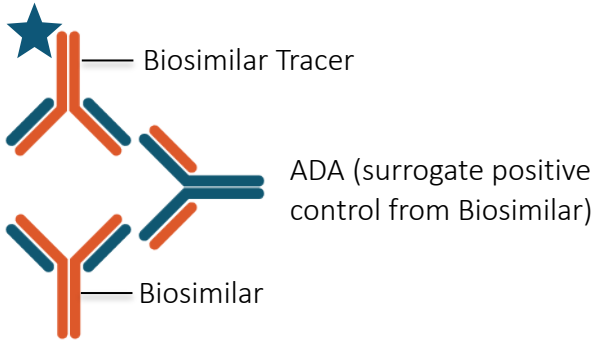
Dialogue Shaping the Journey

- **2012** EBF – breakout session on biosimilars; discussion on one- vs. two-assay approach
- **2012** AAPS NBC – formation of Biosimilars Action Program Committee
- **2013** AAPS Annual Meeting – roundtable session
- **2014** EBF – recommendations from AAPS LBABFG
- **2015** WRIB – discussion on one- vs. two-assay approach
- **2016** WRIB – discussion and recommendation for one-assay approach
- **2016** Biosimilars – Clinical Studies & Analytical Similarity Summit
- **2017** ImmunoTx Summit – Immunogenicity Conference – recommendations from AAPS LBABFG
- **2018** Land O' Lakes Conference – industry and regulators; discussion and consensus on one-assay approach

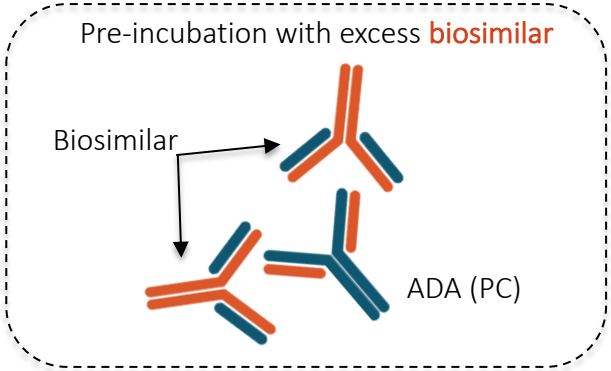
Implement a One-Assay Approach

Strong recommendation: implement a single, biosimilar-based assay, subject to rigorous cross-validation of the biosimilar and originator for **antigenic equivalence**, **drug tolerance**, and performance in the **confirmatory assay**.

Screening Assay Format



Confirmatory Assay Format



…an issue of practical, regulatory, and financial importance…

One-Assay Approach

Advantages:

- ✓ Conservative approach to use biosimilar product for detection of all ADAs
- ✓ Ensures that ADA against biosimilar are reliably detected
- ✓ One validation study with one set of acceptance criteria to evaluate samples from biosimilar and originator products
- ✓ No ‘between-assay’ variability, i.e. minimization of potential impact of assay bias on comparison of immunogenicity of biosimilar vs originator
- ✓ In a comparative blinded trial all samples can be easily analyzed in one assay format

***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 originator drug may not be detected

Selection of Platform & Methodology

Demonstrate similar ADA rates for the biosimilar and the originator in the same study

- ✓ **State-of-the-art technology/methods should be used**
- ✓ **Regulators will expect the most discriminating assays to be utilized**
- ✓ **Developers should not be concerned by increased sensitivity and specificity of next generation assay platforms and/or methodology**

Selection of Positive Control (PC)

The PC's ability to bind equivalently to the biosimilar and originator should be demonstrated during development and validation

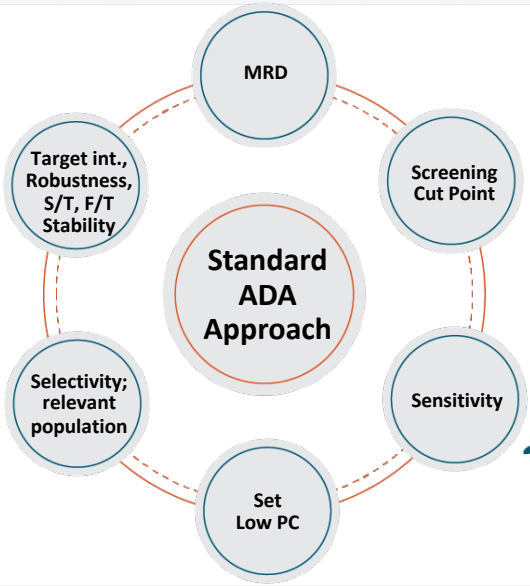
- ✓ **Single PC for samples analysis (anti-biosimilar preferred)**
- ✓ **Potential differences in immunogenicity response in actual clinical studies unlikely to be predicted by surrogate PC**
- ✓ **If biosimilar has lower ADA incidence rates than the originator in clinical studies, compare several PCs to justify clinical results as a "true" observation**

Reagent Labeling -- Limit Variability

Small differences in the labeling of the respective drugs (biosimilar and originator) may impact each assay's ability to detect certain immune responses.

- ✓ **Label originator and biosimilar side-by-side**
- ✓ **Ensure label incorporation ratios are similar**
- ✓ **Re-label, if necessary . . . then re-label again!**

Biosimilar ADA Assessment vs Standard Approach



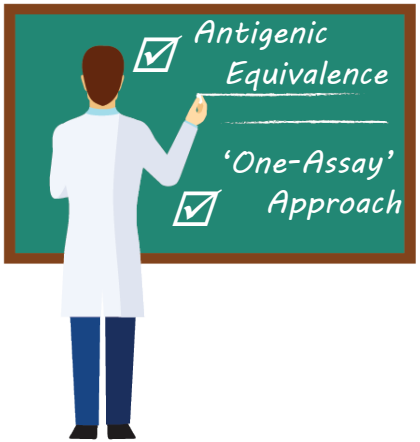
All experiments performed using biosimilar

Biosimilar Assessment -- comparisons w/ originator --	
Guiding Principle	Optimize detection of ADA to Biosimilar & Reference product‡
Antigenic Equivalence (Development)	Essential characteristic of ADA assays for Biosimilar and Reference product
Performance in Confirmatory Assay (Development & Validation)	Establish comparable confirmatory cut-points for Biosimilar and Reference product
Drug Tolerance (Development & Validation)	Demonstrate comparable drug tolerance for Biosimilar and Reference product

‡It is generally acceptable by regulators to resolve any bias in favor of detecting ADA against the biosimilar.

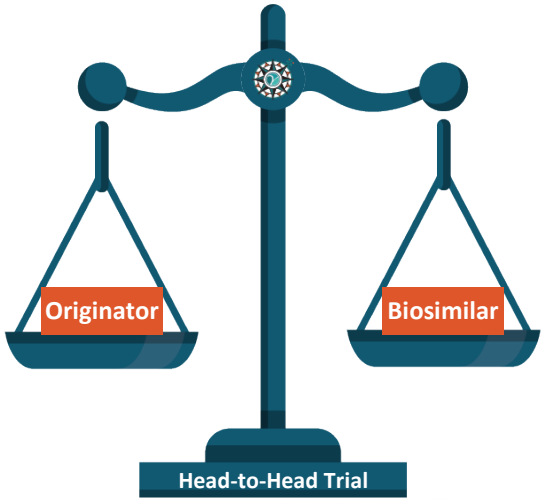
Antigenic Equivalence (Drug Competition Curves)

The ability of the **biosimilar** and the **originator** to bind in a similar manner to the **positive control(s).**



Antigenic equivalence establishes suitability of one-assay approach for support of head-to-head clinical trials.

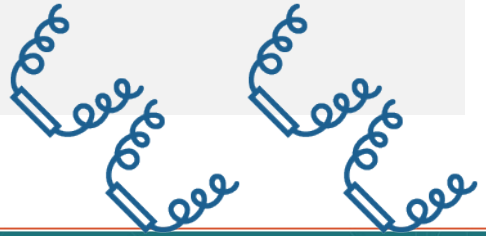
Demonstrates the assay's ability to detect an immune response against the therapeutic administered, irrespective of whether the therapeutic was the originator or the biosimilar.



Antigenic Equivalence (Drug Competition Curves)

Analytical Design:

- ✓ **Spike** matrix with known concentrations of PC
- ✓ Different concentrations of PC should be selected to generate a **high** and **medium/low** signal
- ✓ Analyze the different concentrations of PC with and without increasing concentrations of either the biosimilar and originator drug product
- ✓ Concentrations of drug should be selected to generate a **concentration-response curve** of the competitive inhibition
- ✓ Conduct during development



Antigenic Equivalence (Drug Competition Curves)

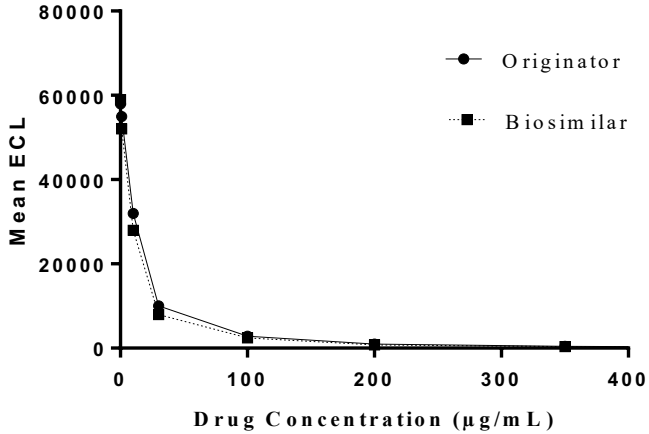
Data Interpretation:

- ✓ Concentration-response curves generated with the biosimilar and the originator should be **visually overlapping** or comparable.
- ✓ Comparison of signal at each concentration of drug:

  %CV of mean signal obtained from both drugs **< 20%** at majority of concentrations

  Confirms that any difference in signal between biosimilar and originator is **within the precision of the assay**.

Successful Demonstration of Antigenic Equivalence



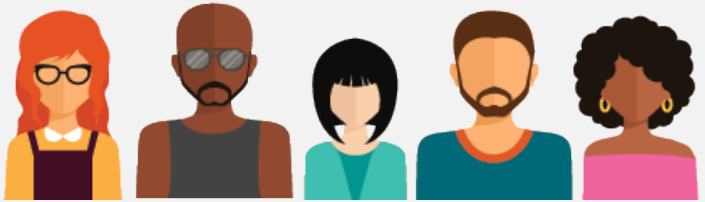
Confirmation that excess concentrations of both the biosimilar and originator inhibit the assay signal of the PC to a similar extent.

Confirmatory Assay - Development

Ensure similar ability to detect antibodies against the biosimilar and the reference product.

Analytical Design:

- ✓ Utilize **concentration** of biosimilar and originator from respective **COA** (not nominal concentration)
- ✓ Choose concentration of excess drug product which produces **substantial inhibition** of the HPC
- ✓ Analyze matrix from **10-15 individuals** once in absence and presence of excess:
  - ✓ Biosimilar
  - ✓ Originator



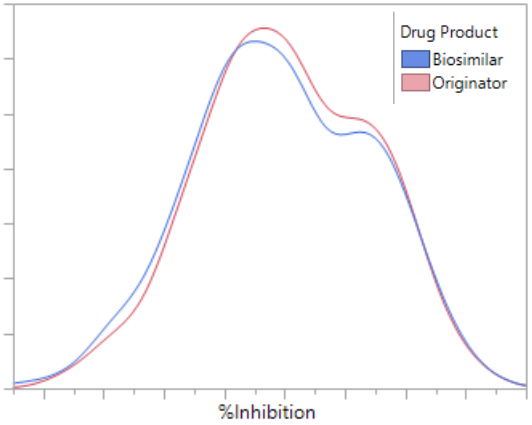
Confirmatory Assay - Development

Data Interpretation:

- ✓ Determine %Inhibition separately for each drug and compare between the biosimilar and originator(s)
- ✓ %Inhibition between the two (or three) drugs should be comparable

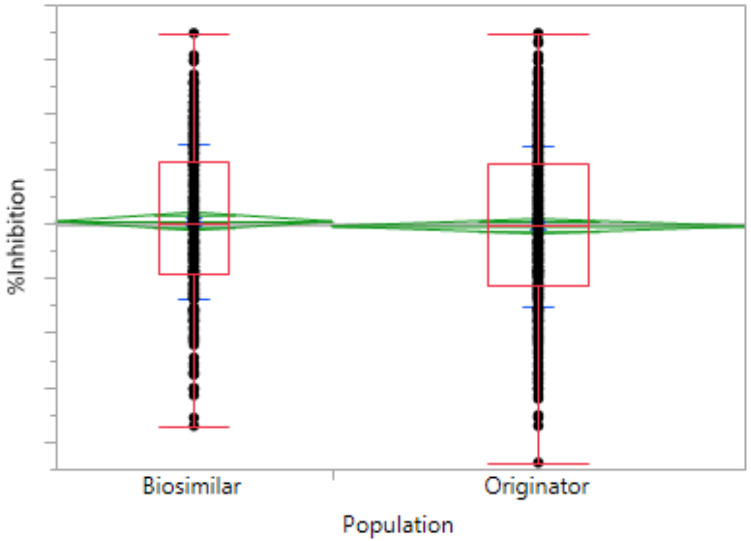
Informs understanding of:

- Subject-to-subject variability
- Effect of biosimilar and originator on assay signal



Confirmatory Assay - Validation

- ✓ Analyze >50 individuals six times across three independent assays by each of two analysts in a balanced analytical design
- ✓ Same samples analyzed in absence and presence of either excess biosimilar or originator on same plate to avoid confounding plate effect
- ✓ Determine %Inhibition for each drug separately
- ✓ Compare distribution of %Inhibition between the drugs:
  - -- **means** by **ANOVA**
  - -- **variances** by **Levene's** test



- One assay approach is supported if no significant difference exists between means/variances
- If there is a significant difference, key point is to demonstrate that the assay is not less likely to detect antibodies against the biosimilar than against the originator

Drug Tolerance

Assessment of assay **sensitivity in the presence** of interfering therapeutic **drug** product.

Analytical Design:

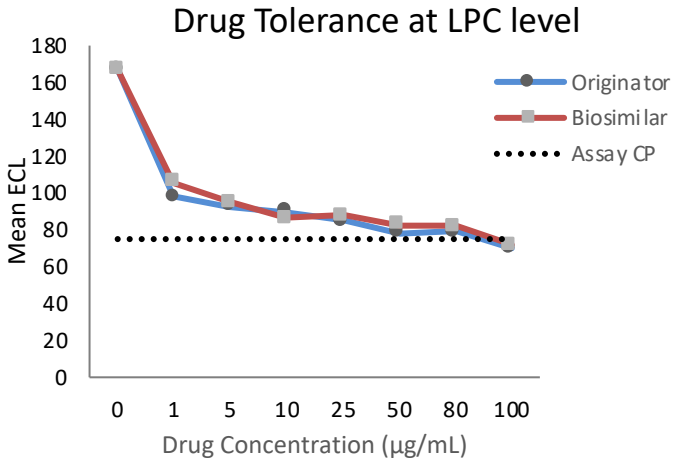
- ✓ **Spike** matrix with a spectrum of known concentrations of PC; to include 100 ng/mL level of PC and HPC, LPC
- ✓ Titrate drug into mock, PC-spiked samples
  - -- 2- or 3-fold dilutions
  - -- Concentrations of drug should span levels expected to be present in clinical samples
- ✓ Conduct in development and validation

Drug Tolerance

Data Interpretation:

- ✓ **Highest drug level** at which the signal generated by PC exceeds the screening cut point is considered the drug tolerance of the assay.
- ✓ Curves for biosimilar and originator should be **visually comparable**.
- ✓ Results obtained in the absence and presence of different quantities of the originator and biosimilar should be compared.

  The assay tolerance to the originator and to the biosimilar should be similar **(within ± one dilution factor)**.



If a difference is observed, alternative control antibodies could be tested to understand the extent of the difference.

If Differences are Observed…

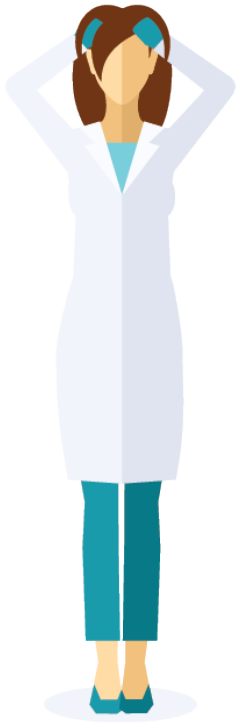
…between the behavior of the Biosimilar and Originator…

…during development…

- Do not move into validation
- Re-visit assay platform, MRD, PCs, other reagents, assay methodology
- Evaluate alternative PC antibodies; re-label drug!
- Discuss with regulators

…during validation…

- Consider the context of the totality of the data
- Re-visit CMC characterization – did the assay detect true differences?
- Discuss with regulators



Sample Analysis **One-Assay Approach**

All study samples (regardless of treatment group) analyzed using one screening and one confirmatory assay (using biosimilar for both assays).

- ✓ **ADA prevalence** (positive rate of ADA pre-dose) may be higher than reported in the literature from originator clinical studies
- ✓ **ADA incidence** for the originator may be higher than observed in historical trials. Comparison with historical ADA rates is irrelevant.

- ✓ If ADA incidence rates for **originator are lower than previously reported**, provide reason and discuss with regulators.
- ✓ If ADA incidence is much **lower for the biosimilar than originator**, a root cause analysis is required.

In Summary

1

The goal is to compare the rate ratio between biosimilar and originator

- ✓ Incidence
- ✓ Titer
- ✓ Clinical Relevance

2

Ensure assay's similar ability to detect antibodies against both biosimilar and originator

- ✓ Antigenic similarity
- ✓ Performance in confirmatory assay
- ✓ Drug tolerance

3

One-assay approach will lead to a more successful program:

- ✓ **Limit variability** and assay bias when there are many contributing factors
- ✓ Streamline **interpretation** of study sample results by analyzing in one assay

BioAgilytix

Thank You!