Recommendations from the AAPS LBABFG Biosimilars Action Program Committee on the Development and Validation of PK and ADA Assays for Biosimilar Drug Development

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on behalf of the AAPS LBABFG Biosimilars Action Program Comittee

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PUBLICATION

White Paper:
"Systematic Verification of Bioanalytical Similarity Between a Biosimilar and a Reference Biotherapeutic: Committee Recommendations for the Development and Validation of a Single Ligand-Binding Assay to Support **Pharmacokinetic** Assessments"

The AAPS Journal
November 2014, Volume 16, Issue 6, pp 1149-1158

DRAFT PAPER

"Systematic Verification of Immunogenicity between a Biosimilar and a Reference Biotherapeutic: Committee Recommendations for the Development and Validation of **Anti-Drug Antibody Assays** to Support Immunogenicity Assessments"

Expected publication Q1 2015

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DEVELOPMENT OF RECOMMENDATIONS

Monthly Team Teleconferences

Discussions with the Bioanalytical Community

Pharmacokinetic Assays

AAPS National Biotech Conference – Hot Topic Session (May 2012)

AAPS National Biotech Conference – Roundtable Session (May 2013)

Anti-Drug Antibody Assays

AAPS Annual Meeting – Roundtable Session (November 2013)

AAPS National Biotech Conference – Open Forum (November 2014)

External Publications

Reviews

AAPS LBABFG Steering Committee

AAPS Executive Council

The AAPS Journal

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An Important Conclusion Guided These Recommendations:

PK and ADA assessment of any biosimilar and its reference therapeutic would be preceded by the generation of substantial CMC data to support structural comparability.

Introduction of a New Term:

"Bioanalytical Similarity" -- used to denote that the two biological products demonstrate an acceptable degree of comparable bioanalytical behavior .

~~**Equivalent Exact Equal**~~

PK ASSAY RECOMMENDATIONS

Use a SINGLE PK ASSAY with one calibration curve and one set of quality control samples to evaluate sample concentrations in Biosimilar and Reference comparison studies.

White Paper recommendations divided into 3 parts:

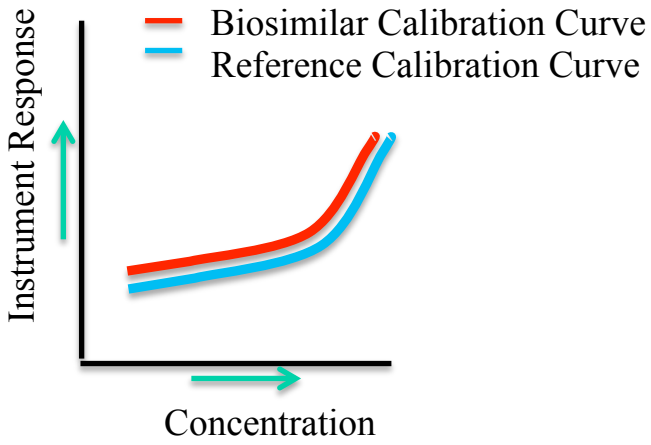
1. **Development Phase**
2. **Validation Phase**
3. **Statistical Analyses for Establishing "Bioanalytical Similarity"**

PK ASSAY RECOMMENDATIONS

Development Phase

Confirm "Bioanalytical Similarity" of Calibration Curves

- Ensure Biosimilar and Reference standard curves are parallel
- Statistical-based approach to compare curves



If "similarity" is not demonstrated, conduct investigation or use two separate assays (with appropriate justification)

If "similarity" is demonstrated, move to Validation Phase with a single calibration curve.

PK ASSAY RECOMMENDATIONS

Validation Phase

Assumptions:

- Biosimilar and Reference calibration curves have demonstrated "bioanalytical similarity" in the Development Phase
- Calibrator curve is made from a single compound (most likely Biosimilar)

Establish "Bioanalytical Similarity" of Quality Control Samples

- Systematic comparison of quality control sample results
  - Intra-batch evaluation
  - Inter-batch evaluation
- Direct comparison of Biosimilar against Reference

Fully validate the single PK assay by assessing specific parameters recommended by standard bioanalytical guidance documents, white papers and other bioanalytical assay publications.

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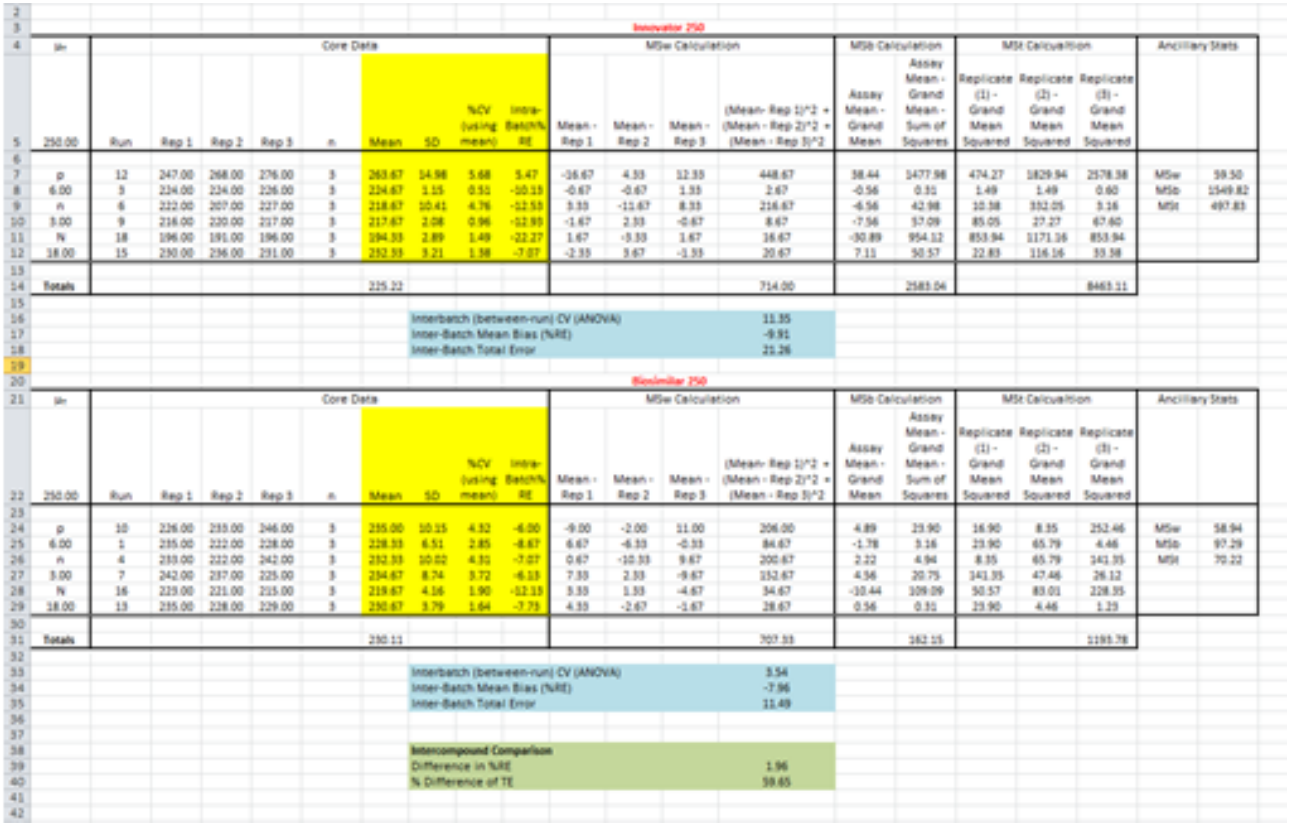
PK ASSAY RECOMMENDATIONS

Statistical Analyses for Establishing "Bioanalytical Similarity"

- Detailed description of how to determine if standard curves are parallel
- Location of free software (ALLFIT) download for assessing parallel curves
- Microsoft Excel workbook that performs all calculations for comparing QCs



Innovator 250

n=	Core Data								MSw Calculation				MSb Calculation		MSt Calculation			Ancillary Stats	
250.00	Run	Rep 1	Rep 2	Rep 3	n	Mean	SD	%CV (using mean)	Intra-Batch% RE	Mean - Rep 1	Mean - Rep 2	Mean - Rep 3	(Mean- Rep 1)^2 + (Mean - Rep 2)^2 + (Mean - Rep 3)^2	Assay Mean - Grand Mean	Assay Mean - Grand Mean - Sum of Squares	Replicate (1) - Grand Mean Squared	Replicate (2) - Grand Mean Squared	Replicate (3) - Grand Mean Squared		
p	12	247.00	268.00	276.00	3	263.67	14.98	5.68	5.47	-16.67	4.33	12.33	448.67	38.44	1477.98	474.27	1829.94	2578.38	MSw	59.50
6.00	3	224.00	224.00	226.00	3	224.67	1.15	0.51	-10.13	-0.67	-0.67	1.33	2.67	-0.56	0.31	1.49	1.49	0.60	MSb	1549.82
n	6	222.00	207.00	227.00	3	218.67	10.41	4.76	-12.53	3.33	-11.67	8.33	216.67	-6.56	42.98	10.38	332.05	3.16	MSt	497.83
3.00	9	216.00	220.00	217.00	3	217.67	2.08	0.96	-12.93	-1.67	2.33	-0.67	8.67	-7.56	57.09	85.05	27.27	67.60		
N	18	196.00	191.00	196.00	3	194.33	2.89	1.49	-22.27	1.67	-3.33	1.67	16.67	-30.89	954.12	853.94	1171.16	853.94		
18.00	15	230.00	236.00	231.00	3	232.33	3.21	1.38	-7.07	-2.33	3.67	-1.33	20.67	7.11	50.57	22.83	116.16	33.38		
Totals						225.22							714.00		2583.04			8463.11		

Interbatch (between-run) CV (ANOVA)	11.35
Inter-Batch Mean Bias (%RE)	-9.91
Inter-Batch Total Error	21.26

Biosimilar 250

n=	Core Data								MSw Calculation				MSb Calculation		MSt Calculation			Ancillary Stats	
250.00	Run	Rep 1	Rep 2	Rep 3	n	Mean	SD	%CV (using mean)	Intra-Batch% RE	Mean - Rep 1	Mean - Rep 2	Mean - Rep 3	(Mean- Rep 1)^2 + (Mean - Rep 2)^2 + (Mean - Rep 3)^2	Assay Mean - Grand Mean	Assay Mean - Grand Mean - Sum of Squares	Replicate (1) - Grand Mean Squared	Replicate (2) - Grand Mean Squared	Replicate (3) - Grand Mean Squared		
p	10	226.00	233.00	246.00	3	235.00	10.15	4.32	-6.00	-9.00	-2.00	11.00	206.00	4.89	23.90	16.90	8.35	252.46	MSw	58.94
6.00	1	235.00	222.00	228.00	3	228.33	6.51	2.85	-8.67	6.67	-6.33	-0.33	84.67	-1.78	3.16	23.90	65.79	4.46	MSb	97.29
n	4	233.00	222.00	242.00	3	232.33	10.02	4.31	-7.07	0.67	-10.33	9.67	200.67	2.22	4.94	8.35	65.79	141.35	MSt	70.22
3.00	7	242.00	237.00	225.00	3	234.67	8.74	3.72	-6.13	7.33	2.33	-9.67	152.67	4.56	20.75	141.35	47.46	26.12		
N	16	223.00	221.00	215.00	3	219.67	4.16	1.90	-12.13	3.33	1.33	-4.67	34.67	-10.44	109.09	50.57	83.01	228.35		
18.00	13	235.00	228.00	229.00	3	230.67	3.79	1.64	-7.73	4.33	-2.67	-1.67	28.67	0.56	0.31	23.90	4.46	1.23		
Totals						230.11							707.33		162.15			1193.78		

Interbatch (between-run) CV (ANOVA)	3.54
Inter-Batch Mean Bias (%RE)	-7.96
Inter-Batch Total Error	11.49

Intercompound Comparison	
Difference in %RE	1.96
% Difference of TE	59.65

PK ASSAY RECOMMENDATIONS -- CONCLUSIONS

1. A single LBA can be used to support PK assessments during Biosimilar drug development.
2. During the Development Phase of an LBA, the standard curve generated using Biosimilar drug should be "bioanalytically similar" to a standard curve generated using a Reference drug.
3. During the Validation Phase of an LBA, the nominal concentration of QC samples generated using Biosimilar drug should be "bioanalytically similar" to the nominal concentration of QC samples generated using a Reference drug.
4. The acceptance criteria provided for the validation should be followed to ensure that one bioanalytical method can be used between the Biosimilar and Reference therapeutic. If any validation parameter does not meet the recommended acceptance criteria, an investigation should be conducted, and a decision should be made to determine if the assay needs to be optimized or if two assays should be used.
5. During Bioanalysis, use one validated assay to assess PK for Biosimilar and Reference study samples.

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ADA ASSAY RECOMMENDATIONS

Objective of ADA Assessment:

"…it is generally only important to demonstrate that the immunogenicity of the proposed product (Biosimilar) is not increased…"

Recommendation will be One Assay or Two Assays

But will try to answer the variety of issues:

What does One Assay look like? What do Two Assays look like?

Is comparison of two positive controls meaningful?

If Two Assays:

- Should cut points be similar?
- Should drug tolerance be similar?
- Run both positive controls in both assays?

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ONE ASSAY PROPOSAL -- ADVANTAGES AND DISADVANTAGES

ADVANTAGES

- Ensures ADAs generated against Biosimilar are reliably detected
- Only need to validate a single assay
- Less inter-assay variation as only one set of reagents are used
  -- minimizes potential impact of assay bias on comparability between Biosimilar and Reference (if two assays are used)
- Blinded study sample analysis possible and only need to analyse the study sample once
- Confirmation of putative positives from the screening step can be obtained either by incubating all the samples with the Biosimilar **or** Reference (if the study is un-blinded) or with Biosimilar **and** Reference (if the study is blinded)
- Sensitivity will be based on performance of one surrogate positive control
- Natural progression of samples from one binding assay to one neutralizing antibody assay

DISADVANTAGES

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

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TWO ASSAYS PROPOSAL -- ADVANTAGES AND DISADVANTAGES

ADVANTAGE:

- Potential for determining the true immunogenicity differences between Biosimilar and Reference using a statistically-powered study.

DISADVANTAGES:

- Need to validate two assays
- Twice as much work using twice as much sample volume and reagents
- Validation criteria has to be very carefully examined for the 2 assays to be "comparable"
  - -- Should assays have same sensitivity (assay cut point, confirmatory cut point)?
  - -- Should assays have same drug tolerance?
  - -- Positive control for Biosimilar, Positive control for Reference?
- Comparing and interpreting data from separate assays may be challenging
  - -- Results of two assays with different properties, different reagents, assay characteristics (screening and confirmatory cut-points, sensitivity, etc.) have to be compared
- Introduction of additional variability / impact of assay bias on comparative evaluation of immunogenicity of the products
- No blinded study bioanalysis – However, if a blinded study– the study samples will have to be analyzed in both assays independently
- Two NAb assays?

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THINGS TO THINK ABOUT

- Regulatory guidances for the development of an assay to support Biosimilar drug development are insufficient at this time. Therefore, use good science.
- ONE ASSAY OR TWO ASSAYS?
  For Non-clinical ADA assessments – one assay is sufficient.

  For Clinical ADA assessments – two assays for early studies, then demonstrate biosimilarity in the results, then move to one assay for later studies?
- Overall objective is to generate data demonstrating that the incidence of ADA of Biosimilar drug is equal to or less than the Reference drug.
  However, if incidence is the same, but titers are different (Reference < Biosimilar), this may have clinical significance.
- Most comparator studies will not be able to detect true differences in immunogenicity because the ADA incidences are low. Large studies would be needed to evaluate meaningful differences. Therefore, a pharmacovigilance program should be put in place to better detect clinical meaningful immunogenicity issues.
- The bioanalytical strategy to assess immunogenicity is the responsibility of the Sponsor. However, it would be smart to discuss the proposed strategy with regulatory agencies prior to beginning development of a Biosimilar.

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