

Outcome of EBF Survey on Biosimilars

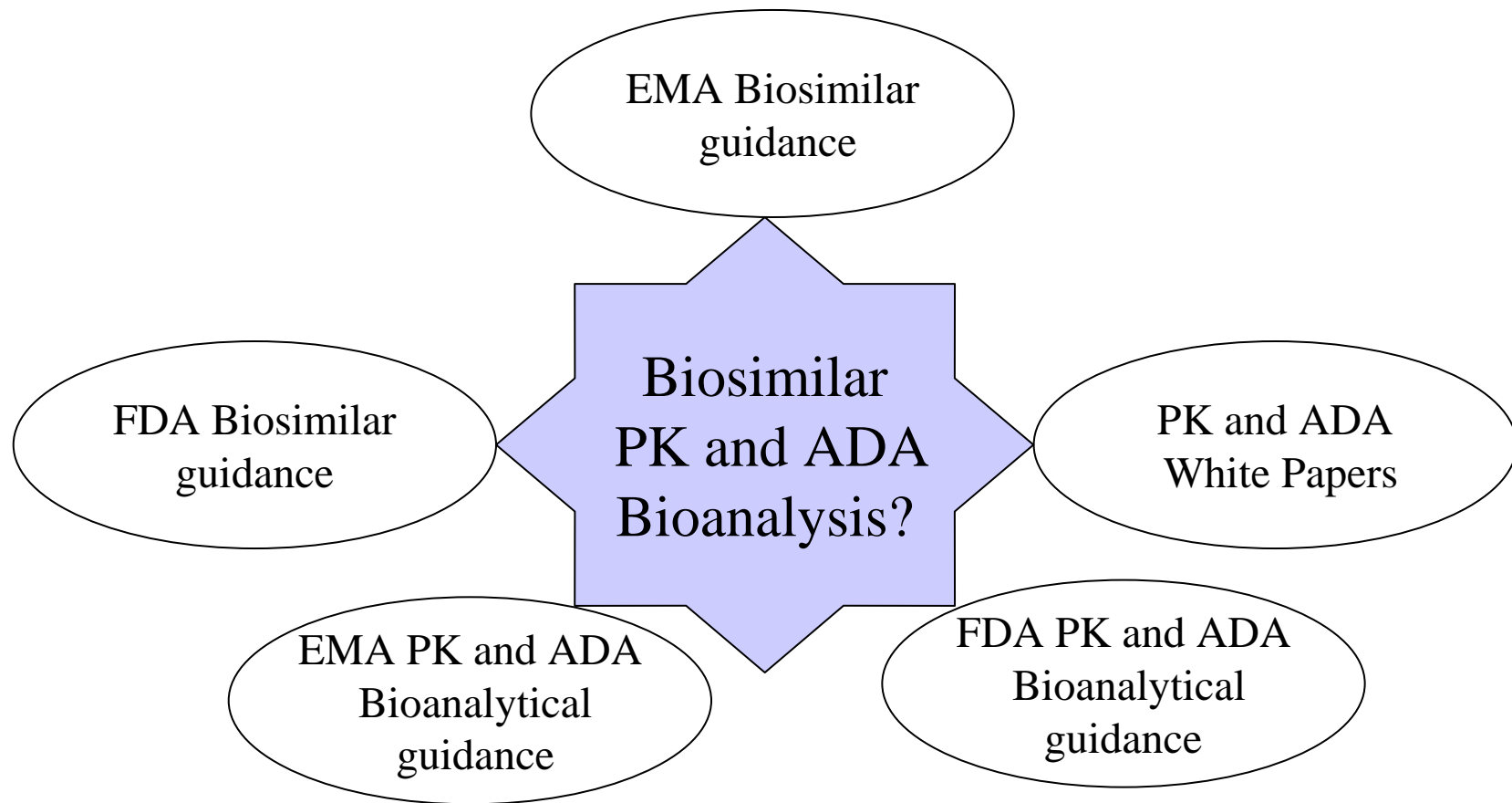
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on behalf of the EBF TT33*

Breakout Session II - Biosimilars
14th November 2012

Overview

- Overall Aim of survey
- Results of PK survey
- Results of ADA survey
- Preliminary Conclusions


Overall Aim of Biosimilar Survey



Wanted to use survey to gauge EBF members opinion on approaches used for Biosimilar PK and ADA bioanalysis

Details of surveys performed

- Surveys used to capture current thinking and approaches used by people across the industry
- 2 surveys, 1 for Biosimilar PK and 1 for Biosimilar ADA bioanalysis
- Survey sent to all EBF members
- Survey conducted 9th to 31st October 2012
- 10 out 33 companies replied for ADA
- 13 out 33 companies replied for PK



Biosimilar PK assay survey

Approaches used for bioanalysis

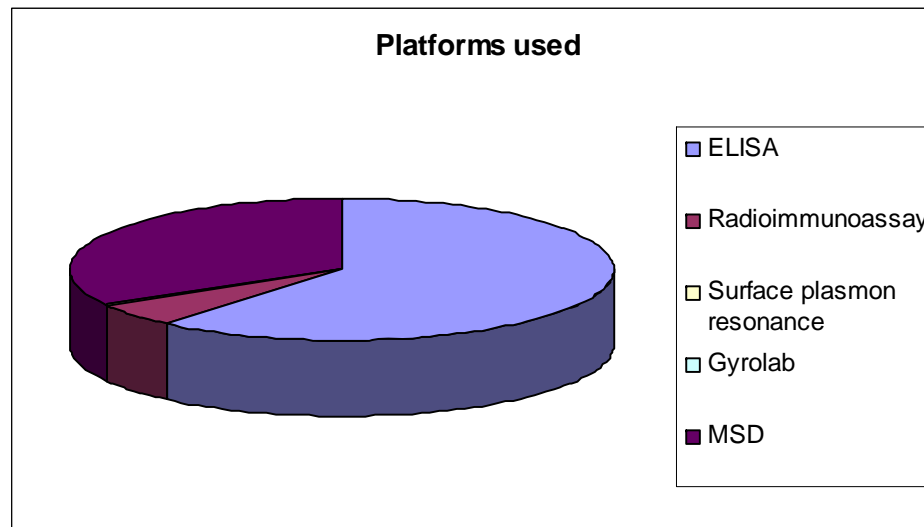
Aim for Biosimilar PK bioanalysis survey

- Survey posed several questions that the topic team considered important for biosimilar PK comparability studies:
 - What platform?
 - How do people define Innovator and Biosimilar Test Articles?
 - Do people use **1 or 2 analytical methods** for Innovator and Biosimilar?
 - Design of bioanalytical testing for comparability studies?
 - Approaches used for validation of Innovator/Biosimilar analytical methods?
 - Approaches used for sample analysis?
 - What regulations are people following?

PK Survey Results – 1 (Platform)

Platform used for biosimilar PK method comparability studies

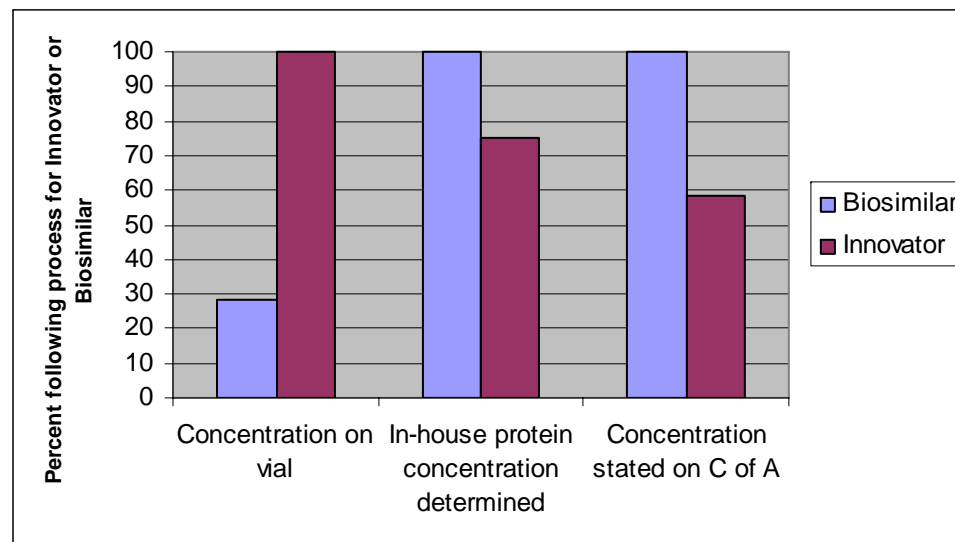
➤ 100% of all respondents used the same platform for the biosimilar method as they did for the innovator



Survey indicated no real differences in the platforms that are used for biosimilar/innovator comparability studies

PK Survey Results – 2 (Test article)

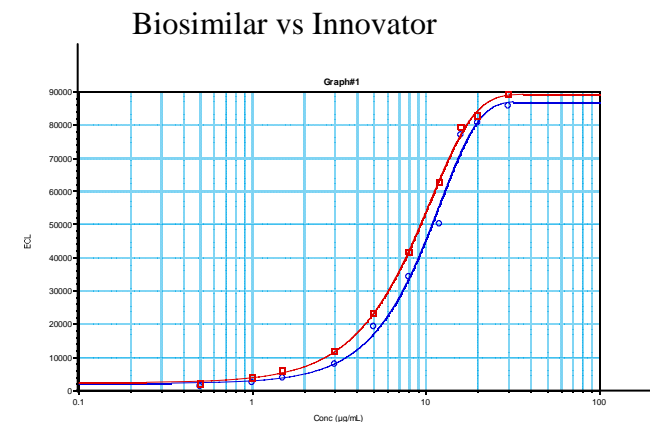
- How do you define the Innovator and Biosimilar Test article for bioanalysis?



Respondents indicated C of A is preferred for defining Innovator and Biosimilar test article but survey demonstrated that it can be difficult to acquire this information for the Innovator product.

PK Survey Results – 3 (1 Analytical Method)

- Design of comparability testing for biosimilar and innovator (**1 Analytical Method**)
 - Do respondents use the biosimilar or innovator product as the calibrator to quantify QCs and samples?
- 58.3% responded biosimilar
- 41.7% responded innovator



No overall trend in biosimilar versus innovator use as calibrator.

PK Survey Results – 4 (1 Analytical Method)

- When using a **biosimilar** calibrator curve do you use biosimilar QCs, innovator QCs or both?

Validation Parameter	Biosimilar only	Innovator only	Both
Accuracy and Precision	25%	0%	75%
Sensitivity	25%	0%	75%
Selectivity	25%	0%	75%
Specificity	50%	0%	50%
Freeze/Thaw stability	50%	0%	50%
Room Temperature stability	50%	0%	50%
Long term stability	50%	0%	50%
Dilutional Linearity	75%	0%	25%

PK Survey Results – 5 (1 Analytical Method)

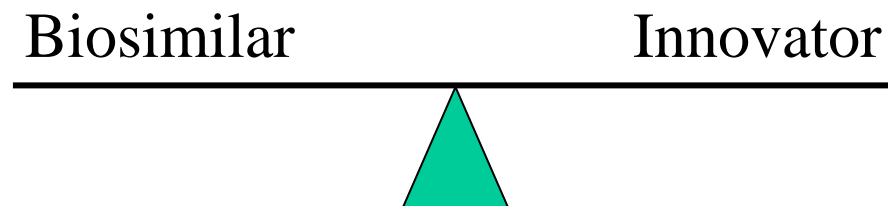
- When using a **Innovator** calibrator curve do you use biosimilar QCs, innovator QCs or both?

Validation Parameter	Biosimilar only	Innovator only	Both
Accuracy and Precision	0%	0%	100%
Sensitivity	0%	0%	100%
Selectivity	0%	14.3%	85.7%
Specificity	0%	14.3%	85.7%
Freeze/Thaw stability	14.3%	14.3%	71.4%
Room Temperature stability	14.3%	14.3%	71.4%
Long term stability	16.7%	0%	83.3%
Dilutional Linearity	14.3%	14.3%	71.4%

PK Survey Results – 6 (1 Analytical Method)

How do you demonstrate the method is comparable for measuring biosimilar and innovator samples?

- 50% Respondents show biosimilar and Innovator are within bioanalytical regulatory guidelines (E.g. Biosimilar and Innovator QCs within $\pm 20\%$ relative error (RE) (25 % at LLOQ and ULOQ))
- 50% Respondents demonstrate that biosimilar and Innovator QC concentration is comparable (E.g. Biosimilar and Innovator QC concentration within $\pm 10\%$ of each other)



There is no current guidelines for validation of methods used in comparability studies

PK Survey Results – 6 (1 Analytical Method)

➤ Sample Analysis considerations when using one analytical method:

- Is the sample analysis performed blinded?
 - 55.6% responded Yes
 - 44.4% responded No

Blinded analysis is more straightforward with 1 analytical method

- What QCs are run during sample analysis?
 - 33.3% responded QCs that are the same as calibrator
 - 66.7% responded QCs for biosimilar and innovator

If you have demonstrated during validation that the analysis is comparable between biosimilar and innovator it is not necessary to run both sets of QCs during sample analysis?

PK Survey Results – 6 (2 Analytical Methods)

- When using 2 analytical methods is there any differences in platform, reagents and conditions?

Question	Responded Yes	Responded No
Do you use the same platform for biosimilar and innovator method?	100%	0%
Do you use the same detection/capture reagents?	100%	0%
Do you use the same labels/tags for the detection reagents?	83.3%	16.7%
Do you use the same assay conditions?	100%	0%

Overall, respondents use the same platform, reagents and conditions when using 2 analytical methods.

PK Survey Results – 7 (2 Analytical Methods)

How do you demonstrate the 2 analytical methods are comparable for measuring biosimilar and innovator samples?

- 57.1% Respondents show biosimilar and Innovator are within bioanalytical regulatory guidelines (E.g. Biosimilar and Innovator QCs within ± 20 % relative error (RE) (25 % at LLOQ and ULOQ))
- 42.9% Respondents demonstrate that biosimilar and Innovator QC concentration is comparable (E.g. Biosimilar and Innovator QC concentration within ± 10 % of each other)

Do you use a correction factor to normalise the two different methods?

- 100% of respondents answered no

PK Survey Results – 8 (2 Analytical Methods)

➤ Sample Analysis considerations when using two analytical method:

– Is the sample analysis performed blinded?

- 40% responded Yes
- 60% responded No

Harder to perform analysis blinded with 2 analytical methods

PK Survey Results – 8 (Regulatory Guidelines)

➤ The following guidelines and publications were cited by the survey respondents:

- EMA and FDA Guidance on analytical method validation
- EMA Guidelines on Biosimilar development
- EMA Guidelines on similar medicinal products containing biotechnology derived proteins
- FDA biosimilar guidelines
- GCP
- Krys J. Miller et al (2001)
- Pharm. Res, Wismanathan et al (2007)

None of the guidelines or publications cited specifically address PK bioanalytical considerations for biosimilar comparability studies



Biosimilar ADA assay survey

Approaches used for bioanalysis

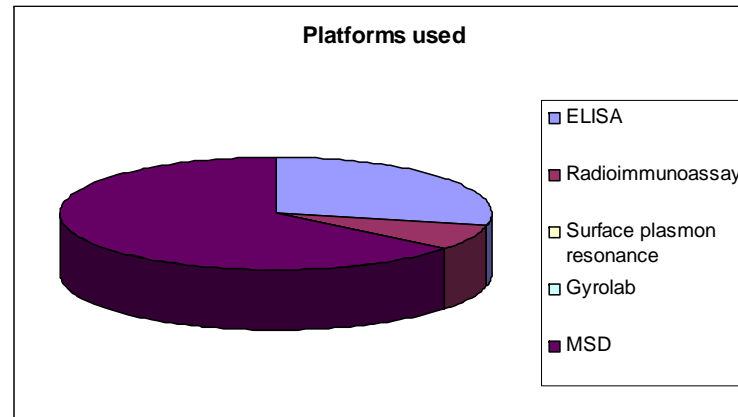
Aim for Biosimilar ADA bioanalysis survey

- Survey posed several questions that the topic team considered important for Biosimilar studies:
 - Details of platform used and format of assay?
 - How many reference materials are used to validate Biosimilar/innovator methods?
 - What is considered the best approach for validating Biosimilar/Innovator ADA assay cut points, specificity cut points?
 - What is considered the best approach for validating the quantification of the Biosimilar/Innovator ADA response?
 - What are the sample analysis considerations for Biosimilar/Innovator ADA methods?
 - What regulations are people following?

ADA Survey Results -1 (Platform/format)

Platform/format used for biosimilar/innovator ADA comparability studies:

- 100% of all respondents used the same platform for the biosimilar method as they did for the innovator
- Types of platform used:



➤ What is your preferred format for setting up ADA comparability studies:

- 90% responded Bridging format
- 10% responded Direct format

ADA Survey Results – 2 (Reference material)

- How many reference materials do you use for validation of biosimilar and innovator ADA methods?
 - 77.8% **One reference** that cross reacts with biosimilar and Innovator
 - 22.2% **Two references** that recognise biosimilar or Innovator

ADA Survey Results – 3 (Assay Cut Point)

➤ Validation of assay cut point for Biosimilar and Innovator ADA methods:

– Do you determine an Innovator assay cut point, Biosimilar assay cut point or both?

Biosimilar assay cut point only = 28.6%

Innovator assay cut point only = 0%

Innovator and Biosimilar assay cut point = 71.4%

– If you assess an Innovator and Biosimilar assay cut point do you determine if the 2 assay cut points are comparable?

Yes = 16.7%

No = 83.3%

Overall, response indicated Biosimilar and Innovator assay cut points are assessed separately

ADA Survey Results – 4 (CCP)

- Validation of Confirmatory Cut Point (CCP) for Biosimilar and Innovator ADA methods:
 - Do you determine an Innovator CCP, Biosimilar CCP or both?
 - Biosimilar CCP only = 33.3%
 - Innovator CCP only = 11.1%
 - Innovator and Biosimilar CCP = 55.6%

 - If you assess an Innovator and Biosimilar CCP do you determine if the 2 CCPs are comparable?
 - Yes = 16.7%
 - No = 83.3%

 - To demonstrate comparability of 2 ADA methods, during CCP assessment do you confirm excess innovator drug can be used to inhibit the detection of the biosimilar ADA response and vice versa?
 - Yes = 60%
 - No = 40%

ADA Survey Results – 5 (Quantification)

➤ If you quantify the antibody response using a reference curve do you demonstrate the PC accuracy is the same for the innovator and biosimilar?

- Yes = 66.7%
- No = 33.3%

Only 3 people responded for this question suggesting this approach is limited

➤ If you perform titre analysis for quantification of ADA response do you do titre analysis with one or two assays?

- Single assay for biosimilar and innovator with one assay cut point = 50%
- Two assays, one for biosimilar and one for innovator = 50%

There is no trend in approach used for biosimilar ADA bioanalysis

ADA Survey Results – 6 (Sample analysis)

- For Biosimilar ADA sample analysis in general is the bioanalysis performed blinded?
 - Yes = 60%
 - No = 40%

Using 2 ADA methods can make performing blinded studies more difficult

ADA Survey Results – 7 (Regulatory guidelines)

➤ The following guidelines and publications were cited by the survey respondents:

- Mire Sluis
- Shanker
- EMA guidance on immunogenicity testing
- Draft FDA immunogenicity guideline
- EMA guide line for immunogenicity of MAbs

None of the guidelines or publications cited specifically address the ADA bioanalytical considerations for biosimilars

Preliminary Conclusions

- Survey shows multiple approaches are being used by EBF members for biosimilar PK and ADA bioanalysis
- Clear need for standardising how Biosimilar PK and ADA bioanalysis is performed
- A standard approach would insure a true assessment of comparability between Innovator and Biosimilar is made
- Clear requirement for a white paper or regulatory guidelines specifically addressing Biosimilar PK and ADA bioanalysis

Acknowledgement

- Michaela Golob
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