2017 ASMS Workshop Report

1. Title of workshop and those presiding:
   Bioanalysis of Biosimilars (Regulated Bioanalysis Interest Group)
   Presided by Dian Su, Ph.D.Genentech), Jiann Wang, Ph.D. (BMS), Fabio Garofolo, Ph.D. (Angelini)

2. Date of workshop
   June 7th, 2017

3. Estimate of attendance
   ~90

4. Summary of program and discussion (Please see pages 2-4)

5. Workshop presentations (Please see pages 5-43)

Summary of Program

1. The workshop was focused on the integration of LC-MS to regulated bioanalysis and areas where it can complement current ligand binding assays.

2. The panel, consisting of representatives from CROs and Pharms, shared their knowledge and practices.

3. The workshop started with an overview of the field of biosimilars given the recent approval 3 new biosimilar biologic drugs. Following a review of the pre-conference survey results for the Regulated Bioanalysis Interest Group, short presentations highlighting various case studies associated with LC-MS and Ligand Binding Assay (LBA) were presented by a panel of experts in the field. The meeting concluded with a panel discussion answering questions from the audience.

Summary of Discussion

1. Overview of the Field (Discussion led by Dian Su, Genentech)
Overview of the biosimilar market and the approach for the development of a biosimilar drugs. The market size for biosimilar drugs will continue to increase and is expected to triple to over 10 billion USD over the next 6 years. The challenges for the development of biosimilars is the need for a multiple-step approach to bioanalytical testing. It is important to demonstrate that all
biosimilar assays possess the ability to measure the biosimilar and innovator reliably and equivalently. Biosimilars also need to demonstrate similarity in sequence, modifications, and drug potency. The methods for biosimilar analysis include ligand binding arrays and LC-MS
using high-resolution mass spectrometers. One question regarding the development of biosimilars is the importance of antibody glycan structures and their effects on the PK profile.

2. Large Molecule Bioanalysis (Discussion led by Barry Jones, Q2labsolutions)
This section focused on the challenges of large molecule bioanalysis. The main difficulties with LBA is potential selectivity issues with reagents. The development of anti-drug antibodies may be difficult depending on the target molecule. One issue with LBA is the inability to obtain whole-molecule information as LBA reagents are insensitive to changes away from the reagent binding regions. LC-MS can complement LBA, but can suffer from sensitivity issues. Cost and throughput are also potential limitations. The ability to obtain comprehensive characterization information is an added benefit. To harmonize LBA and high resolution LC-MS, each technique can be used depending on the challenge. LC-MS offers benefits of better characterization of molecule biotransformation and can utilize generic reagents for multiple studies. Improvements in assay sensitivity can further integrate LC-MS workflows for bioanalysis.

3. Considerations for Assay Development (Discussion led by Moucun Yuan, PPD)
The implementation of a one-assay approach to support structural comparability of CMC produced material was outlined. The main considerations is the number of compounds and the timelines for planned submissions. A one-assay approach allows for easier data interpretation and blinded sample studies in PK analysis. The biosimilar can be used as a reference as the producer has more knowledge of the manufactured molecule. The same biosimilar can be used as a reagent in anti-drug antibody assays.

Summary of Discussion (continued)

4. Quantitation of a Biosimilar (Discussion led by Luca Genovesi, Biotrial)
A case study of regarding the development of LC-MS assays, based on an innovator drug, was presented that can be applied to a biosimilar. A panel of unique peptides were selected for identity as well as ones sufficient for quantitation. A reagent free approach was developed to allow suitable quantitation of an antibody in pre-clinical species by LC-MS/MS. For better sensitivity a functional binding assay using antigen-bound magnetic beads was used combining benefits of LBA with LC-MS quantitation. Both assays, reagent free and functional, were suitable for antibody quantitation in biological matrices.

5. PK Assays for Biosimilars (Discussion led by Xun Wang, QPS)
The final presentation outlined issues with PK assays for biosimilars by LBA or LC-MS. A case study demonstrated how an innovator and biosimilar could be equivalently captured and analyzed by LC-MS/MS when using peptides for quantitation. This data was repeated for
multiple sample lots and concentrations. Important considerations involve the analysis of multiple sample lots by multiple analysts on separate days. Advantages of LC-MS for biosimilar. analysis is the use of the same peptide for comparison and the ability to apply LC-MS throughout the development process. The main challenges to overcome are the issue that the majority of assays are in the LBA format and to decrease the cost of analysis.

6. Panel Discussion (Discussion led by the panel)
Questions from the audience are around demonstration of "similarity" of the Biosimilar compared to the innovator Biotherapeutic and seletion of LBA vs. LC-MS approaches.

The main response from the panel regarding how to draw the line between similarity is one needs to attempt to duplicate the innovator assays. Issues with glycosylation can affect similarity and PK, but no consensus was reached on how to resolve.

Regarding selection of bioanalytical strategies, LBA appears to remain preferred over LC-MS, but LC-MS still has potential to resolve unexpected molecule biotransformation. The main consensus of the panel is if resources are available, it may be best to attempt both LBA and LC-MS both to confirm all methods for biosimilar characterization.

Bioanalysis of Biosimilars
(Regulated Bioanalysis Interest Group)

Presiding: Dian Su, Ph.D. (Genentech)
Jian Wang, Ph.D. (BMS)
Fabio Garofolo, Ph.D. (Angelini)

2017 ASMS 5:45 – 7:00 PM WEDNESDAY WORKSHOPS (June 7th)

Indianapolis, IN

Agenda

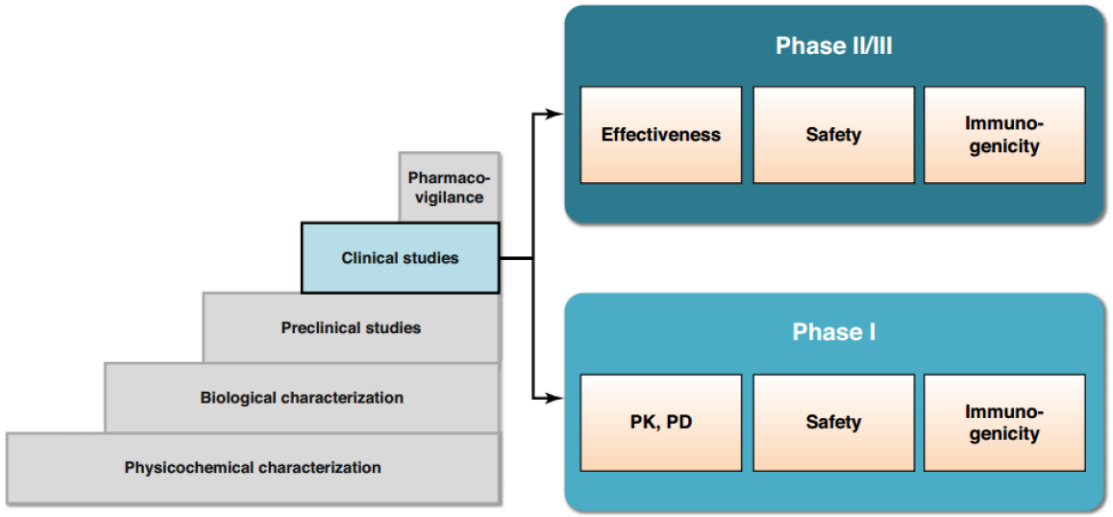
- **Introduction presentation**
  - Increasing market of Biosimilars
  - Challenge in Bioanalysis of Biosimilars
  - Why LCMS rather than LBA in Biosimilars
  - Quick review of the main survey results
  - Intro to the panel list
- **Panel Presentation**
- **Panel Discussion**

Increasing Market of Biosimilars

- **Definition of biosimilar: product highly similar to the reference product without clinically meaningful differences in safety, purity and potency [US Food & Drug Administration (FDA)]**

Biosimilars are not exact duplicates of Innovator Biotherapeutics and require evaluation of "similarity" of the Biosimilar compared to the innovator Biotherapeutic.

The Stepwise Development Approach for a Biosimilar



https://www.pharmacist.com/sites/default/files/files/Biosimilar%20Policy%20Background%20Paper%20-%20FINAL.PDF

- **28 biosimilars are currently approved in Europe and 5 in the U.S.** In 2017, the European Medical Agency (EMA) has approved six biosimilar applications, including applications for biosimilars to two of the best-selling complex biologics, Humira (adalimumab) and MabThera (rituximab).

US Approved Biosimilars as of May 2017

Biosimilar Trade Name	Marketer	Reference Drug	Approval Date
Zarxio (filgrastim-sndz)	Sandoz	Neupogen	March 6, 2015
Inflectra (infliximab-dyyb)	Celltrion	Remicade	April 5, 2016
Erelzi (etanercept-szzs)	Sandoz	Enbrel	August 30, 2016
Amjevita (adalimumab-atto)	Amgen	Humira	September 23, 2016
Renflexis (infliximab-abda)	Samsung Bioepis	Remicade	April 21, 2017

Bioanalytical challenges in the development of biosimilars, *Rafiqul Islam and Clarinda Islam,* Bioanalysis of Biotherapeutics, 2013 , Pages 62-75, eBook ISBN: 978-1-909453-73-9

http://www.jdsupra.com/legalnews/updateonbiosimilarapprovalsand26099/

Increasing Market of Biosimilars

- **Increasing Market of Biosimilars**

- The market size of global biosimilar market was valued over USD 2.5 billion during 2014 and it surpassed USD 3.30 billion during 2016. The global biosimilar market is projected to surpass USD 10.50 billion by 2023, growing with a CAGR 25.0 % -26.0 % from 2017 to 2023

- The major factor driving the growth of biosimilars is their cost-effectiveness*

- Competition is expected to be limited in the market due to the technology required to generate a biosimilar*

- The high cost, the complexity and stringent regulatory processes, and the lack of clear guidelines for the interchangeability or substitution of drugs with bio-similar is a restraint for the growth of the biosimilar market

Table 1. Selected Biosimilars Under Investigation

Reference Product (Brand, Manufacturer)	Est. Patent Expiration (U.S.)	Indication	Biosimilar	Manufacturer	Published Data
Adalimumab (Humira, AbbVie)	2022	RA, psoriatic arthritis, AS, UC, Crohn's disease, psoriasis, HS, JIA	GP2017 PF-06410293 BCD-057	Sandoz Pfizer Biocad	Phase III trial under way Phase I trial under way Phase III (2017)
Bevacizumab (Avastin, Genentech)	2019	Colorectal, lung, and renal cancers	BCD-021 PF-06439535 ABP 215	Biocad Pfizer Amgen	Phase III trial completed Preclinical/phase I trials completed Phase III trials under way
Cetuximab (Erbitux, Eli Lilly)	Expired (2016)	Colorectal, head and neck cancers	ABP 494	Amgen	Phase III trial under way
Darbepoetin alfa (Aranesp, Amgen)	2018	Anemia due to CKD or chemotherapy	BCD-066	Biocad	Phase III trials under way (2017)
Enoxaparin (Lovenox, Sanofi-Aventis)	Expired (2010)	DVT, VTE	BCD-080	Biocad	Phase III trials under way (2016)
Epoetin alfa (Epogen, Amgen)	Expired (2015)	Anemia due to CKD or chemotherapy	HX575	Sandoz	Phase III trial completed
Glatiramer acetate (Copaxone, Teva)	Expired (2014)	Multiple sclerosis	BDC-063	Biocad	Phase III trials under way (2016)
Infliximab (Remicade, Janssen Biotech)	September 2018	Autoimmune diseases including RA, psoriasis, UC, Crohn's disease	GP 1111 PF-06438179 ABP 710 BCD-055	Sandoz Pfizer Amgen Biocad	Phase III trial under way Phase III trial under way No data available Phase III (2017)
Pegfilgrastim (Neulasta, Amgen)	Expired (October 2015)	Chemotherapy-induced neutropenia	LA-2006	Sandoz	File accepted by FDA at the end of 2015
Rituximab (Rituxan, Genentech)	September 2016	Lymphoma	GP2013 BCD-020 PF-05280586 CT-P10 RTXM83 ABP 798	Sandoz Biocad Pfizer Celltrion mAbxience Amgen	Phase II and III trials under way Phase III trials completed Preclinical/phase I trials completed Phase III trials completed Phase III trials completed No data available
Trastuzumab (Herceptin, Genentech)	June 2019	Breast cancer	BCD-022 PF-05280014 ABP 980 CT-P6	Biocad Pfizer Amgen Celltrion	Successful phase I trials Preclinical/phase I trials completed Phase III trials under way Phase III trials completed

AS: ankylosing spondylitis; CKD: chronic kidney disease; DVT: deep venous thrombosis; est: estimated; HS: hidradenitis suppurativa; JIA: juvenile idiopathic arthritis; RA: rheumatoid arthritis; UC: ulcerative colitis; VTE: venous thromboembolism. Source: References 17-22.

*** Inputs from Luca Genovesi (Biotrial)**

Biosimilars: Current Approvals and Pipeline Agents , US Pharm. 2016;41(10):26-29.

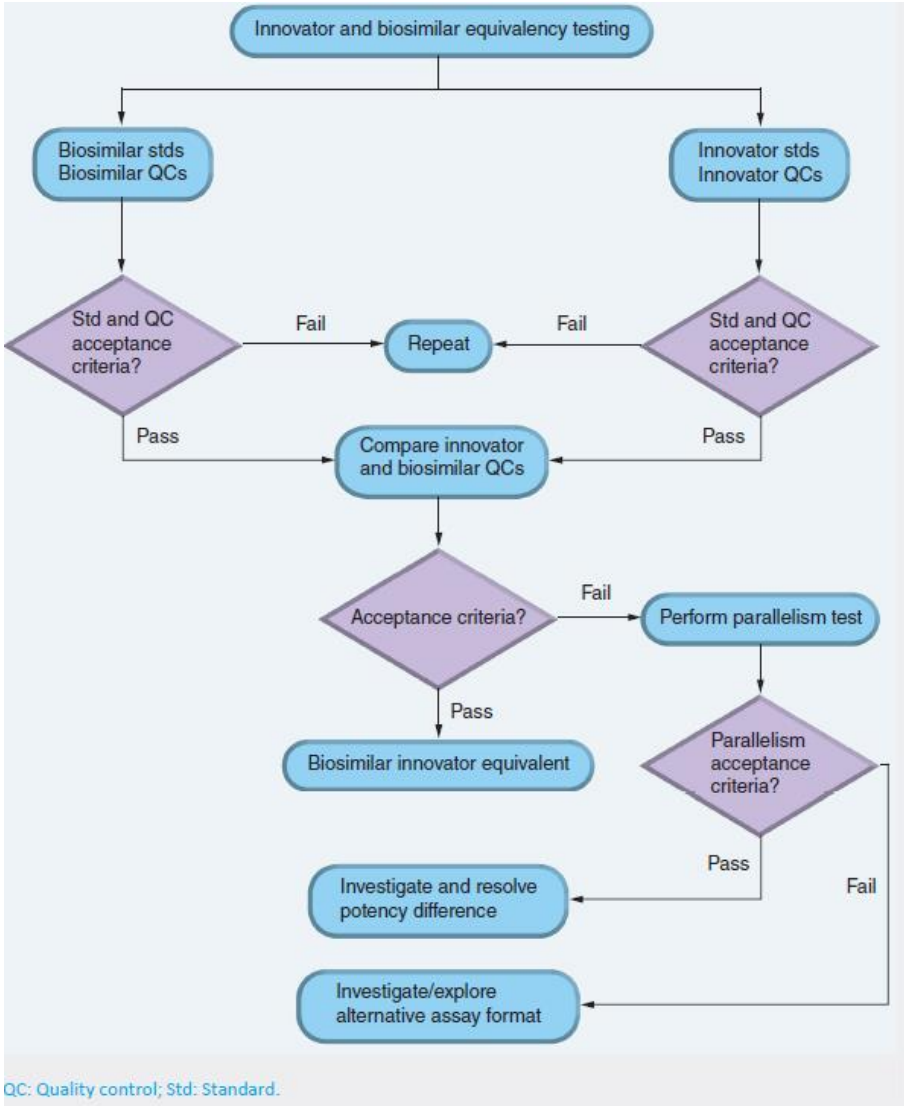
Challenges in Bioanalysis of Biosimilars

- Biosimilars require a multifaceted approach to bioanalytical testing that includes **the quantitative determination of drug (pharmacokinetic assay) and the detection of anti-drug antibodies (immunogenicity assay)**.

- It is important to demonstrate that the **bioanalytical method can measure both the innovator and the biosimilar drug reliably and equivalently**. The PK assay method must be able to permit **demonstration of bioequivalence of the biosimilar**.

- **All the differences (e.g., structural and potency) need to be carefully evaluated and taken into consideration** when developing assays that measure both the biosimilar and the innovator

- Bioanalysis of Biosimilars is subject to endogenous interference, requiring **specific and selective assay to ensure data reliability.**



Bioanalytical challenges in the development of biosimilars, *Rafiqul Islam and Clarinda Islam,* Bioanalysis of Biotherapeutics, 2013 Pages 62-75, eBook ISBN: 978-1-909453-73-9

Why LCMS Rather Than LBA in Biosimilars

- **Ligand Binding Assays – LBA**

  - The specificity and selectivity depend on the interaction of critical reagents to the Biotherapeutic.

  - When the Innovator and the Biosimilar do not have the same binding characteristics towards the assay critical reagents, two assays with different critical reagents may be needed and the demonstration of biocomparability may be more complicated.

- **LCMS**

  - LC-MS/MS and HRMS assays can be developed for the Bioanalysis of Biosimilars without using critical reagents, therefor only a single assay is needed for both Biosimilar and Innovator comparison.

  - LC/MS quantitation of large molecules offers an edge over ligand binding approach*
    - ✓ Classical vs Hybrid approach
    - ✓ Physical Detection is always orthogonal to capture system
    - ✓ Add several degree of separation to obtain specificity
    - ✓ Tailored Assay according to the scientific need (i.e. free, total)
    - ✓ Multiple peptide selection and/or Multiplexing

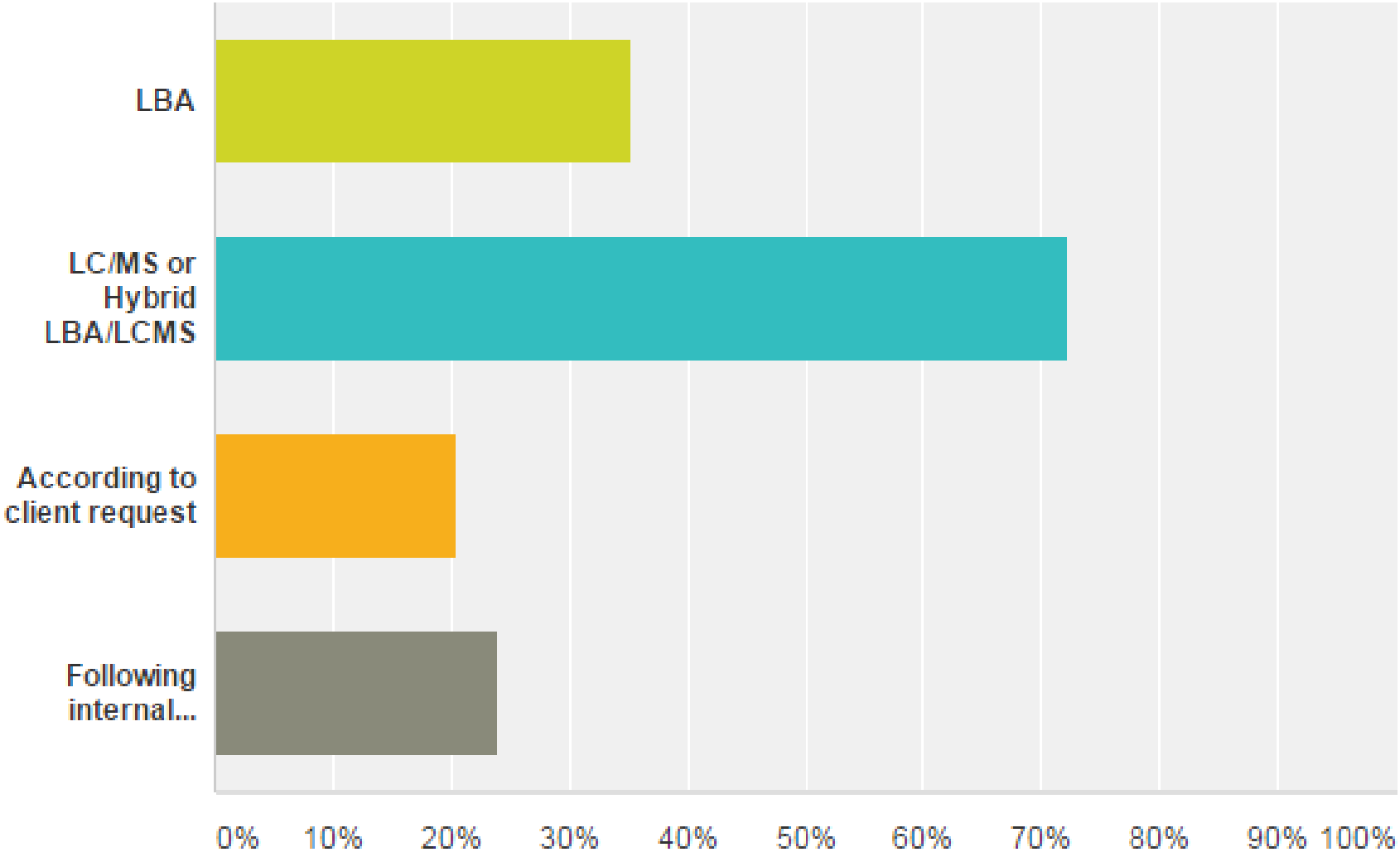
*** Inputs from Luca Genovesi (Biotrial)**

Pre-workshop Survey Results

- https://www.surveymonkey.com/results/SM-LD2LC8SH/

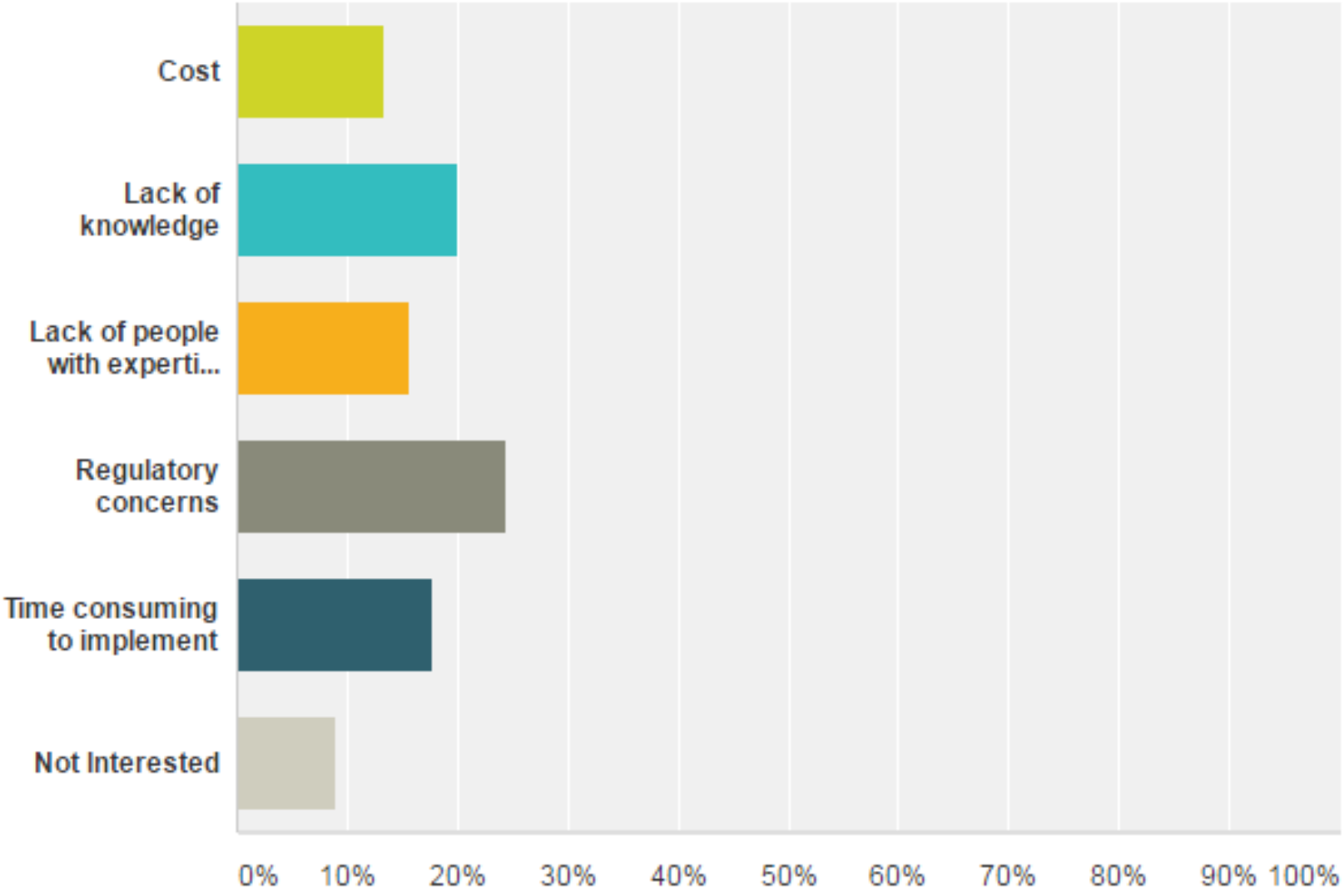
How do you generally do bioanalysis of large molecules? (choose all that apply)

Answered: 54 Skipped: 22



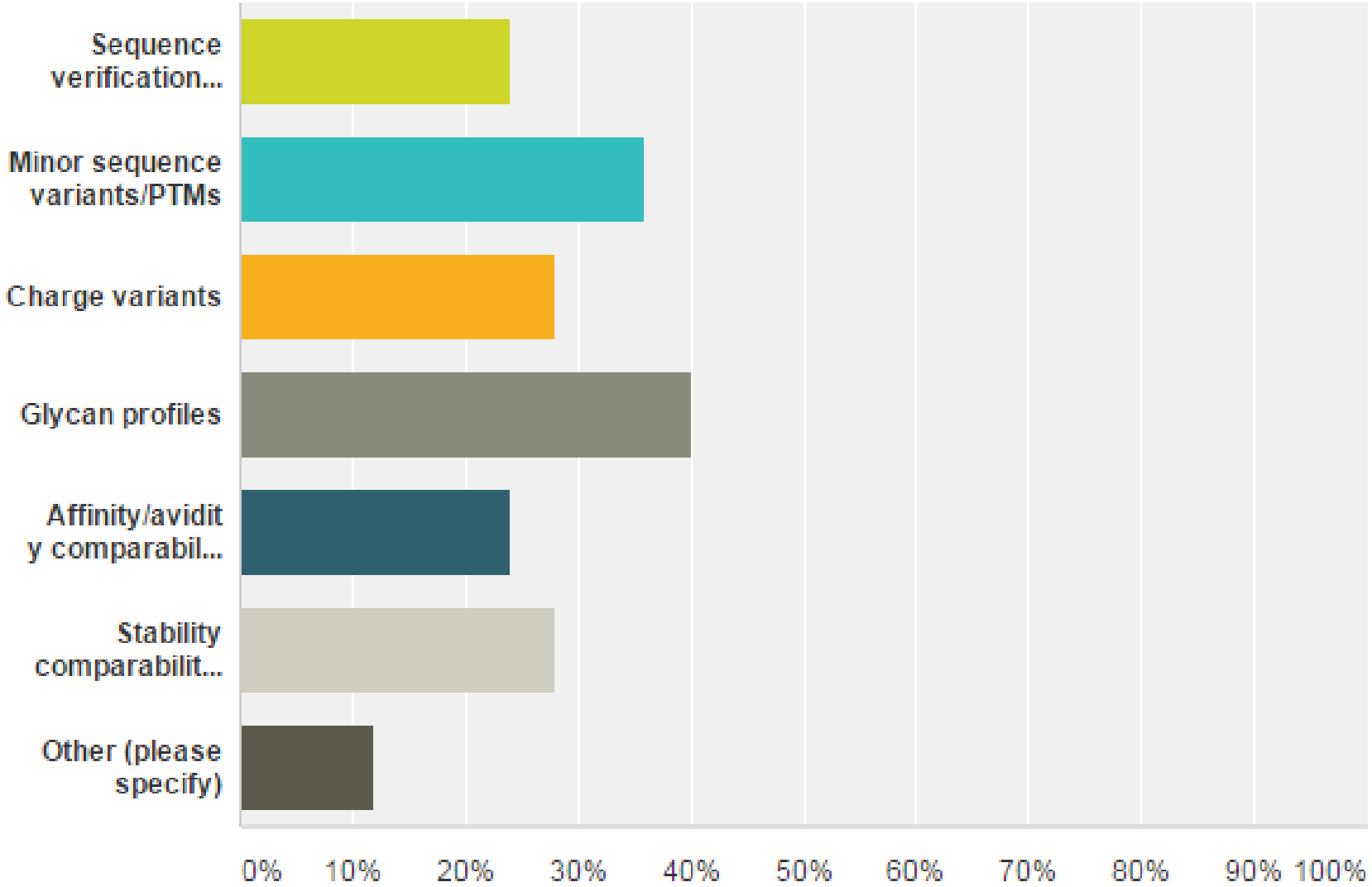
What is the biggest limitation to implement biosimilar bioanalysis by LC/MS or hybrid LBA/LCMS vs. traditional LBA?

Answered: 45 Skipped: 31



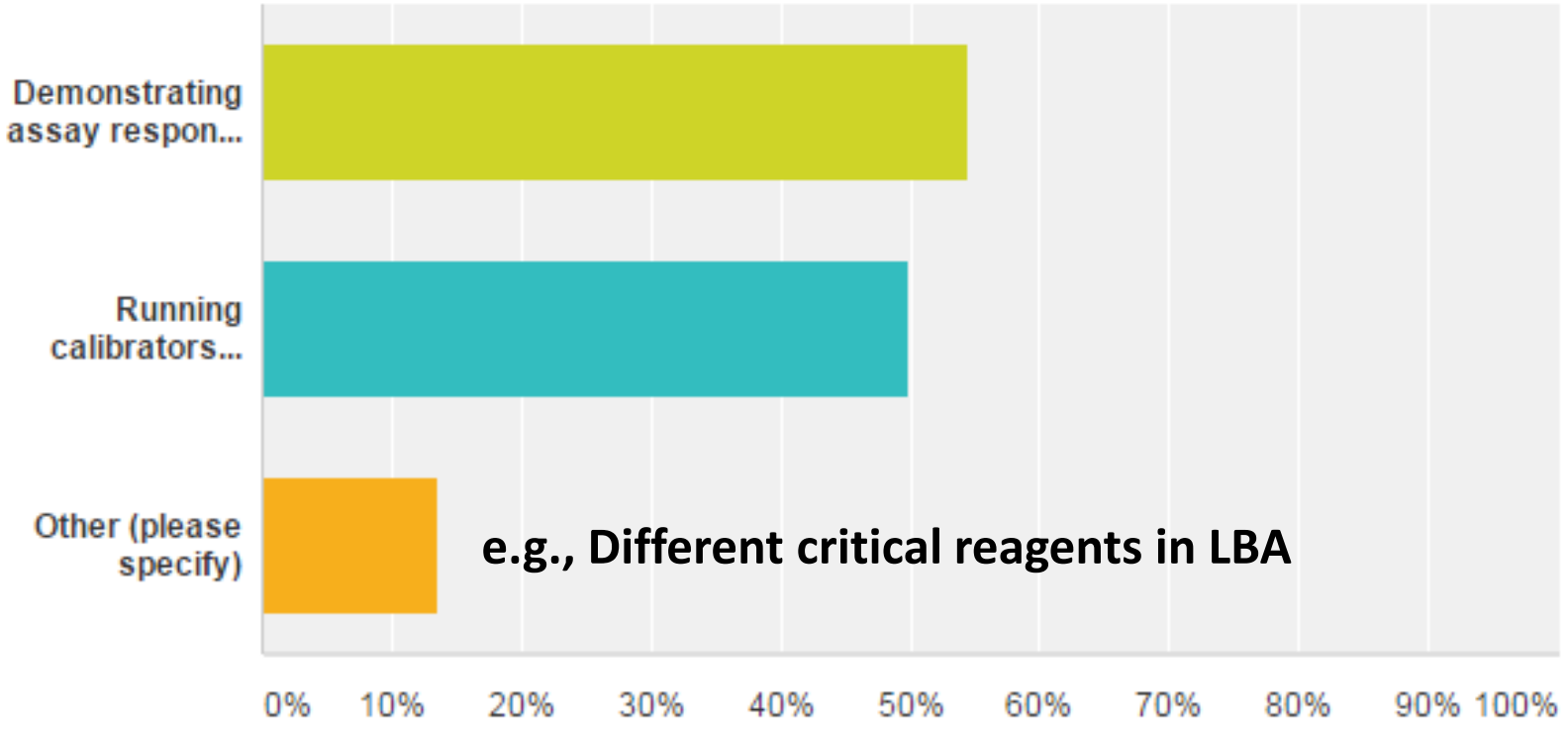
What challenges do you encounter in the bioanalysis of biosimilars? (Choose all that apply)

Answered: 25 Skipped: 51



What challenges do you encounter when quantitatively analyzing biosimilars? (Choose all that apply)

Answered: 22 Skipped: 54



e.g., Different critical reagents in LBA

Answer Choices	Responses	
Demonstrating assay response comparability for both molecules?	54.55%	12
Running calibrators from one vs. QCs from the other or from both?	50.00%	11

Do you see any particular advantages or disadvantages of LBA vs. LC-MS or Hybrid LBA/LCMS for biosimilars?

Answered: 11 Skipped: 65

No
5/16/2017 2:45 PM

+: independent of affnity diffrences of critical reagents + fast assay development - sensitivity diffrences by analyzing biosimilar vs. orginiator
5/16/2017 12:24 PM

Specificity
5/16/2017 12:23 PM

The main disadvantage of LC-MS or hybrid technique for our company is the cost of a new MS instrument because now we have only 1 QTOF for all our purposes; the main disadvantage for Russia entirely is the ossification of our Pharmacopoeia.
5/16/2017 11:22 AM

Hybrid LCMS has better specificity possibilities than traditions LBA, especially when high-res MS is used.
5/16/2017 11:17 AM

LBA advantage: Innovator PK was likely done by LBA. Fast throughput. LCMS advantage: Can get whole molecule information. Not as reliant on reagent performance.
5/24/2017 12:21 PM

LBA is faster in production.
5/24/2017 6:18 AM

advantage of LBA is high throughput and sensitivity. low cost
5/23/2017 8:25 AM

LC-MS/MS has better specificity than LBA
5/17/2017 1:33 AM

Linearity range being limitations but better sensitivity in LBA
5/16/2017 3:27 PM

Where do you see the biosimilar market in 5 years?

Answered: 11 Skipped: 65

increase market share
5/17/2017 1:15 AM

Only increasing
5/16/2017 8:21 PM

It will grow fast and scientists and regulatory bodies will be having more insights.
5/16/2017 3:30 PM

More successful submissions.
5/16/2017 2:46 PM

a lot of top-selling drugs will go off-patent in teh next yeras thus increasing the market for biosimilars
5/16/2017 12:25 PM

I propose a leap forward in a 3-5 years first in the US and EU and then in Russia with subsequent state subsidy areas and protectionism apperrance in the regional markets.
5/16/2017 11:47 AM

Bigger

Do you think that a regulatory agency is ready for biosimilar studies or that regulation should be implemented and why?

Answered: 10 Skipped: 66

Yes, see new FDA draft guidance
5/17/2017 1:35 AM

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not ready due to cost involvement
5/17/2017 1:15 AM

They should be. I would love to hear more about people's experience.
5/16/2017 8:21 PM

Regulatory bodies are also on learning curve. As more biologic will be available for biosimilar in coming years and with advance technology it will improve.
5/16/2017 3:30 PM

Yes
5/16/2017 2:46 PM

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still evolving as new biosimilars reach market
5/16/2017 12:25 PM

I think that a Russia regulatory agency will be ready for biosimilars studies in a 1-2 years because of their relatively low cost and a strong state budget impact on a domestic market. Also, it is obvious that the Ministry of

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What challenges would you like this workshop to address about biosimilars bioanalysis?

Answered: 11 Skipped: 65

Is bottom-up a viable strategy? Does use of qualitative transitions help address? Is middle-down the answer? Is top-down the answer? Is top-down mature enough to be an alternative? Do these approaches give us more information that we can manage?
5/24/2017 12:21 PM

Find out what majority companies/CROs are doing in their practice routinely.
5/24/2017 6:18 AM

Method development for LC/MS and hydrid LBA/LC/MS.
5/23/2017 8:17 AM

Increase the use of LC-MS/MS for Large Molecules
5/17/2017 1:33 AM

Regulatory experiences and types of Questions asked in submissions.
5/16/2017 8:20 PM

Free vs total assay, regulatory acceptance of Immunogenicity methods both for ADA as well as NAb
5/16/2017 3:27 PM

Case study.

how to adress subtle diffrences that account e.g. to diffrences in PK (e.g through glycan expression) regulatory experience of analyzing biosimilars vs. originators
5/16/2017 12:24 PM

Regulatory aspects of setting up an analysis procedure
5/16/2017 12:23 PM

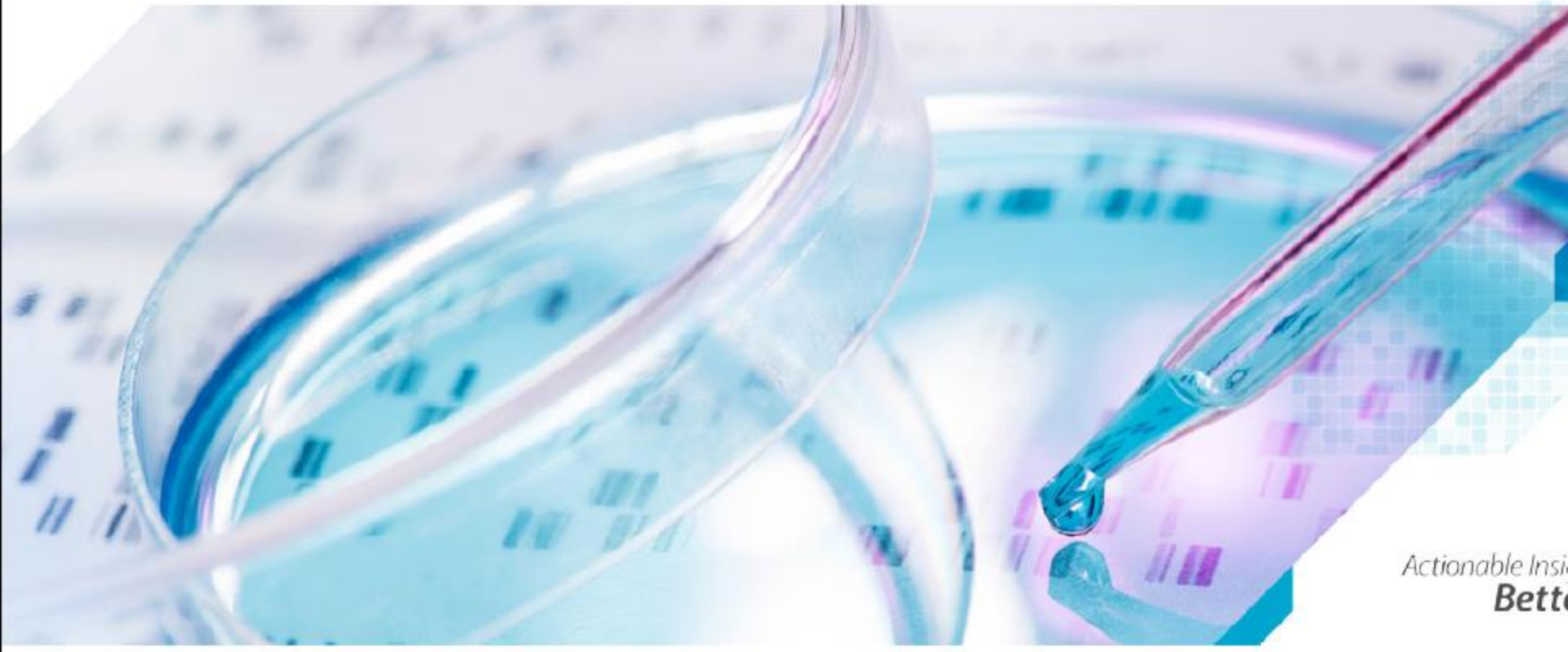
Our Panel

- **Panel List:**
  - Barry Jones (Q2labsolutions)
  - Moucun Yuan (PPD)
  - Luca Genovesi (Biotrial)
  - Xun Wang(QPS)
  - Cong Wei (Vertex Pharmaceuticals. Previous. Pfizer)

- **Minutes:**
  - Jason Hogan (BMS)

Q² Solutions

a Quintiles Quest Joint Venture



Bioanalysis of Large Molecules by LCMS

Challenges in Bioanalysis of large molecules

LBA

- Selectivity challenges
- Anti-drug antibodies
- Ability to obtain whole-molecule information?
  - Insensitive to changes away from binding regions

LCMS

- Sensitivity challenges
- Cost and throughput
  - Serial analysis
- Ability to obtain whole-molecule information
  - Chromatographic, ionization, mass spec detection challenges for intact molecule
  - Regulated targeted quantitation of large molecules by intact LCMS is immature
  - Bottom-up – sequence coverage challenges

Why LCMS rather than LBA in large molecules

- Address difficulty with *selectivity* of LBA method
- Address difficulty with *sensitivity* of LBA method
- Better understand biotransformation and how that impacts bioanalysis (LB LC/MS)
- Multiplexing advantages
- Potential for reagent-free methods
  - ADA-tolerance
- Reduced demands on reagent quality
  - Generic reagents for humanized mAb in pre-clinical species
  - Reagents often used for purification, rather than for specificity
- Reagents do not necessarily define the assay selectivity, rather enable sensitivity
  - Reduce ion suppression, enable low-flow ionization

PPD's Biosimilar Experience

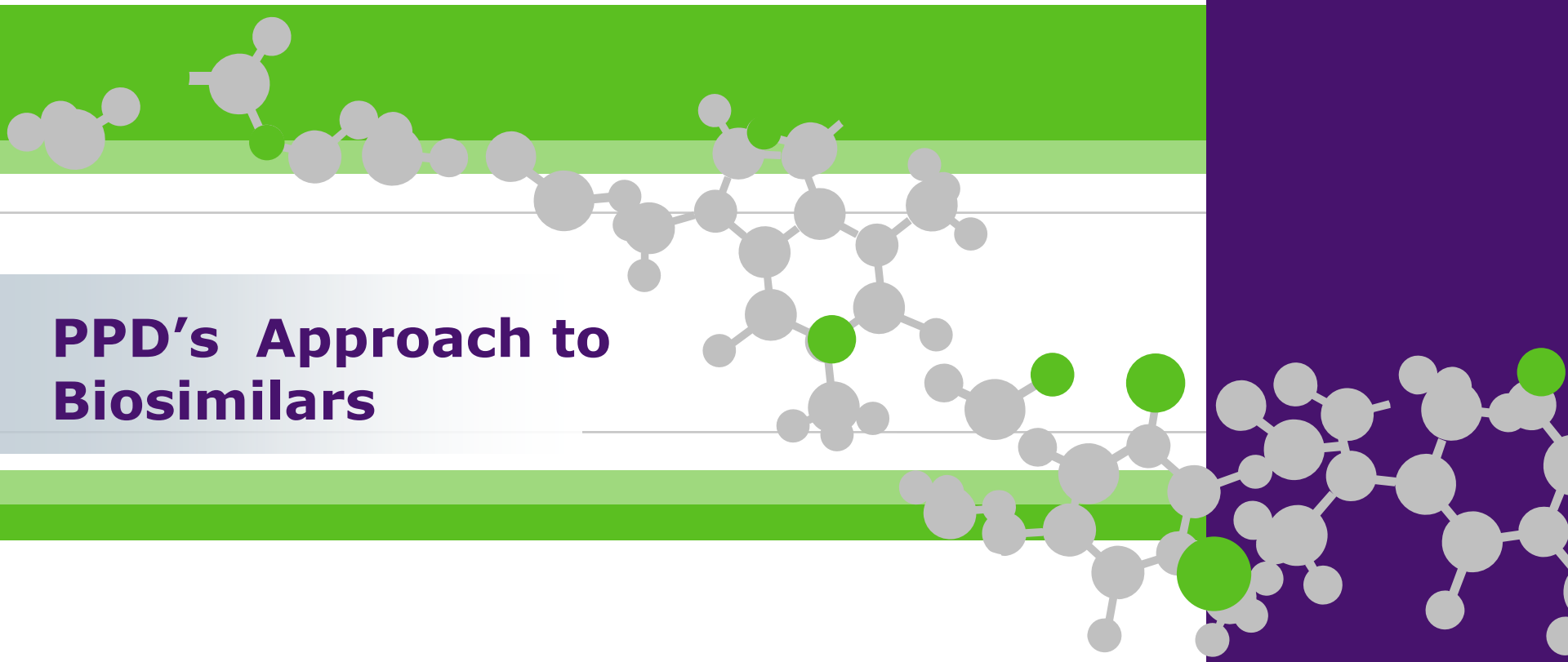
PPD ® Laboratories
Richmond VA

History and Experience

+ We have experience with approximately 22 different biosimilar programs supported within the past 5 years
+ PPD has always used the one assay approach

    - Supported 3 of the first 5 biosimilars approved by the FDA
    - Also supported numerous EMA approved biosimilars

PPD's Approach to Biosimilars



Assumptions prior to assay development

A one-assay approach developed to the biosimilar is recommended as described in the Marini *et al*. White Paper, AAPS Journal Vol. 16 No. 6, Nov 2014

+ CMC (GMP) data to support structural comparability, this should always be evaluated prior to bioanalysis

Considerations for assay development

+ Number of compounds to be compared
  - (e.g. EU innovator, US innovator, additional formulations)
  - Standard curves should be comparable and parallel

+ Planned submissions, including when and to whom.
  - (FDA or EMA, ANVISA especially important to know up front)

+ Potential patient populations and disease states
  - (Earlier the better)

Validated Assays

- For PK assays:
  - One assay approach allows for easier data interpretation and blinded study sample analysis
  - Biosimilar compound is used as the reference standard and the sponsor has more information on the molecule and better control over supply, including lot-to-lot changes

- For Immunogenicity (ADA) assays:
  - Biosimilar compound is labeled for capture and or detection
  - Supply of critical reagents (longer term)
  - Two assay approach has inherent statistical challenges
    - One vs two cut points for the screening assay
  - One assay approach still allows confirmation with multiple compounds

Contact Information

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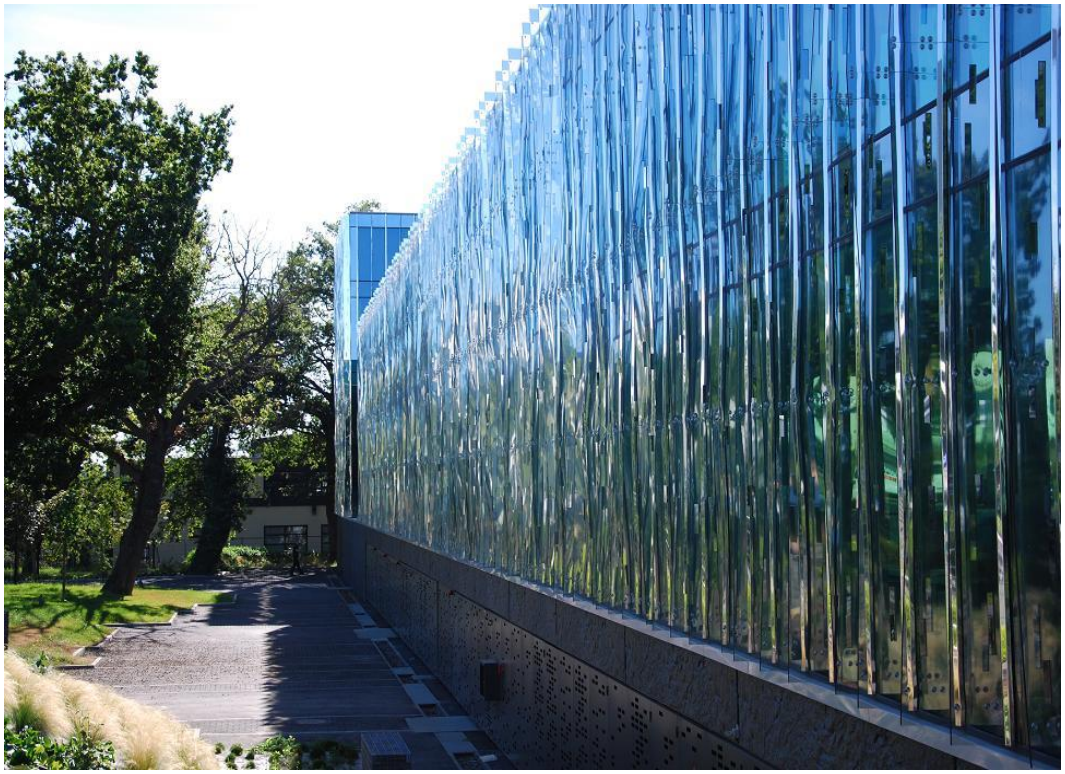
BIOTRIAL

Successful Drug Development



Quantiation of Humira by LC/MS

A gym for Biosimilar?

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Case Study: Humira

- Humira stands for:

  “**Human Monoclonal Antibody In Rheumatoid Arthritis**".

- Humira is used in several treatments for autoimmune disease

- Adalimumab binds to tumor necrosis factor-alpha (TNFα). TNFα normally binds to TNFα receptors, which leads to the inflammatory response of autoimmune diseases. By binding to TNFα, adalimumab reduces this inflammatory response.

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Case Study: Humira

Europe

Segment	Product / Molecule	Patent Expiry
mAbs	Herceptin	2014
	Avastin	2019
	Remicade	2014
	Rituxan / Mabthera	2013
	Humira	2018
	Enbrel	2015
Insulin	Lantus	2015

US

Segment	Product / Molecule	Patent Expiry
mAbs	Rituxan	2016
	Humira	2016
	Xolair	2020
	Erbitux	2018
	Remicade	2018
	Avastin	2019
	Herceptin	2019
	Enbrel	2028
Insulin	Lantus	2015
	NovoMix 30	2017
	Levemir	2019

https://www.biosimilardevelopment.com/doc/factors-driving-global-biosimilar-market-growth-0001

Challenge: Method that is suitable for all the Humira Biosimilar

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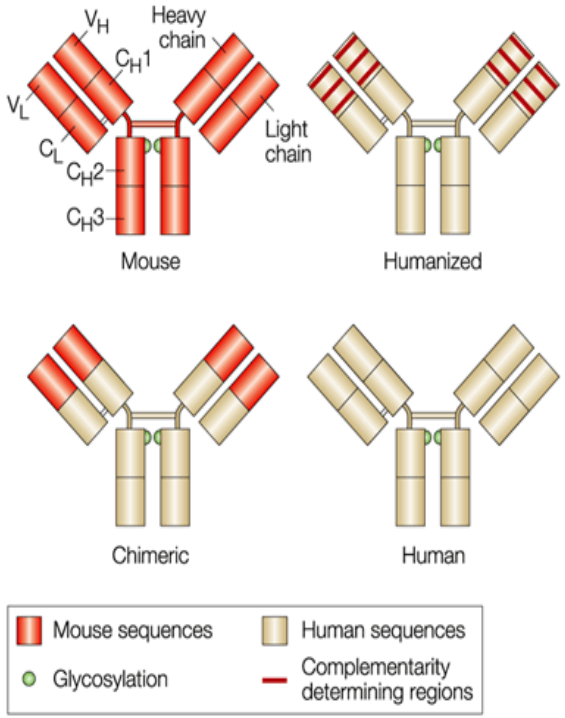
Case Study: Humira

- Humira is a Human Antibody
  - Shares most of its sequence with endogenous IgG
  - Difficult selection of the surrogate peptide



Cartel et al. (2001) Nat. Rev. Cancer

Unique Peptides

- FSGSGSGTDFTLTISSLQPEDVATYYCQR **(LC)**
- GLEWVSAITWNSGHIDYADSVEGR **(HC)**
- VSYLSTASSLDYWGQGTLVTVSSASTK **(HC)**

Peptide Suitable for quantitation

CDR Region

- NYLAWYQQKPGK
- APYTFGQGTK

Challenge: Sensitivity vs. Specificity

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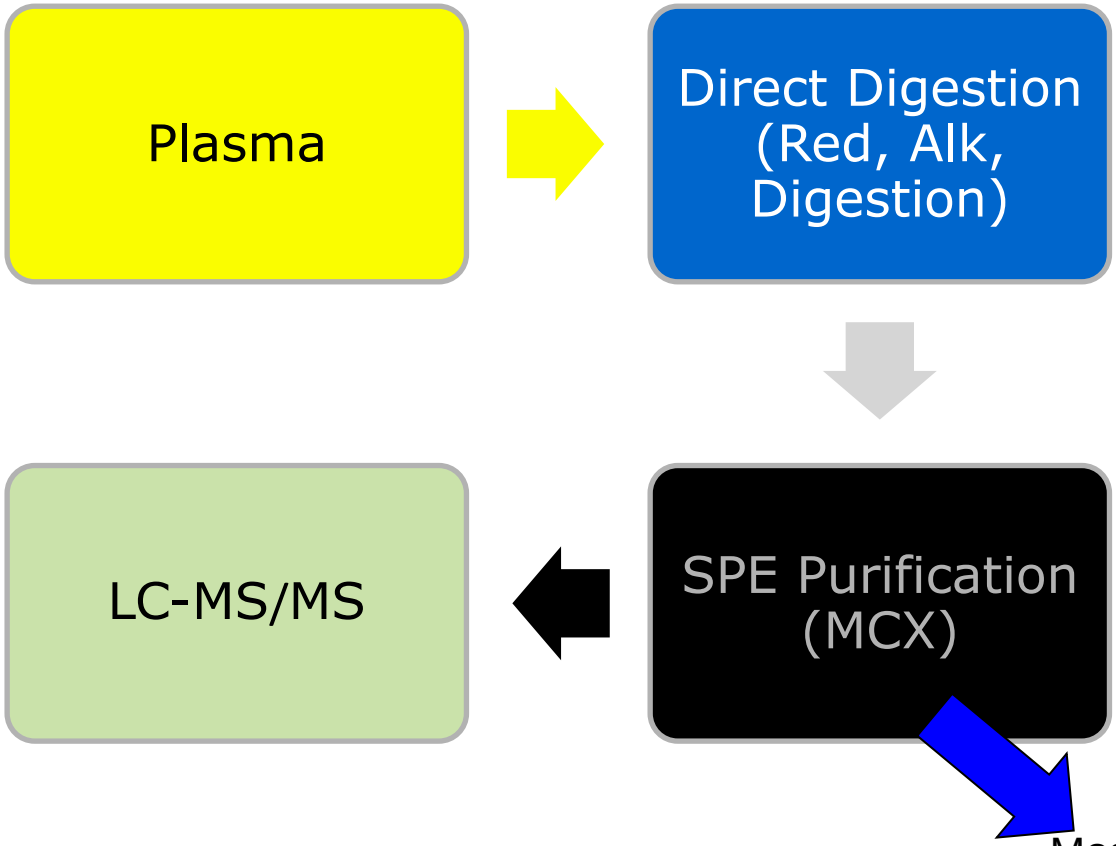
Case Study: Humira

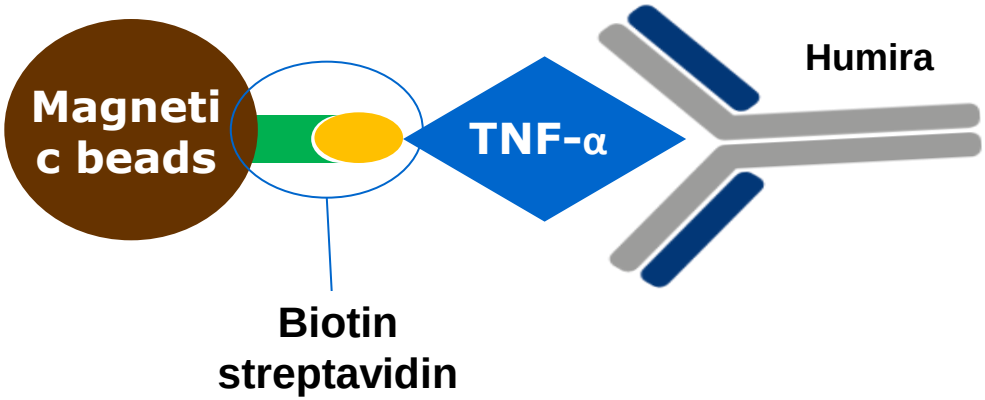
Reagent Free Approach



- Universal Assay suitable for quantitation of Humira in pre-clinical species (i.e. Dog).
- Human give interferences in the range of 1 µg/mL

Case Study: Humira

Functional assay: Confidence in structural integrity



- Better sensitivity than reagent free approach
- Capture of only free or partially free Humira
- Universal assay for all species and all biosimilars

- **Combines the best of LBA and LC-MS to have universal assay**

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Humira: Conclusions

- Both assays are suitable for quantitation of Humira in biological matrices
  - Reagent Free assay → suitable only for pre-clinical, total Humira → not affected by eventual ADA.
  - Functional assay → universal assay → free or partially free Humira →Confidence in biological activity
- Smart design of the assay is the Key for having a successful quantitation method by LC/MS

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Bioanalytical PK Assay for Biosimilars LBA or LC/MS

Xun Wang, Ph.D.

ASMS Workshop, June, 2017

Analytical Similarity (PK) -LBA - AAPS Focus Group Recommendation

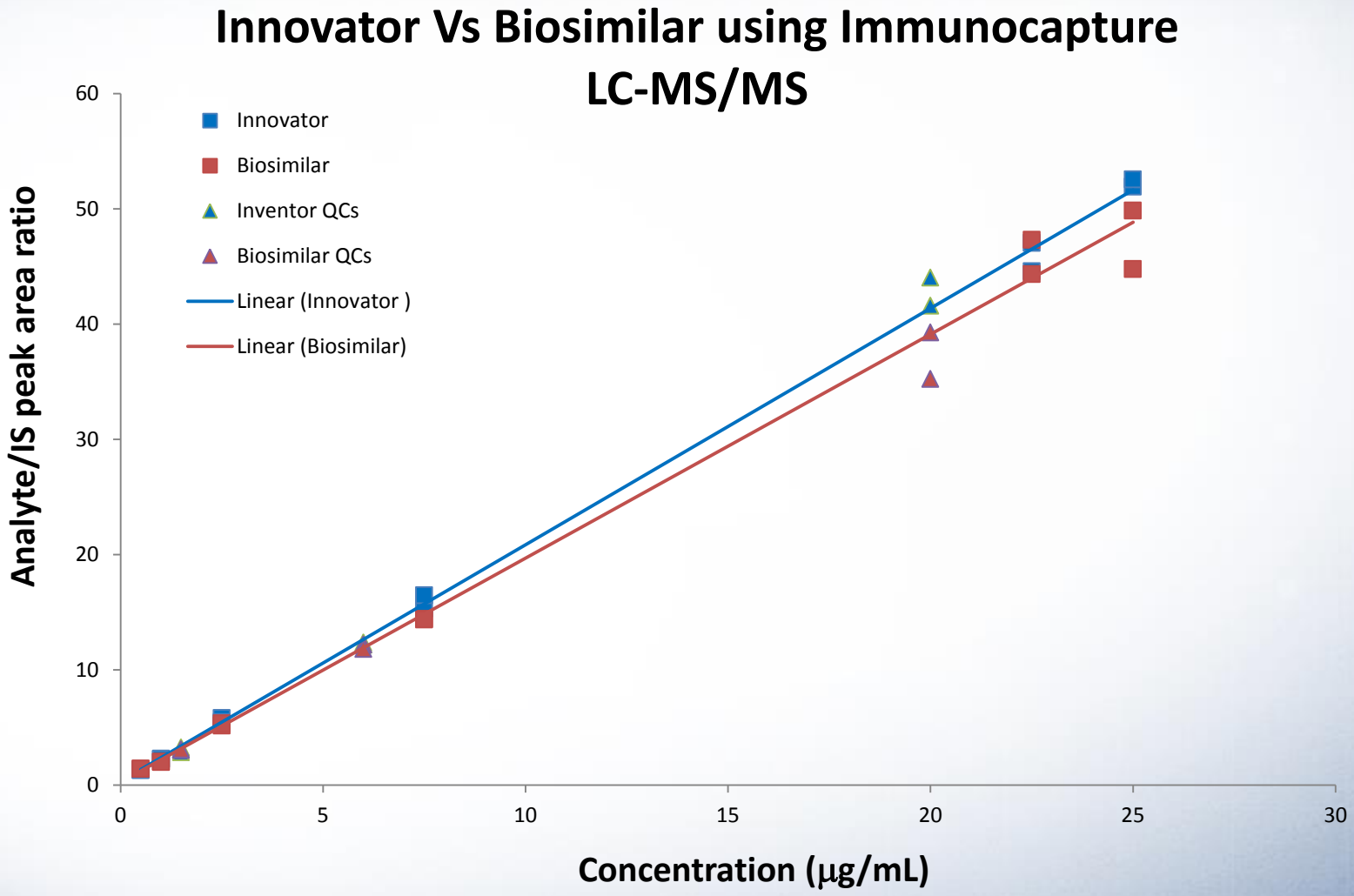
Method Development

- Similarity of CS
- Statistical Approach to compare Innovator and Biosimilar CS

Method Validation

- Intra-Run
- Inter-Run
- Direct comparison of Innovator and Biosimilar QCs

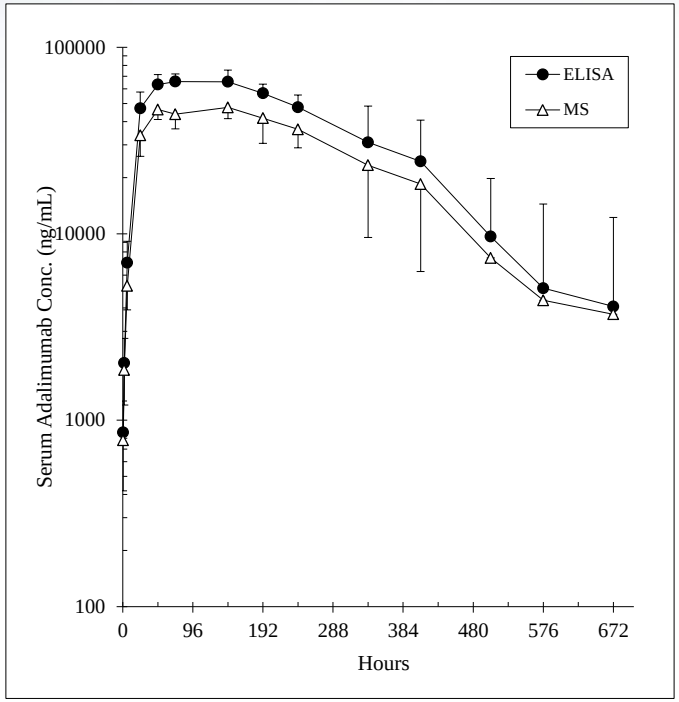
LC/MS: CS Assessment



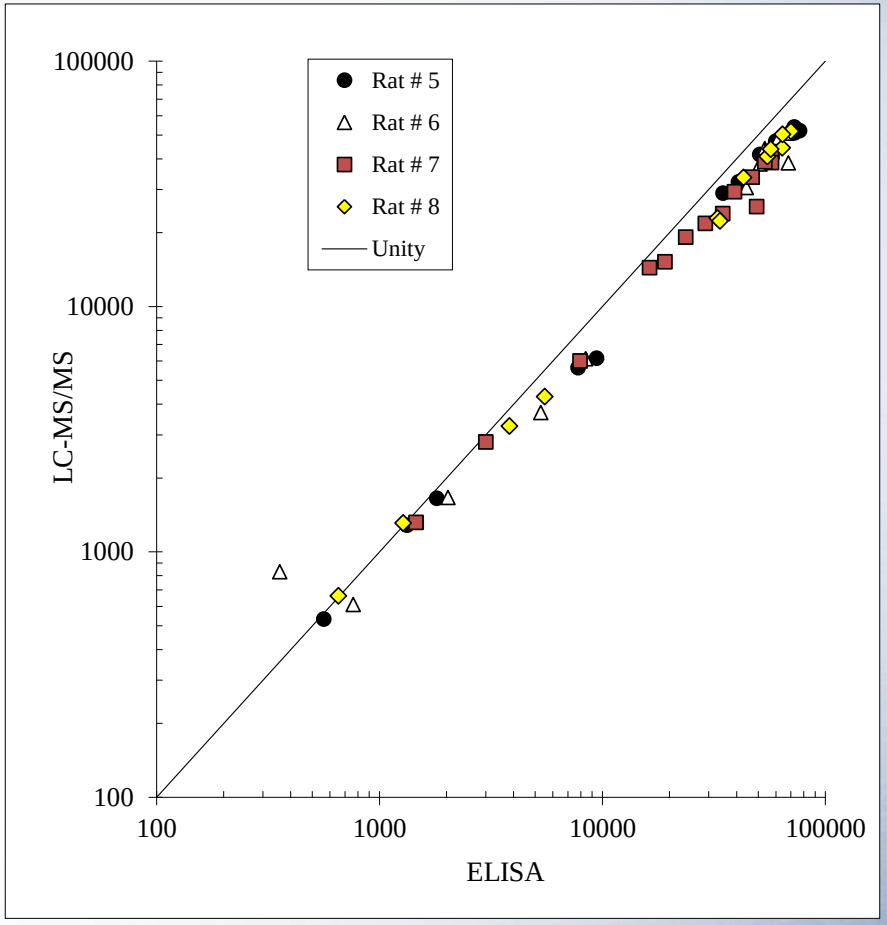
LC/MS: QC Comparison – BSI CS

	US	BSI	US	BSI	US	BSI
Nominal Conc.	**1.50**		**6.00**		**20.0**	
Calculated Conc.	1.51	1.39	6.24	6.25	21.8	18.5
	1.29	1.42	6.34	6.05	23.1	20.6
Mean	1.40	1.41	6.29	6.15	22.5	19.6
S.D.	0.156	0.0212	0.0707	0.141	0.919	1.48
%CV	11.1	1.5	1.1	2.3	4.1	7.6
%RE	-6.7	-6.3	4.8	2.5	12.3	-2.3
%Diff[a]	NA	0.4	NA	-2.2	NA	-12.9

Adalimumab In Rat – LBA vs. LC-MS/MS



Adalimumab (Humira) 10 mg/kg SC				
	ELISA		LC-MS/MS	
	Mean	SD	Mean	SD
C_{max} (ng/mL)	68200	7970	49800	4860
t_{max} (h)	102	49.5	78.0	45.4
AUC_{last} (h*ng/mL)	21900000	4000000	16100000	3210000
$t_{1/2}$ (h)	108	139	132	186



~20% bias

DISCUSSION: Q&A