Regulated Bioanalysis of Large Molecules

Jinhui Zhang Ph.D.
Division of Product Quality Research
Office of Testing and Research, Office of Pharmaceutical Quality
CDER | US FDA
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Disclaimer

*This presentation reflects the views of the author and should not be construed to represent FDA's views or policies

Learning Objectives

- BPCI Act and the Transition of Regulatory Pathway for Certain Biological Products
- Workflow for Regulated Bioanalysis of Large Molecules
- Special Consideration for Bioanalysis of Large Molecules in Biological Matrixes
- Evolution of the Bioanalytical Methods

Outline

- Diversity of large molecule drug entities
- BPCI Act and purple book
- Guidance: Bioanalytical Method Validation (FDA and ICH M10)
  - Case study 1: polypeptide under NDA
  - Case study 2: biosimilar (PEG-protein and monoclonal Ab) under BLA
  - Case study 3: ADC under BLA
- Recent progress: hybrid LBA-LC-MS/MS
- Closing thoughts

Diversity of Large Molecule Drug Entities

https://www.amgenscience.com/features/the-shape-of-drugs-to-come/

BPCI Act and purple book

- Section 7002(e)(4)of the BPCI Act provides:

  An approved application for a biological product under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) shall be deemed to be a license for the biological product under such section 351 [of the PHS Act] on the date that is 10 years after the date of enactment of [the BPCI Act]

- FDA guidance explained that approved NDAs “deemed products” will be transitioned to 351(a) BLAs

- Applicants can seek licensure of products that are biosimilar to, or interchangeable with, transitioned products, via 351(k)

- Purple book
  https://www.fda.gov/drugs/therapeutic-biologics-applications-bla/purple-book-lists-licensed-biological-products-reference-product-exclusivity-and-biosimilarity-or

Evolution of the Assays for Large Molecules*

- RIA
- ELISA
- Immunoassay with multiple detection
- Mass Spectrometry (LC-MS)
- Hybrid Assays-Immunocapture Mass Spectrometry

*Modified from Dr. DeSilva 2018 AAPS

Guidances (Drugs)

Bioanalytical Method Validation Guidance for Industry
https://www.fda.gov/media/70858/download

M10 BIOANALYTICAL METHOD VALIDATION
https://www.fda.gov/media/128343/download

https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs

Bioanalytical Challenges for Large Molecules

- Structural diversity
- Multiple analytes (Ab, ADA, Nab, *etc*)
- Specificity issues (ADA, hemolysis, *etc*)
- Stability
- Critical reagents

Fit-for-purpose

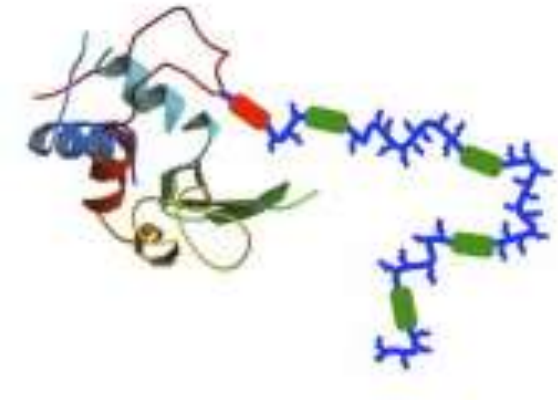
"Validation of a bioanalytical method with scientific rigor for the intended purpose where all applicable parameters may not be evaluated as per regulatory guidance."

Bioanalysis (2013) 5(23), 2903–2918

Case Study 1: Polypeptide

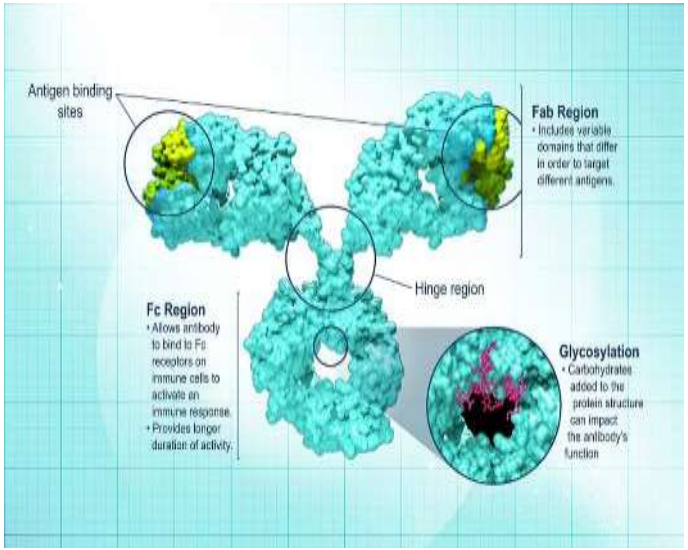
- *NDA Approved 2019*
- *ELISA for the polypeptide (Commercially available kit)*
- *ELISA for the anti-drug antibodies*
- *Cell proliferation based assay for Neutralizing antibodies (Commercially available kit)*

Case Study 2a: PEGylated protein



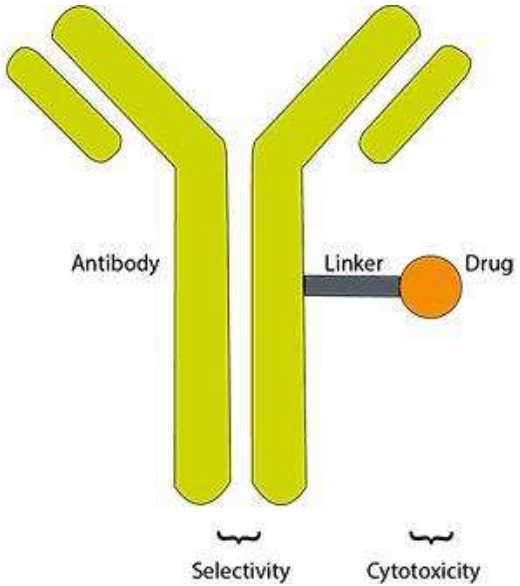
- *BLA 351(k) Biosimilar Approved 2018*
- *ELISA for the PEG-protein using biosimilar as standard*
- *ELISA for the anti-drug antibodies*
- *Cell proliferation based assay for Neutralizing antibodies*

Case Study 2b: Monoclonal Antibody



- *BLA 351(k) Biosimilar Approved 2019*
- *ELISA for the antibody using Reference as standard*
- *Electro-chemiluminescent for the anti-drug antibodies*
- *Cell based assay for Neutralizing antibodies*

Case Study 3: ADC



- *BLA 351 (a)*
  Approved 2019
- *LC-MS/MS for the drug moiety*
- *Electro-chemiluminescent for Intact ADC*
- *Electro-chemiluminescent for anti-ADC*

LBA *vs* LC-MS/MS

Specific antibodies: time consuming

✓ High sensitivity

Limited specificity

Limited multiplexing

✓ High throughput

Method development: straightforward

Relative low sensitivity

✓ High specificity

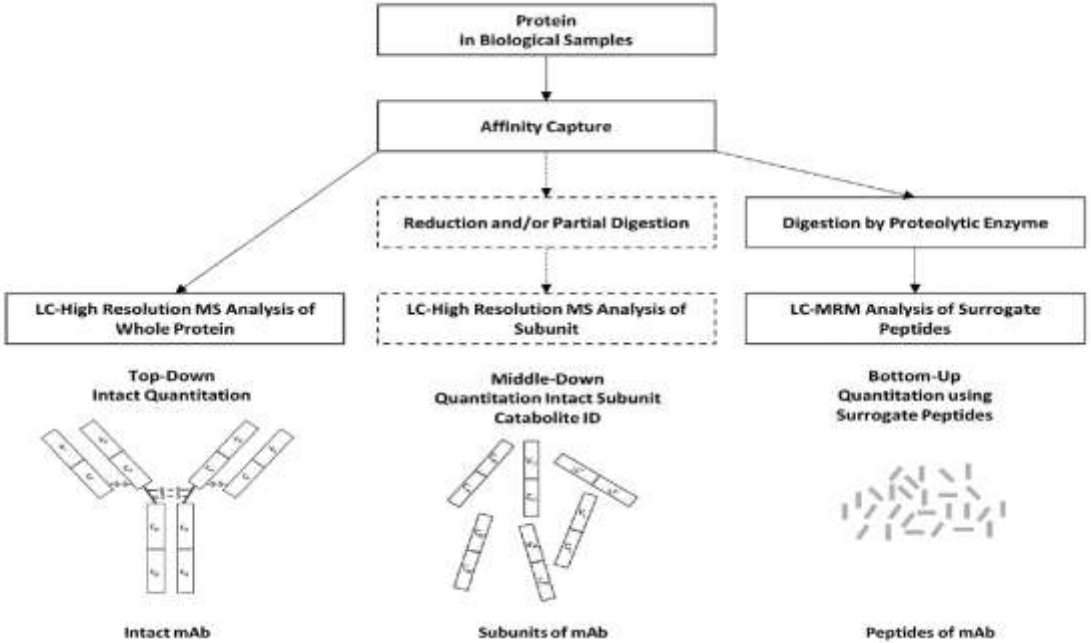
✓ Multiplexing

Complicated workflow

Extensive Discussion on Hybrid-LBA-LC-MS/MS within the Bioanalysis Community

- 2020 White paper: **Intact protein bioanalysis; Hybrid LBA/2D-LCMS**
- 2019 White paper: Part 1, including **"Innovation in Hybrid LBA/LCMS Assays"**
- 2018 White paper: Part 2 **– PK, PD & ADA assays by hybrid LBA/LCMS, *etc***
- 2017 White paper: Part 3, including **(LBA)/LCMS for biotherapeutics**
- 2016 White paper: Part 2 – **Hybrid LBA/LCMS and input from regulatory agencies**
- 2015 White paper: Part 2 – **Hybrid LBA/LCMS and input from regulatory agencies**
- 2014 White paper: Part 2 – **Hybrid LBA/LCMS, *etc***
- 2013 White paper: "Hybrid" – **The best of LBA and LCMS**
- 2012 White paper: **Comparing LBA *v.s.* LCMS - acceptance criteria and duplicates**
- 2011 White paper: **LCMSMS for bioanalysis of PEGylated protein drugs**
- 2010 White paper: **Comparing LBA *v.s.* LCMS; proposing immunoaffinity capture**

Hybrid LBA LC-MS/MS



Biomedical Chromatography. 2020;**34**:e4633.

LC-MS: When and How?

- What to measure?
- Immunoaffinity capture?
- Bottom-up, top-down, or middle-down?
- How to choose internal standard(s)?
- Data acquisition and processing algorithms?

Closing Thoughts

- **Bioanalysis: a core member of the integrated drug development team**
  AAPS, November 2018

- **One size does not fit all**
  AAPS ICH M10 Guidance Workshop, June 2019

- **Each assay may reveal part of puzzle**
  Get a whole picture by putting them together
  Biomedical Chromatography 2020: 34:e4633

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DOI: 10.1208/s12248-014-9685-5

White Paper

Recommendations for Validation of LC-MS/MS Bioanalytical Methods for Protein Biotherapeutics

Rand Jenkins,[1] Jeffrey X. Duggan,[2] Anne-Françoise Aubry,[3] Jianing Zeng,[3] Jean W. Lee,[4] Laura Cojocaru,[5] Dawn Dufield,[6] Fabio Garofolo,[7] Surinder Kaur,[8] Gary A. Schultz,[9] Keyang Xu,[8] Ziping Yang,[10] John Yu,[2] Yan J. Zhang,[3] and Faye Vazvaei[11,12]

Editorial

Hybrid assays: the next big thing?

Brian P Booth*,[1] & Brian Furmanski[1]
[1]US FDA, CDER, Office of Translational Sciences, Office of Clinical Pharmacology, Silver Spring, MD, USA
*Author for correspondence: Brian.booth@fda.hhs.gov

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Questions?

Jinhui Zhang, Ph.D.
Division of Product Quality Research
Office of Testing and Research, Office of Pharmaceutical Quality
CDER | US FDA

druginfo@fda.hhs.gov
Jinhui.zhang@fda.hhs.gov