HELP WANTED: A Regulatory Perspective on Opportunities for Analytical Methods in Biopharmaceutical Development

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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.

Outline

- Background
- Opportunity for Analytical methods
  - Bridging Gap to Clinical Relevance
  - Providing “Quality” Data in Biosimilar Development
  - Supporting Challenging Product Development
- Conclusions
- Acknowledgements

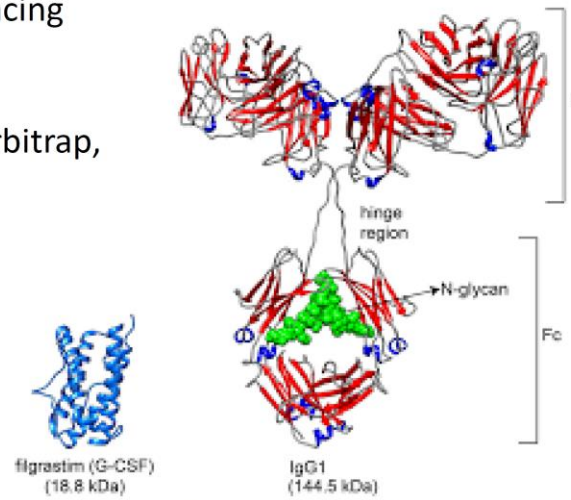
#1 Bridging Gap to Clinical Relevance

The Current Analytical Tool Box

1° Sequence/PTMs
AA analysis
N- and C-term Sequence
Peptide Mapping and Sequencing
LC-MS/MS
Free sulfhydryls
MALDI-TOF, ESI-QTOF-MS, orbitrap, etc….

HOS
Near- and Far-UV CD
FTIR
DSC
HDX-MS
X-ray
NMR

Size/ Purity
SEC-HPLC
HIC-HPLC
RP-HPLC
CE-SDS
CGE
AUC
A4F



Japelj et al Sci Reports 2016

Activity
In vitro Bioassays
Reporter gene assays
Ag/Receptor Binding assays
(mAbs – FcR, C1q)
SPR
Strength (UV A280)

Glycan Analysis
ESI- MS
MALDI-TOF MS
Labeled, PNGaseF released
HPAEC-PAD
HPLC-FD
HILIC (HPLC, UHPLC)
CE-LIF (MS)

Charge
cIEF
icIEF
ICE
IEX- HPLC
CZE

Process Related Impurities
DNA, HCP, Protein A, etc.

Safety
Bioburden
Sterility
Endotoxin
LAL
KT

Adapted from Marjorie Shapiro, CASSS WCBP 2018 and Jeffrey Baker, Recovery Biological Products 2018

Evolution in FDA's Approach to Pharmaceutical Quality

- ICH Q6B: Justification of Specifications:
  - *Specifications are linked to a manufacturing process*
  - *Specifications should account for the stability of drug substance and drug product.*
  - *Specifications are linked to analytical procedures.*
  - *Specifications are linked to preclinical and clinical studies*.

- *Definition of adequate quality: delivers clinical performance described in drug label and is not contaminated*
- *Clinically relevant specifications are based on risk to clinical performance, not what can be achieved by process*
- *Clinically relevant manufacturing standards: deviation should have clear link to risk of substandard clinical performance*

  – ***Janet Woodcock, CDER, "Evolution in FDA's Approach to Pharmaceutical Quality"***

The Use of Process Capability

The types of data and information should be guided by the consideration of clinical impact of impurity levels, as opposed to manufacturing process capability,

For some products, such as certain biotechnology ….for which the relationship to stability, potency, or potential adverse clinical effects is not clear….

…This may be either because the analytical techniques available have not allowed thorough characterization of the impurity, or because data regarding the impact of the impurity on clinical performance are lacking ….may include **greater consideration for manufacturing process capability**

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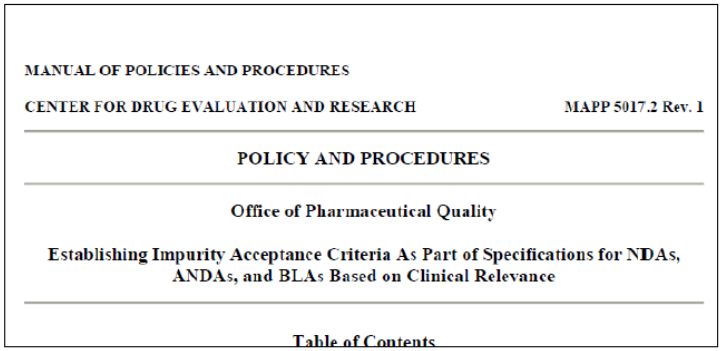


MANUAL OF POLICIES AND PROCEDURES

CENTER FOR DRUG EVALUATION AND RESEARCH MAPP 5017.2 Rev. 1

POLICY AND PROCEDURES

Office of Pharmaceutical Quality

Establishing Impurity Acceptance Criteria As Part of Specifications for NDAs, ANDAs, and BLAs Based on Clinical Relevance

Table of Contents

MAPP 5017.2
Published 2018

~~The Process is the Product~~

- Understanding comes from multiple sources

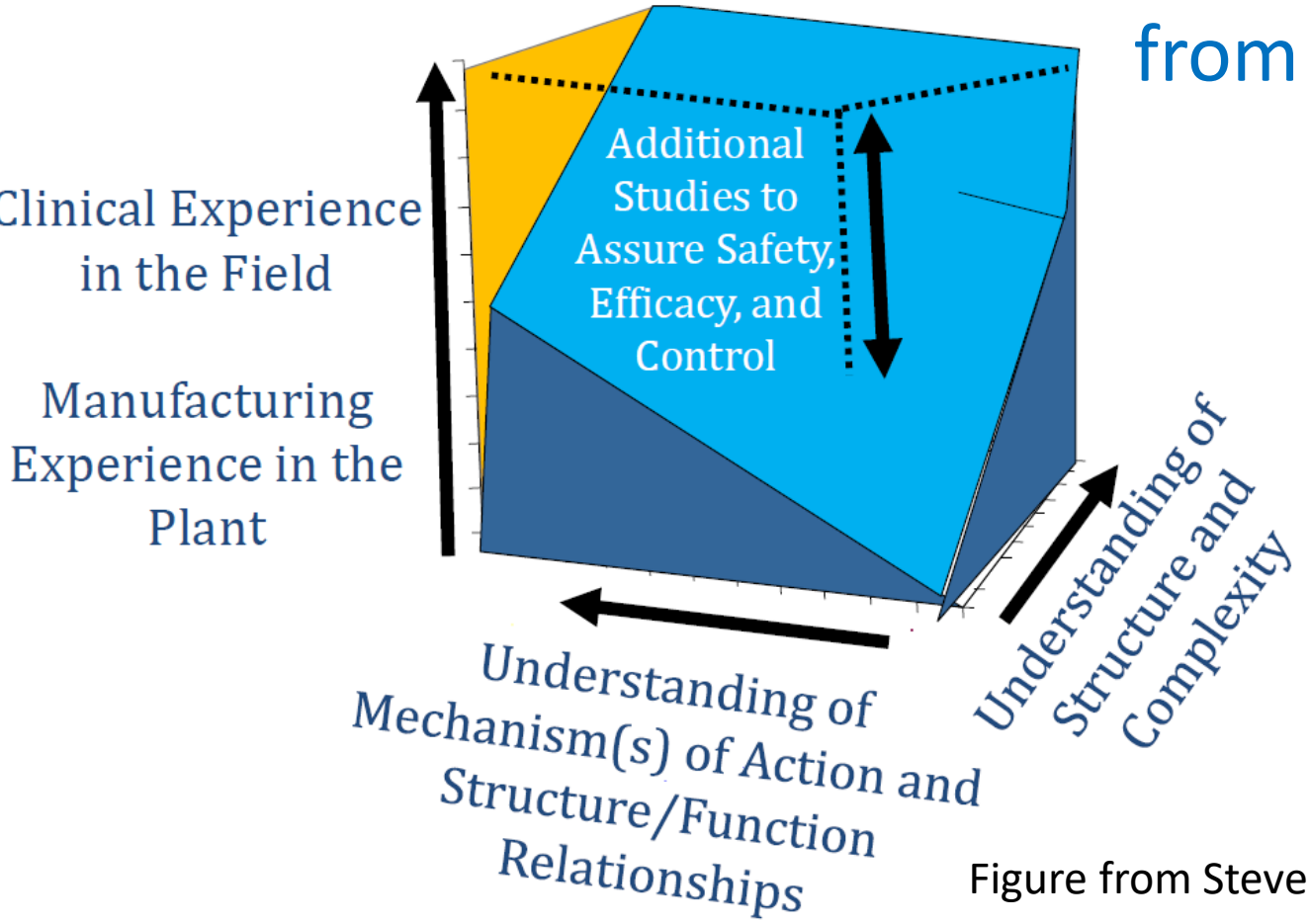


Figure from Steven Kozlowski

Linking CQAs to Clinical Relevance

Boyd 1995 Alemtuzumab
Deglycosylation abolishes CDC/ADCC
Degalactosylation reduces, but does not abolish CDC, no effect on ADCC
Desialyation no effect on CDC/ADCC

Kanda 2006 Rituximab
Afucosylated complex, hybrid and high mannose glycans had higher binding to both FcγRIIIA variants and higher ADCC activity.

Yu 2012 (anti-B cell)
mAb with only high mannose forms has greater ADCC and FcγRIII binding than control mAb, but not as high as 100% afuc version. There was also a decrease in CDC activity

Understanding Evolves….

Shields 2002, Shinkawa 2003, Okazaki 2004
Anti-Her2, anti-IgE, anti-IL5R, anti-CD20
Afucosylation improves binding to FcγRIII and enhances ADCC

Houde 2010, Kiyoshi, 2018
Hyper gal (G2) affects CH2 domain conformation (more rigid), increases binding to FcγRIII

Ferrara 2006 and 2011, Shibata-Koyama 2009
Interactions between FcγRIII glycan and Fc glycan

Hodoniczky 2005
Rituximab, trastuzumab
Degalactosylation reduces, but does not abolish CDC, no effect on ADCC
Bisecting GlcNac enhances ADCC

Chung 2012 anti-CD20
Differences in FcγRIII binding and ADCC activity between 0-10% afuc glycans

Shatz 2015 anti-CD20
Only 1 afuc glycan per mAb has as good ADCC activity as a fully afuc mAb

Scallon 2007, higher levels of sialylation associated with reduced ADCC
Lin 2015 rituximab Homogeneous disialyated (G2) afuc mAb has enhanced FcγRIII binding and ADCC

Adapted from Marjorie Shapiro, CASSS WCBP 2018

Case Study - Specification Setting

- Acidic Charge variants for monoclonal antibody
- Sponsor was able to justify acceptance criteria 15% wider than clinical lots
- How? Know thy molecule!
  - Characterization also revealed which site(s) were most susceptible to deamidation (and don't impact potency)
  - Additional characterization of acidic peaks indicate species are non-CQAs (such as deamidation in non-CDR region)
  - Other CQAs identified that coelute in acidic region are controlled by orthogonal methods
  - "Pooling" Data demonstrate no impact on FcRn binding or potency
- Conclusion: Wider acceptance criteria can be established

#2 Providing “Quality Data” in Biosimilar Development

Definition: Biosimilarity

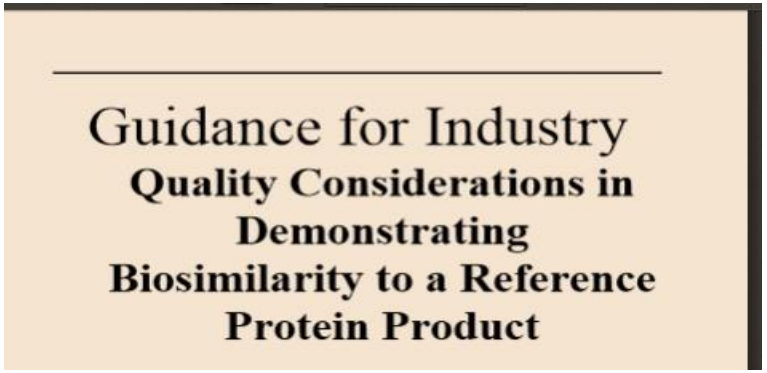
Biosimilar or **Biosimilarity** means:

- that the biological product is **highly similar** to the reference product notwithstanding minor differences in clinically inactive components; and
- there are **no clinically meaningful differences** between the biological product and the reference product in terms of the safety, purity, and potency of the product.

Highly Similar?

Sequence

Expression System

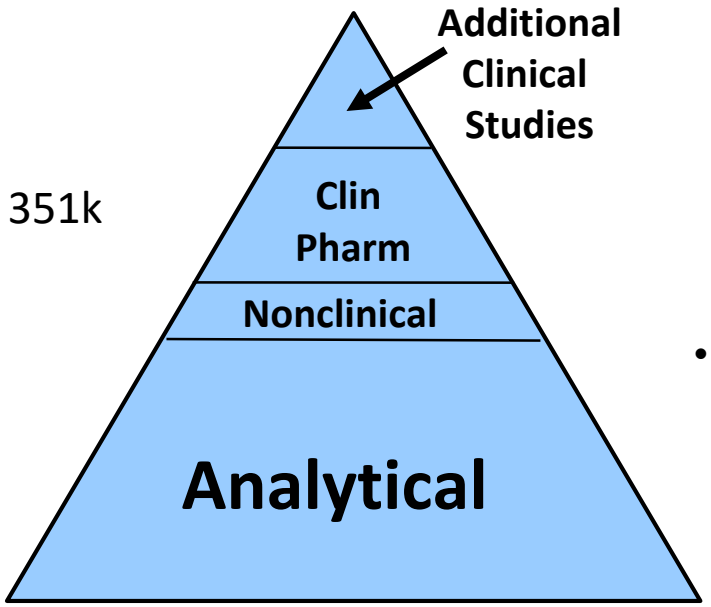


Impurities & Excipients

Adapted from S.Kozlowski, PDA/FDA Biosimilars Conference June 2017

12

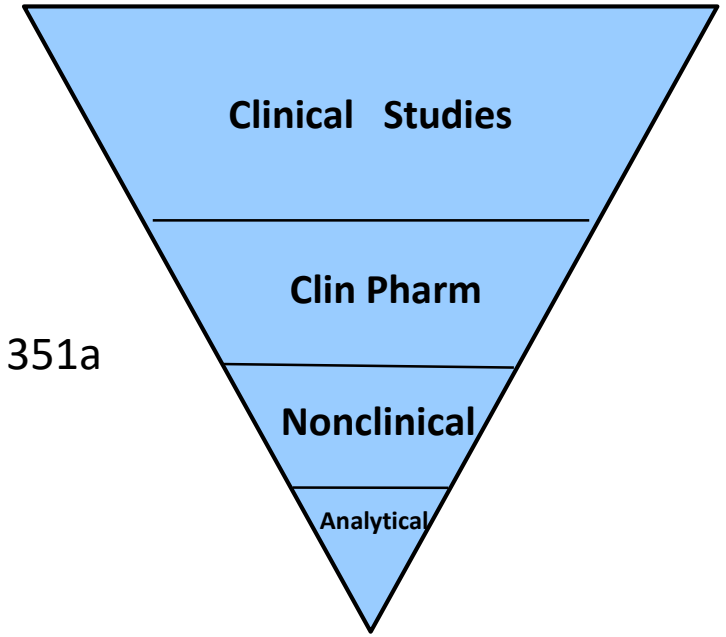
Biosimilar Development



Other Indications:

~~Clinical Efficacy (and Safety)~~

- Extrapolation from information in 351(k) BLA and FDA's finding for the reference product to other indications previously approved for the reference product, considering for each indication:
  - MOA(s), PK, Immunogenicity, Known toxicities



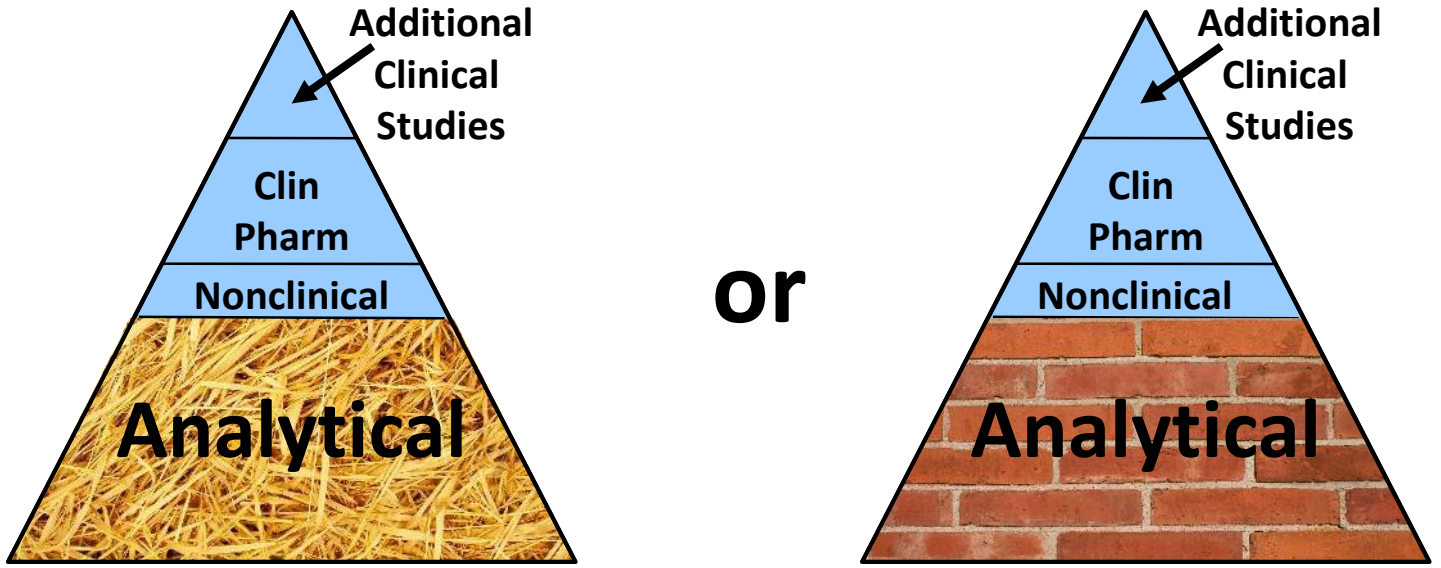
Indication 1

- Clinical Efficacy (and Safety)
- Clin Pharm
- Pharm Tox
- Analytical

Other Indications

- Clinical Efficacy (and Safety)

A Solid Foundation Requires Solid Data



- How solid is the foundation?
- What do we know about the limitations of the analytical methods that generate data?

Adapted from J. Chung, PDA/FDA Biosimilars Conference Sept 2018

A "Typical" Similarity Assessment

Primary structure

- Intact molecular weight
- Amino acid sequence
- Disulfide bonds

Higher order structure

- Secondary structure
- Tertiary structure
- Thermal Stability

Glycosylation

- Afucosylation
- Galactosylation
- High Mannose
- Sialylation

Drug product attributes

- Protein content
- Sub-visible particles
- Deliverable volume
- Appearance, pH, osmolality

Biological activities: Fab-Mediated

- Inhibition of Human Umbilical Vein Endothelial Cell (HUVEC) Proliferation
- VEGFA binding
- Binding kinetics for VEGFA isoforms (165, 121, and 111)
- Binding Specificity

Biological activities: Fc-Mediated

- FcRn
- Fcg Receptors [RIa, RIIa, RIIb, RIIIa (158V and 158F type), RIIIb]
- C1q
- Antibody-dependent cellular cytotoxicity (ADCC)
- Complement-dependent cytotoxicity (CDC)

Product related species

- Charge Variants
  - Acidic
  - Main
  - Basic
- Size Variants
  - Dimers and high-molecular weight species (HMW)
  - Heavy chain (HC) and light chain (LC) fragments

Stability

- Degradation profiles under accelerated and stress conditions

Adapted from J.Chung, FDA presentation for ABP215, ODAC, July 13 2017

Analytical Method Qualification

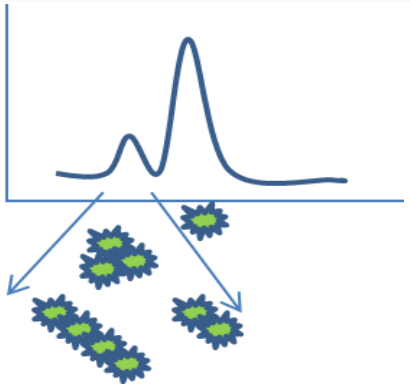
- Why?
  - To ensure that analytical similarity data were generated using methods that are "scientifically sound, *fit for their intended use*, and provide results that are *reproducible* and *reliable*"

    (FDA Guidance on "Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product")
- What does method qualification mean?
  - To demonstrate the suitability of the method for its intended purpose
- Not a new concept or expectation
  - "Validated analytical methods are not necessarily required…when used in characterization studies. Nevertheless, analytical methods should be scientifically sound (e.g., specific, sensitive, and accurate) and provide results that are reliable." (2011 FDA Guidance on Process Validation)
- Expectation is on Developers and Scientists to make a compelling argument

Analytical Method Development and Qualification Strategies

Begin with basic understanding of the method

- Should you use SEC or AUC to detect aggregates?



Understand the method purpose to help design the qualification study

- What is the method going to be used for
  - To quantify a critical quality attribute?
  - To reduce residual uncertainty?
  - To confirm a result?

Evaluate method capabilities and limitations

- specificity, precision, accuracy, etc?
- How sensitive is the method to detect differences?
- How critical are reagents to method performance?

Adapted from J.Chung, PDA FDA Biosimilars, September 2018

#3 Supporting Expedited and Challenging Program Development

Alternative Programs

- Fast Track

  Intended to facilitate the development and expedite the review of drugs to treat serious conditions and fill an unmet medical need:
  - More frequent meetings with FDA,
  - Eligible for priority review or accelerated approval (if respective criteria are met)
  - Eligible for rolling review
- Breakthrough
  - With preliminary clinical evidence that the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint(s)
  - Organizational commitment involving senior managers and experienced review staff
  - "All hands on deck"
- Accelerated Approval
  - Accelerated Approval (approval from surrogate or intermediate clinical endpoint, with post-approval confirmatory studies)
- Priority
  - (6 month BLA review clock instead of 10)
- Orphan
  - Populations of small size (200000 or less)
  - Other requirements per 21 CFR 316.20

Opportunities (and Challenges)

- The pace of development does not fundamentally change the content of BLA CMC sections
- Often a question of not doing less, but doing sooner
- Analytical Method validation and transfers are critical to have in place ahead of need (and bridging data as needed!)
- Fewer batches and less clinical experience may be acquired during these programs
- Extensive characterization can “fill in gap” to bridge to specification setting

Conclusions

- Opportunity for analytical methods beyond just new technologies
  - Methods can help identify what is clinically relevant to aid in specification setting
  - Demonstrating suitability of intended purpose to facility "Quality" Data in Biosimilar Development
  - Supporting Challenging Product Development
    - Addressing challenges of having fewer lots
    - Providing critical characterization data when needed

Acknowledgments

- Marjorie Shapiro
- Steven Kozlowski
- Christopher Downey
- Jee Chung

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See you all in… Bethesda, MD
Sep 29 – Oct 2, 2019