Points to Consider for the CMC Review of Therapeutic Biologics

Willie Wilson, Ph.D.

Division of Biotechnology Review & Research 1
Office of Biotechnology Products
OPQ, CDER, FDA

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FDA Center for Drug Evaluation and Research

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The views and opinions expressed should not be used in place of regulations, published FDA guidances, or discussions with the Agency.

Agenda

- What is a biologic?
- General CMC expectations for therapeutic proteins during IND development
- CMC-related clinical hold issues during Phase 1 IND development

Pop Quiz

Which of the following is NOT considered a biologic?

A. Flu vaccine
B. Stem cell therapy
C. Monoclonal antibody
D. None of the above

Types of Biologic Products

- Vaccines
- Blood and Blood Components
- Allergenics
- Gene Therapy
- Cell Therapy
- Tissues

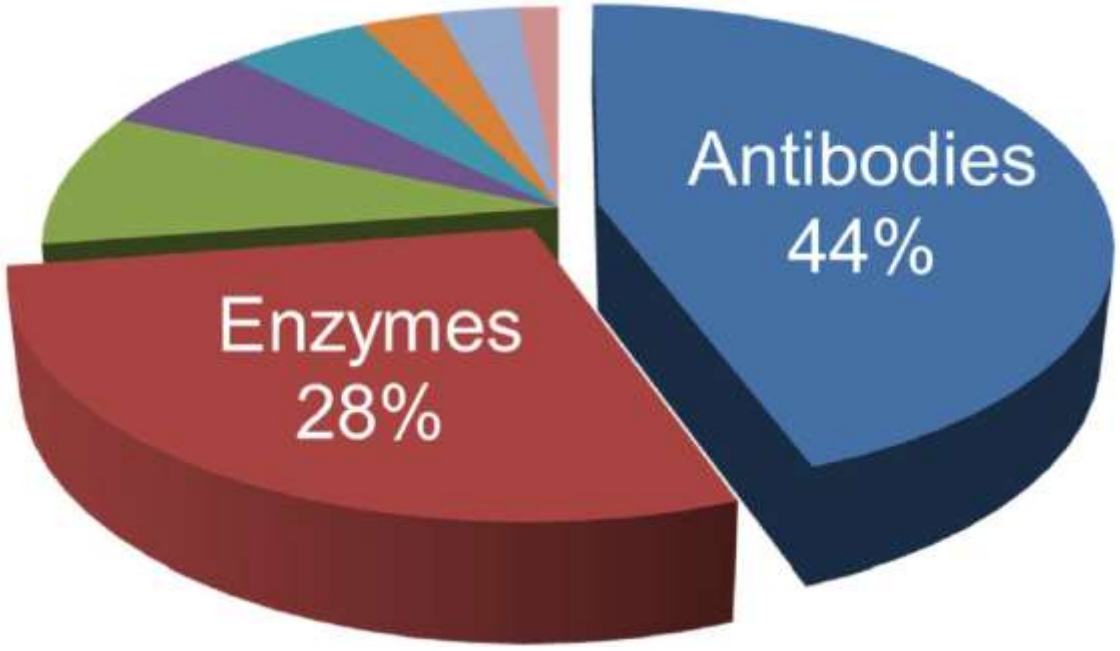
} CBER

- Recombinant Therapeutic Proteins
  * Some Exceptions

} CDER

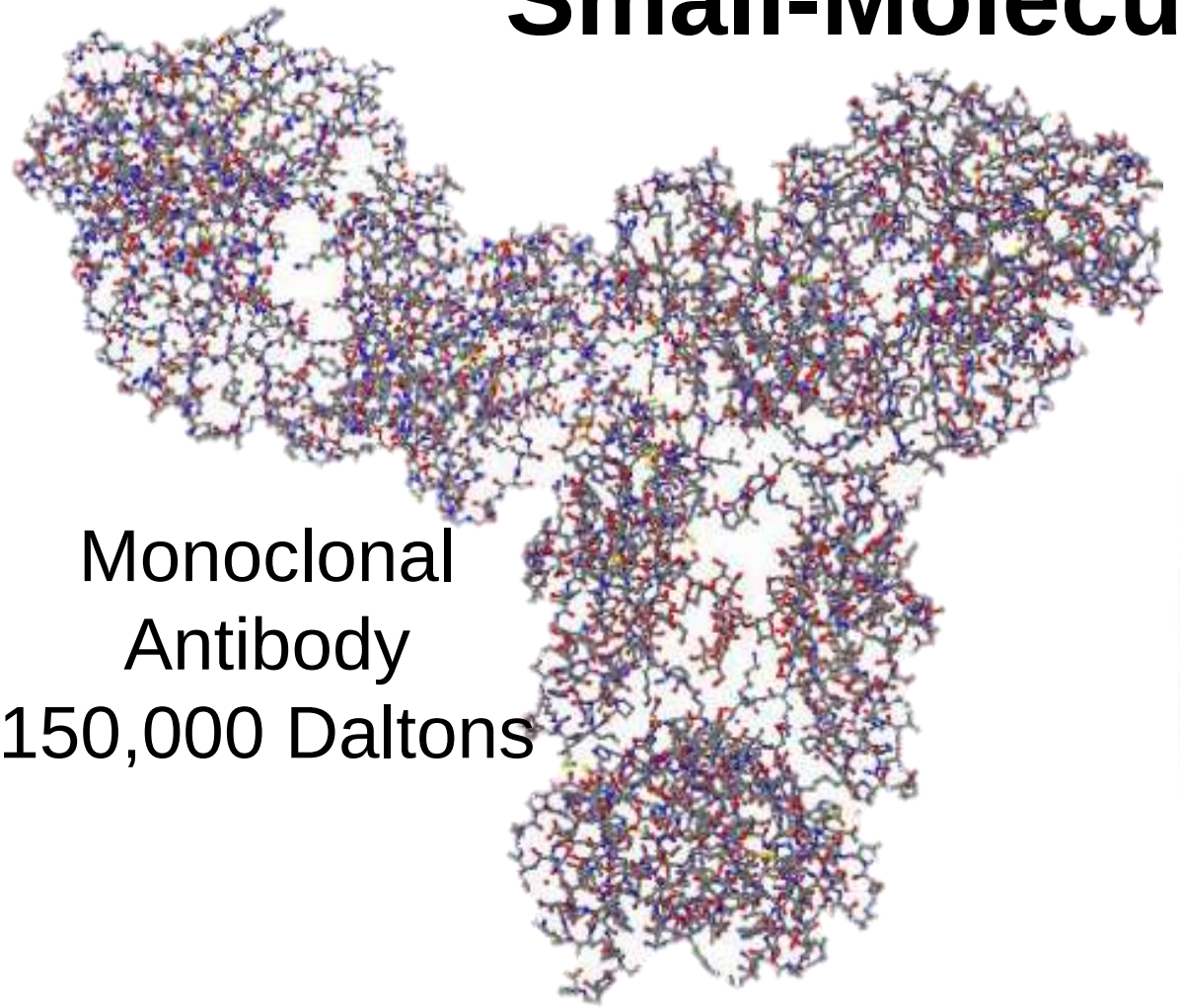
❖ *Remainder of talk will focus on therapeutic proteins*

Licensed Therapeutic Proteins Reviewed by OBP (1950 – 2016)

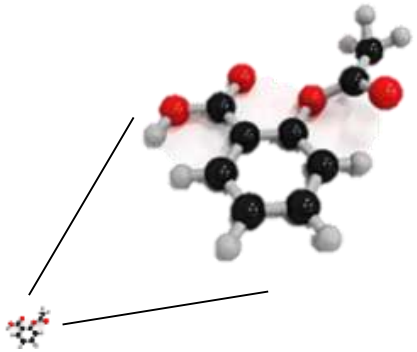


- Cytokines 9%
- CSF 6%
- Biosimilars 2%
- Toxins 3%
- Growth Factors 3%
- Other 5%

Therapeutic Protein Versus Small-Molecule



Monoclonal Antibody
150,000 Daltons



180 Daltons

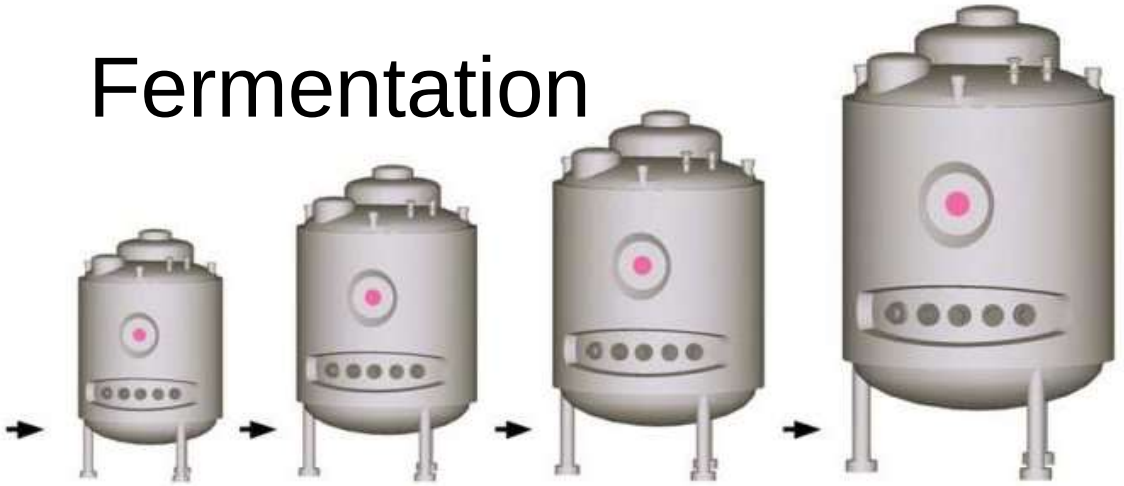
What Distinguishes Therapeutic Proteins from Small-Molecules?

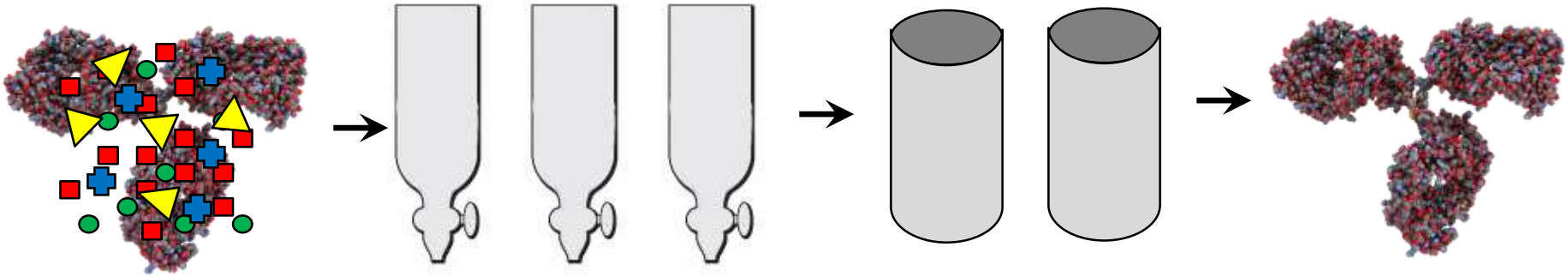
- Isolated from live cells
- Ability to transmit infectious agents
- Cannot be terminally sterilized
- Heterogeneous
  - Mixture of related components and cell line impurities
  - Can impact potency, immunogenicity and pharmacokinetics

Biologic Manufacturing Process
(Therapeutic Proteins)

Cell Bank

Fermentation





Purification

General CMC Expectations for Therapeutic Proteins During IND Development

- Understand what product quality attributes contribute to safety and potency.

- Ensure that the manufacturing process can produce product with consistent quality attributes.

General CMC Expectations for Therapeutic Proteins During IND Development

- Product Characterization
- Lot Release Specifications
- Reference Materials
- Stability Program
- Safety Testing

Product Characterization

- Safety Testing
- General Testing (e.g., particulates)
- Compatibility Testing
- Physicochemical Properties
  - 1^{o}, 2^{o} and 3^{o} structure
  - Post-translational modifications
  - Product variants (e.g., size, charge)
- Biological Activity (Mechanism of Action)

Lot Release Specifications Considerations

- Safety
  - Bioburden, Sterility
  - Endotoxin (≤ 5 EU/kg/hour limit)
- General Testing
  - pH, osmolality, color, particulates
- Identity Test
  - Must distinguish your product from other products in facility

Lot Release Specification Considerations

- Strength (Protein Content)
- Volume in Container Closure
- Process-related Impurities
  - Host cell components (e.g., protein, DNA)
  - Media components
  - Purification components
  - Chemical additives

} Not Always Needed

Lot Release Specification Considerations

Product-related Variants	Method Examples
• Size	• Size-exclusion HPLC • SDS-PAGE • Capillary electrophoresis
• Glycosylation (e.g., N-linked glycan, sialic acid)	• Glycan fluorescent labeling • Capillary electrophoresis, HPLC

Lot Release Specification Considerations

Product-related Variants	Method Examples
• Other Modifications/ Degradation Variants	• Isoelectric focusing (IEF); capillary IEF • Ion exchange chromatography • Reverse-phase HPLC • Hydrophobic interaction chromatography • Peptide Mapping

Lot Release Specification Considerations

- Potency
  - Required to assess biologic activity. 21 CFR 600.3(s) and 610.10
  - Should represent mechanism(s) of action
  - <u>Typical Methods:</u>
    - Cell-based Assay
    - Biochemical Assay
    - Binding Assay

Reference Material Expectations

- Substance prepared for use as the standard in an assay, identification or purity test
- Expected for IND development
- Should be representative of the clinical manufacturing process
- Should be fully characterized (product quality, stability)

Stability Program Expectations

- Protocol should include appropriate testing intervals and specifications
- Real-time storage condition expected
- Recommend accelerated and stressed storage
- Clinical versus toxicology stability lots

Ensure product quality over time; understand degradation pathway(s)

Mammalian Cell Bank Characterization

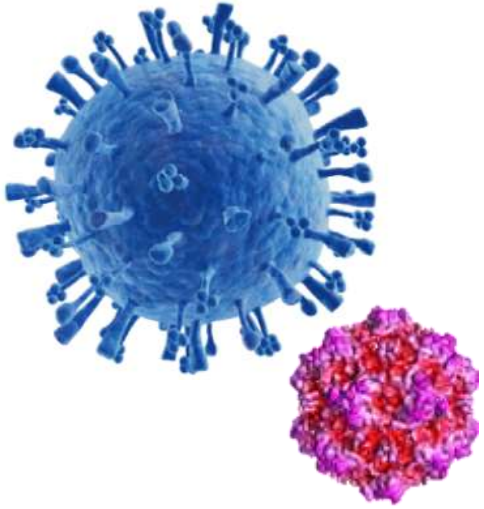
Test	MCB	WCB
Sterility	X	X
Mycoplasma	X	X
Adventitious virus *(in vitro/ in vivo)*	X	
Species-specific virus *(MAP, HAP, RAP)*	X	
Retrovirus	X	
Authenticity	X	

- *Other substrates should be tested as appropriate for the cell type*

Viral Safety Expectations
(Mammalian Cell Substrates)

<u>Virus Reduction:</u>

Include at least two orthogonal viral clearance steps in purification process



- Virus filter (15 – 140 nm pore)
- Low pH incubation
- Solvent/ detergent
- Chromatography steps

Viral Safety Expectations

- Viral Clearance Studies – Phase 1 IND
  - Small-scale model of purification steps
  - Represents clinical manufacturing process
  - Spike starting material with model virus
- Types of Model Viruses:
  - DNA/ RNA
  - Enveloped/ non-enveloped
  - Physicochemical resistant/ non-resistant

Use of a representative retrovirus model (e.g., xMuLV) is generally expected

TSE Safety Expectations

Transmissible Spongiform Encephalopathy

- Contamination risk for animal-derived raw materials (e.g., fetal bovine serum)
- No adequate test for TSE
- Provide identity, source and country of origin for animal-derived raw materials
- Recommend developing process free of all animal-derived raw materials

Common CMC Speed Bumps for Phase 1 IND Development

Clinical Hold Issues - CMC

21 CFR 312.42(b)(1)(i)

Exposure to a significant and unreasonable risk

- Unacceptable safety specifications (e.g., sterility, endotoxin)
- Evidence of product or cell line contamination
- Use of β-lactam antibiotics in culture medium

Clinical Hold Issues – CMC

<u>21 CFR 312.42(b)(1)(iv)</u>

Insufficient information submitted to assess risks to subjects

- Clinical lots not comparable to toxicology lots
- Inadequate manufacturing process description

Clinical Hold Issues – CMC

21 CFR 312.42(b)(1)(iv)

Insufficient information submitted to assess risks to subjects

- Insufficient assurance of product stability
- Inadequate release specifications (potency)

Clinical Hold Issues – CMC

21 CFR 312.42(b)(1)(iv)

Insufficient information submitted to assess risks to subjects

- Insufficient viral safety assurance
  - Retrovirus removal or inactivation
  - Cell line testing and raw materials
  - Link between viral clearance study and manufacturing process

Take Home Message

- Biologics require extensive manufacturing control
- Know your product and process
- Pay close attention to potential safety risks of your product

Acknowledgements

- Sarah Kennett
- Division of Biotechnology Review and Research 1 (DBRR1)

References

FDA Guidance

- Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use. CBER (1997)

- Guidance for Industry: Characterization and Qualification of Cell Substrates and Other Biological Materials Used in the Production of Viral Vaccines for Infectious Disease Indications. CBER. (2010)

- Guidance for Industry: Content and Format of IND Applications for Phase 1 Studies of Drugs, including Well-Characterized, Therapeutic, Biotechnology-derived Products. CDER/CBER (1995).

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- ICH Q5A: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin. (1999)
- ICH Q5C: Stability Testing of Biotechnological/ Biological Products. (1995)

World Health Organization (WHO)

- Recommendations for the Evaluation of Animal Cell Cultures as Substrates for the Manufacture of Biological Medicinal Products and for the Characterization of Cell Banks. (2010)

Thank You!

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