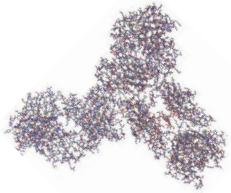
Pre-License Inspections for Biologics: What Industry Should Know

Christopher Downey, Ph.D.
Director
Division of Biotechnology Manufacturing
Office of Pharmaceutical Manufacturing Assessment,
Office of Pharmaceutical Quality
CDER | US FDA

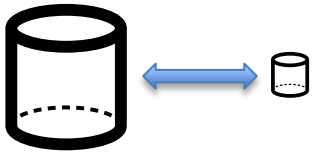
SBIA Pharmaceutical Quality Symposium
October 31, 2023

Biologics are Distinct from Small Molecules

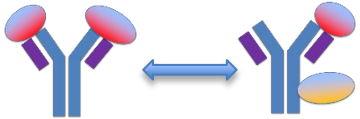
Biological Products can be highly complex



Many controls/parameters must be established based on small scale models (e.g., viral clearance)

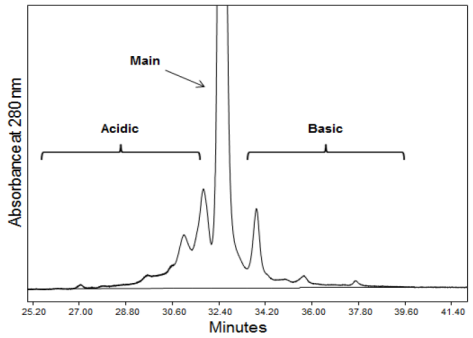


Molecules may have indication specific CQAs



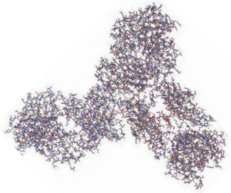
Biological products may contain product-related substances (retaining activity) as well as product-related impurities

CQAs may not always be fully resolved by a given method



Biologics are Distinct from Small Molecules

Biological Products can be highly complex



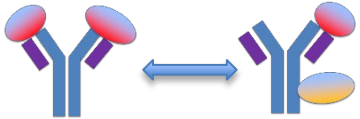
Biological products may cont… product-related substances (…vity) as well as product…

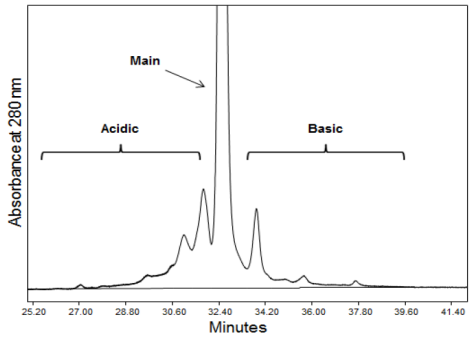
Many controls/parameters must be … based on small scale model… clearance)

…ys be fully resolved by a

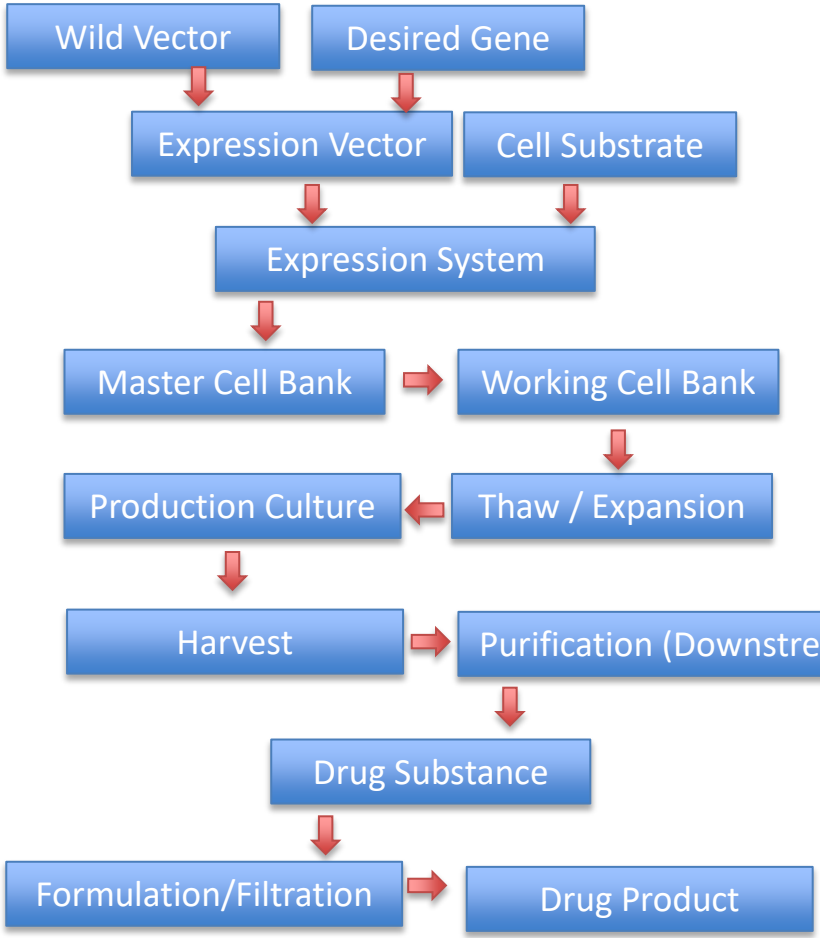
Biologics process characterization, process validation, and process control are critical…and make pre-license inspections more complex

Molecul… …indication specific C…





A "Typical" Recombinant Protein Manufacturing Process



Genetic Development

Cell Banking

Drug Substance Production

Drug Product Production

Q5A
Q5B
Q5D
Q5E

Q5AR1
Q5C
Q5E
Q6B
Q11
Q5E

Q6B
Q8R2

Q7

M4Q
Q9
Q10
Q12

Process Validation Expectations Differ Between BLAs and NDA/ANDAs

- For NDAs/ANDAs:
  - Process performance qualification (PPQ) phase must be *completed before commercial distribution*
- For BLAs:
  - PPQ phase *complete prior to submission* of the BLA
  - PPQ Data provided in the application
  - Commercial process inspected during application review
- BLA inspectors expect to see final commercial process in operation

Often overlooked information

- Data supporting routine manufacturing operations and ongoing commitments:
  - Virus clearance
  - Membrane Reuse
  - Chromatographic Purification Resin Reuse
  - Shipping Qualification and Validation
  - Stability Monitoring and Requalification Protocols for Reference Materials
  - Monitoring Protocols for Cell Banks
- Risk from other products manufactured on shared equipment
- *These items may also be evaluated during pre-license inspections*

Why Pre-license inspections?

Biologics Licenses: Issuance and Conditions:

- The facility in which the biological product is manufactured, processed, packed, or held meets standards designed to assure that the biological product continues to be safe, pure, and potent (**PHS Act)**
- The applicant consents to the inspection of the facility that is the subject of the application (**PHS Act**)
- A biologics license application shall be approved only upon examination of the product and upon a determination that the product complies with the standards established in the biologics license application and the requirements prescribed in the regulations **(21CFR Sec. 601.20(a))**
- A biologics license application shall be approved only after inspection of the establishment(s) listed in the biologics license application and upon a determination that the establishment(s) complies with the standards established in the biologics license application and the requirements prescribed in applicable regulations **(21 CFR Sec. 601.20(d))**

Key Items to Consider

- All facilities must be registered with FDA at the time of the BLA submission and ready for inspection (see 21 CFR 600.21 and 601.20(b)(2))
- A preliminary manufacturing schedule for the drug substance and drug product should be provided in the BLA submission to support inspection planning
- Manufacturing facilities should be in operation and manufacturing the product under review during the inspection
- Type II DMFs for Drug Substance, Drug Substance Intermediate and Drug Product are typically not permissible for BLAs (except small molecule components)
- Identical laws and regulations, expectations, and inspection processes for standard or biosimilar applications

Pre-License Inspections (PLIs) are Distinct From Surveillance Inspections

- Product- and process-specific evaluation
  - A BLA licenses the product and the process
- PLIs observes the BLA subject product and its to-be-commercial process specifically
- PLIs are led by CDER staff who are experts in biotechnology review and inspection
  - Same inspection teams for new molecules or biosimilars
- Acceptable outcomes of both application assessment and facility inspections and are required for BLA approval

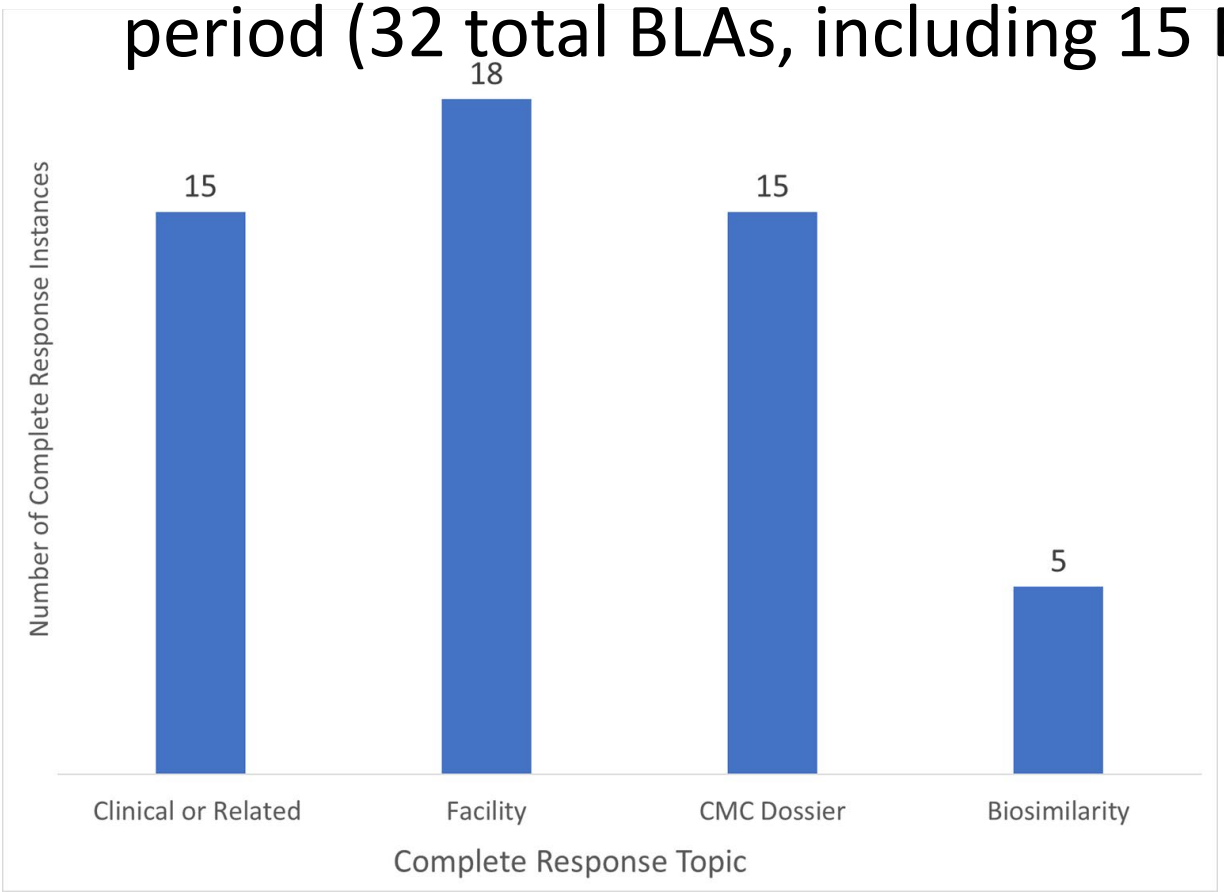
Pre-License Inspection Objectives

- Systems-based evaluation of CGMP readiness for the BLA
  - Quality System
  - Facilities and Equipment System
  - Materials System
  - Production System
  - Packaging and Labeling System
  - Laboratory Control System
- Conformance of process, controls, and supporting data with those in the application
- Data integrity and security

Key Items to Consider

- Robust Product Quality System in place
  - Process changes, deviations, failures, are adequately and promptly evaluated, investigated, controlled, corrected, as applicable
  - Proactively identifies problems and takes corrective actions, does not merely react to and justify problems
- Equipment, procedures, and controls prevent contamination and cross-contamination and assure bioburden control and sterility
  - *Do not rely only on detectability or clearance for microbiology control*
- Process, controls, and monitoring assure product CQAs
- Personnel involved in manufacturing & testing are appropriately trained
- Applicant must have knowledge and control of all stages of the manufacturing process
  - Quality agreement may be requested on inspection

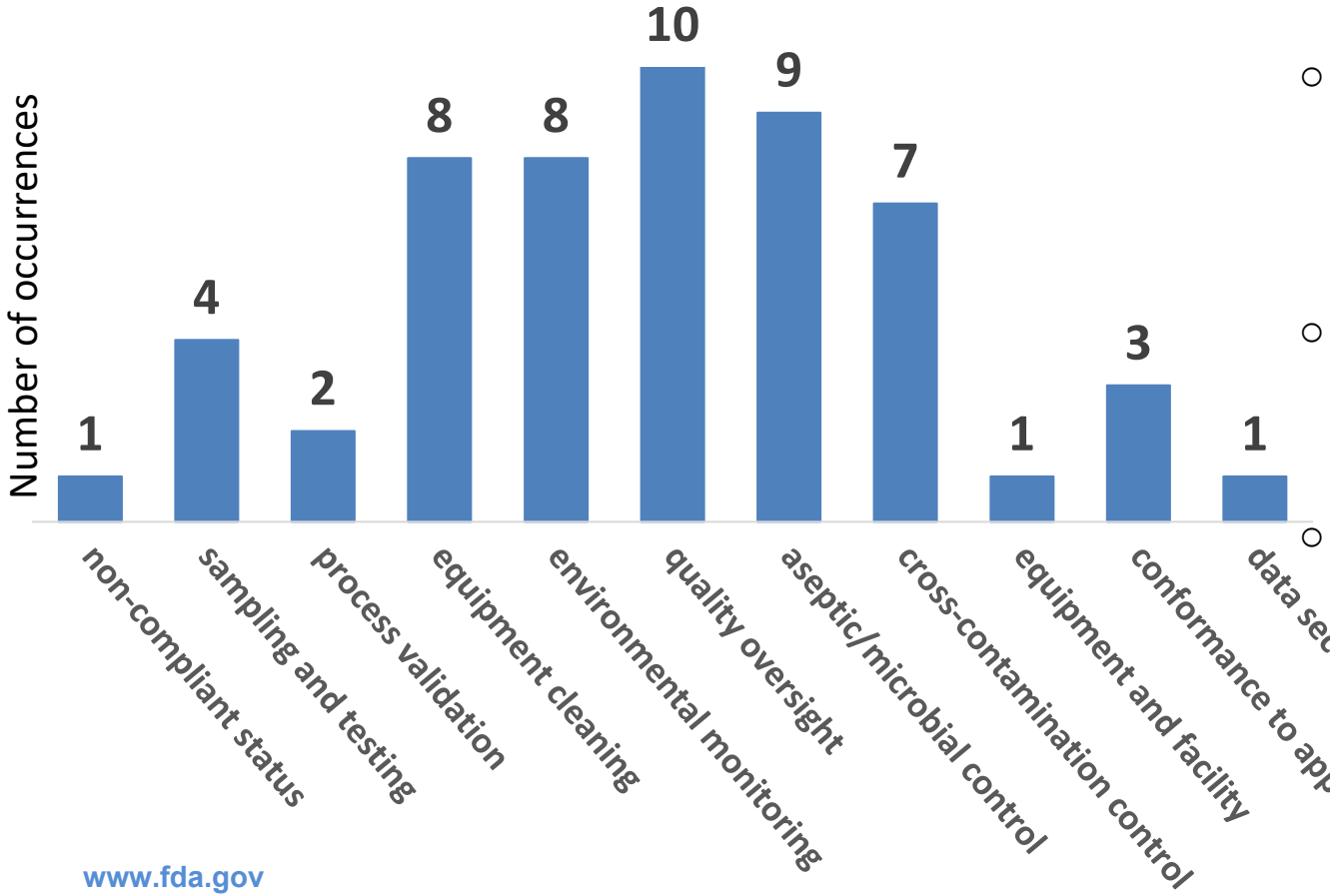
Survey of CR Deficiency types over a recent 3 year period (32 total BLAs, including 15 Biosimilars)



Key Takeaways:

- Issues identified during inspection are the most common deficiency type
- For biosimilars, facility deficiencies are more common than lack of biosimilarity to reference product

Summary of Inspection CR Issues (18 CRs)



- Corrective actions often need data supporting their effectiveness or verification on a follow-up inspection—takes time to generate
- Aseptic procedures, bioburden control, and environmental monitoring are common issues
- Effective Quality Management System is critical

Summary

- Successful development of biologics includes ensuring manufacturing facilities are ready for commercial production
- For biologics, facility- and inspection-related issues have been the most common CR deficiencies in recent years
- Common biologics inspection (PLI) issues include aseptic procedures, contamination/cross-contamination controls, environmental monitoring
- Insufficient quality oversight is a recurring theme

Resources

- ICH Quality Guidelines, e.g. Q5A, Q7, Q9, Q10, Q11, Q12
- 21 CFR: Parts 210 and 211; Parts 600, 601, and 610
- FDA Guidance "Process Validation: General Principles and Practices"
- FDA Guidance: Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice
- FDA Guidance: "Conducting Remote Regulatory Assessments Questions and Answers" Draft Guidance for Industry
- FDA Guidance: "Remote Interactive Evaluations of Drug Manufacturing and Bioresearch Monitoring Facilities During the COVID-19 Public Health Emergency"
- "Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use"
- FDA Guidance: Analytical Procedures and Methods Validation for Drugs and Biologics
- FDA Drug Compliance Programs: e.g. 7346.832 Pre-Approval Inspections, FDA Compliance Program 7356.002M Surveillance Inspections of Protein Drug Substance Manufacturers, 7356.002A: Sterile Drug Process Inspections
- EU GMP Annex 1: Manufacture of Sterile Medicinal Products


FDA
U.S. FOOD & DRUG
ADMINISTRATION