

Pre-License Inspections for Biologics: What Industry Should Know

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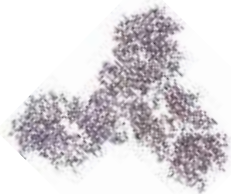
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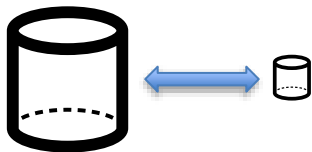
Biologics are Distinct from Small Molecules



Biological Products can be highly complex



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



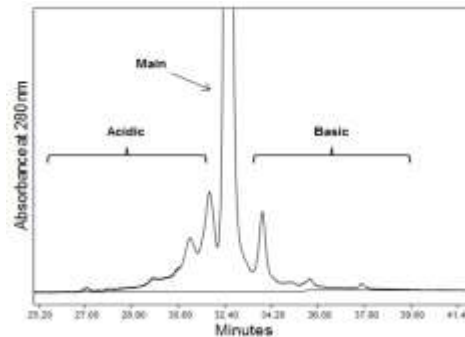
Molecules may have indication specific CQAs



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



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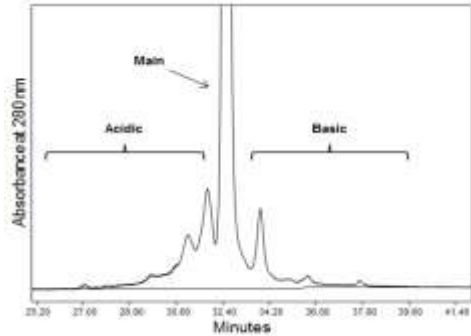
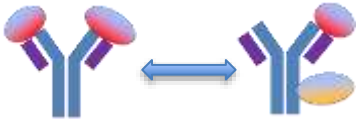
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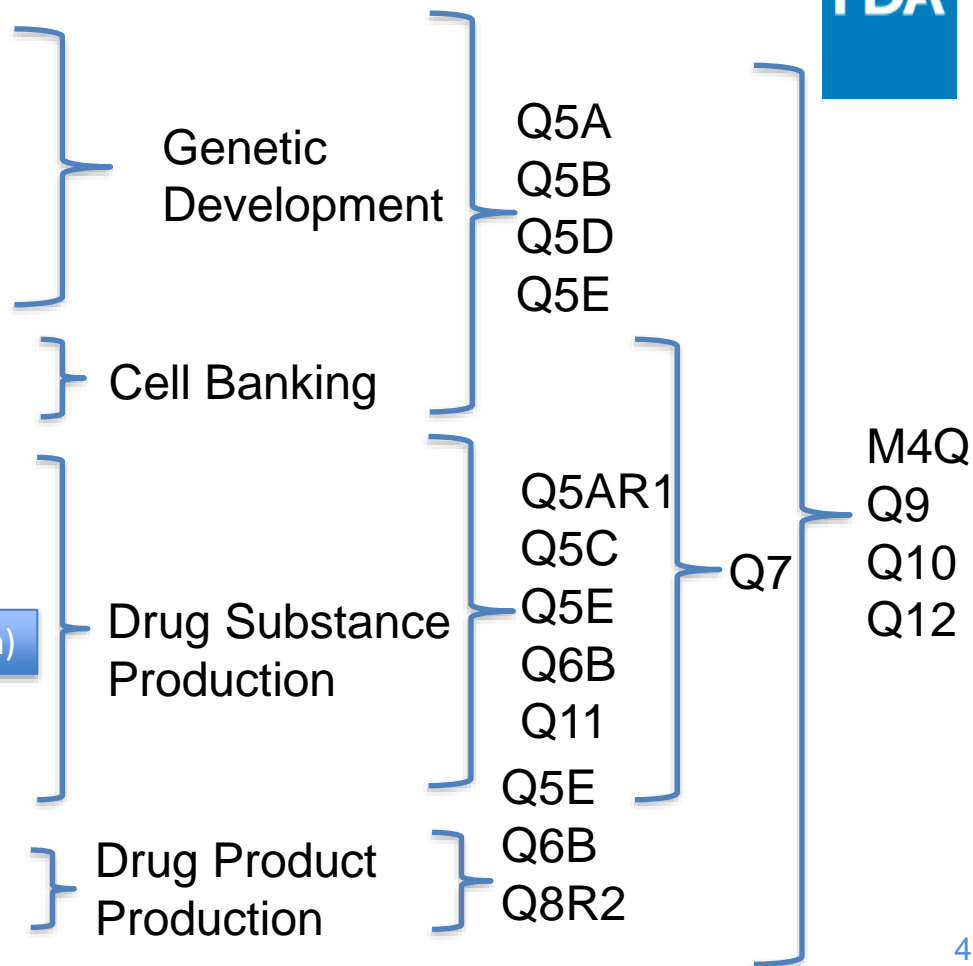
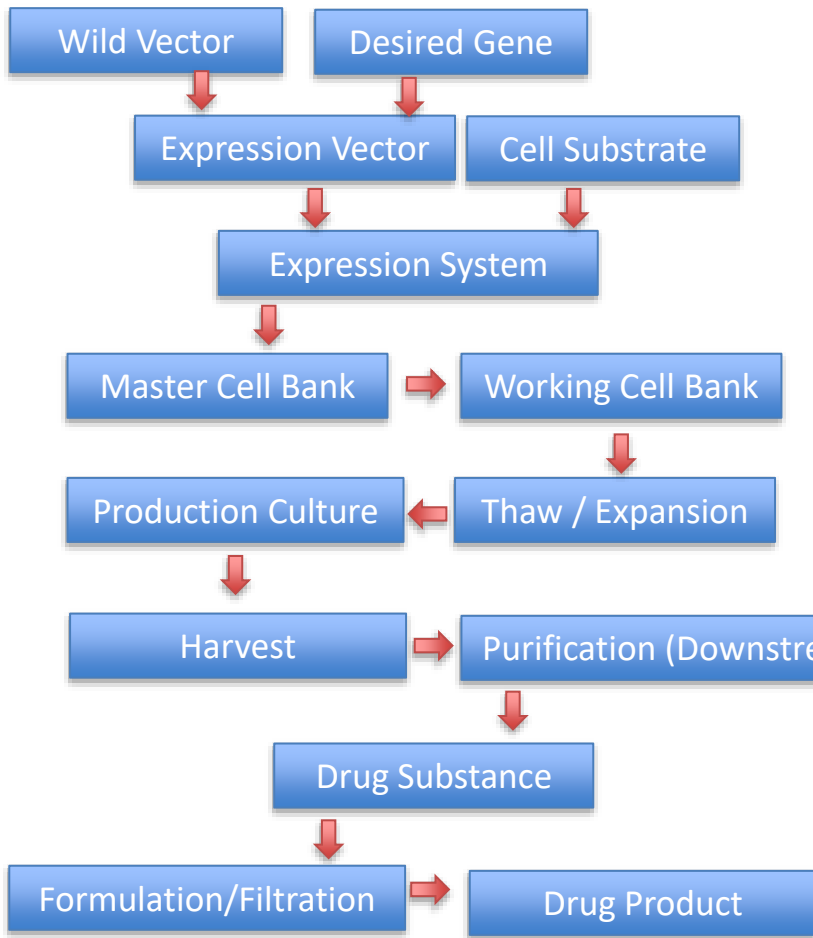
Biologics process characterization, process validation, and process control are critical...and make pre-license inspections more complex

Molecular specific C

indication



A "Typical" Recombinant Protein Manufacturing Process



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



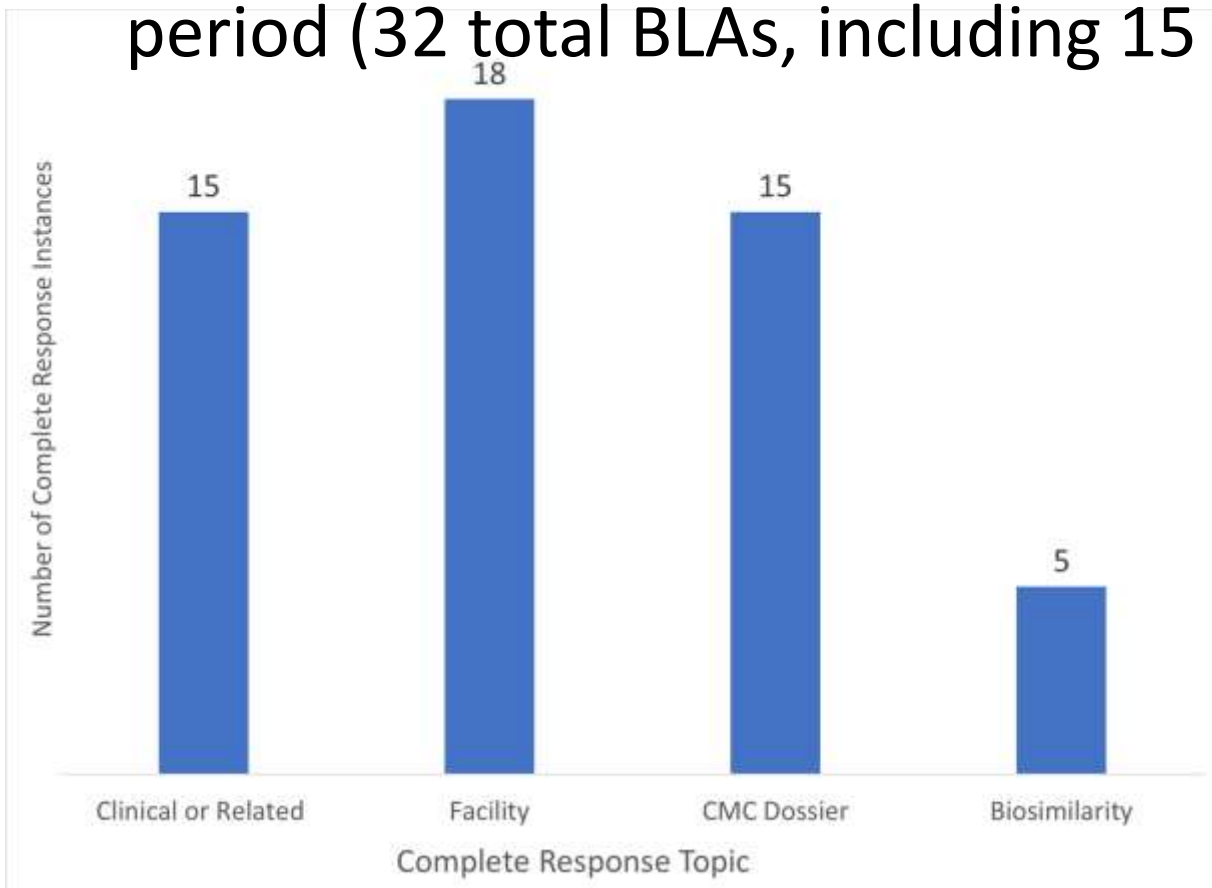
- Systems-based evaluation of CGMP readiness for the BLA
 - Quality System
 - Facilities and Equipment System
 - Materials System
 - Production System
 - Packaging and Labeling System
 - Laboratory Control System
- Conformance of process, controls, and supporting data with those in the application
-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

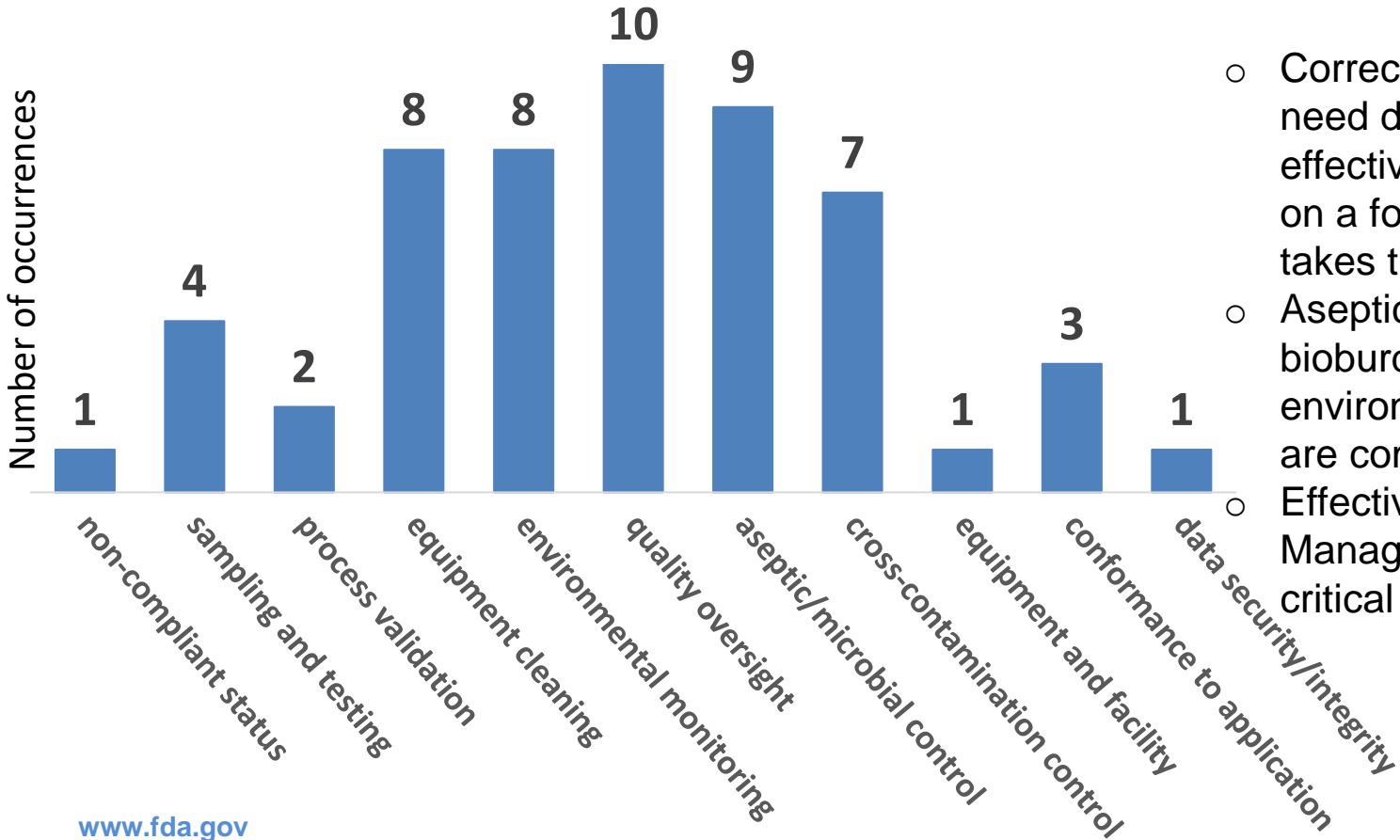
Survey of CR Deficiency types over a recent 3 year period (32 total BLAs, including 15 Biosimilars)



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](#)

