

A Quick-Start Guide to Biologics Manufacturing

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Everyone deserves
confidence in their *next* dose
of medicine.

Pharmaceutical quality
assures the
availability,
safety,
and efficacy
of *every* dose.

Learning Objectives

- Describe how biological products are regulated
- Discuss unique factors for biological products
 - Key Scientific Features
 - Key Regulatory Features
- Describe how CDER approaches inspectional activities for biological products
- Identify common themes for complete responses for CDER Biological Products



Scientific and Regulatory Considerations

How FDA Regulates Biologics



CDER Regulates these Biologics:

- Monoclonal antibodies for *in vivo* use
- Most proteins intended for therapeutic use (e.g., cytokines, enzymes)

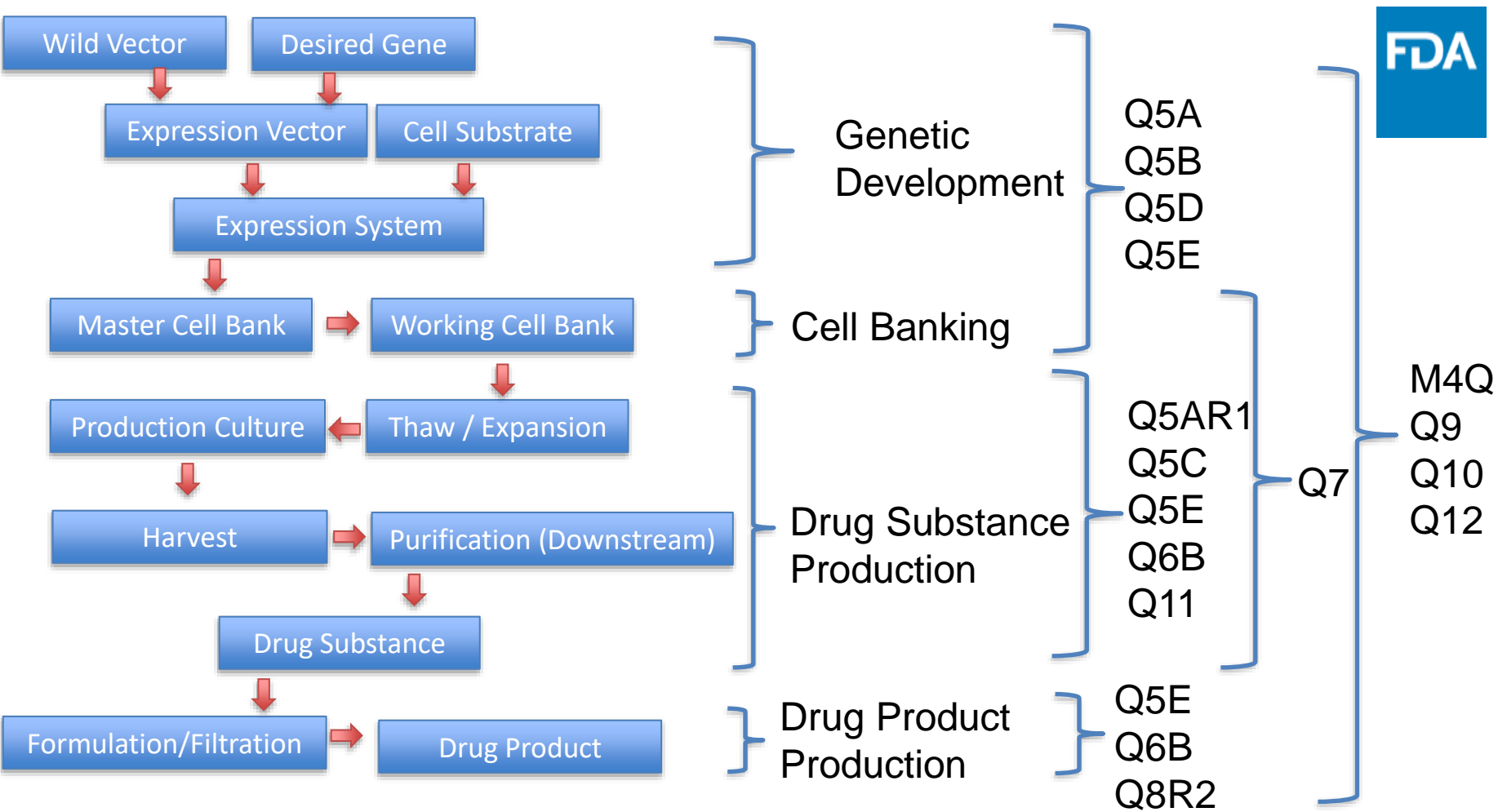
CBER Regulates these Biologics:

- Cellular products, including products composed of human, bacterial or animal cells or from physical parts of those cells
- Gene therapy products
- Vaccines and vaccine-associated products: regardless of their composition or manufacture
- Allergenic extracts used for the diagnosis and treatment of allergic diseases
- Antitoxins, antivenins, and venoms
- Blood, blood components, plasma derived products (for example, albumin, immunoglobulins)
- Human cells, tissues and cellular and tissue-based products

Quality Assessment Responsibility in OPQ in CDER for Products Containing Drug Substances Composed of Amino Acid Polymers

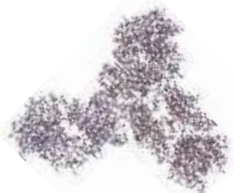


Size (# aa)	Manufacturing Process
≤ 40 (NDA and subsequent ANDAs)	<ul style="list-style-type: none">• Made entirely by chemical synthesis• Derived from a biological source
> 40 (BLA)	<ul style="list-style-type: none">• Derived from a biological source• Made entirely by chemical synthesis

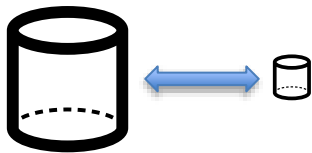


How Do Biological Products Differ From Small Molecules?

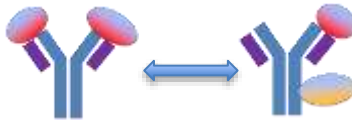
Biological Products can be highly complex



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



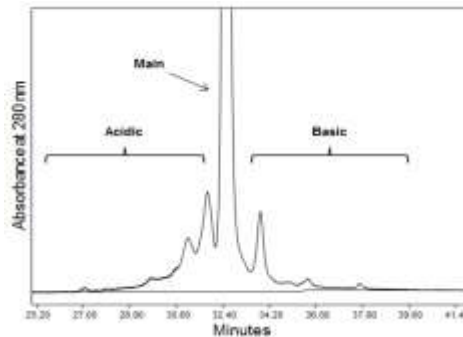
Molecules may have indication specific CQAs



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 and Process Validation

- Described in the 2011 FDA Process Validation Guidance
- Includes collection and evaluation of data from process design, through commercialization and beyond.
- Three stages:
 - Stage 1 Process Design (definition based on knowledge gained through development)
 - Stage 2 Process Qualification (Evaluation if the process is capable)
 - Stage 3 Continued Process Verification (Ongoing assurance is gained through routine production)

Process Validation Expectations

- For NDAs/ANDAs:
 - PPQ (Stage 2) must be completed before commercial distribution
- For BLAs:
 - PPQ studies must be performed prior to submission of the BLA
 - PPQ Data should be provided in the application
 - Facilities must be ready for inspection at the time of submission and manufacturing the complete product within the review cycle

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)**)
- **Applies equally to 351(a) and 351(k)**



Key Items to Consider

- All facilities should be **registered with FDA** at the time of the BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2)
- A preliminary **manufacturing schedule** for the antibody intermediate, the drug substance and drug product should be provided in the BLA submission to facilitate the planning of pre-license inspections during the review cycle.
- 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 new BLAs (except small molecule components)

More Key Items to Consider

- Often overlooked are data/information needed for the manufacturing process for both routine operation and to support ongoing commitments:
 - Shipping Qualification and Validation
 - Membrane Reuse
 - Chromatographic Purification Resin Reuse
 - Monitoring Protocols for Reference Material Stability and Requalification
 - Monitoring Protocols for Cell Banks
- Can include “nice to have” elements too
 - Protocols for qualification of new Reference Material, new Working Cell Bank
- This is not a complete list!

Challenge Question #1

When is Stage 2 Process Validation Data Required for a new BLA submission?

- A. Never
- B. In All Instances
- C. Upon the Request of the Review Team
- D. Only for Combination Products

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Inspection Considerations



Pre-License Inspections (PLI)

- Conducted during BLA review
- Distinct from surveillance inspections
- Product and process specific
- Observe the BLA product in production
 - Applicant provides manufacturing schedule for DS and DP production at time of submission
- Applicant expected to have knowledge and control of all stages of manufacturing process
- Acceptable outcome of facility inspection and application assessment are required for approval

Pre-License Inspection Objectives

CDER Biologics PLIs include the following assessments:

- Readiness for Commercial Manufacturing
- Quality System has sufficient knowledge and control over the facility and commercial manufacturing operations to assure quality of the product
 - CGMP
 - Changes, trends, deviations, failures, are adequately evaluated, investigated, controlled, corrected, as applicable
 - Facility and equipment procedures and controls prevent contamination and cross-contamination
 - Process, controls, monitoring assure low bioburden, sterility, and product CQAs
 - Personnel involved in manufacturing & testing are appropriately trained and knowledgeable of process and product CQAs
- Conformance of process and controls with those in the Application
- Data integrity and security

Biologic Facility Inspection Decisions are Risk-Based



- All facilities listed in application are assessed for inspection coverage
- Prior inspection history
 - New facility/building/filling line without inspection history?
 - Do previous inspection reports suggest potential risks?
- Does facility have experience with a similar manufacturing process?
- Information shared by other trusted Regulatory Agencies
 - CGMP issues relevant to application product?
 - Product- and process-specific risks?
- Risks identified during application review?
- Extent/significance/novelty/risk of process (or process changes for approved products)

Inspectional Assessment Tools Available



- Inspection – in person
- Records requests under the Section 704(a)(4) of the FD&C Act in advance of or in lieu of an inspection
 - Mandatory for facility
- Remote Interactive Evaluation
 - Voluntary for facility
- Inspection reports from other trusted foreign regulatory partners
 - Information from MRA partner inspections used to understand facility capabilities and CGMP compliance and inform risk assessment
 - Mutual Recognition Agreement (MRA) -- *Does not replace PLI/PAIs*
 - Confidentiality agreements allow FDA and other Regulatory Authorities to share information

Use of remote regulatory tools as alternatives to BLA inspections



- Decision made by FDA – FDA does not consider “requests”
- Depends on risk factors identified by FDA (product, process, facility, micro, inspection history etc.)
- Remote tools used when they will assist in facility evaluation or to support regulatory decisions
 - Can either support or mitigate the need for inspectional activities
 - Potential to save time and resources for both the firm and Agency
- Can be used when travel restrictions prevent inspections

Challenge Question #2

Can a BLA be approved with outstanding facility deficiencies?

- A. Yes, if the facility commits to correcting them
- B. Yes, if the facility requests a follow-up remote regulatory evaluation
- C. No. Satisfactory facility evaluations are required for approval
- D. Yes, but only for 351(a) applications



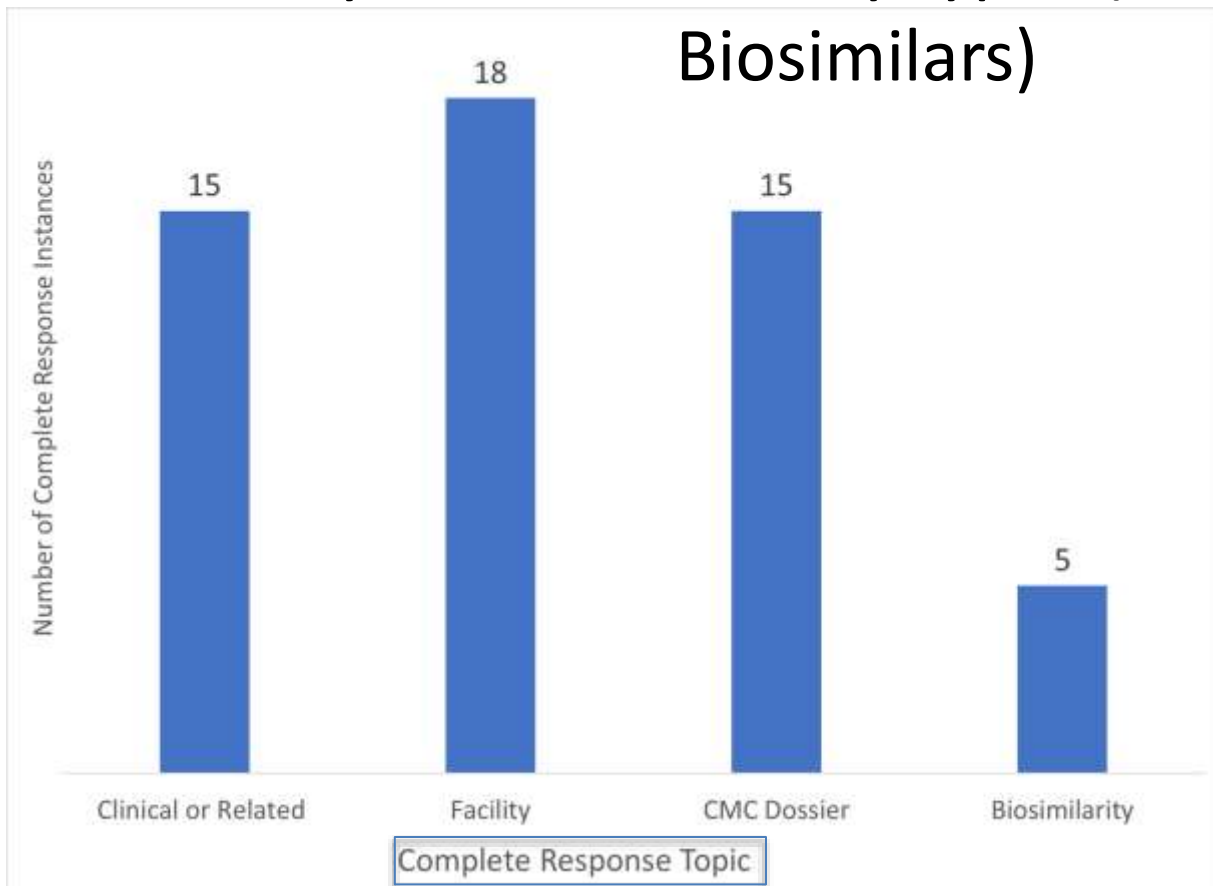
Reflections on Complete Responses

Evaluation of Complete Responses (CR)



- We surveyed a predetermined subset of recent CRs for CDER BLAs in an approximately three-year window
- A total of 32 CRs were collected, each CR letter may include more than one deficiency
- Multiple CRs to a single BLA were included in some instances
- There were 15 biosimilar BLAs included among the group

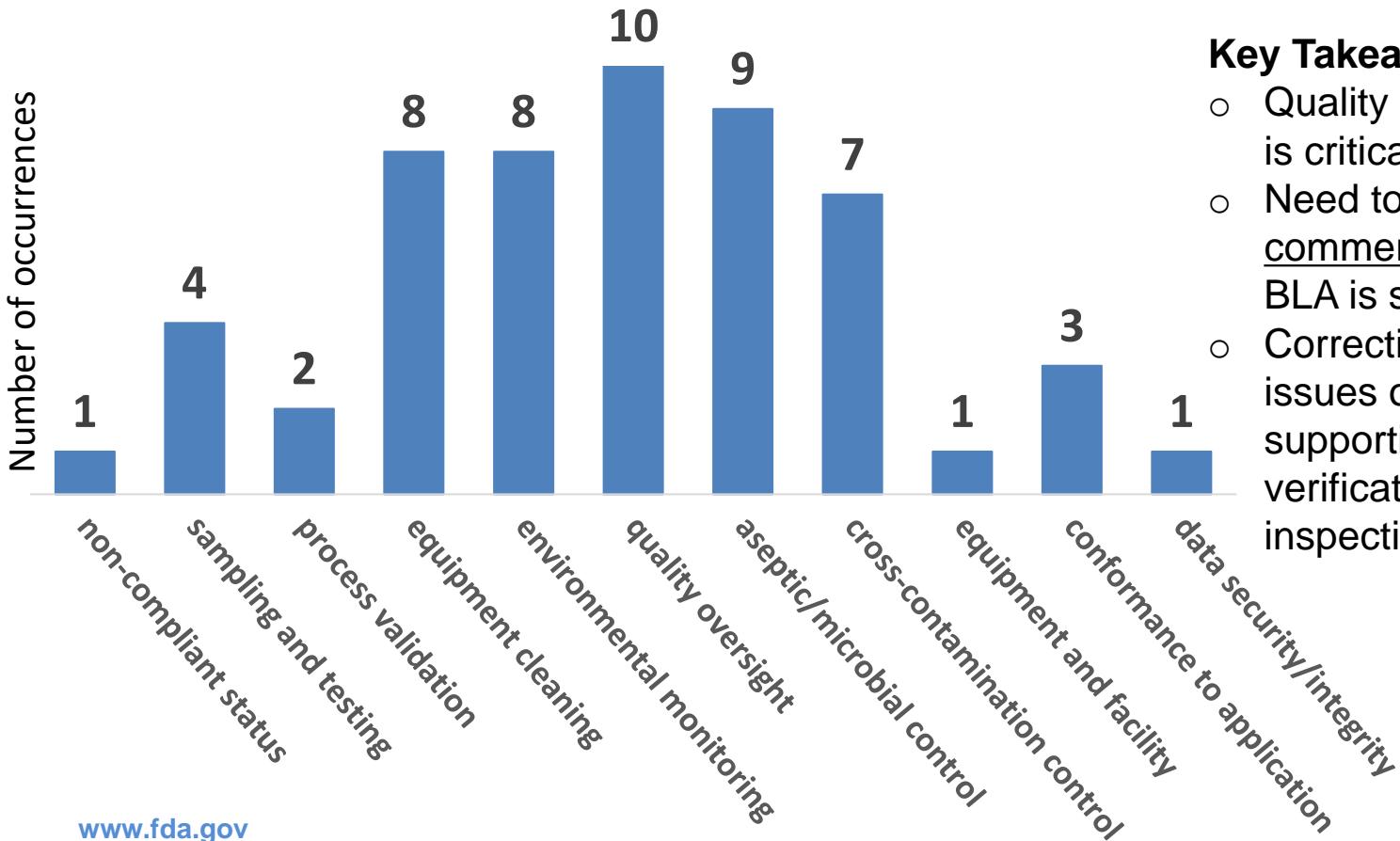
Summary of CR Deficiency types (32 total BLAs/15 Biosimilars)



Key Takeaways:

- Facility and manufacturing issues identified on inspection are the most common deficiency
- Lack of biosimilarity to the reference product is not the most common deficiency for CRs of biosimilars

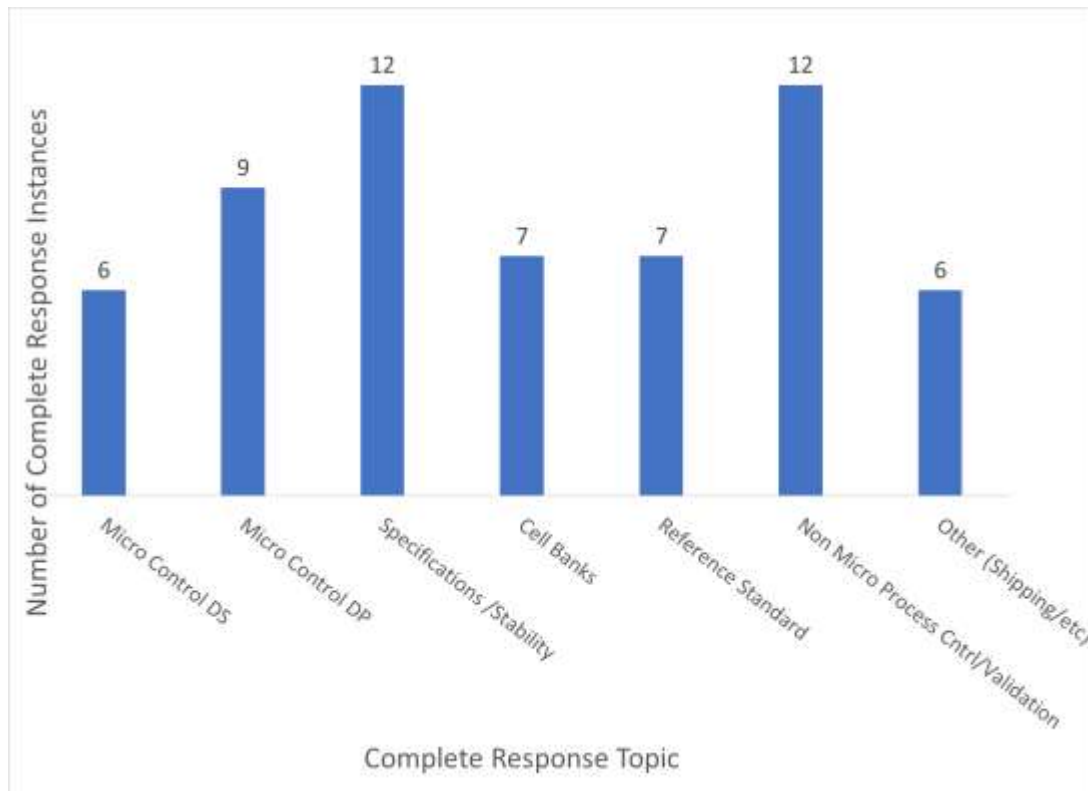
Summary of Inspection Issues (18 CRs)



Key Takeaways:

- Quality Management System is critical
- Need to be ready for commercial production when BLA is submitted
- Corrective actions for CR-issues often need data supporting effectiveness and verification on a follow-up inspection

Summary of CMC Dossier Issues (n=15)



Key Takeaways:

- Basic Manufacturing Controls including Microbiological Control are critical
- Specifications and Stability are frequently issues, including for Reference Standards
- Control of key inputs such as Cell Banks is critical

Key Conclusions for CR Evaluation



- Facility issues are the most common reason for CR, even exceeding clinical issues
- For biosimilars, facility and CMC deficiencies are more than deficiencies in demonstration of biosimilarity to the reference product
- CMC issues span a variety of topics, with basic manufacturing controls (including microbiology) the largest category
- Specs/Methods/Stability (including Reference Standards) and Cell Banking are frequent CR issues
- Inspection issues span variety of topics, with insufficient quality oversight a recurring theme

Challenge Question #3

For BLAs in CDER which receive a complete response what are some potential causes?

- A. CRs may only occur for clinical reasons
- B. CRs may only occur for manufacturing facility reasons
- C. Clinical, product quality, and manufacturing facility reasons are all common causes
- D. None of the Above

Resources

- www.ich.org
- ["Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products"](#)
- ["Content and Format of INDs for Phase I Studies of Drugs Including Well-Characterized, Therapeutic, Biotechnology-derived products"](#)
- ["Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use"](#)
- ["Process Validation: General Principles and Practices"](#)
- [Analytical Procedures and Methods Validation for Drugs and Biologics](#)
- [Drug Compliance Programs](#)
- ["Conducting Remote Regulatory Assessments Questions and Answers" Draft Guidance for Industry](#)
- ["Remote Interactive Evaluations of Drug Manufacturing and Bioresearch Monitoring Facilities During the COVID-19 Public Health Emergency" Guidance for Industry](#)

Summary

- Biological Products have unique scientific and regulatory considerations
- Inspection plays a critical role in BLA assessment, and a variety of tools are used
- The successful development of biologics requires CMC development along with clinical development, including ensuring the readiness of manufacturing facilities for commercial production

Questions?