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:

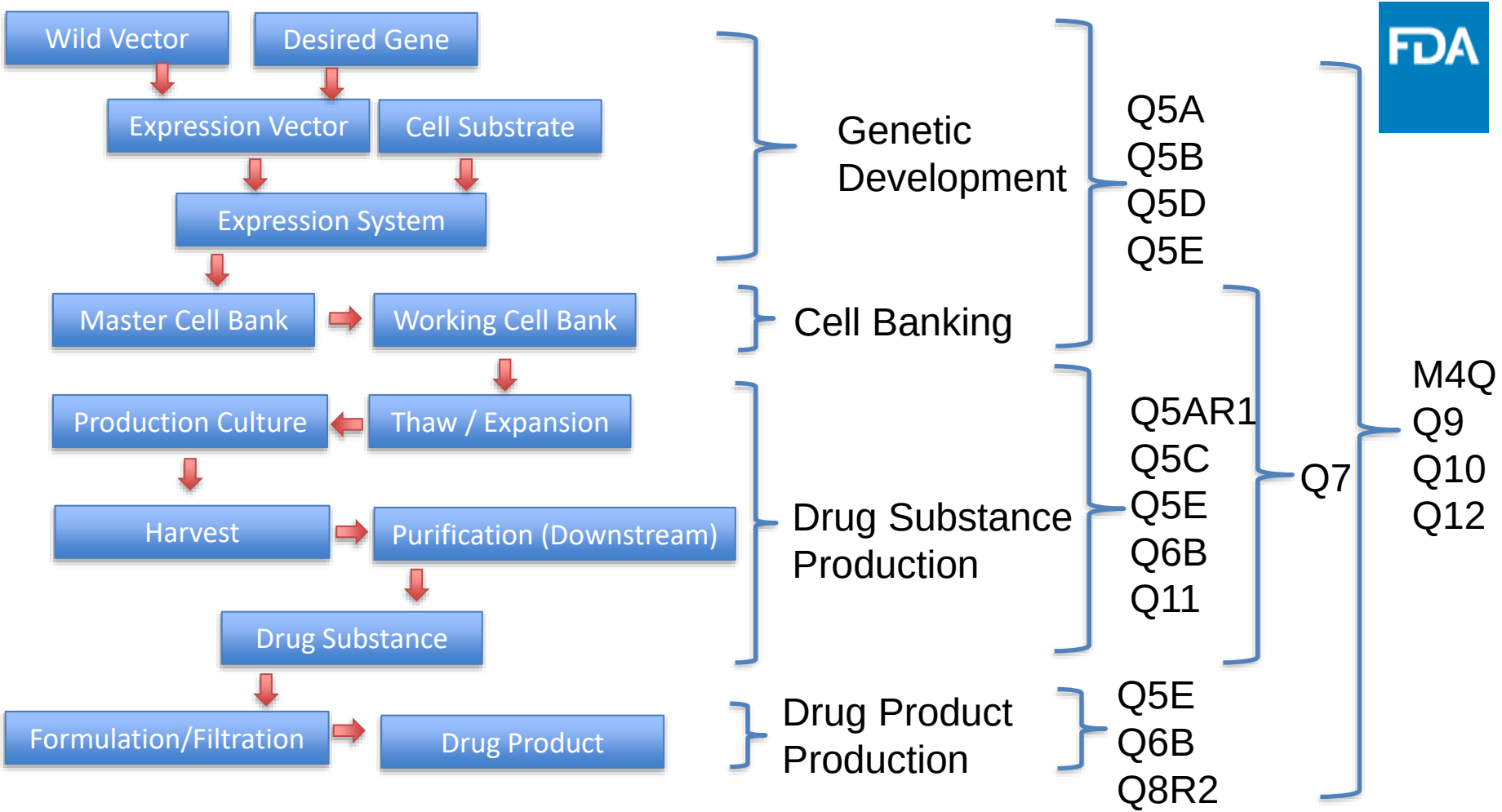
- Monoclonal antibodies for *in vivo* use
- Most proteins intended for therapeutic use (e.g., cytokines, enzymes)

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

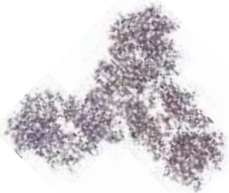
Size (# aa)	Manufacturing Process
≤ 40 (NDA and subsequent ANDAs)	• Made entirely by chemical synthesis • Derived from a biological source
> 40 (BLA)	• Derived from a biological source • Made entirely by chemical synthesis



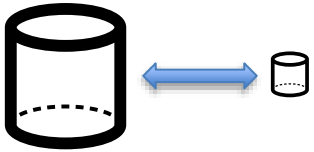
A "Typical" Recombinant Protein Manufacturing Process

How Do Biological Products Differ From Small Molecules?

Biological Products can be highly complex

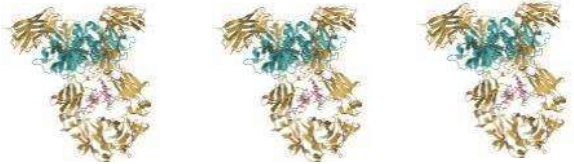


Many controls/parameters must be established based on small scale models (e.g., viral clearance)

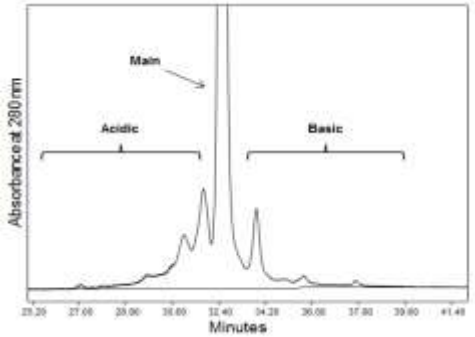


Molecules may have indication specific CQAs

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

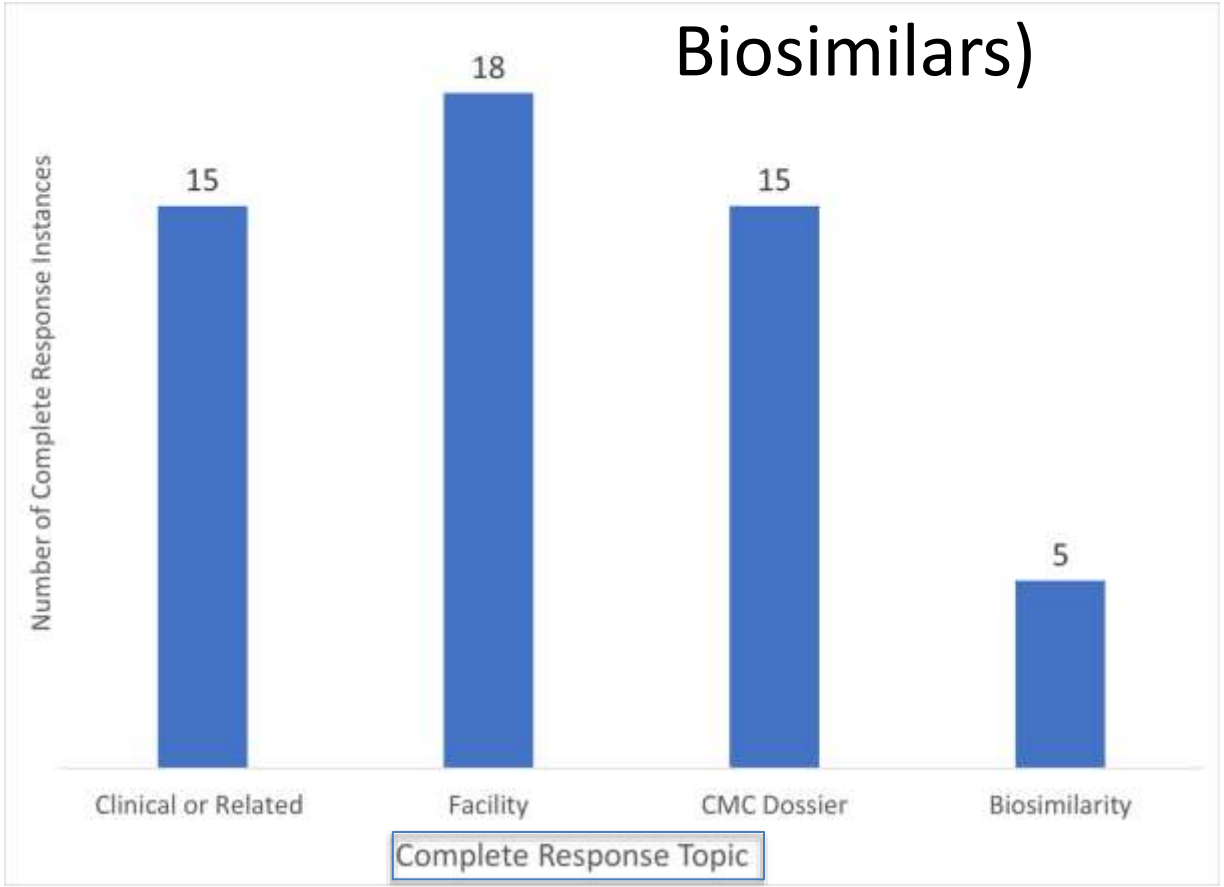
D. Yes, but only for 351(a) applications

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

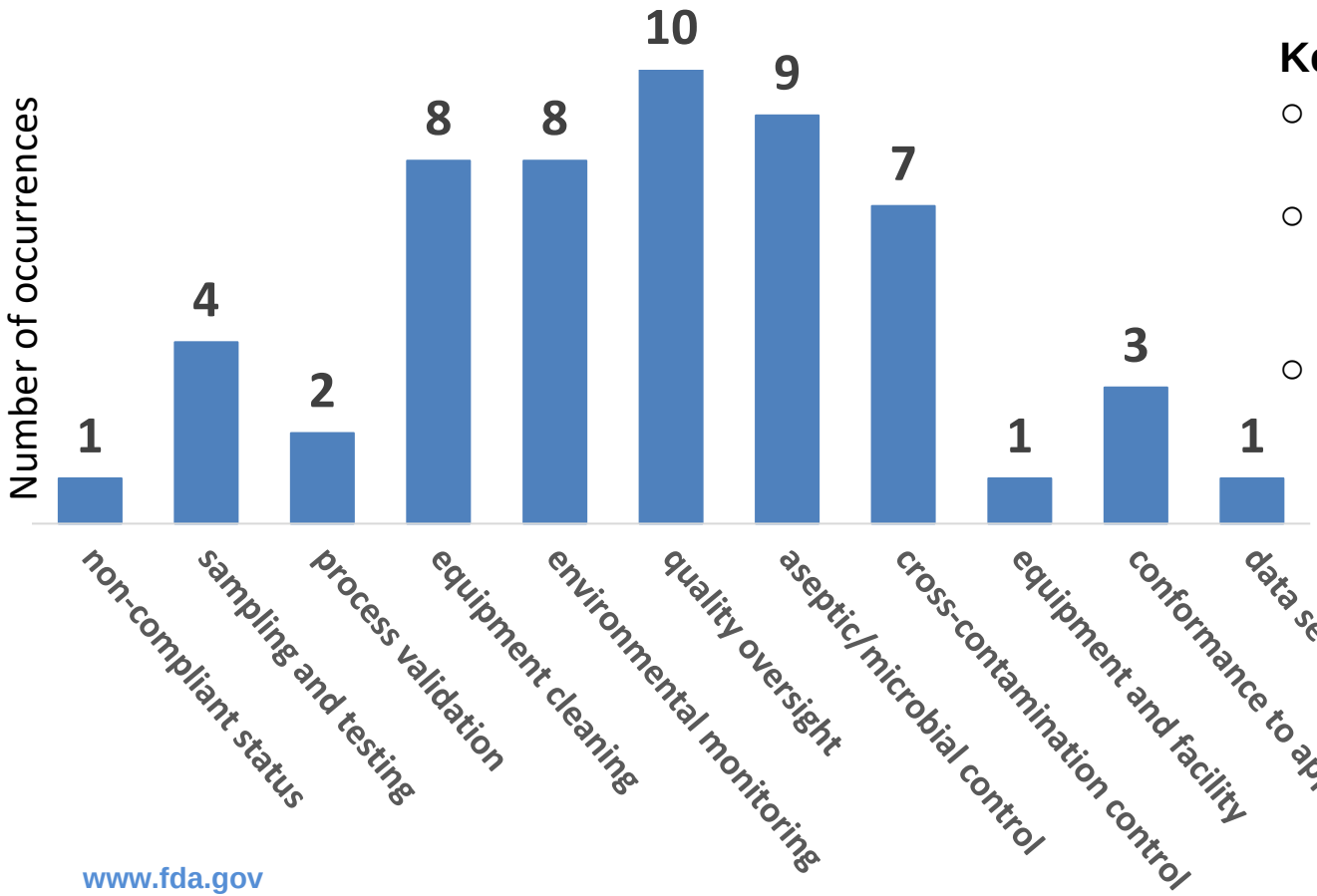
Summary of CR Deficiency types (32 total BLAs/15 Biosimilars)



Key Takeaways:

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

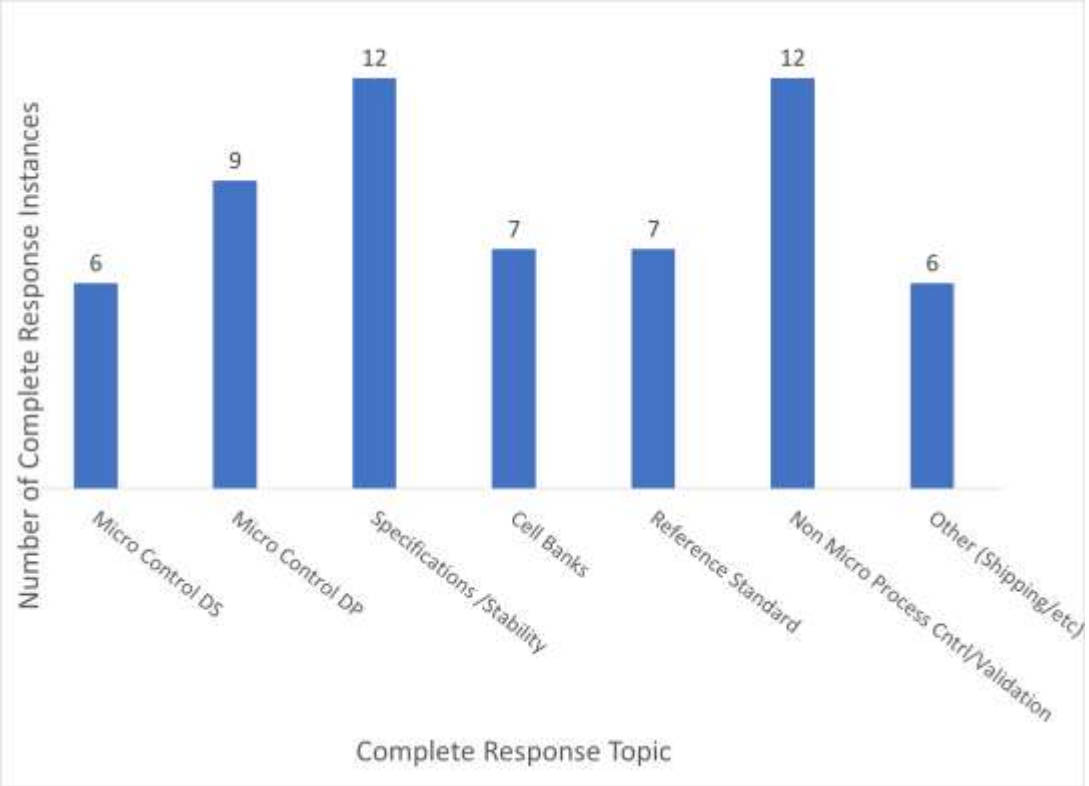
Summary of Inspection Issues (18 CRs)



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

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Questions?