CHAPTER 46—NEW DRUG EVALUATION

SUBJECT:	IMPLEMENTATION DATE:
Prelicense and Preapproval Inspections of CDER-Regulated Biological Product Manufacturers	05/14/2026

DATA REPORTING

PRODUCT CODES	PROGRAMASSIGNMENT CODES
Human Drugs Industry Codes: 50, 55-56, 57-59, 60-66	**PAC Subject** Domestic/Foreign Inspections: 46832M Pre-License Therapeutic Biological Product Inspections 46832S BLA Pre-License Inspections—Biosimilars 56R927 Remote Interactive Evaluation (RIE) Activities—Human Drugs 56R928 704a4 Activities—Human Drugs

Remarks:

1. The Center for Drug Evaluation and Research (CDER) should use this compliance program for prelicense inspections (PLIs) and preapproval inspections (PAIs) of manufacturing establishments[1] to support approval of original and supplemental biologics license applications (BLAs).
2. For assessments of sterility assurance during a PLI or PAI of biological product[2] fill /finish operations, follow instructions in compliance program 7356.002A—*Sterile Drug Process Inspections*.
3. If an inspection is necessary to support an investigational new drug (IND), including treatment INDs, a for-cause assignment will be initiated.

REPORTING REQUIREMENTS:

1. CDER PLI and PAI Requests in the Appropriate Component of the CDER Informatics Platform

The facility assessor in the Office of Pharmaceutical Manufacturing Assessment (OPMA), in CDER's Office of Pharmaceutical Quality (OPQ), enters the decision for conducting a PLI or PAI of

[1] In this compliance program, the terms *establishment*, *facility*, and *firm* are used synonymously to cover entities subject to FDA drug manufacturing regulations and statutory authority. See also 21 CFR 207.1 and 21 CFR 600.3(w).

[2] In this compliance program, unless otherwise specified, the term *biological product* means the subset of drugs regulated under section 351 of the Public Health Service Act (PHS Act; 42 U.S.C. 262) and includes both CDER-regulated protein drug substances and drug products.

establishments manufacturing protein drug substance (DS) or drug product (DP) during the assessment[3] of an original or supplemental BLA.

2. Instructions for Firm Responses to Form FDA 483

At the end of the PLI or PAI, if a Form FDA 483 is issued, the inspection team lead[4] instructs the establishment's management to submit responses to the observations itemized on Form FDA 483 to the OPMA mailbox OPMABLAInspection483Responses@fda.hhs.gov, with a copy to the inspection team lead, within 15 business days.

3. Communication of Inspectional Results

- The inspection team lead communicates inspectional findings within 2 business days of closing the inspection and provides Form FDA 483 (if issued) with an initial field recommendation to the OPMA Division Director, the inspection team lead's supervisor, and the OPMA mailbox OPMABLAInspection483Responses@fda.hhs.gov.
- In collaboration with the inspection team, the inspection team lead completes the establishment inspection report (EIR), which includes attachments and exhibits.
- The inspection team lead informs the OPMA assessor assigned to the inspection review that the EIR has been completed.

4. Facility Recommendations

The OPMA assessor makes the appropriate final recommendation (to **approve** or **withhold)** when the inspection review is complete.

- The recommendation to **approve** is entered when none of the criteria for withholding apply (see Part V of this compliance program).
- The recommendation to **withhold** is entered when there are significant deficiencies (see Part V of this compliance program).

5. Facility Alerts

- When a PLI or PAI uncovers deficiencies that only affect the manufacturing and control operations relevant to the biological product described in the application, do not enter a potential Official Action Indicated (pOAI) alert in the CDER Informatics Platform.
- When a PLI or PAI uncovers critical or systemic CGMP deficiencies (e.g., deficiencies related to data integrity) that affect manufacturing and control operations for other approved products produced in the establishment, communicate the deficiencies to CDER's Office of Compliance (OC) (CDEROMQPMTRACK@fda.hhs.gov) as soon as possible and discuss

[3] In this compliance program, the term *assessment* is synonymous with *review* and means the process of evaluating and analyzing data and information submitted in an application to determine whether the application meets the requirements for approval and documenting that determination.

[4] See Part II.1.A for more information about inspection team leads and the makeup of the inspection team.

with CDER's OC to determine the appropriate next steps (e.g., a pOAI alert in the CDER Informatics Platform or a follow-up future inspection).[5]

6. Establishment Profile Class Code Updates

The status (acceptable or unacceptable) of profile class codes covered during establishment inspections are managed in accordance with Exhibit 5-14.6.3 in the *Investigations Operations Manual* (IOM).

- Profiles are **not** updated for PLIs or PAIs unless the inspection covers a new profile class code.
- For a PLI or PAI of an establishment with a new profile class code, the inspection team lead can add the new profile class code to the appropriate system and the OPMA assessor can finalize it if the inspection is classified as No Action Indicated (NAI) or Voluntary Action Indicated (VAI) and an **approve** recommendation for the application is made.
- If a PLI or PAI involving a new profile class code results in a **withhold** recommendation, no profile class code recommendation is made. This ensures that the establishment will not be considered an acceptable manufacturer of the biological product described in the application (or related products) until a follow-up inspection, if needed, verifies implementation of appropriate corrective actions or until corrections are verified through other appropriate means (i.e., alternative tools).[6]

7. Other Reporting for Marketed Products at the Inspected Establishment

During a PLI or PAI, if the inspection team obtains information about inadequate adverse drug experience reporting, unapproved drug issues, or postapproval reporting violations (e.g., failure to submit application supplements, biological product deviation reports (BPDRs)), the inspection team should notify OPQ's Office of Quality Surveillance (OQS) and the OC in a timely manner by emailing CDERDossierProgram@fda.hhs.gov and CDERCompliance@fda.hhs.gov and copying CDERBIOTECHINSPECT@fda.hhs.gov.

8. Sample-Related Reporting Requirements

When needed, sample collection during PLIs and PAIs is performed in accordance with IOM (chapter 4) and section 702 of the Federal Food, Drug, and Cosmetic Act (FD&C Act, 21 U.S.C. 372) to ensure evidentiary sample controls are maintained. Sampling can be performed by the establishment's personnel under FDA observation. When official samples are collected for method verification or profile analyses, the inspection team lead should identify them by using the appropriate product/assignment codes (PACs). These samples are then sent to OPQ laboratories for testing (e.g., method verification or profile analysis).

The inspection team lead, when needed, may contact OQS by emailing

[5] For examples of critical deficiencies, see Part V of compliance program 7356.002M—*Surveillance Inspections of Protein Drug Substance Manufacturers*.

[6] See Part II.1.B(3) for more information about alternative tools.

CDERBIOTECHINSPECT@fda.hhs.gov and cc'ing CDERSurveillance@fda.hhs.gov to gain clarity on procedural details for collecting samples during the PLI or PAI.

Contents

PART I—BACKGROUND

1. Applicable Statutes, Regulations, and Guidance

Biological products, including those regulated by CDER, must meet requirements articulated in section 351 of the Public Health Service Act (PHS Act, 42 U.S.C. 262) as codified in 21 CFR parts 600 and 601 to ensure that products are safe, pure, and potent. They must also meet current good manufacturing practice (CGMP) requirements in the FD&C Act and applicable CGMP regulations found in 21 CFR parts 210 and 211. Additionally, combination products with biological product and device constituent parts are subject to the CGMP requirements applicable to each constituent part, which include drug CGMP regulations (21 CFR parts 210, 211, 600 and 601) and the device quality management system regulation (QMSR) (21 CFR part 820).[7]

Regulations for the licensing of biological products include the following:

- Per 601.20(a): "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 in this chapter including but not limited to the good manufacturing practice requirements set forth in parts 210, 211, 600, 606, and 820 of this chapter."
- Per 601.20(d): "A biologics license shall be issued or a biologics license application 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." Consequently, coverage under this compliance program and the application assessment process have been designed to determine whether those requirements have been met.

Although FDA has not issued CGMP regulations specific to DS, all drugs are required to be manufactured in compliance with CGMP per section 501(a)(2)(B) of the FD&C Act (21 U.S.C. 351(a)(2)(B)). As such, FDA's current thinking on CGMP for DS manufacture, including protein DS, can be found in the International Council for Harmonisation (ICH) guidance for industry *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* (September 2016).[8] ICH

[7] See 21 CFR part 820 provisions required by 21 CFR part 4. On February 2, 2024, the CGMP Final Rule for combination products (21 CFR Part 4) was amended to reflect the issuance of the Quality Management System Regulation (QMSR) (21 CFR part 820), which replaces the Quality System regulation (QS regulation) (See 89 FR 7496, available at https://www.federalregister.gov/d/2024-01709). The QMSR amends Part 820, primarily through incorporating by reference the 2016 edition of ISO 13485 (ISO 13485) quality management system requirements. The requirements in ISO 13485, when taken in totality, are substantially similar to the requirements of the QS regulation and provide a similar level of assurance in a firm's quality management system. The QMSR also incorporates by reference Clause 3 of ISO 9000:2015(E), Quality management systems-Fundamentals and vocabulary, (ISO 9000). In addition to incorporating by reference ISO 13485 and ISO 9000, the QMSR establishes additional requirements and provisions that clarify certain expectations and concepts used in ISO 13485. These additions ensure that the incorporation by reference of ISO 13485 does not create inconsistencies with other applicable FDA requirements (Medical Devices; Quality Management System Regulation Technical Amendments (90 FR 55978, December 4, 2025).

[8] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

Q7 does not establish requirements but provides guidance for manufacturers in complying with CGMP for protein DS manufacturing operations. Establishments that follow ICH Q7 generally will be considered to comply with the statutory requirement of section 501(a)(2)(B) of the FD&C Act.

To facilitate the management of postapproval chemistry, manufacturing, and controls (CMC) changes in a more predictable and efficient manner, FDA published ICH guidance for industry *Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management* (May 2021) and its Annexes and draft guidance for industry *ICH Q12: Implementation Considerations for FDA-Regulated Products* (ICH Q12 implementation guidance, May 2021).[9] When ICH Q12 and the ICH Q12 implementation guidance are used jointly with sufficient product and process knowledge and in the context of the risk management principles articulated in ICH guidance for industry *Q9(R1) Quality Risk Management* (May 2023) and an effective quality system as described in ICH guidance for industry *Q10 Pharmaceutical Quality System* (April 2009), applicants and manufacturers have opportunities to manage CMC changes effectively with less need for extensive regulatory oversight before change implementation.[10]

Evaluation of the change management system during an inspection of the establishment's quality system is an important component in FDA's assessment of applications, particularly those that propose the use of ICH Q12 regulatory tools such as established conditions (ECs). The evaluation of an establishment's change management system helps inform FDA's assessment of whether the establishment will manage changes appropriately and facilitate the applicant's ability to appropriately report changes in ECs that are consistent with the applicant's product lifecycle management document or its comparability protocols if submitted in the application.[11] Comparability protocols can be submitted independent of any prior identification of ECs in the original or supplemental application.

Further, FDA employs a risk-based strategy to determine the need for, and timing and conduct of a PLI or PAI in support of the regulatory action on an application. The risk-based approach considers information gained from inspections and utilization of alternative tools, streamlines FDA's oversight of pharmaceutical manufacturing establishments and operations and enables prompt and efficient evaluation of establishments' preparedness to conduct commercial manufacturing operations as described in the application.[12] See Part II.1.B of this compliance program for information about risk-based inspection strategy.

[9] When final, the ICH Q12 implementation guidance will represent FDA's current thinking on this topic.

[10] In this compliance program, the term *quality system* is synonymous with *pharmaceutical quality system* (PQS) as described in ICH Q10. The PQS is a management system to direct and control a pharmaceutical company with regard to quality.

[11] Comparability protocols are synonymous with *protocols* as defined in 21 CFR 601.12(e) and *postapproval change management protocols* as used in ICH Q12. See guidance for industry *Comparability Protocols for Postapproval Changes to the Chemistry, Manufacturing, and Controls Information in an NDA, ANDA, or BLA* (October 2022).

[12] See guidance for industry *Alternative Tools: Assessing Drug Manufacturing Facilities Identified in Pending Applications* (September 2025).

2. General Overview of Biological Product Manufacturing Operations

A. Drug Substance

Proteins—one of the statutory categories of biological products in section 351(i)(1) of the PHS Act—can be extracted and purified from the tissue, fluids, or eggs of animals or transgenic animals. In most cases, however, they are recovered and purified following expression in cell culture. Mammalian and bacterial cells are the most common host cells used to express biological products' protein DS, but yeast, plant, and other cell lines can also be used as the host cell. Most biological products that are recombinantly derived and produced through cell culture or fermentation use a tiered cell banking system. A master cell bank (MCB) is created that expresses the protein. A vial of the MCB is used to manufacture the working cell bank (WCB). During upstream manufacturing operations, cells from a WCB vial are inoculated into a growth medium to begin cell culture or fermentation, and the cell culture is sequentially expanded into increasingly larger vessels up to the production-scale fermentor or bioreactor. Following controlled growth and expression, the crude protein DS is harvested and clarified from the production-scale fermentor or bioreactor at the end of a predetermined culture duration. Depending on the final fermentor or bioreactor type (e.g., fed batch versus perfusion), harvesting can be continuous or performed in batches, with subsequent pooling of the clarified harvested liquid.

Harvesting processes such as centrifugation and filtration are intended to stop cell growth and to separate the protein product and soluble liquid components in the fermentation mixture from the host cells and other debris to condition the resulting fermentor liquid for downstream purification unit operations. When the protein is not secreted into the growth medium (i.e., it remains intracellular), the cells can be subjected to lytic enzymes, or mechanical treatments such as homogenization, to release the protein. In some cases (generally bacterial expression systems), the expressed protein aggregates to form inclusion bodies; therefore, the protein is denatured (unfolded) and renatured (refolded) to produce a soluble, active form of the protein, which is then subjected to further purification through downstream manufacturing operations.

Purification steps can include precipitation, ultrafiltration/diafiltration (UF/DF), and bind-and-elute or flow-through chromatography. These steps are designed to separate the target protein from process- and product-related impurities such as media components; aggregated, low-molecular weight, and misfolded target proteins; host DNA; host cell proteins; and endotoxins). Depending on the host expression system used to produce the protein, there may also be steps to inactivate or clear adventitious agents, such as viruses. These steps include column purification steps and viral inactivation-dedicated steps (i.e., detergent inactivation, low pH hold, viral filtration, and/or heat treatment). Generally, at the end of the purification process, the DS is formulated, filled into the DS container closure system, and stored at the appropriate temperature. The bulk DS (BDS) is then prepared for shipment and use at a DP fill/finish manufacturing establishment.

For some biological products, DS production follows a different process than that outlined above:

- In some cases, individual component amino acids are synthetically coupled to create the protein. After synthesis, the purification steps typically proceed as described above to remove product-related impurities (e.g., isomers, degradation impurities) or process-related impurities (e.g., organic solvents used in the synthesis processes).

- In other cases, the purified protein is conjugated, or chemically linked, to a small molecule drug (e.g., antibody-drug conjugate (ADC)) and may also encompass synthetically derived proteins conjugated to a radioactive molecule or other marker for imaging purposes. Synthetic chemicals such as polyethylene glycol can also be conjugated to the protein to extend protein half-life. In protein-small molecule conjugate manufacturing operations, both the purified protein and the small molecule are considered DS intermediates (DSIs). There are typically two manufacturing operations for conjugated products: First, the protein component is manufactured, as described in the cell growth and purification processes or peptide synthesis process, to yield the protein DSI. This protein DSI is then conjugated to the small molecule intermediate to form the BDS, which is processed into the DP. The processes of protein intermediate production and protein-drug conjugation can be conducted at the same or separate establishments (The inspection coverage guide specific to ADCs is provided in Attachment A).[13]
- For some protein DS, steps include lyophilization or freeze-drying before the final DS fill to improve product stability. Typically, lyophilization starts by decanting the DS (as a slurry or liquid) into trays that are then loaded into the lyophilizer. After lyophilization is completed, the DS is milled to a homogenous powder and filled into the appropriate DS container closure system (e.g., bags or bottles) (The inspection coverage guide specific to lyophilization or freeze-drying is provided in Attachment D).
- Some protein DSIs are precipitated or crystallized as a type of purification step or to reduce volume. These precipitated or crystallized intermediates can sometimes be used as intermediate hold points or, in some cases, can be generated before lyophilization.

B. Drug Product

At the DP facility, the BDS solution can be pooled or, if frozen, thawed and then pooled. If necessary, the BDS can be further formulated. The BDS solution can be filtered through a bioburden reduction filter and then through a 0.2 µm sterilizing filter to create the bulk DP. The sterile filtered bulk DP is aseptically filled into the appropriate sterile container closure system (e.g., vials, prefilled syringes, cartridges), and the filled container is closed with a sterile, suitable stopper to produce DP solution-filled dosage units. The manufacture of some DPs includes a lyophilization step during which the DP dosage units are partially stoppered, and water is removed to produce a powder for reconstitution and dilution before patient administration. DP-filled vials and cartridges are sealed with a cap during crimping. DP-filled cartridges and some prefilled syringes can be further assembled into devices (e.g., autoinjectors, on-body delivery systems). Less frequently, the DP can be tableted or encapsulated. Finally, the DP's primary container closure system is visually inspected, labeled, and packaged into secondary packaging for release and distribution.

[13] Commercial manufacturing operations of small molecules used as intermediates and linkers are not within the scope of this compliance program. For inspectional coverage of their manufacturing operations, refer to compliance program 7346.832—*Preapproval Inspections*.

PART II—IMPLEMENTATION

1. Objective

A. Scope

This compliance program covers PLIs and PAIs of DS and DP manufacturers[14] of CDER-regulated biological products that meet the definition of *protein* articulated in 21 CFR 600.3(h)(6).[15] Some examples of these types of products follow:

- Enzymes.
- Monoclonal antibodies.
- ADCs.
- Fusion proteins (e.g., antibody Fc region-containing fusion proteins).
- Growth factors.
- Cytokines (e.g., interleukins, interferons, tumor necrosis factors).
- Botulinum toxins.
- Insulin and insulin analogues.
- Synthetically derived proteins.

CDER is responsible for conducting PLIs and PAIs covered under this compliance program:

- A **PLI** is an inspection of an establishment (new or existing)[16] that manufactures a new biological product subject to an original application. This includes inspections of establishments that already manufacture other currently approved biological products.
- A **PAI** is an inspection of an establishment (new or existing) that manufactures a licensed biological product for which the applicant has submitted a supplement for a significant manufacturing change (e.g., prior approval supplement) that requires on-site review of the change.

These PLIs and PAIs are conducted by CDER to evaluate establishment readiness for commercial manufacturing operations[17] of biological products or combination products with biological product and device constituent parts described in original and supplemental BLAs under assessment (hereinafter *products of interest*), and ultimately to support regulatory decisions for these

[14] 21 CFR 600.3(t) defines *manufacturer* as "any legal person or entity engaged in the manufacture of a product subject to license under the act" and "...any legal person or entity who is an applicant for a license where the applicant assumes responsibility for compliance with the applicable product and establishment standards."

[15] Under 21 CFR 600.3(h)(6), a protein is any alpha amino acid polymer with a specific, defined sequence that is greater than 40 amino acids in size.

[16] In this compliance program, new establishments are those with no compliance history, and existing establishments are those with a compliance history.

[17] In this compliance program, the term *commercial manufacturing operations* refers to the manufacturing processes resulting in commercial biological product.

applications.[18,19] The inspections help CDER determine whether proposed manufacturing operations and control strategies ensure product quality and conform with licensing requirements, including standards established in applications and applicable CGMP requirements.[20] The compliance program can be used in conjunction with compliance program 7356.002A to cover the evaluation of certain sterile manufacturing operations (e.g., aseptic filling operation).

Under this compliance program, inspection teams within CDER (in collaboration with the Office of Inspections and Investigations (OII), when needed) conduct PLIs and PAIs using the strategy described in Part II.1.B and cover the objectives detailed in Part III. Inspectional coverage outlined in Part III applies to both DS and DP unless specifically noted. Inspection teams include an inspection team lead (typically from OPMA) and, as needed, assessors from other OPQ offices (e.g., Office of Product Quality Assessment III (OPQA III).[21]

If the inspection team discovers systemic CGMP deficiencies during a PLI or PAI, the inspection coverage may be expanded to cover the commercial manufacture of other FDA approved products at the establishment, as time permits. This expanded coverage would generate evidence and appropriate documentation of these deficiencies[22] to support potential enforcement actions for marketed products and to inform future inspection planning and strategy.[23]

B. Strategy

(1) Risk-Based Inspection Determination

In general, PLIs and PAIs are performed to provide assurance that data and information submitted in original and supplemental BLAs under review are accurate and complete and to evaluate whether establishment operations are performed as described in applications under review and in conformance with applicable requirements.

The CDER integrated quality assessment (IQA) team[24] takes a holistic, risk-based approach to determine whether a PLI or PAI is needed for an establishment listed in a BLA. In conducting the risk assessment, the IQA team assesses the manufacturing operations and activities of the facility as described in the application in relation to those previously evaluated or inspected in the facility (e.g., profile codes), evaluates the information about the facility's compliance with CGMP (e.g.,

[18] For the purpose of this compliance program, there is no distinction between inspectional approaches to support approval of original or supplemental 351(a) or 351(k) BLAs. Throughout the rest of this compliance program, the term *application* is used to describe both original and supplemental BLAs, unless a distinction between the two is necessary.

[19] This compliance program covers certain combination products containing both biological and device constituent parts, with coverage determined by the risk of the device component.

[20] See 21 CFR parts 210, 211, and 610 and 21 CFR 600.21, 601.2, 601.20, and 601.22, and 21 CFR parts 4.

[21] Inspections are conducted by officers or employees duly designated by the Secretary who are authorized to conduct inspections under 704(a)(1) under FD&C Act.

[22] See footnote 5.

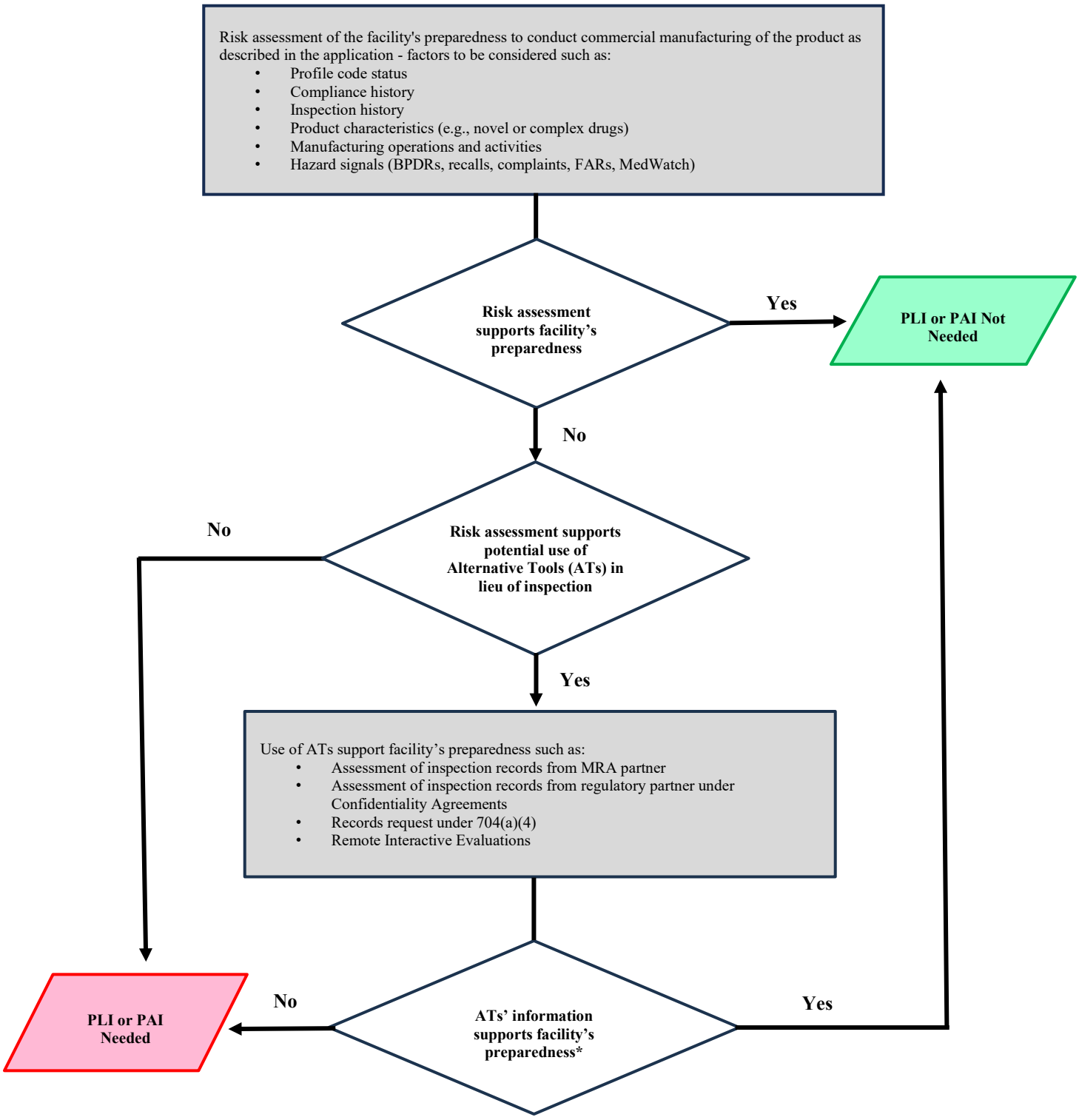
[23] See Facility Alerts in the Reporting Requirements section for additional pOAI details for U.S.-marketed products manufactured at the establishment being inspected.

[24] The IQA team consists of assessors from OPMA and OPQA III but can also include assessors from other disciplines as needed.

compliance status, inspection history), and identifies potential risk associated with the operations for the proposed product (e.g., complexity of the operation, the product itself, or both). Using the knowledge of the facility along with the understanding of the proposed manufacturing operations and activities, as well as relevant hazard signals (e.g., BPDRs, recalls), the IQA team assesses the overall risk of the operations and determines the preparedness of the facility and necessity of an inspection. Based on the risk assessment, the IQA team decides whether existing information is sufficient to demonstrate that the facility meets applicable approval standards, or there is a need for an inspection, a further assessment through alternative tools (see Part II. 1.B(3)), or both, to determine whether the facility is in compliance with applicable statutory and regulatory requirements to meet the approval standards for the BLA.[25] The holistic, risk-based approach used to facilitate a prompt decision on the necessity of a PLI or PAI is illustrated in the flow diagram below:

[25] 351 PHS Act, 42 U.S.C. 262, and 21 CFR parts 4, 210, 211, 600, and 601.

Flow Diagram: Risk-Based Inspection Determination



*Information from ATs may also be used in support of a regulatory action.

(2) Risk-Based Determination of the Inspection Scope and Depth

Once the IQA determines that a PLI or PAI is needed, the IQA team and the inspection team will determine the scope and depth of the inspection by considering the following:

- The novelty and complexity of the product of interest and manufacturing operations and activities described in the application (e.g., combination products with biological and device constituent parts[26]).
- The inherent risk of the product of interest (e.g., a biological product that is classified as highly potent).
- For supplemental applications, the novelty and complexity of the proposed manufacturing change(s), and the risk of the proposed change(s) to the product quality.
- Other considerations (e.g., significance of issues identified during the application assessment, type of inspections (PLI versus PAI)).

The scope and depth of coverage can be adjusted during an inspection based on the inspection team's findings.

(3) Alternative Tools

FDA can use alternative tools to support evaluation of establishments and regulatory decisions regarding applications, such as the following[27]: (1) requesting existing inspection reports and other information from trusted foreign regulatory partners through Mutual Recognition Agreements (MRAs) and other confidentiality agreements;[28] and (2) conducting remote regulatory assessments,[29] including (a) requesting records and other information directly from establishments and other inspected entities related to the application under section 704(a)(4) of the FD&C Act (21 U.S.C. 374(a)(4)), and (b) conducting remote interactive evaluations where appropriate.[30] With regards to this compliance program, a request of records under section 704(a)(4) can be used in lieu of or in advance of a PLI or PAI to support assessment of an application.[31]

---

[26] For inspections of combination products with biological and device constituent parts, per compliance program 7356.000– *Inspections of CDER-led or CDRH-led Combination Products*, the lead center will engage expertise from other agency components, including other center(s), as needed.

[27] For these and other alternative tools, see guidance for industry *Alternative Tools: Assessing Drug Manufacturing Facilities Identified in Pending Applications* (September 2025).

[28] For existing FDA MRAs with the European Union, United Kingdom, and SwissMedic, this includes the use of official inspection reports issued by a recognized authority for manufacturing establishments located inside and outside the territory of the issuing authority. For more information, see https://www.fda.gov/international-programs/international-arrangements/mutual-recognition-agreement-mra.

[29] A remote regulatory assessment is an examination of an FDA-regulated establishment or its records, conducted entirely remotely, to evaluate compliance with applicable FDA requirements. For more information, see guidance for industry *Conducting Remote Regulatory Assessments: Questions and Answers* (June 2025).

[30] See draft guidance for industry *Remote Interactive Evaluations of Drug Manufacturing and Bioresearch Monitoring Facilities* (October 2023). When final, this guidance will represent FDA's current thinking on this topic.

[31] See Staff Manual Guide 6001.1, Agency Program Directives, Volume IV – *Food and Drug Administration Inspection,*

(4) Inspection by Objectives

The objectives identified in this compliance program reflect FDA's risk-based inspectional approach described in Part II.1B(1), building on the knowledge acquired by FDA over decades of inspections. PLIs and PAIs incorporate this risk-based approach in the systematic evaluation of a facility to determine its ability to produce a biological product that meets the identity, strength, quality, safety, purity, and potency standards described in the application.

The primary objectives to be covered on every PLI and PAI follow:

- Objective 1: Application Commitments and Applicable CGMP Requirements Compliance[32]
- Objective 2: Data Integrity Audit

The following table outlines high-level examples of the areas under each objective that should be evaluated during an inspection. Knowledge about the establishment and its capabilities, such as that gained from previous inspections or assessments through alternative tools, should inform the breadth of coverage needed to assess the establishment in support of the subject application(s). Coverage under each objective is described in more detail in Part III of this compliance program. Part V provides administrative/regulatory guidance regarding the evaluation of inspectional findings and examples of Form FDA 483 observations.

High-Level Examples of Areas To Evaluate, by Objective	
Objectives	**Examples**
Objective 1: Application Commitments and Applicable CGMP Requirements Compliance	
Objective 1a: Evaluation of the Effectiveness of Quality System Oversight	• Deviation reports and associated corrective actions and preventive actions • Personnel training and qualification • Document control and distribution records (including batch records) and procedures • Change control activities • Quality and contract agreements

FDA Remote Regulatory Assessment Standard Practices (January 2025). See also guidance for industry *Alternative Tools: Assessing Drug Manufacturing Facilities Identified in Pending Applications* (September 2025).

[32] Inspectional coverage described in Objective 1 is organized following the six-system inspection model. For more information about the six-system inspection model, see guidance for industry *Quality Systems Approach to Pharmaceutical CGMP Regulations* (September 2006) and compliance program 7356.002—*Drug Manufacturing Inspections.*

High-Level Examples of Areas To Evaluate, by Objective	
Objectives	**Examples**
Objective 1b: Evaluation of the Suitability of Facilities and Equipment	• Design and layout of the facility to include qualification and maintenance of room classification • Critical equipment operations, qualification, and cleaning • Product cross-contamination preventive measures • Water and clean steam systems
Objective 1c: Evaluation of Material Management to Support Commercial Manufacturing	• Raw material/component testing, examination, release, and documentation • Critical raw material supplier qualification • Storage, distribution, and quarantine of materials (including cell banks)
Objective 1d: Evaluation of Production and Process Controls in Commercial Manufacturing Operations	• Relevant procedures and records of commercial manufacturing operations • Manufacturing unit operations • Microbial monitoring and control • Process performance qualification results
Objective 1e: Evaluation of the Laboratory Control System	• Out-of-specification investigation and procedures • Test sample and reference standard tracking and storage • Laboratory equipment qualification, maintenance, and calibration • Stability testing program and records
Objective 1f: Evaluation of Packaging, Labeling, Storage, and Shipping Operations	• Packaging and labeling procedures and controls • Storage of in-process and final material • 21 CFR 610.14 identity test fulfillment
Objective 2: Data Integrity Audit	• Computerized systems validation • Completeness and accuracy of CGMP data • Computerized systems access control and audit trail

2. Program Management Instructions

Inspection activities conducted under this compliance program involve a collaborative effort between the IQA team and the inspection team. Both teams should be knowledgeable of the manufacturing operations, testing methodologies, and control strategies used to manufacture the product of interest.[33] They should also be knowledgeable of the applicable statutory and regulatory requirements, including CGMP requirements. When applicable, the OPMA invites investigators from OII to participate in the inspection. The inspection team has access to electronic product applications and should refer to these applications when appropriate. If needed, the inspection team lead can ask product specialists to assist in obtaining copies of relevant sections of paper-based product applications.

[33] See 21 CFR 600.20.

A. Establishment Evaluation and Inspection

- The OPMA assessor verifies that relevant establishments listed in the application are entered in the appropriate component of the CDER Informatics Platform.
- The OPMA assessor places a request in the appropriate component of the CDER Informatics Platform for a PLI or PAI.
    - If a PLI or PAI is not needed based on the risk assessment, the OPMA assessor enters appropriate justification in the appropriate component of the CDER Informatics Platform.
- The inspection team lead schedules the date for the inspection.
- During the inspection, the inspection team documents significant CGMP deficiencies regarding the manufacturing of the product of interest on Form FDA 483, as applicable, with sufficient supporting evidence. Deficiencies that are solely application assessment issues are not included on Form FDA 483.
- All participants on the inspection team are responsible for writing and submitting their portion of the EIR to the inspection team lead, along with supporting exhibits.

B. Scheduling the Inspection

FDA expects the establishment to be ready for an inspection at the time of application submission, and, in general, to be operational and manufacturing the complete product for which a biologics license is sought at the time of inspection.[34] Because of the complexity and duration of biological product manufacturing operations, in most cases, the inspection is scheduled to observe operations considered to be relatively high risk from a quality perspective.

When scheduling a PLI or PAI, the OPQ inspection team considers the manufacturing schedule at the establishment to be inspected as provided by the applicant. The IQA team or inspection team lead, as applicable, generally contacts applicants and establishments to confirm the establishment's manufacturing schedule for the product of interest and to coordinate inspectional logistics, respectively. For original applications, FDA's goal is to notify the applicant of its intent to inspect a manufacturing facility at least 60 days before the inspection and no later than midcycle.[35] For any application, FDA reserves the right to conduct inspections of the manufacturing establishment at any time during the assessment cycle, whether or not the Agency has communicated to the establishment the intent to inspect. If the proposed manufacturing schedule changes, applicants and establishments have been advised to immediately provide a written explanation and provide a new proposed manufacturing schedule.

3. Importance of Application Assessment Integration

Achieving a science- and risk-based approval decision for each application from a pharmaceutical quality perspective requires an integrated assessment of the application and inspection of the

[34] See 21 CFR 600.21 and 601.20(b)(2).

[35] See the PDUFA VII and BsUFA III commitment letters, available on the FDA User Fee Programs website.

establishments named in the application. Because multiple disciplines within the FDA contribute to the integrated assessment, differences of opinion might occur. FDA offices involved in PLIs or PAIs supporting regulatory decisions for applications are covered by an "equal voice" philosophy. Under this philosophy, all appropriate expertise should be considered in the important decisions made about applications, and the perspective from each FDA office assigned a role in assessing and evaluating drug applications is valuable.[36]

[36] See MAPP 4151.8, Rev. 2, *Equal Voice: Collaboration and Regulatory and Policy Decision-Making in CDER* (August 12, 2025).

PART III—INSPECTIONAL

1. Operations

This section provides instructions for the inspection team on evaluating whether establishments comply with licensing requirements, including standards established in applications and applicable CGMP requirements,[37] and on confirming the integrity of data submitted in applications.

The instructions fall under two primary objectives, as listed below. The IQA team and inspection team decide the scope and depth of coverage for each objective based on the risk-based approach and considerations described in Part II.1.B(1) of this compliance program. While conducting inspectional activities related to each objective, the inspection team focuses on the product of interest as defined in the Scope section of this compliance program (Part II.1.A).

The inspection coverage outlined in Part III applies generally to both DS and DP, unless stated otherwise. DP-specific inspection coverage elements are clearly identified in the narrative, when appropriate.[38]

- Objective 1: Application Commitments and Applicable CGMP Requirements Compliance
  - Objective 1a: Evaluation of the Effectiveness of Quality System Oversight
  - Objective 1b: Evaluation of the Suitability of Facilities and Equipment
  - Objective 1c: Evaluation of Material Management to Support Commercial Manufacturing
  - Objective 1d: Evaluation of Production and Process Controls in Commercial Manufacturing Operations
  - Objective 1e: Evaluation of the Laboratory Control System
  - Objective 1f: Evaluation of Packaging, Labeling, Storage, and Shipping Operations
- Objective 2: Data Integrity Audit

This section explains objectives 1 and 2 in more detail, provides coverage instructions for the inspection team, and includes applicable references.

A. Objective 1: Application Commitments and Applicable CGMP Requirements Compliance

(1) Objective 1a: Evaluation of the Effectiveness of Quality System Oversight

Under this objective, the inspection team evaluates the establishment's quality system to determine its ability to provide effective oversight of the commercial manufacturing operations described in the application and to ensure that the quality of the product of interest consistently meets established specifications.

[37] See 21 CFR parts 4, 210, 211, and 610 and 21 CFR 600.21, 601.2, 601.20, and 601.22.

[38] In this compliance program, the inspection coverage specific to DS follows ICH Q7 for meeting statutory CGMP requirements. Inspection coverage specific to DP follows the requirements set forth in 21 CFR parts 4, 210, 211, 600, and 601.

Parts III.1.A(1)(a) through (o) below outline specific areas under Objective 1a that should be verified by the inspection team **as they relate to the product of interest.**

(a) Quality Unit

The establishment's quality system includes the quality unit, which is responsible for, among other duties[39]:

- Establishing a system to release or reject materials, including DS, DP, intermediates, packaging, and labeling materials.
- Approving specifications and instructions provided in master production records.
- Reviewing and approving validation protocols and reports and completed batch production and laboratory control records before release or distribution of materials.
- Ensuring that product quality-related complaints, unexplained excursions, adverse trends, deviations, and failures are fully investigated and resolved.
- Ensuring that there are stability data, generated through an adequate stability program, to support expiry dates and storage conditions.
- Performing product quality reviews.
- Overseeing facilities and equipment, including manufacturing and laboratory testing. This includes ensuring that systems are in place that are used for maintaining and calibrating equipment used in establishments to manufacture or test materials.
- Ensuring that regular internal audits (self-inspections) are performed to confirm that operations conform with CGMP requirements.[40]
- Approving contractors and relevant quality agreements between the applicant and contractors that define in detail the responsibilities of each party.

The inspection team should, at a minimum:

- Verify that the quality unit:
  - Reviews and approves relevant documents—including validation protocols and reports, operating procedures, manufacturing records, laboratory control records, associated deviations, corrective actions and preventive actions (CAPAs), and change controls—before lots are released or distributed.
  - Reviews and approves changes that potentially affect the quality of intermediates or products before implementation.
  - Ensures that there is an adequate number of trained personnel, training programs are periodically assessed, and training is adequate.
- Verify that an effective system is in place for maintaining and calibrating critical equipment.

[39] See 21 CFR 211.22 and ICH Q7, section II.B, Responsibilities of the Quality Unit(s).

[40] See ICH Q7, section II.D, Internal Audits (Self Inspection).

- Verify that an effective system is in place to release or reject materials, including raw materials, intermediates, DS or DP, packaging, and labeling materials.
- Verify that the establishment has adequate oversight in place to detect potential quality issues and respond appropriately to ensure defective products are not released to the market. This includes determining whether the establishment is operating in a state of control employing conditions and practices that ensure compliance with regulatory requirements.
- Verify that the establishment has adequate oversight and a robust change management system to evaluate manufacturing changes and risks associated with them.

FDA can consider the outcomes of these evaluations when assessing whether appropriate regulatory oversight can be maintained for products for which flexible regulatory approaches have been proposed (e.g., in applications with proposed ECs as described in ICH Q12), or when assessing how effectively establishments are applying principles of continual improvement.

References:

- 21 CFR 211.22, 211.25, 211.28, 600.10, 600.12, and parts 601 and 610
- ICH Q7, section II, Quality Management
- ICH Q10
- ICH Q12
- Guidance for industry *ICH Q12 Implementation Considerations for FDA-Regulated Products* (May 2021)
- Guidance for industry *Advancement of Emerging Technology Applications for Pharmaceutical Innovation and Modernization* (September 2017)
- Guidance for industry *Quality Systems Approach to Pharmaceutical CGMP Regulations* (October 2006)

(b) Senior Management Responsibility

Senior management should demonstrate a commitment to quality. This includes a commitment to meeting applicable regulatory requirements (e.g., supporting the quality management system addressing specific requirements for combination products that include device constituent parts (e.g., conducting management reviews to assess the suitability and effectiveness of the quality management system at defined intervals)), developing quality policy, among other aspects.

The inspection team should, at a minimum:

- Evaluate whether the responsibilities and authority of operations and quality organization units are clearly delineated by senior management.
- Evaluate whether management commits appropriate resources (e.g., investigate quality issues and implement appropriate CAPAs, upgrading facilities and equipment, adequate staffing levels).

References:

- 21 CFR 4.4
- ICH Q10, section III, Management Responsibility
- Guidance for industry *Quality Systems Approach to Pharmaceutical CGMP Regulations*

(c) Internal Audits

The establishment should perform regular internal audits to confirm that manufacturing operations are in conformance with CGMP requirements.

The inspection team should, at a minimum:

- Evaluate whether there are written procedures to conduct regular internal audits and critical review of processes and procedures pertaining to manufacturing operations are reviewed and approved by the quality unit and that they are in place and being followed.
- Evaluate whether internal audits are conducted regularly according to an approved, defined schedule.
- Evaluate whether the reporting procedures ensure the internal audit results are reported to management.

Reference:

- ICH Q7, section II.D, Internal Audits (Self Inspection)

(d) Contract Agreements

Applicants and contract manufacturing organizations (CMOs) share the responsibility of ensuring that manufacturing operations are conducted in compliance with CGMP. CMOs are subject to CGMP requirements and may not violate them at the direction of applicants.

Contract agreements can be extremely valuable in delineating the activities of all parties involved. For contract agreements in place, the inspection team should, at a minimum:

- Verify that there is a written and approved contract or formal agreement between the applicant and CMO and other contracted parties (e.g., testing laboratories) defining in detail the CGMP responsibilities of each party, including quality measures and other considerations relevant to the contract agreement.
- Confirm that the contract agreement describes each party's involvement in investigations, CAPAs, and product disposition.
- Verify that the contract agreement indicates that the applicant should be notified by the contracted party of deviations or changes pertaining to or affecting the product or its established conditions.
- Verify that batch production records have been reviewed and approved for batch release in accordance with the quality agreement.
- Confirm that the contract agreement allows for on-site audits of contracted establishments.

References:

- 21 CFR 210.2(b), 211.22(b) and 211.22(d)
- ICH Q7, section XVI, Contract Manufacturers (Including Laboratories)
- Guidance for industry *Contract Manufacturing Arrangements for Drugs: Quality Agreements* (November 2016)

(e) Personnel Training

The establishment is expected to provide adequate training to ensure that personnel are trained and qualified to perform their functions.

The inspection team should, at a minimum:

- Verify that there is an adequate number of trained personnel, including supervisors, for assigned functions and operations.
- Verify that the establishment has adequate standard operating procedures (SOPs) and other training procedures in place to appropriately train personnel on essential documents, including training on changes to SOPs, batch production records, or other pertinent work instructions.
- Verify that training is regularly conducted by qualified individuals and that it covers, at a minimum, the particular operations that the employee performs and applicable CGMP requirements as they relate to the employee's functions.
- Verify that personnel are trained in appropriate sanitation and health habits for the establishment's production processes.
- Verify that training records are maintained.
- Confirm that training is periodically assessed.

References:

- 21 CFR 211.25 and 600.10(b)
- ICH Q7, section III, Personnel

(f) Personnel Gowning and Qualifications

Commercial manufacturing operators are expected to be trained in proper gowning technique.

The inspection team should, at a minimum:

- Evaluate whether appropriate gowning procedures, including those governing hygiene, behavior, and health, have been established and are followed by observing personnel during the inspection. Focus on personnel who might have direct contact with product intermediates or manufacturing operations.
- Verify that personnel with apparent illnesses or open lesions are excluded from manufacturing activities.

- Verify that the establishment's gowning procedure is adequate to prevent cross-contamination when operators move from one product suite to another within the establishment, especially when operators pass from highly potent or toxic compound manufacturing areas to other areas.

References:

- 21 CFR 211.25, 211.28, and 600.10(c)(2)
- ICH Q7, section III.B, Personnel Hygiene

(g) Document Control Procedures

Production, control, and distribution records are expected to be maintained for not fewer than 5 years after the batch records have been completed or 6 months after the latest expiry date of the batch. These records should be readily available during an inspection.

The inspection team should, at a minimum:

- Evaluate whether master production and control records are completed to ensure uniformity from batch to batch according to approved procedure.
- Verify the adequacy of the document control procedures, including issuance, version control, accessibility to manufacturing personnel, and archiving.
- For combination products with biological product and device constituent parts, verify that the manufacturer has established and maintained a design and development file for the device constituent part.

References:

- 21 CFR 211.186, 600.12, and Clause 7.3 and its subclauses of ISO 13485:2016, as required by 21 CFR parts 4.4(b)(1)(ii)
- ICH Q7, section VI, Documentation and Records

(h) Batch Production Record Review and Control

Master and batch production records are expected to include complete information related to batch production and control. The quality unit should review and approve these batch production records to determine compliance with established, approved written procedures before a batch is released or distributed.

The inspection team should, at a minimum:

- Verify that manufacturing operations use the same unit operations and control strategies described in the batch production records. (The inspection team should do this while observing the manufacturing operations being performed, if possible.)
- Confirm that the batch production records submitted in the application correspond to the batch production records used at the establishment (as appropriate; batch production records can be updated following application submission).

- Verify that the methods listed in the batch production records align with those described in the application (including those used to assess the quality and stability of the batch, in-process materials, intermediates, and raw materials, as applicable).
- Verify that the master production record provides sufficient instructions for manufacturing operations if such information is not provided in other procedures. In addition, confirm that there are no operations or procedures performed that are not described in the batch production records or incorporated by reference in other quality unit-approved procedures.
- Verify that manufacturing unit operations recorded in the batch production records are within validated operational parameters as described in the application.
- Verify that all equipment is listed in the batch production records and that the equipment meets performance parameters.
- Verify that the quality unit has reviewed deviation, investigation, and out-of-specification (OOS) reports as part of the batch production record review.
- Verify that the documentation system for batch production records is appropriately validated and controlled to prevent unauthorized access and changes to data.
- For computerized batch production records that list exceptions that will not be part of a deviation investigation, review the exceptions for their potential impact on the product.
- Verify that the quality unit reviews and approves relevant documents, including manufacturing and laboratory control records, before releasing lots for distribution.
- For combination products with biological product and device constituent parts, verify that the quality unit has procedures to conduct formal documented reviews of design and development results to ensure that the device constituent parts design meet the established standards. Also, verify that the design and development reviews are conducted by personnel with expertise in relevant operational functions for the design and development stage being reviewed, as well as specialists and the individual(s) who does/do not have direct responsibility for the design and development stage being reviewed. In addition, verify that the results of a design and development review, including identification of the design, date, and individuals performing the review, are documented appropriately in the design and development file.

See Objective 1d in Part III.1.A(4) of this compliance program for further inspectional activities regarding batch production records.

References:

- 21 CFR 211.180(e), 211.188, 211.192, and Clause 7.3 and its subclauses of ISO 13485:2016, as required by 21 CFR parts 4.4(b)(1)(ii)
- ICH Q7, section VI.E, Batch Production Records (Batch Production and Control Records)

(i) Computerized Systems

Computerized systems used to support commercial manufacturing operations are expected to have controls to ensure that data generated by these systems are reliable, accurate, complete, and secure.[41] They should have sufficient controls to prevent unauthorized access and unauthorized changes to data. If changes are made, computerized systems should be able to trace the change, who made it, and when it was made and should also be able to capture the original entry before the change was made. Changes to computerized systems should be made according to an approved change procedure and should be formally authorized, documented, and validated. Records should be kept of changes, including modifications and enhancements made to hardware, software, and other critical components of the system.

The inspection team should, at a minimum:

- Confirm that computerized systems involved in product manufacturing operations are validated for their intended use.[42]
- Verify that written procedures are available for the operation and maintenance of computerized systems.
- Verify that user access controls to computerized systems are appropriately configured and enforced to prohibit unauthorized access, unauthorized changes to data, and deletion of data.
- Verify that the system administrator role and any rights to alter files and settings are assigned to personnel independent from those responsible for the record content and verify that the quality unit maintains and controls a list of authorized individuals for each system.
- Verify that audit trail functionalities for computerized systems are properly configured, enabled, and locked and that audit trails for critical data are independently reviewed during data review and batch release. Verify that the production and control records, which include audit trails, have been reviewed and approved by the quality unit. Verify that aborted or incomplete analyses/runs are captured in audit trails and that they have been investigated and justified.
- Verify that changes to computerized systems are authorized, documented, and validated and that records of changes are maintained to ensure that the computer system remains in a validated state.
- Verify that original manufacturing and testing data and relevant metadata, including audit trails, are backed up periodically using a secure and commercial process, and confirm that efficient, reliable restoration of the backup/archived data is verified.

References:

- 21 CFR 211.68(b) and 211.192

[41] Computerized or related systems can refer to computer hardware, software, peripheral devices, networks, cloud infrastructure, personnel, and associated documents (e.g., user manuals, SOPs).

[42] See ICH Q7, which defines *validation* as providing assurance that a specific process, method, or system will consistently produce results meeting predetermined acceptance criteria.

- ICH Q7, section V.D, Computerized Systems
- Guidance for industry *Data Integrity and Compliance With Drug CGMP: Questions and Answers* (December 2018)
- Guidance for industry and FDA staff *General Principles of Software Validation* (January 2002)

(j) Change Management

Changes to manufacturing operations, controls, materials, analytical methods, computer hardware and software, facilities, and equipment are expected to be evaluated for their potential to impact product quality. CGMP-related changes that can potentially affect product identity, strength, quality, safety, purity, and potency should be implemented following approval by the quality unit and other relevant disciplines.

Evaluation and verification of an establishment's change management system are particularly important when an applicant proposes specific ECs for the application, comparability protocols to modify ECs, or the reporting categories for ECs differ from FDA regulations and guidance.

The inspection team should, at a minimum:

- Determine whether there is a strategy for evaluating the effect that changes in manufacturing operations have on the product's identity, strength, quality, safety, purity, and potency.
- Verify that changes are reviewed and approved by the quality unit and relevant disciplines and that if the establishment conducts additional testing and validation studies, they are appropriate to justify the changes.
- Verify that there is a robust change control system and major changes made to manufacturing operations after process validation are reported with the appropriate reporting category to FDA.
- For combination products with biological product and device constituent parts, verify that the quality unit and relevant disciplines review and approve procedures for the identification, documentation, validation, and, where appropriate, review and approve design and development changes of device constituent parts before their implementation.

References:

- 21 CFR 211.100, 211.160, 601.12, and Clause 7.3 and its subclauses of ISO 13485:2016, as required by 21 CFR parts 4.4(b)(1)(ii)
- ICH Q7, section XIII, Change Control
- ICH Q9(R1)
- ICH Q10
- ICH Q12
- Guidance for industry C*hanges to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products* (July 1997)

- Guidance for industry *CMC Postapproval Manufacturing Changes To Be Documented in Annual Reports* (March 2014)

(k) Validation Protocols and Reports

Manufacturing and testing in conformance with CGMP requirements require validation activities; manufacturers are expected to collect and evaluate data demonstrating that equipment, processes, and test methods are capable of consistently performing as intended to produce high-quality product for commercial distribution. For biological products, applications need to include sufficient data and information demonstrating that the commercial manufacturing process consistently delivers a product that is safe, pure, and potent. The demonstration of consistency is supported by data and information derived from process validation Stage 2 – process performance qualification (PPQ). For combination products with biological product and device constituent parts, pharmaceutical development practices such as *Quality by Design*[43] can be used and built upon to demonstrate compliance with design and development requirements. However, the manufacturer should have documentation supporting their claim that the device constituent part design and control procedures are in alignment with the design and development requirements.

The quality unit is responsible for overseeing validation activities, including reviewing and approving validation protocols and reports.

The inspection team should, at a minimum:

- Verify that the quality unit reviews and approves validation protocols and reports and ensures that procedures are executed as written.
- Verify that validation reports contain results that meet predetermined acceptance criteria as submitted to FDA.
- Determine whether deviations or investigations occurred during execution of the validation protocol and, if so, whether the deviation investigations and associated CAPAs and change controls were adequate. Consider the potential impact of the deviation on FDA's assessment of validation data submitted to the application.
- Determine whether associated change management activities are indicative of inadequate validation efforts.
- For combination products with biological product and device constituent parts, verify that the manufacturer has procedures that describe the process for design and development verification and design and development validation for each device constituent part specific to its use and ensure that the procedures are executed as written.[44]

References:

[43] See the guidance for industry *Q8(R2) Pharmaceutical Development* (November 2009).

[44] Design and development verification and design and development validation data are evaluated during BLA assessment.

- 21 CFR part 211, subparts F—Production and Process Controls and I—Laboratory Controls, 21 CFR 601.2(a), and Clause 7.3 and its subclauses of ISO 13485:2016, as required by 21 CFR parts 4.4(b)(1)(ii)
- ICH Q7, section XII, Validation
- Guidance for industry *Process Validation: General Principles and Practices* (January 2011)

(l) Product Review

Products are expected to be regularly reviewed for quality with the objective of verifying the consistency of manufacturing operations after approval. These product reviews are expected to be performed and documented at least annually and generally include a review of the following:

- Critical in-process controls.
- Trending of release data.
- Batches that failed to meet established specifications.
- Critical deviations or nonconformances and related investigations.
- Changes introduced to commercial manufacturing and testing operations.
- Results of the stability monitoring program.
- Environmental monitoring data.
- Utility systems (e.g., water, gas) monitoring data.

The inspection team should, at a minimum:

- Verify that the establishment has developed procedures or will sufficiently incorporate the pending drug into existing procedures to conduct product reviews at least annually.
- Determine whether the product review procedure is comprehensive and covers relevant quality reports.

References:

- 21 CFR 211.180(e)
- ICH Q7, section II.E, Product Quality Review

(m) Stability Program

A stability monitoring program is expected to be in place to confirm product stability. In general, at least one product batch is subjected to stability testing annually, and additional batches should be placed on stability following major deviations or anomalies that occur during production.

The inspection team should, at a minimum:

- Verify that stability records are aligned with data and information submitted in the application.

- Verify that procedures are in place and are followed within the establishment, as appropriate, for the storage and testing of stability samples as specified in the application.
- Verify that validation and continuous monitoring of stability chambers used for storage of stability samples are operated and maintained at storage conditions specified in the application. Review deviations related to stability chambers.
- During PAIs, verify that adequate investigation and documentation of stability failures occur and, if necessary, stability failures are reported through BPDRs.

References:

- 21 CFR 211.137, 211.166, 211.170, 211.194, and 610.50
- ICH guidance for industry *Q1A(R2) Stability Testing of New Drug Substances and Products* (November 2003)
- ICH guidance for industry *Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products* (July 1996)
- ICH Q7, section XI.E, Stability Monitoring of APIs[45]

(n) Deviation and Failure Investigations

The effectiveness of the establishment's quality system is in part evaluated based on the established practices in place to mitigate and prevent excursions, adverse trends, deviations, failures, and changes in product quality. When excursions, adverse trends, deviations, or failures occur, the establishment's quality system is expected to conduct thorough and meaningful investigations with scientifically supported conclusions, relevant CAPAs, and associated change controls as needed. The effectiveness of CAPAs is expected to be documented and evaluated by the quality unit in a timely manner.

The inspection team should, at a minimum:

- Verify that the quality unit reviews production records to investigate unexplained excursions, adverse trends, deviations, and failures and that it fully investigates errors. Verify that the quality unit's investigation includes an evaluation of relevant product batches, including aborted batches.
- Verify that the establishment has and follows quality unit-approved procedures for handling deviation-and-failure investigations.
- Evaluate a sufficient number of investigation records across multiple systems for commercial manufacturing operations to confirm the adequacy of investigations, product disposition decisions, and CAPA implementations.
- For combination products with biological product and device constituent parts, verify that the manufacturer has established and maintained procedures for implementing analysis of data, improvement, and complaint handling to address nonconformance associated with the device constituent part and the combination product as a whole. Verify that there are effectiveness

[45] API=active pharmaceutical ingredient.

checks that consider the combination product as a whole even if the analysis of data, improvement, and complaint handling applies only to a single constituent part.

References:

- 21 CFR 211.192, and Clause 7.3 and its subclauses of ISO 13485:2016, as required by 21 CFR parts 4.4(b)(1)(iv)
- ICH Q7, section II.A, Principles
- ICH Q9(R1)

(o) Product Complaints, Adverse Event Reports, BPDRs, Recalls, and Returns

Adequate procedures are expected to be in place to handle product complaints, adverse event reports (AERs), BPDRs, recalls, and returns.

The inspection team should, at a minimum:

- Verify that adequate procedures are in place for proper handling of product complaints, AERs, BPDRs, recalls, and returns.
- If applicable, review records of product complaints, AERs, BPDRs, recalls, and returns and verify if approved procedures were followed, adequate investigations were conducted, and CAPAs were implemented.

References:

- 21 CFR 7.40, 211.180(e)(2), 211.198, 600.14, and 600.80
- ICH Q7, section XV, Complaints and Recalls
- Guidance for industry *Biological Product Deviation Reporting for Licensed Manufacturers of Biological Products Other than Blood and Blood Components* (October 2006)
- Compliance program 7356.002M—*Surveillance Inspections of Protein Drug Substance Manufacturers*[46]

(2) Objective 1b: Evaluation of the Suitability of Facilities and Equipment

Under this objective, the inspection team evaluates a facility's design, layout, and equipment—including utilities and equipment qualification, calibration, and maintenance—supporting the commercial operations described in the application. During the inspection, the inspection team observes the commercial manufacturing operations related to the product of interest and verifies that they are performed in the areas and with the equipment as described in the application.

Facilities might conduct aseptic processing operations (e.g., DP filling operations) where product sterility must be maintained.[47] In such cases, the inspection team should refer to compliance program

[46] Compliance program 7356.002M applies only to surveillance inspections of **CDER-regulated** protein DS manufacturers.

[47] 21 CFR 211.113(b).

7356.002A to appropriately evaluate aseptic processing operations performed for DP operations and, when appropriate, for DS operations. In addition, the inspection team should refer to FDA's recommendations regarding aseptic processing in the guidance for industry *Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice* (September 2004).

Parts III.1.A(2)(a) through (c) below outline specific areas under Objective 1b that should be verified by the inspection team **as they relate to the product of interest.**

(a) Facilities

The buildings and facilities housing manufacturing operations are expected to be of suitable size and design and are expected to be constructed to facilitate cleaning, maintenance, and operations that are appropriate for the type of manufacturing being performed. Facilities are expected to be designed to minimize potential exposure of the product stream to contaminants. Adequate changeover activities are critical when commercial manufacturing operations are conducted in a multiproduct establishment.

The inspection team should, at a minimum:

- Review the design and layout of the facility (e.g., personnel flow, material flow, equipment flow, product flow, waste flow, area classifications) on paper and on the manufacturing floor to confirm their suitability.
- Verify: (a) appropriate segregation with adequate space to prevent mix-ups, (b) appropriate area classification, and (c) adequate pressure differential controls (e.g., cascades, sinks, or bubbles for personnel/material airlocks) are established to prevent cross-contamination and microbiological contamination.
- Verify that pertinent buildings and facilities are in an appropriate state of repair during the inspection walk-through.
- Verify the suitability of the type of water used in manufacturing.
- Verify that clean utilities are qualified and monitored and that actions are taken when limits are exceeded.
- Verify that cleaning and disinfecting procedures are sufficiently detailed (e.g., concentrations of cleaning and disinfectant solutions, contact time, use of sporicidal agents) and that they adequately ensure microbial control based on environmental monitoring data.
- Evaluate whether a response plan is in place to guide decontamination activities during catastrophic spills and potential viral contamination events.

References:

- 21 CFR 211.42 through 211.58, 211.63 through 211.72, and 600.11(a) and (b)
- ICH Q7, sections IV.A, Design and Construction, and V, Process Equipment
- Guidance for industry *Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice*, section IV, Buildings and Facilities

i. HVAC system/Area classifications

Heating, ventilation, and air conditioning (HVAC) systems are essential for providing suitable manufacturing environments for biological products, which are usually manufactured using mammalian cell cultures that are susceptible to contamination by adventitious agents (e.g., viruses, mycoplasma). HVAC systems are expected to be designed to contain or protect biological products from risks of contamination and cross-contamination.

The inspection team should, at a minimum:

- Determine if the HVAC system, including air-handling unit segregation, area classifications, and pressure differential controls, is appropriately designed to prevent cross-contamination and the spread of adventitious agents.
- Review environmental monitoring data (see Part III.1.A(2)(a)(v)—Environmental monitoring for more details) and pressure differential data to determine whether there is adequate establishment control.
- Verify that the cell culture/fermentation microbial contamination rates and in-process bioburden and endotoxin data for harvesting and purification confirm the suitability of the environmental classifications for production areas.
- Determine whether there is environmental segregation of manufacturing operations that occur before viral clearance/inactivation and those that occur after viral clearance/inactivation, with separate air handling units or a once-through HVAC system. In the case where there is no physical segregation of pre- and post-viral operations, evaluate whether procedural controls or other controls are in place to sufficiently mitigate viral contamination risks and that available information and data support this practice.
- Determine whether there is physical segregation of live cell and cell-free areas for microbial-derived products.
- Determine whether there are adequate records on the HVAC system's installation, qualification, and recertifications (e.g., documentation of testing for flow laminarity, air velocity, particle counts, leaks). Review the qualification and recertification data and confirm that high-efficiency particulate air (HEPA) filters are tested for integrity at installation and recertified at least annually.

References:

- 21 CFR 211.46(a) through (c) and 600.11(a)
- ICH Q7, section IV.B, Utilities
- Guidance for industry *Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice,* section IV, Buildings and Facilities

ii. Water system and clean steam system

Water used in manufacturing is expected to be suitable for its intended use. In general, water for injection (WFI) is used in the production of biological products. Purified water can be used for initial equipment rinses when cleaning. Purified water can also be used in fermentation and early-stage

purification steps for microbial processes using Gram-negative organisms. The downstream purification process is generally designed to remove levels of endotoxin generated by the microbial cultures, after which it is more appropriate to use WFI. It may also be possible to justify the suitability of purified water in other cases, such as fermentation processes for fungal or Gram-positive host organisms. However, WFI should generally be used for all DS manufacturing steps of mammalian cell-derived products. WFI is expected to have appropriate specifications for physical/chemical attributes, total microbial counts, objectionable organisms, and endotoxins.

Clean steam condensate quality specifications should not be inferior to compendial (United States Pharmacopeia (USP)) standards for WFI for physical/chemical attributes and endotoxins.

The inspection team should, at a minimum:

- Verify that the primary source of water complies with applicable standards (e.g., U.S. Environmental Protection Agency, World Health Organization, European Union) and that water production systems (including purified water and WFI) produce water of a quality that is suitable for its intended use.
- Verify the adequacy of the water system's design (e.g., no dead legs) and qualification.
- Evaluate the adequacy of the facility's water system maintenance program (e.g., no visible leaks) and related procedures to determine whether the program maintains a constant state of control over the system.
- Verify the adequacy of the facility's water monitoring program and associated procedures and data. Similarly, determine whether the establishment adequately investigates and documents water and clean steam monitoring excursions and implements appropriate CAPAs in a timely manner.
- Determine whether the level of steam saturation or dryness, amount of non-condensable gas, and amount of superheat are suitable for the intended pure steam application.

References:

- 21 CFR 211.48, 211.63, 211.67(b), 211.100(a) and (b), and 211.192
- ICH Q7, section IV.C, Water
- Guidance for industry *Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice,* section VI, Components and Containers/Closures
- USP General Chapter <1231> *Water for Pharmaceutical Purposes*

iii. Other utilities

Other utilities (such as process gases) that can impact product quality are expected to be qualified and appropriately monitored as actions need to be taken when limits are exceeded. These utilities can be used in both upstream and downstream manufacturing operations.

The inspection team should, at a minimum:

- Review the sampling points, frequency of testing, acceptance criteria, monitoring data, and maintenance records.

- Verify the locations of the filters used to remove bioburden and particulates (if applicable) from process gases during manufacturing operations and verify the frequency of integrity testing and replacement of these filters.

References:

- 21 CFR 211.46 and 600.11
- ICH Q7, section IV.B, Utilities

iv. Pest control

A pest control program is necessary to prevent infestations and contamination of raw materials, equipment, and other components that can impact manufacturing operations.

The inspection team should, at a minimum:

- Verify the adequacy of the establishment's pest control program.
- Evaluate the adequacy of pest monitoring limits and determine whether the frequency of trap inspections is adequate.
- Evaluate the establishment's pest control data, pest control deviations, and associated investigations and CAPAs.

References:

- 21 CFR 211.56
- ICH Q7, section IV.G, Sanitation and Maintenance

v. Environmental monitoring

Establishments should use appropriate environmental controls to minimize the risk of contamination. When determining acceptance criteria for air quality and monitoring frequency, establishments should factor in the stages of production and the types of operations conducted in specific areas (open, closed, or contained systems).

The inspection team should, at a minimum:

- Determine the adequacy of the establishment's environmental monitoring program, including monitoring methods, locations, frequency, and alert and action limits. Confirm monitoring methods and locations on the manufacturing floor.
- Review environmental monitoring data and trend reports to verify that the HVAC control and cleaning and sanitization programs are adequate and effective (see Part III.1.A(2)(a)(i)—HVAC system/Area classifications for more details).
- Determine whether the establishment promptly responds to, adequately investigates, and documents environmental monitoring excursions and performs appropriate CAPAs in a timely manner.

References:

- ICH Q7, section XVIII.A, General

- Guidance for industry *Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice*, section X.A, Environmental Monitoring

(b) Equipment

Manufacturing equipment is expected to be of appropriate design and size and be suitable for its intended use. A cleaning, sterilization/sanitization (where appropriate), and maintenance program is expected to be in place and followed at appropriate intervals to prevent equipment malfunctions and contamination.

The inspection team should, at a minimum:

- Confirm that product contact surfaces are constructed from materials that are not reactive, additive, or absorptive.
- Confirm that substances associated with equipment operation, such as lubricants, heating fluids, and coolants, do not contact products directly or alter their quality.
- Confirm that equipment failures and deviations related to equipment function are evaluated for their impact on product quality.
- Verify that critical equipment specified in the application is the same equipment used during commercial manufacturing operations.
- Confirm that the establishment has effective preventive maintenance and calibration programs for its equipment.
- Review records associated with the qualification, requalification, preventive maintenance, calibration, cleaning, and sterilization/sanitization of manufacturing and laboratory testing equipment, as applicable.
- Verify the effectiveness of microbial control and equipment sterilization/sanitization procedures as demonstrated by low rates of cell culture/fermentation process contamination and acceptable in-process harvesting and purification bioburden and endotoxin data.
- Verify that deviations related to manufacturing equipment have been appropriately investigated and CAPAs implemented in a timely manner. Confirm that the effectiveness of CAPAs after implementation has been evaluated and documented. As appropriate, verify the adequacy of the implemented CAPAs on the manufacturing floor.
- For protein DS manufacturing using critical equipment with specialized qualification activities (e.g., fermentors or bioreactors, centrifuges, depth filtration, UF/DF, column chromatography equipment), evaluate the verification activities related to equipment maintenance and requalification/continued performance.[48] This includes:
    - Adhering to chromatography resin or UF/DF membrane lifetimes as established and concurrently validated at commercial scale, including a periodic review of the qualified state and requalification of these lifetimes as needed.

[48] Information on qualification activities is also evaluated as part of the application assessment.

- Ensuring that instruments used to measure or monitor critical in-process parameters such as pH or dissolved oxygen are maintained and calibrated at appropriate intervals using appropriate standards. These calibration procedures should also contain limits for accuracy over the relevant range and limits for precision.

References:

- 21 CFR 211.63, 211.65, 211.67, and 211.113
- ICH Q7, section V.A, Design and Construction
- Guidance for industry *Sterile Drug Products Produced by Aseptic Processing —Current Good Manufacturing Practice*, section IX.C, Sterilization of Equipment, Containers, and Closures
- Compliance program 7356.002A—*Sterile Drug Process Inspections*
- International Organization for Standardization (ISO) 17665, *Sterilization of Health Care Products—Moist Heat —Requirements for the Development, Validation and Routine Control of a Sterilization Process for Medical Devices* (2024)

i. Equipment cleaning

Equipment used to manufacture products are expected to be cleaned, stored, and, where appropriate, sanitized or sterilized to prevent contamination or carryover of a material that would alter product identity, strength, quality, safety, purity, and potency. Equipment cleaning validation studies are expected to include an evaluation of the cleaning efficacy for dedicated and shared equipment. In general, cleaning validation includes preestablished residual limits assessed by assays demonstrated to detect residues. For shared equipment and utensils, the cleaning validation ensures that there is no carryover between products such that product safety and efficacy are compromised. A periodic monitoring program is expected to be in place to verify that equipment and utensils continue to be effectively cleaned.

The inspection team should, at a minimum:

- Review equipment cleaning validation data to determine the adequacy of the cleaning-in-place system, washer cycles, and manual cleaning operations in removing cleaning agents and product residues. Highest priority should be placed on equipment shared with other products and on equipment used to process high-risk products (e.g., spore-forming organisms or highly potent or toxic products).[49] If cleaning validation has not been completed, evaluate whether the establishment has adequate cleaning verification procedures in place. Verify that cleaning validation and verification includes a visual inspection (e.g., for lyophilizers, a periodic monitoring for leaks of silicon oil or alternate shelf heat fluids).
- Verify that the cleaning validation acceptance criteria are suitable for the equipment's intended use.
- Verify that the validated cleaning procedures are followed during routine equipment cleaning.
- Review the frequency of and resulting data for periodic equipment cleaning verification.

[49] See Attachments B and C of this compliance program.

- Review the validation of equipment's dirty and clean hold times, if applicable. Confirm adherence to the validated dirty and clean hold times.
- Visually check equipment cleanliness.

References:

- 21 CFR 211.67 and 600.11(b)
- ICH Q7, section V.B, Equipment Maintenance and Cleaning
- Guidance for industry *Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice*, sections VI, Components and Containers/Closures, and VII, Endotoxin Control

ii. Equipment sanitization and sterilization

Establishments are expected to use sterile equipment for cell culture and fermentation processes. Equipment used in purification processes can be sterilized or sanitized to prevent cross-contamination.

The inspection team should, at a minimum:

- Review the validation and requalification records of sterilization processes for cell culture and fermentation equipment as detailed in the application to determine whether there is effective equipment sterilization.
- Verify the sterilization and/or sanitization validation and requalification of purification equipment to determine whether there is effective microbial control of equipment.

References:

- 21 CFR 211.67
- Guidance for industry *Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice*, sections VI, Components and Containers/Closures, and VII, Endotoxin Control
- ICH Q7, sections XVIII, Specific Guidance for APIs Manufactured by Cell Culture/Fermentation

iii. Equipment maintenance and calibration

Equipment used in the manufacture and testing of raw materials, in-process materials, intermediates, and products are expected to be calibrated according to written procedures and an established schedule. The equipment maintenance and calibration schedule should be based on the criticality of the equipment or the frequency of the equipment use to ensure that relevant range and limits for precision are maintained as appropriate. Equipment calibrations are expected to be performed using certified standards or equipment manufacturer's recommended standards. Deviations from approved standards of calibration involving critical instruments should be investigated to determine if those deviations could have influenced the determination of the product quality.

The inspection team should, at a minimum:

- Determine if the procedures and schedules of the equipment maintenance program are adequate to support the equipment's intended use.
- Confirm that appropriate documentation is maintained.
- Verify that appropriate and timely actions are taken in response to identified or potential equipment issues or deviations.
- For manufacturing and laboratory equipment, verify that the establishment follows a calibration SOP that includes:
  - Specific directions on how to conduct the equipment calibration.
  - Limits for the equipment's accuracy and precision.
  - A schedule for the equipment calibration that details its frequency.
  - Provisions for implementing CAPAs and an evaluation of the impact on product quality involving batches affected by calibration deviations.
- Verify that calibration standards are maintained, and that current calibration status is known and verifiable.
- Evaluate calibration records.
- For disposable or single-use equipment:
  - Verify that disposable equipment has been appropriately qualified (e.g., for extractables/leachables, compatibility, and other suitability issues).
  - Verify that appropriate and timely actions are taken in response to disposable equipment leakage incidents and that the incidents are not recurring.
  - Confirm that there is an approved SOP to address leakage incidents involving disposable containers. Verify that the SOP includes provisions for evaluating and addressing contamination and cross-contamination of buffers, media, cell cultures, in-process intermediates, and DS affected by the leakage.

References:

- 21 CFR 211.58, 211.67, and 211.68
- ICH Q7, section V.C, Calibration

(c) Cross-Contamination Prevention

Cross-contamination is a risk to product safety. Cross-contamination can occur through mix-ups, retention, mechanical transfer, and airborne transfer in a multiproduct establishment.

The inspection team should, at a minimum:

- Evaluate the establishment's cross-contamination prevention measures, including HVAC design and area segregation as described in Part III.1.A.(2)(a)i of this compliance program.

- Determine whether changeover procedures (e.g., personnel, equipment, product) are appropriate to prevent cross-contamination and mix-ups.
    - Obtain a list of changeover activities and determine whether procedures are followed and are adequate. Verify that shared equipment and areas are cleaned and released for use according to quality unit-approved procedures to prevent mix-ups and cross-contamination of raw materials, equipment, and products.
    - Verify that adequate cleaning procedures for shared product contact equipment are in place to prevent product carryover. Verify that acceptance criteria for residuals are adequately calculated and justified. Pay special attention to changeover of production areas from one product with a higher risk profile (e.g., highly potent or toxic product) to another product.
    - For products for which cleaning validation has not been completed, confirm that cleaning verification is conducted for shared equipment during changeover. Verify that cleaning verification data from previous changeover processes are documented in sufficient detail.
- Verify that adequate procedures are in place to govern the flow of products, raw materials, personnel, waste, and equipment to prevent cross-contamination. Evaluate product crossover points that might allow cross-contamination between different products.
- Observe personnel working in more than one area and verify that employees are following appropriate cross-contamination measures and have been trained to take adequate precautions to prevent cross-contamination when they pass from one area to another.
- Evaluate crossover points that might allow cross-contamination between different process steps. Of particular importance are crossover points between upstream and downstream steps and crossover points between pre- and post-viral clearance steps.

References:

- 21 CFR 211.42(b) and (c)
- ICH Q7, section IV.D, Containment
- International Society for Pharmaceutical Engineering (ISPE) Baseline Guide Volume 7, *Risk Based Manufacture of Pharmaceutical Products (Risk-MaPP)* (2017)

(3) Objective 1c: Evaluation of Material Management to Support Commercial Manufacturing

Under this objective, the inspection team evaluates the control of materials (e.g., raw materials, cell lines) used in the commercial manufacturing operations described in the application.[50]

References:

- 21 CFR 211.42(a), 211.58, 211.80, 211.82, 211.84 through 211.94, 600.11(h), and 601.2
- ICH Q7, section VII, Materials Management

[50] Coverage of the water system and process gases is provided under Objective 1b of this compliance program.

Parts III.1.A(3)(a) through (d) below outline specific areas under Objective 1c that should be verified by the inspection team **as they relate to the product of interest.**

(a) Receipt, Inventory, and Storage of Materials

The establishment is expected to have adequate written procedures for the receipt, identification, quarantine, handling, sampling, storage, and approval or rejection of materials. Materials to be used in commercial manufacturing operations should be stored under conditions that are appropriate to prevent degradation, contamination, and cross-contamination. The establishment's warehouses and storage areas are expected to be maintained in a clean and orderly manner and should be of suitable size and design to accommodate appropriate materials management.

Materials are expected to be stored off the warehouse floor and, when appropriate, suitably spaced to permit cleaning and inspection. Inappropriate storage conditions increase the risk that critical materials (e.g., raw materials) or equipment can become the source of unintended variability, which could affect the product's identity, strength, quality, safety, purity, and potency.

The inspection team should, at a minimum:

- Observe receiving, quarantine, sampling, and storage areas to verify the appropriate handling and inventory of materials coming into the establishment as specified in the application.
    - Verify that materials are stored under conditions (e.g., light exposure, temperature, humidity) that are appropriate to prevent deterioration and contamination (microbial or otherwise) and that they are protected from rodents and other pests.
    - Verify that the unpacking and handling of materials, instruments or equipment is performed following approved procedures that safeguard equipment integrity (e.g., protecting from damage by sharp tools, preventing damaging or kinking flexible tubing).
    - Confirm that storage areas are appropriately sized and spaced to allow for cleaning and inspection.
    - Verify that appropriate expiry or retest dates have been assigned to materials in storage areas and that they are clearly identifiable.
- Confirm during an inspection walk-through that rejected materials are clearly identified and controlled under a quarantine system that prevents unauthorized use.
- Verify that there are inventory control processes that account for material storage, distribution controls, quarantine practices, and documentation for incoming materials. Confirm that the control processes adequately ensure the traceability of material lots used in commercial batch production and prohibit the use of quarantined, expired, or rejected material.
- Confirm that the establishment maintains an inventory of critical materials and that it includes their source, use, and criticality ranking for their potential to introduce contaminants or alter the final product, if their sourcing is altered.
- Verify that the establishment has a plan to address potential supply chain vulnerabilities in a timely manner.

References:

- 21 CFR 211.80, 211.82, and 211.84
- ICH Q7, section VII, Materials Management
- ICH Q10

(b) Supplier Qualifications

The establishment is expected to have adequate procedures for selecting, qualifying, and monitoring raw material suppliers. Supplier qualification includes an evaluation of whether a supplier is able to consistently provide material meeting the quality unit-approved specifications. Complete analyses of the supplier material should be conducted on at least three batches of each acquired material before reducing its in-house testing provisions. At a minimum, a complete analysis needs to be performed at appropriate intervals and compared with the certificates of analysis (COAs) of the acquired material to verify the reliability of COAs at regular intervals. Where appropriate, establishments can rely on COAs from the supplier once the reliability of the supplier's analysis has been established and one specific identity test is conducted (if applicable) upon receiving the raw material.

The inspection team should, at a minimum:

- Verify that there are adequate procedures in place to select, qualify, and monitor raw material suppliers. Confirm that critical and high-risk materials, including disposable equipment, are sourced and supported by an appropriate risk-based qualification program.
- If the establishment relies on COAs in lieu of testing every lot of materials for conformance to specifications, confirm that the reliability of the supplier's analysis has been established through initial and periodic verification of the supplier's test results.
- Evaluate the establishment's raw material and component supplier qualification program. Determine whether the approach, including initial and ongoing audits, is appropriately risk-based, considering the criticality of materials and their potential impact on product quality. Note any materials for which an initial on-site audit of the supplier was not conducted by the establishment or a qualified third party and determine the establishment's justification for not doing so, including their documented risk-based assessment.
- Verify that quality agreements between the manufacturer and suppliers include supplier qualification and auditing that are appropriately performed considering material risks.
- Note if there were recent changes in the supply of critical raw materials and verify that the changes were handled per established and appropriate change management procedures. Confirm that an evaluation of the potential impacts to product quality was conducted.

References:

- 21 CFR 211.84
- ICH Q7, section VII, Materials Management

(c) Raw Material and Component Testing, Examination, Release, and Documentation

Manufacturers are expected to purchase raw materials and components against agreed specifications, from suppliers, approved by the quality unit.

The inspection team should, at a minimum:

- Verify that there are appropriate written specifications approved by the quality unit for raw materials noted in the application.
- Confirm that released materials meet specifications through testing of representative samples or through the examination of a COA from an appropriately qualified vendor. Confirm that materials intended for release that do not meet the specifications are rejected and documented.
- Verify that procedures are in place and are followed for the quarantine, testing, and release of raw materials.
- Verify that source materials of animal origin are tested as described in the application. Specifically:
  - Verify that the establishment has determined, through testing or verification by manufacturer COA, that biological raw materials are free from adventitious agents.
  - Verify that raw materials with the potential for microbiological contamination undergo microbiological tests before use.
- If the establishment administered a conditional release of material or components, verify that the material or components were confirmed to be fit for use before distribution. Note that conditional release of DP components is not allowed (21 CFR 211.84(a) and (b)), including BDS (ICH Q7).
- For synthetic processes, if the starting material is not commercially supplied, confirm that processes exist and are followed to ensure changes in the defined chemical properties and structures did not occur before use in manufacturing operations.
- For combination products with biological product and device constituent parts, verify that the device constituent parts (or their components) are purchased from a supplier that meets purchasing requirements as described in Compliance Program 7356.000 Attachment B.

References:

- 21 CFR 211.84, 600.11, and 21 CFR part 4.4
- ICH Q7, section VI.C, Records of Raw Materials, Intermediates, API Labeling and Packaging Materials
- Compliance program 7356.000—*Inspections of CDER-led or CDRH-led Combination Products*

(d) Cell Banks

Storage conditions for cell banks (MCB or WCB) are expected to be clearly defined, with control systems in place to maintain viability and prevent contamination and mix-ups. Monitoring of temperature readings and a working alarm system are essential to ensure that cell banks are stored within established storage conditions. Additionally, to maintain the integrity of the cell banks, it is essential to have a system in place to maintain records of cell bank inventory and the consistency of storage conditions. Limiting access to authorized personnel is critical for maintaining the security and integrity of cell banks.

The inspection team should, at a minimum:

- Review records for inventory and handling of cell banks. Confirm that the records trace the use of specific WCB vials and lots, including whether the vial was used in a completed or failed manufacturing campaign. Also confirm that the establishment investigates whether manufacturing campaign failures correlate with cell bank-related issues.
- If cell banks are not stored on-site but are received from other establishments, verify that adequate procedures are in place to (1) confirm the identity of received cell bank vials, (2) verify that cell bank vials are appropriately controlled to prevent temperature excursions during shipping, and (3) verify that adequate storage conditions are used until production as specified elsewhere in this section.
- Verify that procedures are in place to adequately segregate cell banks used for production from uncharacterized or quarantined cell banks. For multiproduct establishments, verify that there is adequate segregation of cell lines either physically or through controlled procedures to prevent misuse of other products' cell bank vials in production.
- Determine whether there are procedures in place to address resupply or requalification of cell banks when a specific point in the inventory of cell bank vials is met. Verify that the procedures ensure timely resupply or requalification of cell banks.
- Verify that storage conditions for cell banks are adequately monitored, and review freezer temperature logs and maintenance activities to confirm that freezers are appropriately maintained to protect cell banks. Confirm these storage conditions and monitoring activities on-site during the cell bank storage area inspection.

References:

- 21 CFR 610.18
- ICH guidance for industry *Q5A(R2) Viral Safety Evaluation of Biotechnology Products Derived From Cell Lines of Human or Animal Origin* (January 2024)
- ICH Q7, section XVIII.B, Cell Bank Maintenance and Record Keeping
- ICH guidance for industry *Q11 Development and Manufacture of Drug Substances* (November 2012)

(4) Objective 1d: Evaluation of Production and Process Controls in Manufacturing Operations

Under this objective, the inspection team evaluates whether the product of interest is being manufactured in accordance with the validated commercial manufacturing operations described in the application. This objective directs the inspection team to evaluate validated manufacturing operations associated with critical quality attributes and process controls, such as clearance of impurities, viral clearance, microbial control, and contamination and cross-contamination controls (see also Objective 1b of this compliance program) to verify their conformance to the standards described in the application. For biological products, data demonstrating the process performance qualification (PPQ) of the commercial process is submitted in the application.

References:

- 21 CFR 211 subpart F—Production and Process Controls
- ICH Q7, section VIII, Production and In-Process Controls

Parts III.1.A(4)(a) through (k) below outline specific areas under Objective 1d that should be verified by the inspection team **as they relate to the product of interest.** Not all biologics-related unit operations are covered in this compliance program; contact the IQA team for additional information regarding unit operations not described in this document.

(a) Process Validation

Process validation data are evaluated during application assessment. During the inspection, the inspection team observes the ongoing commercial manufacturing operations to verify that they are consistent with the commercial process as described in the application.

The inspection team should, at a minimum:

- Verify that deviation investigations related to process validation activities follow established procedures.
- Determine whether the establishment has pending change management activities that might be indicative of incomplete/inadequate process validation.
- Verify that all failed campaigns during the PPQ batch manufacturing were reported in the application.
- Verify that the establishment is capable of manufacturing commercial batches using the validated process that produced the PPQ batches, (e.g., manufacturing equipment used to produce the PPQ batches remains in a qualified state).
- For commercial manufacturing operations, verify that the process is as described in the application and follows quality standards by reviewing records, observing, and verifying critical manufacturing steps.

References:

- 21 CFR 211.100

- Guidance for industry *Process Validation: General Principles and Practices*
- ICH Q7, section XII, Validation

(b) In-Process Sampling and Controls

The establishment is expected to have written procedures to monitor the performance of manufacturing operations.

The inspection team should, at a minimum:

- Review the records of in-process testing and confirm that test results are recorded as described in the application.
- If a material failed an in-process test, verify that the establishment conducted appropriate investigations, identified actual or potential root causes, implemented appropriate CAPAs, and properly disposed of the failed material.
- Review the records of in-process control trends and excursions from established action limits and determine whether procedures are in place to monitor the maximum number of exceeded alerts and action limits before implementation of appropriate CAPAs.
- If the material that failed an in-process test was used in a finished product, review the records of the justification for disposition of the batch in question and verify that the establishment had adequate justification.

References:

- 21 CFR 211.110
- ICH Q7, section VIII.C, In-Process Sampling and Controls

(c) Manufacturing Operations

Manufacturing of commercial biological products in compliance with CGMP requirements and in accordance with approved processes, as appropriate, exercising appropriate change controls, and ensuring adequate microbial control are important concepts in the manufacture of biological products. These concepts take on added relevance for biological product manufacturing due to the increased likelihood for failures in these areas. Accordingly, they deserve increased scrutiny during inspection. It is of particular importance that biological product manufacturing operations are being executed as described in the application because it is possible for manufacturing changes presumed to be inconsequential to result in a product change that might not be detectable. For example, a change in a cell culture parameter could potentially shift DS post-translational modification in a way that affects product safety and efficacy.

The inspection team should, at a minimum:

- Verify that instructions related to batch production records are followed for different unit operations.

- Verify that unit operations are conducted as currently defined in the application, including that:
  - Operating ranges for process parameters and hold times for process intermediates are not wider or longer than those listed in the application, respectively. If not, determine whether these changes were reported to FDA, as appropriate.
  - If manufacturing operations include steps for pooling of sub-batches, they are performed according to validated protocols described in the application and include confirmation that pooled sub-batches met defined criteria (identical to the application) before pooling.
- Review release and in-process testing data for product batches manufactured to date to determine the consistency of manufacturing. If release and in-process testing limits were exceeded, determine whether the establishment followed approved procedures for investigation; conducted an appropriate, scientifically based investigation; and implemented CAPAs, as needed. Determine whether the product disposition decision is adequate.
- Review deviations to determine whether there are recurring problems or negative trends in manufacturing operations.
- If automated systems are used during the production process, verify that the systems were appropriately qualified and calibrated.
- Verify that there are no open operations during which the DS or DP is exposed to the immediate environment. If the process described in the application includes open operation(s), confirm that the open operation is conducted in a suitable environment and manner to prevent contamination and cross-contamination of the in-process material.
- For combination products with biological product and device constituent parts, verify that the manufacturer has established and maintained procedures for the transfer of the device constituent part design (or design of the components thereof) to manufacturing, including procedures to ensure that the device constituent part design is suitable for manufacturing before becoming final product specifications and production capability can meet commercial production specifications.

References:

- 21 CFR 211.42, and Clause 7.3 and its subclauses of ISO 13485:2016, as required by 21 CFR parts 4.4(b)(1)(ii)
- ICH Q7, section VIII.A, Production Operations
- Guidance for industry *Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use* (February 1997)

(d) Weighing and Dispensing

Raw materials used for the manufacturing of biological products (including product intermediates) are expected to be weighed or measured under appropriate conditions that do not affect their suitability for use.

The inspection team should, at a minimum:

- Verify that SOPs for tracking and weighing of materials are complete and accurate. This should include procedures for release of materials and components before use and accurate recording of information in batch production records.
- Verify that changeover procedures between the handling of different raw materials are adequate to prevent cross-contamination and are followed in weighing and dispensing areas.
- Observe weighing, measuring, and subdividing operations when feasible to verify that the materials are those specified in the batch production record for the product and its intermediate and that there is adequate segregation, tracking, and recording.
- Verify that storage containers are appropriate to maintain material suitability and that they are clearly labeled.

References:

- 21 CFR 211.101
- ICH Q7, section VIII.A, Production Operations
- Guidance for industry *Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use* (February 1997)

(e) Media and Buffers

Growth media is used at all stages of cell culture unit operations. The media can be of different composition at different stages and can be supplemented by various components, including salts, sugars, and antifoaming agents. Process buffers are used throughout manufacturing, but their use is prominent for the biological product purification and formulation steps. Particular care should be taken for formulation buffers with excipients. Excipient sourcing and storage conditions are of high importance.

The inspection team should, at a minimum:

- Confirm that buffers and media are used as defined in the application and are accurately described in the master production record.
- Evaluate whether adequate procedures are in place to prepare, label, store, and trace buffers and media throughout manufacturing operations.
- Evaluate whether, in production, the predefined hold times for buffers and media are supported by microbiological and chemical stability data.

- If contamination control procedures are used for cell culture media such as high-temperature, short-time treatment, confirm that validated parameters (e.g., temperature, time, flow rate) are used.
- Confirm that the buffer and media preparation process includes adequate environmental and procedural controls to prevent contamination.

References:

- ICH Q7, section VIII.A, Production Operations
- Guidance for industry *Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use* (February 1997)

(f) Cell Culture Processes

Upstream manufacturing operations such as cell culture processes are considered high risk from a microbial contamination perspective, and it is essential that they are conducted in a manner to avoid contamination events.[51] Manufacturers are expected to test unprocessed bulk from the end of the upstream manufacturing steps for the presence of adventitious agents. This testing is critical for detecting microbial contaminants (e.g., viruses, mycoplasma) early in the manufacturing process to ensure the product purity and safety.

The inspection team should, at a minimum:

- Review available cell culture performance trends such as cell growth and titer to identify issues with cell culture performance. Gross deviations in cell culture parameter profiles can be indicative of raw material failures or adventitious agent contamination.
- Evaluate the success rate for the cell culture or the fermentation process starting from cell bank thawing. Confirm that the establishment investigates instances of a WCB failing to generate the growth necessary for production.
- Review bioburden data and determine whether acceptance criteria or limits are met as specified in the application. Verify that the batch is rejected in the case of a confirmed culture contamination. Confirm that an investigation was conducted to identify root causes and that subsequent CAPAs were implemented. Verify that procedures were followed to decontaminate the contaminated equipment and establishment (if applicable) as described in Objective 1b.
- Verify that unprocessed bulk safety tests (viral or microbial as relevant) were conducted using the assays and acceptance criteria outlined in the application.
- Confirm that in-process parameters and controls for each step—from initial thaw of the cell bank vial to production of the bioreactor culture—adhere to application commitments.
- Verify that procedures exist and are followed to maintain and expand cell cultures with appropriate controls to minimize the risk of contamination and cross-contamination during

[51] See Part I.2 of this compliance program for a description of steps involved in typical upstream manufacturing operations.

cell culture expansion. Evaluate changeover procedures to determine whether they are appropriate to prevent cross-contamination between different products.

- Verify that appropriate records for cell culture activities include cell passage numbers that are consistent with the end of production or limits of in vitro cell age specified in the application.

References:

- 21 CFR 211.42
- ICH Q7, sections VIII.A, Production Operations, and XVIII, Specific Guidance for APIs Manufactured by Cell Culture/Fermentation
- ICH Q5A(R2)
- Guidance for industry *Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use* (February 1997)
- USP General Chapter <1237> *Virology Test Methods*

(g) Final Fermentor/Bioreactor Harvesting

Harvesting can include centrifugation, filtration, or both of these unit operations, resulting in a clarified liquid that can be more readily purified.

The inspection team should, at a minimum:

- Evaluate whether the end-of-production adventitious agent samples were taken before harvesting.
- Evaluate whether cell culture end-of-production procedures, harvesting storage temperatures, and elapsed times were within the ranges as specified in the application.
- Determine whether unanticipated clogging or fouling events initiated the need for unplanned additional depth filtration or filtration steps; this can be indicative of an upstream cell culture issue not detected by viability or cell number.

References:

- ICH Q7, section XVIII.D, Harvesting, Isolation and Purification
- Guidance for industry *Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use*

(h) Homogenization

Some biological products produced in microorganisms might require liberation of the protein product intermediate from the bacterial cells after harvesting and before downstream processing. This can be accomplished through the disruption of cell walls by sonication or mechanical homogenization of the cells followed by physical separation, such as centrifugation.

The inspection team should, at a minimum:

- Confirm that operating temperatures of the cellular disruption do not exceed the validated range.

References:

- ICH Q7, section XVIII.D, Harvesting, Isolation and Purification
- Guidance for industry *Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use* (February 1997)

(i) Purification Processes

Special considerations for purification manufacturing steps are listed below, organized by overall unit operation.

i. Chromatography

Although chromatography resins or adsorbers can be reused, they should be product-dedicated. Chromatography column housing (the hardware containing the purification resins) need not be product-dedicated; however, the establishment should have adequate cleaning validation and changeover procedures for nondedicated column housing. The resin or adsorber lifetimes can be initially validated using small-scale models, but concurrent validation at commercial scale is expected to be ongoing at the time of approval. The effectiveness of cleaning, sanitization, and storage of resins should be verified at scale.

The inspection team should, at a minimum:

- Confirm that the establishment reviews and trends column chromatography traces, step yields, impurities, and other measures of performance to ensure the column chromatography steps are consistent batch to batch, as described in the application.
- Confirm that column housings are clean and free of leaks. Visually confirm that packed columns are free from discoloration, channels throughout the column, or pockets of air at seals.
- Confirm that resins are product-dedicated and consistent with the application.
- Evaluate whether appropriate cleaning validation and changeover procedures for column housings exist and whether they are followed if column housings are not product-dedicated.
- Review protocols for packing and unpacking of columns and determine whether packing criteria are adequate (e.g., post-use resin/adsorber testing is conducted and demonstrates adequate column performance). Evaluate whether segregation and changeover procedures at the resin packing/unpacking area are adequate to prevent mix-up and cross-contamination. Evaluate whether the packing/unpacking procedures are as closed as possible to reduce resin exposure to the environment and prevent resin microbial contamination.
- Review and evaluate whether procedures for cleaning, sanitizing, and storing resins are adequate and followed. From a microbial control perspective, review available data from validation/verification studies of the sanitization and storage solution for chromatography resins.

- If full-scale lifetime validation studies were completed, determine whether resins were used within their validated lifetimes. If not, evaluate whether protocols and reports, including interim reports, are available for full-scale lifetime studies that support the performance of the resins.

References:

- ICH Q7, section XVIII.D, Harvesting, Isolation and Purification
- Guidance for industry *Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use* (February 1997)

ii. Viral clearance/inactivation

During cell expansion or while in the final fermentor or bioreactor, the cell culture can be contaminated by adventitious agents, potentially posing a safety risk to patients. Materials, personnel, or contaminated equipment can be the source of adventitious agents. The downstream process has multiple orthogonal viral reduction unit operations (e.g., column chromatography), and separating the desired product from the culture medium can also reduce adventitious agent load. Furthermore, the manufacturing process will contain unit operations that are designed specifically to inactivate or remove adventitious agents, such as viruses. These unit operations can include a low pH treatment step, a detergent or solvent treatment step, a heating step, and a specific viral nanofiltration step.

The inspection team should, at a minimum:

- Confirm that the minimum exposure times for treatment steps are met.
- Confirm that column chromatography and nanofiltration steps are performed within their validated parameters, as described in the application.
- Evaluate whether the viral filters pass the integrity testing.
- Evaluate whether process pauses in nanofiltration steps, which can impact clearance of viruses, were validated during small-scale viral clearance studies.
- Evaluate whether deviations associated with adventitious agent clearance or inactivation unit operations are thoroughly investigated and resolved.

References:

- ICH Q7, section XVIII.E, Viral Removal/Inactivation Steps
- Guidance for industry *Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use* (February 1997)

iii. Precipitation/Crystallization

A protein DS intermediate can be concentrated, or purified, using precipitation or crystallization unit operations. This process can be induced by the addition of salts or polymers and the alteration of a solution's temperature, pH, or ionic strength. The resulting crystals or precipitates can be collected by decanting, centrifugation, or other physical/mechanical separation methods.

The inspection team should, at a minimum:

- Evaluate whether temperatures, agitation rates, and reaction times during the precipitation or crystallization incubation period are within validated ranges.
- Evaluate whether the resulting intermediate manual transport and decanting are conducted in a suitable environment and manner to prevent contamination and cross-contamination if conducted in open environmental conditions.

References:

- ICH Q7, section VIII.D, Blending Batches of Intermediates or APIs
- Guidance for industry *Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use* (February 1997)

iv. UF/DF

UF/DF can be used at any point in the production process where volume reduction (product concentration) or buffer exchange is desired. As such, it might be used before, in between, or after column chromatography steps. UF/DF membranes can be reused but should be product-dedicated, and membrane lifetimes are expected to be validated, and can be done concurrently during commercial production. The effectiveness of cleaning, sanitization, and storage are expected to be verified at scale.

The inspection team should, at a minimum:

- Determine whether establishments that reuse UF/DF membranes confirm their suitability with supporting data. Confirm that UF/DF membranes are not used beyond the qualified lifetime supported by the UF/DF membrane lifetime qualification protocol outlined in the application, as applicable. If not, determine whether protocols and reports, including interim reports, are available for full-scale lifetime studies that support the performance of the membranes.
- Confirm that the establishment complies with the minimum number of buffer exchanges as defined in the application.
- Confirm that the UF/DF membranes are product-dedicated and that the cleaning, sanitizing, and storage procedures are followed between manufacturing operations. From a microbial control perspective, review available data from validation/verification studies of the sanitization and storage solution.

Reference:

- Guidance for industry *Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use* (February 1997)

(j) BDS Filtration and Fill

Most protein BDS is not typically tested for sterility. However, liquid forms are typically filtered using 0.22 µm filtration to reduce bioburden to predefined acceptance levels. The bulk fill process should be conducted under conditions designed to ensure microbial control during storage and handling. The environment where the bulk fill process takes place is evaluated on a case-by-case basis based on risk, typically during the PLI or PAI. Factors affecting microbial control include use of

open or closed systems, the growth promoting potential of the BDS, and the storage temperature of the protein DS.

The inspection team should, at a minimum:

- Evaluate whether sensitive excipients (e.g., Polysorbate-80) are within their validated expiry dates before compounding the BDS.
- Evaluate whether adequate procedures are in place for integrity testing of the bioburden reduction filter used during final DS filling and that these procedures outline an appropriate course of action if the integrity test fails. Confirm that adequate investigation and documentation of integrity test failures occurs and appropriate CAPAs are performed in a timely manner.
- If filling processes are not closed, evaluate whether the fill procedure is adequate to prevent contamination and cross-contamination, and microbiology samples represent the worst-case scenario.
- Confirm that the DS container closure system used is as indicated in the application and is closed as described in the application (e.g., to a specified torque for screw-cap containers).
- As applicable, confirm that the manufacturer investigates leakage events, evaluates their potential impact on the product, and provides sound, scientific reasoning for the related disposition decision.
- Confirm that sampling is performed on representative homogeneous DS.
- For lyophilized DS milling and fill[52]:
    - Evaluate whether the validation was confirmed by appropriate lyophilized DS tray sampling to ensure homogenous lyophilized DS is filled into BDS container closure systems.
    - Evaluate whether the transfer of BDS after lyophilization is conducted in a manner that does not increase risk of contamination.

Reference:

- Guidance for industry *Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use* (February 1997)

(k) Reworking and Reprocessing

Manufacturers are expected to identify products or in-process materials or intermediates that fail to meet established limits or specifications. Adequate investigation and documentation of discrepancies and failures that prompted reprocessing steps are essential to ensure that the root causes are properly identified and corrected.[53] Reprocessing steps are expected to be appropriately justified through

[52] See Attachment D for inspection coverage guide specific to lyophilization or freeze-drying.

[53] *Reprocessing* of a biological intermediate is defined as the repetition of a unit operation when the process has shifted out of the validated operating ranges. *Reworking* is defined per ICH Q7 as "Subjecting an intermediate or API that does

validation studies, including when the reprocessing was done according to a previously approved protocol. The final disposition of reprocessed or reworked material is expected to be recorded as per the establishment's written procedures. Reprocessing steps for biological products should be a rare occurrence and generally limited to exigent circumstances, such as to avoid a drug shortage situation. Reprocessing must be performed with the review and approval of the quality unit. If reprocessing activities have been approved in a prior approval supplement, reprocessing can be performed without an approved protocol, prior to releasing the reprocessed batch(es). If reprocessing is performed with an approved protocol, the reprocessing activities should be submitted in an annual report.[54]

The inspection team should, at a minimum:

- Verify that the manufacturer has established quality unit-approved procedures for reprocessing, if applicable. Review updates to concurrent reprocessing validation reports if available.
- If evidence of reprocessing activities is found for approved processes, verify that these activities have been communicated to FDA in a timely manner or that material was reprocessed per the products' FDA-approved and validated procedures. Confirm that batches manufactured using reprocessing steps meet specifications. If unapproved reprocessing is discovered, notify the IQA team, in a timely manner.
- Release of reworked material should not occur for biological intermediates unless reworking has been approved by FDA. If reworked material for marketed product is discovered, confirm that FDA has approved such reworking. If reworked material for marketed product has been distributed or is intended for distribution to the United States without FDA notification, immediately contact OQS by emailing CDERBIOTECHINSPECT@fda.hhs.gov and cc'ing CDERSurveillance@fda.hhs.gov, providing evidence of distributed reworked material, as applicable.

References:

- 21 CFR 211.115
- ICH Q7, section XIV, Rejection and Re-Use of Materials

(5) Objective 1e: Evaluation of the Laboratory Control System

Under this objective, the inspection team evaluates the establishment's laboratory control system, which includes evaluating various activities related to laboratory procedures, validation and verification of analytical methods, and sample testing associated with the product of interest.

Parts III.1.A.(5)(a) through (g) outline specific areas under Objective 1e that should be verified by the inspection team **as they relate to the product of interest.**

not conform to standards or specifications to one or more processing steps that are different from the established manufacturing process to obtain acceptable quality intermediate or API."

[54] For additional information on the adequate reporting categories for reprocessing activities, see guidance for industry *Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products* (June 2021).

(a) General Laboratory Operations

The establishment is expected to have documented procedures describing sampling, testing, approval or rejection of materials, and recording and storage of laboratory data, among other aspects, to routinely track method performance parameters and effectively manage trends. In addition, laboratory equipment used in analytical testing is expected to be appropriately qualified for its intended use.

The inspection team should, at a minimum:

- Verify that the laboratory raw data match the data that are formally recorded in a laboratory information management system or other computer data storage system.
- Verify that laboratory record-keeping practices align with record-keeping principles outlined in Objective 2 of this compliance program.
- Verify that the noncompendial method validation data are consistent with the data provided in the submission. Confirm that compendial methods were verified under actual conditions of use.
- Verify that there is adequate test sample tracking and that there is an adequate system in place to ensure that samples are stored appropriately and that correct samples are tested within the appropriate time frames per the SOP.
- Verify that laboratory analysts and management staff are qualified to analyze, review, and evaluate data.
- Review laboratory equipment qualification, maintenance, and calibration records (see Part III.1.A(2)(b) of this compliance program for more details).
- Evaluate the establishment's management of laboratory reagents and chemicals, including adherence to storage conditions and expiry dates, as outlined in Part III.1.A(3)(a) of this compliance program.

References:

- 21 CFR 211.160(a), 211.194, 610.9, 610.12 through 610.15, and 610.18
- ICH guidance for industry *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products* (August 1999)
- ICH Q7, section XI, Laboratory Controls
- Guidance for industry *Analytical Procedures and Methods Validation for Drugs and Biologics* (July 2015)
- Guidance for industry *Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production,* Revision 1 (May 2022)

(b) Biochemical and Microbiology Methods

In general, biological products are tested for potency, sterility, and identity, among other biochemical and microbiological characteristics. Because of the nature of biological product manufacturing, the

inspection team should expect to see protein-specific testing as well as microbiological testing, including in-process control, release, and stability testing. It is common for some testing, such as adventitious agent testing (e.g., mycoplasma testing, viral safety testing) to be conducted at establishments other than the product manufacturer.

The inspection team should, at a minimum:

- Corroborate that data (e.g., release data, stability data) collected for batches manufactured and tested using the validated commercial-scale process and laboratory testing methods align with data and information submitted in the application (see Objective 2 for additional details).
- Confirm that methods are consistently executed within their validated ranges and performance parameters and that they meet their predetermined system suitability criteria.
- Evaluate repeat incidents of failed or invalid test results and confirm they were resolved appropriately (Assay failure rates are important indicator of assay performance and cannot be determined solely by reviewing OOS investigations).
- Verify that laboratory method/test investigations or deviations that occurred during or after validation were appropriately documented.
- Review discrepancies in the method validation or technical transfer results from those submitted in the application, verify that the analytical methods described in the application have not changed or that changes are justified, and confirm that the establishment intends to notify FDA during submission assessment and amend the pending submission accordingly.
- Confirm that off-site testing laboratories have quality agreements that detail the responsibilities for reporting deviations, reviewing and reporting OOS results, reviewing the raw data, and validating test methods and on-site audits.

References:

- 21 CFR 610.10, 610.12, and 610.14
- ICH Q7, section XII.H, Validation of Analytical Methods
- Guidance for industry *Contract Manufacturing Arrangements for Drugs: Quality Agreements* (November 2016)

(c) Sampling

Laboratory and production documents are expected to include procedures on sampling, sampling frequency, and testing (in-line or off-line) of raw materials, in-process materials, intermediates, and DS and DP.

The inspection team should, at a minimum:

- Verify that procedures for sampling and testing of raw materials are adequate to ensure their proper control and disposition. Confirm implementation of procedures on the manufacturing floor and in the raw materials testing laboratory.

- Confirm that in-process material sampling and sampling plans for product release are consistent with the established sampling plan in the application, which should be appropriately justified.
- Verify that the procedures in place for tracking samples (raw material, in-process, or release) are adequate to ensure that samples are stored appropriately and that the correct samples are tested within the time frames specified by SOPs. Storage conditions for microbial and endotoxin samples generally should not be longer than 24 hours at 2-8°C. Review supporting data of these microbial and endotoxin samples if stored otherwise.

References:

- 21 CFR 211.84, 211.110, 211.160, and 211.165(c)
- ICH Q7, section XI, Laboratory Controls
- ICH Q7, section VII.C, Sampling and Testing of Incoming Production Materials
- ICH Q7, section VIII.C, In-Process Sampling and Controls

(d) Stability Testing

The establishment's quality system is expected to have procedures for the stability testing program to monitor the stability characteristics of the biological product, critical intermediates, and reference standards (see Part III.1.A(5)(e)—Reference Standards—for more detail). The stability data are expected to be available to review if needed. Generally, stability data are submitted in the application, and the OPQ assessment division uses the stability data to evaluate the adequacy of the proposed long-term storage conditions and expiry date. Stability samples are expected to be stored using the appropriate container closure system (i.e., representative of the manufacturing container closure system) under appropriate storage conditions, supported by data or records associated with stability chamber monitoring. In general, the manufacturer should place the first three commercial batches on the stability monitoring program to confirm the retest or expiry date.

The inspection team should, at a minimum:

- Confirm that stability samples are collected, stored, and tested per the stability protocol described in the application.
- Verify that the stability data collected since application submission display no new stability trends.
- Verify that the appropriate container and storage conditions are used for stability samples and reserve samples.

References:

- 21 CFR 211.137, 211.166, and 610.50
- ICH Q1A(R2)
- ICH Q5C
- ICH Q7, section XI.E, Stability Monitoring of APIs

(e) Reference Standards

Reference standards should be appropriately prepared, identified, tested, approved, and stored. The establishment's laboratory control system should document the source of each reference standard. Each batch of the reference standard should be periodically requalified in accordance with an FDA-approved protocol.

The inspection team should, at a minimum:

- Determine whether the reference standards used in product testing are as described in the application and whether the establishment's laboratory control system follows approved procedures for reference standard storage conditions, usage conditions, and handling instructions.
- Confirm that procedures are in place to adequately track the reference standard inventory.
- Confirm that there are reference standard requalification and stability testing protocols in place that align with the application submission. If a new reference standard was qualified since submission of the application, confirm that it was qualified using an FDA-approved protocol and reported to the Agency, as appropriate.

References:

- ICH Q6B, section II.B.1, Reference Standards and Reference Materials
- ICH Q7, section XI.A, General Controls

(f) OOS Procedures and Investigations

The establishment's laboratory control system is expected to investigate OOS results obtained from product testing. OOS investigations should be documented according to approved procedures, which should detail the investigation as well as the procedures in place for retesting (if any) and conclusions. Retesting after OOS results might be allowed under an approved documented procedure.

The inspection team should, at a minimum:

- Confirm that OOS investigation procedures are followed and that they clearly outline or reference other procedures that dictate the disposition of material that does not meet preestablished acceptance criteria.
- Obtain a complete list of OOS results associated with the product for in-process, release, and stability tests, including those that were invalidated, and confirm that the OOS results were evaluated and resolved appropriately (see Objective 2 for additional details).
- If retesting is performed, verify that there are procedures in place to determine when retesting is appropriate, how retesting should be performed (e.g., sampling, duplicates), and how results should be interpreted.
- For contract testing laboratories, verify that the establishment has procedures in place to ensure receipt of reports and results (including initial and confirmed OOS results) signed by

the contract testing laboratory's quality assurance department and that the establishment is able to obtain raw data upon request.

References:

- 21 CFR 211.160(a) and 211.192
- Guidance for industry *Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production,* Revision 1

(g) Reserve Sample Tracking

The establishment's laboratory control system is expected to have procedures for retaining reserve samples of each batch. Reserve samples are for the purpose of potential future evaluation of the product quality of batches. These procedures are in place to ensure that a sufficient quantity of each reserve sample is retained for an appropriate length of time (e.g., 3 years after distribution of the batch of the DS).[55]

The inspection team should, at a minimum:

- Confirm that reserve samples are stored in the same container closure system and recommended temperatures as specified for the bulk DP in the application.
- Verify that reserve samples are retained for the specified length of time.

References:

- 21 CFR 211.170 and 600.13
- ICH Q7

(6) Objective 1f: Evaluation of Packaging, Labeling, Storage, and Shipping Operations

Under this objective, the inspection team determines whether the establishment packages, labels, and ships the product as described in the application to confirm that the quality of the product of interest meets established standards. In addition, the inspection team verifies that the establishment has suitable written and approved procedures describing the receipt, identification, quarantine, disposition, sampling, examination or testing, release, and handling of packaging and labeling materials of the product of interest.

References:

- 21 CFR 211 subparts G—Packaging and Labeling Control and H—Holding and Distribution
- ICH Q7, sections IX, Packaging and Identification Labeling of APIs and Intermediates, and X, Storage and Distribution

Parts III.1.A.(6)(a) through (c) outline specific areas under Objective 1f that should be verified by the inspection team **as they relate to the product of interest.**

[55] See ICH Q7, section XI.G.

(a) Packaging and Labeling

Packaging and labeling materials (including those for DS) are expected to conform to appropriate written specifications established by the quality unit. Those materials that do not comply with such specifications are expected to be rejected to prevent their use in operations for which they are unsuitable.

The inspection team should, at a minimum:

- Review the establishment's procedures that prevent mix-ups, including those related to label issuance, storage, removal from designated areas, and destruction.
- Verify that the numbers of labels issued and used are reconciled and that discrepancies are investigated and corrected as appropriate.
- Verify that printed labels contain the correct information as described in the master production record or in the application.
- Verify that containers are clearly and accurately labeled during the inspection walk-through.

For DP, the inspection team should also, at a minimum:

- Verify that the dating of each lot of DP is consistent with the final sterile filtration before the filling of a BDS solution into the DP. This is because some bulk solutions are held after sterile filtration and before filling.
- Verify that the contents of the final DP container of each filling of each lot are tested for identity after labeling operations are completed.

References:

- 21 CFR part 211, subpart G; 21 CFR 610.14 and 610.50
- ICH Q7, section IX, Packaging and Identification Labelling of APIs and Intermediates

(b) Storage

Appropriate storage conditions (e.g., controlled temperature, light, humidity when necessary) for materials are expected to be used. Maintaining and monitoring establishments and equipment storage conditions are essential to ensure the quality of the product.

The inspection team should, at a minimum:

- Confirm that in-process or final material is stored at an appropriate temperature as described in the application, which may be in a controlled and monitored freezer or other cooling device.
- Confirm that containers containing in-process or final material are appropriately segregated and stored in areas with controlled access.
- Confirm that separate storage areas are assigned for temporary storage of quarantined, rejected, returned, or recalled materials until the decision as to their future use has been made, unless there is an alternative system to prevent unintentional or unauthorized use.

- Confirm that records demonstrate that specified storage conditions have been maintained, including temperature measurements at appropriate intervals.

References:

- 21 CFR 211.122 and 211.142(b)
- ICH Q7, section VII.D, Storage

(c) Shipping

Manufacturers are expected to follow validated and documented shipping procedures to ship the product in qualified shipping containers. For each shipment of materials, records are expected to be maintained that show receipt and examination or testing and whether the shipment was accepted or rejected.

The inspection team should, at a minimum:

- Confirm that batches are shipped using the validated shipping processes described in the application.
- Confirm that the product is maintained at the appropriate temperature throughout the shipping process.

References:

- 21 CFR 211.150
- ICH Q7, section X.B, Distribution Procedures

B. Objective 2: Data Integrity Audit

Under this objective, the inspection team evaluates the integrity of data submitted in the application. The inspection team should select a subset of data filed in the application to audit on-site for accuracy and completeness and should audit data with issues or risks identified during the application assessment. The subset of data should include process validation data (including in-process testing, release, and stability data). Additional data available on-site that are useful in assessing data integrity are identity assay results, product and process-related impurities results, reference standard qualification testing, and critical analytical method validation packages (e.g., potency assays, stability-indicating assays). The inspection team should note that some of the content in this section is an extension of the content covered under Objective 1a (e.g., computerized systems).

The inspection team should verify that data selected for evaluation have factual and contextual integrity[56] and have been reported accurately in the application. Data integrity issues, such as those

[56] *Factual integrity* refers to the correspondence between the data and information observed during inspection and that submitted in the application (e.g., a chromatography image in the application corresponds to the chromatographic result on record for the specified test on the specified date). *Contextual integrity* refers to the information submitted in the application as being representative of the testing or manufacturing area and related products or processes (e.g., the chromatography results (successes and failures) for assayed samples using the described method). Missing or

below, could indicate that the information submitted in the application is neither complete nor accurate:

- Changes of original data and records without appropriate justification.
- Inconsistencies in the documentation of manufacturing operations.
- Exclusion of specific batches from the stability program to avoid submitting failed stability results.
- Backdating stability test results to meet required commitments.
- Reprocessing or reworking steps not described in the application.
- Manipulation of data to obtain passing results.
- Repeated testing without appropriate justification.
- Unjustified revisions to test results.
- Lack of traceability of test results reported in the application (e.g., the establishment has no records of the testing occurrence or raw data).
- Use of test results from one batch to substitute testing for another batch.
- Test results that do not have records supporting the conduct of the test.

The inspection team should, at a minimum, conduct the following activities with the product of interest in mind:

- Audit and evaluate the accuracy and completeness of data associated with the product.
- Evaluate validated systems (e.g., storage and accessibility controls) in place to manage data associated with biological product manufacturing operations to verify that the data submitted in the application are relevant, accurate, complete, and reliable.
- Verify that the original raw data collected or generated from batch production and testing and other pertinent controls are documented by means of written records or electronic systems. For example, compare the original raw data such as chromatograms, spectrograms, laboratory analyst notebooks, and additional information from the laboratory with summary data filed in the application. Original raw data files should support a conclusion that the data and information reported by the establishment are complete and accurate.
- Confirm that access controls to computerized systems are followed.
- Review selected audit trails to confirm that analytical equipment software used to support the application, as applicable, has verifiable audit trails for the recording and processing of raw data. Review selected audit trails.
- Verify that electronic records have appropriately controlled electronic signatures when used in place of handwritten signatures and that electronic signatures are not shared.

unauthorized changes to records related to the production and testing of the product of interest, as well as unexplained losses of inventory or testing components, challenges the factual and contextual integrity of data and information provided in the application.

- Verify that the quality unit is appropriately ensuring the integrity of data supporting CGMP operations.
- When data discrepancies are observed, determine which actions or inactions contributed to the data integrity problem and whether CAPAs were or are to be taken, including retraining of personnel if needed. Document instances of failure to report data that should have been included in the application. Depending on the severity of the data discrepancy, the issue might result in a **withhold** recommendation for the application. See a discussion of withhold items in Part V of this compliance program.

References:

- 21 CFR 211.160, 211.165, 211.166 and 211.167
- Guidance for industry *Data Integrity and Compliance With CGMP: Questions and Answers*
- Guidance for industry *Part 11, Electronic Records; Electronic Signatures—Scope and Application* (August 2003)
- Guidance for industry *Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production,* Revision 1(May 2022)
- ORA Laboratory Manual, *Volume III Section 3—Recording of Results Analyst Worksheet*, Rev. 4 (December 2023)

2. Reporting

In preparing the inspection report, the inspection team should follow instructions in chapter 5 of the IOM. A single inspection report, and, when applicable, Form FDA 483 should be used to document all inspection observations, including those made during an inspection at a combination product with biological and device constituent part manufacturer.

In the "Objectionable Conditions and Management's Response" section of the inspection report, the inspection team should summarize its findings with sufficient details, supporting evidence, and relevance to quality/safety for each Form FDA 483 observation as appropriate.

PART IV—ANALYTICAL

Routine sample collection and analysis under this compliance program are not anticipated.

As discussed in the Reporting Requirements section of this compliance program (under 8. Sample-Related Reporting Requirements), the inspection team should contact OQS before samples are collected.

PART V—REGULATORY/ADMINISTRATIVE STRATEGY

1. CDER Recommendations

The outcome of the inspection results in either an **approve** or a **withhold** recommendation for the facility in the appropriate component of the CDER Informatics Platform and application assessment.

A. Approve Recommendation

For a BLA to be approved, the facility in which the biological product is manufactured, processed, packed, or held must meet standards designed to ensure that the biological product continues to be safe, pure, and potent. OPQ makes an **approve** recommendation if there are no significant CGMP issues that could adversely affect the establishment's ability to perform the manufacturing operations described in the application and if no data integrity concerns were observed.

B. Withhold Recommendation

OPQ makes a **withhold** recommendation if there are significant CGMP issues that would adversely impact the establishment's ability to perform its designated functions described in the application or if significant data integrity issues are observed. Deficiencies discovered during the PLI or PAI that are not related to the facility's CGMP compliance or the manufacturing of the product of interest but are solely application assessment issues can be addressed and communicated through established assessment practices and should not be considered in PLI and PAI withhold decisions.

(1) Overarching Examples of Significant Deficiencies

Examples of significant deficiencies associated with the manufacture of the product of interest that could result in a **withhold** recommendation that are not limited to a specific system or objective follow:

- Failure to perform the manufacturing operations as described in the application or failure to comply with applicable CGMP requirements.
- Significant documentation deficiencies impacting equipment cleaning and maintenance, methods validation/verification, or process parameters used to produce the protein DS or DP as described in the application (21 CFR 211.67, 211.160, 211.165, and 211.100).
- Significant data integrity issues. (See examples under Part III.1.B of this compliance program.)
- Delaying, denying, limiting, or refusing a drug inspection.[57]

[57] See guidance for industry *Circumstances That Constitute Delaying, Denying, Limiting, or Refusing a Drug or Device Inspection* (June 2024).

(2) Examples of Significant Deficiencies, Arranged by Objective

This section includes examples of deficiencies associated with the manufacture of the product of interest that could result in a **withhold** recommendation, arranged by objective. The examples are not exhaustive.

(a) Objective 1a: Quality System

- Deficient or unsupported instructions (e.g., records, SOPs) to conduct manufacturing operations in compliance with regulations.
- Failure of the quality unit to review and approve complete batch production records before batch release (21 CFR 211.22(a) and ICH Q7, section VI.E).
- Failure to investigate when the suitability of a batch is in doubt, including the failure to investigate OOS testing results (21 CFR 211.192 and ICH Q7, section II).
- Release of affected batches without appropriately reporting significant production process changes, reprocessing (that has not been approved in the product application), or product rework (21 CFR 211.115 and 601.20 and ICH Q7, section XIV).
- Release of affected batches with major unapproved changes to the application, including using a process, material, or equipment that was neither submitted to the application under review nor in an approved application (21 CFR 601.12(b)).
- Operators are or were not trained in the particular operation that they performed or in CGMP requirements related to their job functions (21 CFR 211.25(a) and ICH Q7, section III).
- Significant stability study deficiencies or failures, which raise questions about the stability of the DS or DP.

(b) Objective 1b: Facilities and Equipment

- Failures or deficiencies in the qualification and maintenance/calibration of utilities or other establishment controls/operations and equipment that can lead to batch failures (21 CFR 211.58), such as water systems; HVAC systems; fermentors or bioreactors; centrifuges; chromatography columns; UF/DF equipment; cold storage equipment used for product intermediates, DS, and DP; and DP aseptic filling-related equipment, including restricted access barrier systems (RABS), isolators, filling machines, and so forth (21 CFR 211.68(a) and ICH Q7, section IV.A).
- Failure to ensure the prevention of product contamination and cross-contamination, especially from live viruses and highly potent or toxic compounds (21 CFR 211.63, 211.130(a), 600.10(c)(1) through (3), 600.11(e)(2) and (3), and ICH Q7, section IV.D).
- Evidence that the establishment is not compliant with 21 CFR 211.56 or 211.58 due to its lack of cleanliness or state of disrepair (see also ICH Q7, sections IV.A and V.B).

(c) Objective 1c: Material Management

- Use of raw material (including critical raw material) that does not meet specifications or was not appropriately qualified (21 CFR 211.84(e) and ICH Q7, section VII.C).
- Failure to ensure that materials are free from adventitious agents as required (21 CFR 600.11(e)(5)).
- Failure to store cell banks under conditions that maintain the initial characteristics of the organisms and prevent mix-ups, contamination, and deterioration (21 CFR 610.18 and ICH Q7, section XVIII.B).

(d) Objective 1d: Production and Process Controls

- The product cannot be consistently manufactured using the proposed commercial process or cannot meet established quality specifications described in the application (21 CFR 601.2(d)).
- Performing production steps inconsistent with written procedures involving production and process controls designed to ensure that products have the identity, strength, quality, safety, purity, and potency they purport or are represented to possess (21 CFR 211.100 and ICH Q7, section VIII.A).
- Batch production and control records are or were not prepared for each product batch (21 CFR 211.188, 600.12, and ICH Q7, section VI.E).
- Significant trend of endotoxin or bioburden excursions beyond action limits (21 CFR 211.110, and ICH Q7, section XVIII.A).
- Recurrent cell culture contaminations, including viral, mycoplasma, and bacterial contaminations (21 CFR 211.113(b), 600.11(b), and ICH Q7, section XVIII.C).
- Release of DS produced under conditions in which viral inactivation or clearance operations were not performed in conformance with application commitments or without data to support DS suitability (ICH Q5A(R2)).
- Evidence that manufacturing operations, including analytical methods, are operating outside validation/qualification acceptance criteria described in the application (21 CFR 211.110 and ICH Q7, section XVIII).
- Lack of complete manufacturing and control instructions in the master production record or lack of data to support those instructions (21 CFR 211.186 and ICH Q7, section VI).
- Release of DP from a facility with a history of unresolved DP media fill failures (21 CFR 211.165).

(e) Objective 1e: Laboratory Control System

- A significant, unresolved history of in-process testing results exceeding action limits (21 CFR 211.110 and ICH Q7, section XI.A).

- Failure to conduct required adventitious agent testing, including mycoplasma and viral safety testing, in accordance with the application (21 CFR 211.113 and 600.11).
- Failure to establish an adequate OOS procedure, follow the established OOS procedure, or provide justification for repeated testing (21 CFR 211.192, 211.194, and ICH Q7, section XI).
- Failure to conduct testing as indicated in the application or a pattern of failure to perform tests in accordance with established procedures (21 CFR 211.165, 211.166, 211.167, and ICH Q7, section XI.B).
- Failure to properly validate/qualify test methods for assessment of quality, safety, or efficacy attributes (21 CFR 211.194, 211.165(e), and ICH Q7, section XI.C).

(f) Objective 1f: Packaging, Labeling, Storage, and Shipping Operations

- Failure to package BDS or DP in the approved container or properly label BDS or DP containers, respectively (21 CFR 211.94, 600.11(h), and ICH Q7, section IX.D).
- Pattern of failure to adequately investigate BDS leakage events (21 CFR 600.11(h)).
- Failure to ensure that each DP batch conforms to label claims or specifications described in the application.

(g) Objective 2: Data Integrity

- Significant data integrity problems, including misrepresented data or other conditions related to the batches manufactured by the proposed commercial process as described in the application.
- Significant factual and contextual integrity of data issues, including failure to report failed test data (21 CFR 211.68, 211.100, 211.160, 211.180, 211.188, and 211.194). For example:
  - Repeated analyses of the same sample without adequate justification.
  - Use of test results from previous batches to substitute testing for another batch.
  - Fabrication of acceptable test results without performing the test.
- Failure to provide CGMP record traceability, failure to protect data files and systems from changes made by unauthorized personnel, or manipulation of audit trails and data.
- Pattern of discrepancy between raw data results and formally recorded results or to maintain complete and original copies of data, including relevant metadata.

2. Additional Considerations

- OPQ evaluates the inspection's evidentiary records (e.g., EIRs, records pursuant to a request under section 704(a)(4) of the FD&C Act, Form FDA 483s, establishment responses to communicated deficiencies) and enters an application recommendation in the appropriate component of the CDER Informatics Platform.
- In the case of an **approve** recommendation, OPMA updates the final decision and

establishment's profile (as appropriate) in the appropriate system and shares with the IQA team the recommendation for facilities listed in the application to support regulatory action.

- When a **withhold** recommendation is made for a facility that does not market FDA-regulated products, a warning letter is not usually an appropriate regulatory action. However, if a **withhold** recommendation is made for a facility on the basis of systemic CGMP deficiencies that could impact marketed products, OPQ will discuss the deficiencies with OC in a timely manner to determine the appropriate next steps.
- For combination products with biological and device constituent parts, the inspection team may need to engage expertise from other agency components, including other center(s), as needed.

PART VI—REFERENCES, ATTACHMENTS, PROGRAM CONTACTS, AND ACRONYMS

1. References

A. Code of Federal Regulations, Title 21
https://www.ecfr.gov/current/title-21

Part 4: Regulation of Combination Products

Part 210: Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; General

Part 211: Current Good Manufacturing Practice for Finished Pharmaceuticals

Part 600: Biological Products: General

Part 601: Licensing

Part 610: General Biological Products Standard

B. Compliance Programs (CDER Drugs)
https://www.fda.gov/drugs/guidance-compliance-regulatory-information/drug-compliance-programs

7356.000—*Inspections of CDER-led or CDRH-led Combination Products*

7356.002—*Drug Manufacturing Inspections*

7356.002A—*Sterile Drug Process Inspections*

7356.002M—*Surveillance Inspections of Protein Drug Substance Manufacturers*[58]

C. Guidances

https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs

(1) Guidances for Industry

Advancement of Emerging Technology Applications for Pharmaceutical Innovation and Modernization (September 2017)

Alternative Tools: Assessing Drug Manufacturing Facilities Identified in Pending Applications (September 2025)

Analytical Procedures and Methods Validation for Drugs and Biologics (July 2015)

Biological Product Deviation Reporting for Licensed Manufacturers of Biological Products Other than Blood and Blood Components (October 2006)

[58] This compliance program applies only to surveillance inspections of **CDER-regulated** protein DS manufacturers.

Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products (July 1997)

Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products (June 2021)

Circumstances That Constitute Delaying, Denying, Limiting, or Refusing a Drug or Device Inspection (June 2024)

CMC Postapproval Manufacturing Changes To Be Documented in Annual Reports (March 2014)

Comparability Protocols for Postapproval Changes to the Chemistry, Manufacturing, and Controls Information in an NDA, ANDA, or BLA (October 2022)

Conducting Remote Regulatory Assessments—Questions and Answers (June 2025)

Contract Manufacturing Arrangements for Drugs: Quality Agreements (November 2016)

Cooperative Manufacturing Arrangements for Licensed Biologics (November 2008)

Data Integrity and Compliance With Drug CGMP: Questions and Answers (December 2018)

General Principles of Software Validation (January 2002)

Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production, Revision 1 *(May 2022)*

Manufacturing Biological Intermediates and Biological Drug Substances Using Spore-Forming Microorganisms (September 2007)

Part 11, Electronic Records; Electronic Signatures—Scope and Application (August 2003)

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

Process Validation: General Principles and Practices (January 2011)

Quality Systems Approach to Pharmaceutical CGMP Regulations (September 2006)

Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice (September 2004)

(2) Draft Guidances for Industry[59]

ICH Q12: Implementation Considerations for FDA-Regulated Products (May 2021)

Inspection of Injectable Products for Visible Particulates (December 2021)

(3) ICH Guidances for Industry

Q1A(R2) Stability Testing of New Drug Substances and Products (November 2003)

Q2(R2) Validation of Analytical Procedures (March 2024)

[59] When final, these guidances will represent FDA's current thinking on these topics.

Q5A(R2) Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin (January 2024)

Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products (July 1996)

Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products (August 1999)

Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients (September 2016)

Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients - Questions and Answers (April 2018)

Q8(R2) Pharmaceutical Development (November 2009)

Q8, Q9 & Q10 Questions and Answers; *Appendix Q&As from Training Sessions* (July 2012)

Q9(R1) Quality Risk Management (May 2023)

Q10 Pharmaceutical Quality System (April 2009)

Q11 Development and Manufacture of Drug Substances (November 2012)

Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management (May 2021))

Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management Annexes (May 2021)

Q13 Continuous Manufacturing of Drug Substances and Drug Products (March 2023)

(4) FDA Procedures and References

Investigations Operations Manual, https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/investigations-operations-manual

MAPP 4151.8, Rev. 2, *Equal Voice: Collaboration and Regulatory and Policy Decision-Making in CDER* (August 12, 2025), https://www.fda.gov/media/188211/download?attachment

ORA Laboratory Manual, *Volume III Section 3—Recording of Results Analyst Worksheet,* Rev. 4 (December 2023), https://www.fda.gov/media/74012/download?attachment

Staff Manual Guide 6001.1, *FDA Remote Regulatory Assessment Standard Practices* (January 2025), https://www.fda.gov/media/186992/download?attachment

D. FDA User Fee Programs
https://www.fda.gov/industry/fda-user-fee-programs

Prescription Drug User Fee Act (PDUFA)

Biosimilars User Fee Act (BsUFA)

E. Non-FDA References

ISO 17665, *Sterilization of Health Care Products—Moist Heat—Requirements for the Development, Validation and Routine Control of a Sterilization Process for Medical Devices* (2024)

ISPE Baseline Guide Volume 7, *Risk Based Manufacture of Pharmaceutical Products (Risk-MaPP)* (2017)

USP General Chapter <1231> *Water for Pharmaceutical Purposes*

USP General Chapter <1237> *Virology Test Methods*

2. Program Contacts

A. Center for Drug Evaluation and Research

CGMP- or Quality-Related Policy Questions

For CGMP- or quality-related policy, technical, or scientific questions or information needs, including questions about this compliance program, send an email to the following address and it will be handled as a top priority: OPQPolicy@fda.hhs.gov.

Office of Compliance: Enforcement-Related Guidance or Policy

For enforcement-related guidance or policy, including evidence need and sufficiency, citations, and case evaluation/recommendation advice related to marketed products or surveillance coverage, send an email to the following address and it will be handled as a top priority: CDEROMQCompliance@fda.hhs.gov.

Laboratories

Division of Pharmaceutical Analysis
645 South Newstead Avenue
St. Louis, MO 63110

Drug Applications

Submission information (general):

- Forms & Submission Requirements web page: https://www.fda.gov/drugs/development-approval-process-drugs/forms-submission-requirements
- Guidance Documents for Drug Applications web page: https://www.fda.gov/drugs/development-approval-process-drugs/guidance-documents-drug-applications

B. Office of Inspections and Investigations

Office of Medical Products and Tobacco Operations

Office of Pharmaceutical Quality Operations, Division of Pharmaceutical Quality Programs, Pharmaceutical Quality Initiatives Branch

ORA program coordinators: See the ORA Directory in the IOM for updated references,

https://www.fda.gov/files/inspections,%20compliance,%20enforcement,%20and%20criminal%20investigations/published/ORA--Directory.pdf

3. Acronyms

ADC	antibody-drug conjugate
ADE	acceptable daily exposure
AER	adverse event report
ATs	Alternative Tools
ANDA	abbreviated new drug application
API	active pharmaceutical ingredient
BDS	bulk drug substance
BLA	biologics license application
BPDR	biological product deviation report
BsUFA	Biosimilar User Fee Act
CAPA	corrective action and preventive action
CDER	Center for Drug Evaluation and Research
CGMP	current good manufacturing practice
CMC	chemistry, manufacturing, and controls
CMO	contract manufacturing organization
COA	certificate of analysis
DP	drug product
DS	drug substance
DSI	drug substance intermediate
EC	established condition
EIR	establishment inspection report
FD&C Act	Federal Food, Drug, and Cosmetic Act
FARs	Field Alert Reports
HEPA	high-efficiency particulate air
HVAC	heating, ventilation, and air conditioning
ICH	International Council for Harmonisation
IND	investigational new drug
IOM	Investigations Operations Manual
IQA	integrated quality assessment
ISO	International Organization for Standardization
ISPE	International Society for Pharmaceutical Engineering
MAPP	Manual of Policies and Procedures
MCB	master cell bank
MRA	mutual recognition agreement
NAI	No Action Indicated
NDA	new drug application
OC	Office of Compliance
OII	Office of Inspections and Investigations
OOS	out-of-specification
OPMA	Office of Pharmaceutical Manufacturing Assessment
OPQ	Office of Pharmaceutical Quality

OQS	Office of Quality Surveillance
PAC	product/assignment code
PAI	preapproval inspection
PDUFA	Prescription Drug User Fee Act
PHS Act	Public Health Service Act
PLI	prelicense inspection
pOAI	potential Official Action Indicated
PPQ	process performance qualification
PQS	pharmaceutical quality system
QMSR	quality management system regulation
RABS	restricted access barrier system
RIE	Remote Interactive Evaluations
SOP	standard operating procedure
UF/DF	ultrafiltration/diafiltration
USP	United States Pharmacopeia
VAI	Voluntary Action Indicated
WCB	working cell bank
WFI	water for injection

PART VII—CENTER RESPONSIBILITIES

This Part is intentionally left blank.

ATTACHMENT A: ANTIBODY-DRUG CONJUGATE PRODUCTS

ADCs are a type of biological product whereby a recombinant protein is purified and then conjugated to a small molecule drug via a chemical linker. Conjugation manufacturing can be performed at the DSI manufacturer but has typically been performed at a dedicated CMO due to the specialized manufacturing involved. The protein intermediate is purified and stored as a DSI, which is then conjugated to the small molecule payload, either through a linker or direct conjugation. Conjugation technologies employed are typically random conjugation processes, site-specific conjugation via engineered cysteine or other non-natural amino acids, or enzyme-mediated, facility-specific conjugation (e.g., transglutaminase). After conjugation, the ADC undergoes purification and formulation for the final DS.

The inspection team should, at a minimum:

- Evaluate the identity of the recombinant protein in the DSI.
- Evaluate whether the linker-payload raw material has been stored at the validated storage conditions before conjugation.
- When the conjugation reaction is enzyme-mediated, pay special attention to the raw material control strategy for the enzyme, including potential contamination concerns involving the use of animal-derived material in the production of the enzyme.
- Confirm that the conjugation procedure and subsequent quenching reaction are performed at the appropriate temperatures and time frames as described in the application.
- Confirm that subsequent purification steps after conjugation consistently remove unconjugated payload to appropriate safety levels as outlined in the application.

Reference:

- Guidance for industry *Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use* (February 1997)

ATTACHMENT B: PRODUCTS DERIVED FROM SPORE-FORMING MICROORGANISMS

Product manufacturing operations using spore-forming microorganisms conducted in a multiproduct establishment are expected to be performed under appropriate controls to prevent contamination of other products and areas within the establishment. Appropriate process containment control procedures are expected to be in place to prevent the potential spread of spore-forming microorganisms. Spore contamination prevention can be achieved by using a dedicated building or by using process containment if manufacturing is conducted in a multiproduct manufacturing building.

The inspection team should, at a minimum:

- If spore-forming microorganisms are used for manufacturing operations, regardless of whether production is in a dedicated building or multiproduct establishment:
    - Verify that a distinct crossover point is established in manufacturing operations, after which viable spore-forming microorganisms (both vegetative and spore forms) are not part of the process or process solutions.
    - Verify that the establishment's design, including air-handling unit segregation, airlocks, and pressure differentials, is appropriate to prevent the potential spread of spore-forming microorganisms to downstream of the crossover point.
    - Verify the adequacy of equipment segregation, personnel training, gowning, and flow of products, raw materials, personnel, waste, and equipment to prevent the spread of spores over the crossover point. Observe personnel during gowning and manufacturing operations.
- Verify that equipment exposed to pathogenic or potentially pathogenic microorganisms (e.g., *Clostridium botulinum*) is disposable or dedicated.
- For multiproduct establishments:
    - Determine whether the establishment design and procedures that are in place appropriately ensure containment. Verify that the movement of product and personnel between the spore-forming microorganisms manufacturing area and other manufacturing areas is appropriately designed to prevent the introduction of spores into other areas of the establishment.
    - Confirm that major processing equipment is disposable or dedicated to a specific product and is decontaminated and removed from the area during changeover. If equipment dedication and removal are not feasible, verify that effective equipment decontamination and cleaning procedures are in place. Review decontamination efficacy and cleaning validation/verification data.
    - Verify that procedures to decontaminate and remove potentially spore-contaminated materials (including ancillary room items), equipment, waste, and disposable or product-dedicated items during changeover are followed.
    - Determine whether environmental monitoring of the spore-forming microorganisms in adjacent areas is conducted during manufacturing operations with adequate results.

- Determine whether the environmental monitoring data demonstrate the effective removal of spore-forming production microorganisms from the manufacturing area after cleaning and decontamination are complete and before subsequent manufacture of other products.
- Verify that the quality unit reviews campaign changeover data (including environmental monitoring data) and that the quality unit executes area inspections before releasing the manufacturing area for the next product.

References:

- 21 CFR 600.11(e)(2), (3), and (5); 600.10(b); and 600.10(c)(1), (2), and (3)
- ICH Q7, section IV.D, Containment
- Guidance for industry *Manufacturing Biological Intermediates and Biological Drug Substances Using Spore-Forming Microorganisms* (September 2007)

ATTACHMENT C: HIGHLY POTENT OR TOXIC PRODUCTS

Multiproduct establishments that manufacture highly potent or toxic products are expected to identify hazards appropriately and minimize and prevent cross-contamination by having appropriate establishment design, segregation, process containment, and procedural controls. Establishments are expected to establish product carryover limits for shared product contact equipment based on toxicologically-derived acceptable daily exposure (ADE)—an exposure dose unlikely to cause an adverse effect when an individual is exposed, by any route, at or below the dose every day for a lifetime.

The inspection team should, at a minimum:

- Evaluate the adequacy of the establishment's strategies, including risk assessment documents, to control identified cross-contamination risks associated with highly potent or toxic products.
- Evaluate whether the establishment updates its risk assessment and risk mitigation strategies as new products are introduced or when new toxicological data become available indicating additional risks for cross-contamination.
- Evaluate whether toxicologically derived ADE is used in establishing the product carryover limits for shared product contact equipment and the analytical methods for cleaning validation are sufficiently sensitive in recovering highly potent or toxic compounds. Confirm that dedicated or disposable equipment is used if the predetermined product carryover limit for the cleaning of a toxic or highly potent product cannot be achieved.
- If ADE is not used for product carryover limit calculation for shared product contact equipment and the establishment claims product inactivation and degradation by equipment cleaning agents as the justification for the high product carryover limit, review product inactivation and degradation validation data using the worst-case cleaning simulation conditions.

References:

- ICH Q7, section IV.D, Containment
- ICH Q9(R1)
- ISPE Baseline Guide Volume 7, *Risk Based Manufacture of Pharmaceutical Products (Risk-MaPP)*

ATTACHMENT D: LYOPHILIZATION OR FREEZE-DRYING

Some DS and DP are lyophilized or freeze-dried to improve their storage stability. This section outlines inspectional activities specific to the lyophilization or freeze-drying operations of DS and DP manufacturing that are not covered in compliance program 7356.002A.

For DS operations, the inspection team should, at a minimum:

- Confirm that multiple trays were used for shelf temperature mapping during temperature uniformity studies for bulk lyophilization of DS and evaluate the data from the worst-case scenario mapping experiments.
- For the bulk lyophilization of DS, confirm that the volume, concentration, and fill height of DS are within validated ranges.
- Evaluate whether DSI decanting, tray filling, tray transport, and loading conditions are conducted as validated.

For DP operations, the inspection team should, at a minimum:

- Evaluate the establishment's visual inspection program (100% and acceptance quality limit), the effectiveness of inspection, and actions taken when defect limits are exceeded. Determine whether lyophilization DP vial defects are appropriately categorized and trended.
- Confirm that visual inspectors are appropriately trained and qualified and that training and qualification involves the use of defect libraries that incorporate relevant or expected defects such as melt back or cracks in the cake appearance for lyophilized product.
- Evaluate whether a small sample of units is reconstituted and inspected for visible particles in addition to the 100% inspection of the cakes for visible particles in the DP. Review the justification for the number of samples reconstituted.
- Evaluate whether the identity of the lyophilizer manufacturer is as described in the application.
- Confirm that the lyophilized product parameters (e.g., general appearance, cake appearance, melt back, reconstitution time, moisture) and their acceptance criteria are those described in the application.

References (for DP only):

- Draft guidance for industry *Inspection of Injectable Products for Visible Particulates* (December 2021)[1]
- Compliance program 7356.002A—*Sterile Drug Process Inspections*

[1] When final, this guidance will represent FDA's current thinking on this topic.